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ORAL ABSTRACT SESSION

Plenary Session 3: Proffered Papers: Clinical Trials

1 **Oral**

Phase 1 trial and translational study of the glutaminase-1 (GLS1) inhibitor IACS-6274 in combination with bevacizumab and paclitaxel in patients with advanced ovarian cancer

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Background: GLS1 drives glutamine-dependent metabolic pathways that support tumor survival under bevacizumab-induced hypoxic stress and paclitaxel-mediated cytotoxic pressure. Preclinical studies demonstrated that GLS1 inhibition synergistically disrupts adaptive metabolic reprogramming, resulting in enhanced antitumor activity. IACS-6274 is a potent oral GLS1 inhibitor with excellent pharmacokinetics (PK) and antitumor activity as monotherapy (NCT05039801; Yap et al ASCO 2021).

Materials and Methods: Advanced ovarian cancer patients (pts) received IACS-6274 at 120 mg or 180 mg BID in combination with bevacizumab (10 mg/Kg IV, D1 & D15) and paclitaxel (80 mg/m^2 IV, D1, D8 & D15) in 21-day cycles. PK and translational analyses were conducted using serial tumor and/or blood samples for ASNS IHC loss, differential gene expression, pathway enrichment, immune cell deconvolution, and transcriptional profiling analyses.

Results: 14 pts (mean age 56y [45-75y]; ECOG PS 0-1; median of 3 [1-6] prior lines of therapy) received IACS-6274 at 120 mg (n = 7) or 180mg (n = 7) BID with bevacizumab/paclitaxel. 13 of 14 (93%) pts had platinum-resistant disease and 8/14 (57%) had ASNS loss. Both dose levels were generally well tolerated; common treatment-related adverse events (TRAEs; ≥20%) were G1-2 nausea, fatigue, alopecia, anemia, epistaxis, ALT/AST elevation, leukopenia, nail disorders and photopsia. G3-4 TRAEs were reversible neutropenia (6/14), hypertension (4/14) and anemia (3/14). No dose-limiting toxicities were observed. PK at dose level 1: C_{max} 21.2 μM, $AUC_{0\text{-}12h}$ 191.4 h*μM, and C_{trough} 9.6 μM. Nine of 13 (69%) efficacy-evaluable pts achieved confirmed partial responses (PR) and 3 had stable disease (SD) by RECISTv1.1. Notably, 6/8 (75%) pts with ASNS loss tumors achieved PRs. Disease control at 12 weeks was 85% (11/13), with treatment durations lasting beyond 37 months. Durable tumor regression with PR or SD ≥ 6 months was observed in 10/13 (77%) pts.

Translational analyses showed substantial treatment-associated remodeling of the tumor microenvironment, with increased immune cell infiltration, induction of inflammatory/immune activation pathways, and suppression of proliferative/oxidative phosphorylation programs. Baseline transcriptional profiling identified epithelial-to-mesenchymal transition (EMT) and neural-like transcriptional states as candidate determinants of therapeutic response. Reduced PCDH10 expression, together with EMT-associated compensatory activation of ASNS pathway, may represent adaptive resistance mechanisms and potential targets for therapeutic intervention.

Conclusions: IACS-6274 in combination with bevacizumab/paclitaxel had a favorable safety profile and encouraging, durable antitumor activity in heavily pretreated, predominantly platinum-resistant ovarian cancer. A 2-stage expansion cohort in pts with advanced ovarian cancer is underway.

Conflict of interest: Other Substantive Relationships: We acknowledge that IACS-6274 was invented at The University of Texas MD Anderson Cancer Center and authors are inventors on patents related to this work.

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2 **Oral**

Phase 1 study of BHV-1530, a first-in-class FGFR3 ADC in Advanced Tumors

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Background: Fibroblast growth factor receptor 3 (FGFR3) is a validated oncogenic driver in multiple solid tumor types, with FGFR3 alterations and overexpression prevalent in urothelial carcinoma (UC) and other histologies. Despite this, no FGFR3-directed ADCs are approved or currently in clinical development. BHV-1530 is a novel, FGFR3-directed ADC with a proprietary topoisomerase I inhibitor payload with site-specific, highly stable conjugation, designed to enhance efficacy while differentiating on safety. Unlike small molecule inhibitors, which are limited to genomically altered tumors, BHV-1530's ADC mechanism has the potential to address a broader range of cancers, including both FGFR3-altered and FGFR3 wild-type overexpressing tumors. BHV-1530 also has the potential to synergize with checkpoint inhibitors, further expanding its therapeutic potential.

Materials and methods: BHV1530-101 (NCT06874335) is the ongoing, Phase 1 First-In-Human trial of BHV-1530 in patients (pts) with advanced solid tumors. The primary endpoint is safety; the secondary endpoint is preliminary efficacy. We report interim results from the dose escalation portion of BHV-1530-101.

Results: As of June 23, 2026, 20 pts had received BHV-1530 at doses from 1mg/kg to 9mg/kg, IV every 3 weeks, including UC (N = 5), HNSCC (N = 3), and NSCLC (N = 2). No dose-limiting toxicities, treatment-related serious adverse events, or deaths have been reported. Treatment emergent adverse events, (TEAEs) occurred in 19 pts (95%) and were mostly Grade 1-2, including nausea (40.0%) and fatigue (25%). Notably, TEAEs frequently reported with approved pan-FGFR inhibitors including hyperphosphatemia, nail dystrophy, stomatitis, and central serous retinopathy were not reported as TEAEs in this study, nor were any cases of interstitial lung disease. The maximum tolerated dose has not been reached.

Tumor reductions have been reported at doses $\geq$3.3mg/kg in both FGFR3-mutated and wild-type overexpressing tumors, including confirmed partial responses in FGFR3-mutated UC and HNSCC. Notably, responses were observed in pts with disease progression on prior EV and FGFR TKIs, suggesting independence from established resistance mechanisms. Preliminary pharmacokinetic (PK) data were favorable, demonstrating a dose-dependent increase in exposure, a half-life (approximately 8 days or longer) suitable for Q3W dosing, and a highly stable ADC with the unconjugated-payload-to-ADC molar ratio $<$1%.

Conclusions: BHV-1530, a first-in-class FGFR3-directed ADC in clinical development, has demonstrated a favorable safety profile with no FGFR class-related toxicities and confirmed objective responses across multiple tumor types. Enrollment is ongoing; updated clinical and PK data from current and additional pts will be presented.

Conflict of interest:

Ownership: SS: Revolution Medicine, Pfizer, Moderna, Oscar Health

WM: Recursion Pharmaceuticals

SC: Biohaven Pharmaceuticals Inc.

NK: Biohaven Pharmaceuticals Inc.

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SG: Pfizer, Merck, BMS, Novartis, Convergent Therapeutics, Flare Therapeutics

JRA: Novartis, Blueprint Medicines, Spectrum Pharmaceuticals, Symphogen, BioAtla, Black Diamond, Pfizer, GenMab, Kelun-Biotech, GlaxoSmithKline, Merck Sharp & Dohme, Hummingbird, Yingli, Bicycle Therapeutics, Taiho, Roche Pharmaceuticals, Merus, Curis, Aadi Bioscience, ForeBio, Loxo Oncology, Ideaya, Amgen, Tango Therapeutics, Mirati, Linnaeus Therapeutics, Hutchinson MediPharma

Other Substantive Relationships:

GF: Travel -BMS, EMD Serono, Fujifilm, Millennium, Sarah Cannon Research Institute (employer), Amgen, Synthorx / Sanofi. Wolters Kluwer (Royalties)

GI: Invited Speaker- Pfizer, Curio Science

SS: Consultant- Guidepoint Global

DB: Speakers' Bureau-Merck Sharpe Dohme, Accommodation-DAVA Oncology, Merck KGaA, Merck Sharpe Dohme, Seagen.

SG: Gilead Sciences (Research Grant)

JP: Biohaven (paid consultant)

JRA: Consultancy for Pfizer, Sardona Therapeutics, Vall d'Hebron Institute of Oncology/Ministero De Empleo Y Seguridad, Chinese University of Hong Kong, Boxer Capital, LLC, Tang Advisors, LLC, Alnylam Pharmaceuticals, Bridgebio Pharma, Mekanistic, Amgen, Guidepoint, Axiom, Merus, Vall d'Hebron Institute of Oncology/ Cancer Core Europe (research funding)

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3 **Oral**

Dose-exploration results of a phase 1 study of AMG 305, a dual-targeting MSLN/CDH3 x CD3 T-cell engager, in patients with advanced solid tumors

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Background: AMG 305 is a novel mesothelin (MSLN) and P-cadherin (CDH3) dual-targeting half-life extended (HLE) bispecific T-cell engager (BiTE®) designed to preferentially redirect T cells towards tumor cells co-expressing MSLN and CDH3, aiming to expand the therapeutic index in solid tumors. We report dose-exploration results of AMG 305 monotherapy in a first-in-human study in patients (pts) with advanced solid tumors.

Material and methods: This open-label phase 1 study enrolled adults with selected advanced/metastatic solid tumors who had exhausted standard of care treatment options or were not candidates for available therapy. AMG 305 was administered intravenously across escalating dose levels / various schedules in dose-exploration cohorts 1-8; cohort 8 incorporated rituximab B-cell depletion preconditioning to mitigate anti-drug antibody (ADA) formation. Primary objectives were to evaluate safety/tolerability and identify OBD, MTD, and RP2D. Secondary objectives included PK and preliminary antitumor activity.

Results: As of 8 April 2026, 37 pts across 8 cohorts received $>=1$ dose of AMG 305, 32 were DLT-evaluable. Median (range) age was 55.0 (33-76) years. Tumor types included colorectal cancer (n = 17), pancreatic ductal adenocarcinoma (n = 12), non-small cell lung cancer (n = 2), mesothelioma (n = 2), endometrial cancer (n = 2), cervical carcinoma (n = 1), and ovarian epithelial cancer (n = 1); 28 (75.7%) pts had 2 or more prior lines of therapy. Treatment-emergent adverse events (TEAEs) occurred in 36 (97.3%) pts [grades (gr) 3 and 4: 26 (70.3%); no gr5]; treatment-related adverse events (TRAEs) occurred in 34 (91.9%) pts, including gr 3/4 events in 11 (29.7%). The most common TEAEs were cytokine release syndrome (CRS; 28 [75.7%]), fatigue (15 [40.5%]), abdominal pain (14 [37.8%]), anemia (10 [27.0%]), rash and cough (9 [24.3%] each). CRS was gr 1 in 19 (51.4%), gr 2 in 5 (13.5%), gr 3 in 4 (10.8%) pts; no gr 4. DLTs (CRS, pneumonitis) were observed in 4 pts across 3 cohorts; an MTD was not defined. Preliminary PK showed dose-proportional increase in exposure. Among 36 response-evaluable pts, tumor shrinkage was observed in 4, without confirmed response per RECIST 1.1. Treatment-emergent ADAs were developed in 60.0% of evaluable pts (median onset of 22 days after the 1st dose of AMG 305) and were associated with lower AMG 305 concentrations in some pts. Findings in cohort 8 (N = 6) suggest B-cell depletion preconditioning had no meaningful impact on ADA profile and no new safety signal.

Conclusions: Across dose-exploration cohorts, AMG 305 had a manageable safety profile. Dose-proportional PK was observed; however, treatment-emergent ADAs limited sustained drug exposure, no confirmed RECIST responses were achieved. These findings provide important insights for the development of future T-cell engagers in solid tumors.

Clinical trial identification: NCT05800964

Conflict of interest:

Advisory Board: BB: Tempus AI, Fate Therapeutics, Artios Pharma

BT: for Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Ipsen, IQVIA, Janssen, Merck, MSD, Novartis, Pfizer, Roche, Sanofi, Tolmar, VIR Biotechnology

MH: IQVIA, Abbvie

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VC: Immuneering and Revolution Medicine

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Novartis, Ono Pharmaceuticals, Pionyr Immunopharma, RAScal Therapeutics, Synnovation Therapeutics, Tarveda Therapeutics.

TWK: Genentech, Inocras

MS: Bristol Myers Squibb, Johnson & Johnson

BT: Amgen, Astellas, AstraZeneca, Bayer, BMS, Genentech, Ipsen, Janssen, Pfizer, Movember, MSD

MH: Novartis, Roche

MW: Roche, Iovance Biotherapeutics, Boehringer Ingelheim

VC: Merck

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Other Substantive Relationships:

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NS, JZ, BiB: employment Amgen Inc.

JS, NS, JZ and BiB: Amgen Inc. stock ownership

BB: Department of Defense CDRMP Research Funding, Speaker's Bureau Guadrant Health

MS: consultant –Amgen, AstraZeneca, Bristol Myers Squibb, Gilead, GlaxoSmithKline, Johnson & Johnson, Lilly, MSD, Novartis, Regeneron, Roche, Sanofi and •Honoraria for CME presentations: Amgen, Bristol Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Lilly, MSD, Roche

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MH: honoraria Roche, Speaker's Bureau Roche, MSD

MW: Honoriaria, Lilly, Boehringer Ingelheim, Synlab, Janssen, Merck Serono, GWT, Amgen, Novartis, Pfizer, BMS, Regeneron, MJH/PER, Takeda, AstraZeneca, Travel expenses: Amgen, Astra Zeneca, BMS, Daiichi Sankyo Europe, GEMoaB, immatics, Iovance Biotherapeutics, Janssen Oncology, Merck Serono, Pfizer, Sanofi/Aventis

EC: President and Founder of Foundation INTHEOS (Investigational Therapeutics in Oncological Sciences), Non for profit Foundation PharmaMar, Non-for-profit CRIS Cancer Foundation, Stock or other ownership: START, Oncoart Associated, HM Hospitales, employment: START, HM Hospitales Group, Leadership: START, PharmaMar, EORTC, Sanofi, BeiGene, CHUV, Oncomatryx, Shionogi

MG: Shareholder - Outcomes Matter Innovations LLC, Genomic Testing Cooperative, COTA

MJ: Travel, accommodations, expenses – AbbVie, AstraZeneca, Genentech, Incyte, Merck, Pfizer, Sanofi.

SP: Travel, accommodations, expenses - Revolution Medicines.

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5 **Oral**

First clinical data of SYN818, a selective POLθ helicase domain inhibitor, in combination with olaparib in patients with BRCA-mutated solid tumors

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Background: DNA polymerase theta (POLθ) plays a critical role in replication fork protection. In homologous recombination deficient tumors, POLθ inhibition is synthetically lethal with PARP inhibition. SYN818 is a first-in-class, highly potent oral inhibitor specifically targeting the helicase domain of POLθ. This combination is expected to deepen clinical response and improve outcomes in BRCA-mutated cancers.

Methods: This ongoing first-in-human, open-label, multicenter Phase Ib dose-escalation study (NCT07156253; CTR20253189) evaluates the safety, pharmacokinetics (PK), and preliminary antitumor activity of SYN818 plus olaparib for advanced BRCA-mutated solid tumors. SYN818 was administered orally once daily (50-200 mg) in combination with olaparib 300 mg BID. Primary objectives included

safety and tolerability. Secondary objectives included PK and antitumor activity per RECIST v1.1.

Results: As of 17 April 2026, 16 patients had been enrolled in the dose-escalation phase. No dose-limiting toxicities occurred. The safety profile was consistent with olaparib monotherapy, with no evidence of additive or overlapping toxicity from SYN818. Olaparib PK parameters were comparable to historical data in Chinese patients, indicating minimal drug–drug interaction risk. Among enrolled patients, the median number of prior lines of therapy was 3 (range, 1–7); prior treatment with PARP inhibitors or antibody–drug conjugates was permitted. 10 patients were evaluable for efficacy, yielding an objective response rate (ORR) of 70%. In the subgroup of eight patients with HER2-negative metastatic breast cancer, six partial responses were observed (ORR 75%; disease control rate 87.5%). At data cut-off, median follow-up was 3 months, with most patients continuing treatment. Updated follow-up 7 months (longest treatment duration ~10 months) will be presented at the congress.

Conclusions: This represents the first clinical disclosure of SYN818, a novel POLθ helicase domain inhibitor. The combination of SYN818 with olaparib was well tolerated and demonstrated highly encouraging preliminary antitumor activity in patients with BRCA-mutated solid tumors, particularly in HER2-negative metastatic breast cancer. These data provide the first human evidence that dual targeting of PARP and POLθ helicase domain yields robust clinical responses, and support further development of this combination as a potential new standard-of-care option for patients with BRCA-mutated tumors.

No conflict of interest

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ORAL ABSTRACT SESSION

Plenary Session 6: Proffered Papers: Advances in Targeting RAS

6 **Oral**

MYC Inhibition with OMO-103 Restores TNF-Superfamily Signaling and Uncovers Actionable Immunotherapy Vulnerabilities in KRAS-Mutant NSCLC

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Background: MYC is a central transcriptional regulator downstream of oncogenic KRAS that contributes to immune exclusion and therapeutic resistance in non-small cell lung cancer (NSCLC). Analysis of KRAS-mutant NSCLC patient datasets identified suppression of Tumor Necrosis Factor (TNF) superfamily signaling as a prominent feature associated with elevated MYC activity. We investigated whether MYC inhibition with OMO-103 (a.k.a. Omomyc), the first clinically viable direct MYC inhibitor, restores TNF-dependent immune programs and reveals therapeutically exploitable vulnerabilities within the tumor immune microenvironment (TIME).

Materials and Methods: Transcriptomic analyses were performed in KRAS-mutant NSCLC patient cohorts and genetically engineered mouse models. MYC-dependent NSCLC cell lines were used to assess the impact of OMO-103 on proliferation and immune-related transcriptional programs. Multiple KRAS-driven NSCLC mouse models were employed to characterize changes in immune composition and TNF-superfamily signaling following MYC inhibition. Translational relevance was evaluated using paired tumor and serum samples from patients enrolled in the MYCure Phase I trial (NCT04808362).

Results: Elevated MYC activity in KRAS-mutant NSCLC was associated with reduced expression of TNF-superfamily components and diminished immune engagement. OMO-103 treatment induced broad transcriptional remodeling characterized by activation of inflammatory pathways, enhanced antigen presentation and restoration of TNF-superfamily signaling. In vivo MYC inhibition increased infiltration of effector immune populations and promoted elevated expression of co-stimulatory TNF receptor family members, including OX40 and 4-1BB, on tumor-infiltrating T cells. Functional activation of these pathways was accompanied by increased production of interferon-γ and TNF-α and durable tumor control. Importantly, TNF-superfamily activation emerged as a consistent pharmacodynamic consequence of MYC blockade across preclinical models and clinical samples. In MYCure patients, clinical benefit was associated with increased expression of TNF-superfamily genes in tumors and elevated circulating TNF-related mediators, with the strongest induction observed in the KRAS-mutant NSCLC patient.

Conclusions: These findings identify suppression of TNF-superfamily signaling as a previously underappreciated mechanism of MYC-driven immune evasion in KRAS-mutant NSCLC. OMO-103 restores these pathways and converts immunologically restricted tumors into immune-responsive states, providing mechanistic rationale for biomarker-driven combinations of MYC inhibition with TNFR-targeted immunotherapies.

Conflict of interest

Ownership:

L.S., M.E.B., and S.C.-S. are or were shareholders of Peptomyc S.L. at the time the results were generated.

Advisory Board:

J.Z. received advisory honoraria from multiple companies (Boehringer-Ingelheim, Janssen, Pierre Fabre, Takeda, Sanofi, BMS, AstraZeneca, MSD, Roche, Pfizer, Novartis, NanoString). S.V. is a scientific advisor for Libera Bio and has received consulting fees from Roche and Revolution Medicines. L.S. received consulting fees from Peptomyc S.L.

Board of Directors:

LS is board member of Peptomyc S.L.

Corporate-sponsored Research: J.Z. received research support/grants from AstraZeneca, Roche, and BMS. S.V. received research funding from Roche and Revolution Medicines.

Other Substantive Relationships:

M.A., S.M.-M., L.S.-B., L.F., and H.T. are employees of Peptomyc S.L. L.S., M.E.B., and S.C.-S. are or were employees of Peptomyc S.L. L.S., M.E.B., I.G.-L., and S.C.-S. are inventors/authors on patents related to OMO-103. J.Z. received speaker and travel honoraria from multiple companies.

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7 **Oral**

ARV-806, a PROTAC KRAS G12D Degrader, in Patients with KRAS G12D–Mutated Advanced Solid Tumors: Preliminary Phase 1 Results

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Background: No approved therapies target KRAS G12D, the most common oncogenic *KRAS* alteration. ARV-806, a PROteolysis TArgeting Chimera (PROTAC) KRAS G12D degrader, is a bifunctional small molecule that induces ubiquitination and subsequent proteasomal degradation of KRAS G12D. ARV-806 targets both active (GTP-bound) and inactive (GDP-bound) forms of KRAS G12D. Preclinically, ARV-806 demonstrated tumor growth inhibition and tumor regressions in pancreatic, colorectal, and lung cancer models. We report initial results of a first-in-human, multicenter study of ARV-806 in patients (pts) with *KRAS* G12D–mutated cancer.

Material and methods: The phase 1 dose-escalation part of this phase 1/2 study (NCT07023731) enrolled pts with *KRAS* G12D–mutated advanced solid tumors who received prior standard of care therapy and had ≥1 measurable lesion. Pts received intravenous ARV-806 once weekly (QW) or every 2 weeks (Q2W) in 28-day cycles. Primary endpoints were dose-limiting toxicities (DLTs) during cycle 1 and treatment-emergent adverse events (TEAEs); secondary endpoints included pharmacokinetics (PK) and investigator-assessed objective response. Exploratory biomarker analyses included KRAS G12D degradation in tumor tissue and change in *KRAS* G12D in ctDNA.

Results: As of Jun 12, 2026, 76 pts received ARV-806 QW (10 mg n = 4; 20 mg n = 9; 40 mg n = 13; 65 mg n = 13; 100 mg n = 10) or Q2W (65 mg n = 12; 100 mg n = 15); 50 (66%) had pancreatic ductal adenocarcinoma (PDAC), 16 (21%) colorectal cancer (CRC), 4 (5%) non-small cell lung cancer, 3 (4%) cholangiocarcinoma (CCA), 2 (3%) appendiceal carcinoma, and 1 (1%) ovarian cancer. Median age was 64 y (range 35 − 82); 53% of pts were female. Median number of prior lines of systemic therapy was 2 (range 1 − 8). At data cutoff, 25 (33%) pts remained on treatment. No DLTs were reported. Any grade TEAEs occurred in 70 (92%) pts, grade ≥3 TEAEs in 43 (57%), and serious TEAEs in 37 (49%). TEAEs led to dose interruption in 29 (38%) pts; 5 (7%) discontinued ARV-806 due to TEAEs (1 treatment-related). Treatment-related TEAEs (TRAEs; ≥5%) were fatigue (26%), nausea (20%), diarrhea (9%), vomiting (9%), increased aspartate aminotransferase (AST; 5%), dysgeusia (5%), infusion-related reaction (IRR; 5%), and maculopapular rash (5%). Most TRAEs were grade 1/2; 3 pts had grade 3 TRAEs (IRR/stomatitis, increased AST, and anemia [n = 1 each]). Preliminary PK suggested ARV-806 exposure increased in a dose-proportional manner and reached the preclinical exposure threshold for efficacy at doses ≥20 mg QW. In response-evaluable pts, 7 responses (5 confirmed) were observed across dose levels, including 5 in PDAC (4 confirmed), 1 in CRC, and 1 in CCA (confirmed).

Conclusions: ARV-806 was well tolerated, with no DLTs observed at any dose tested, and demonstrated preliminary antitumor activity in pts with *KRAS* G12D–mutated advanced solid tumors.

Conflict of interest:

Ownership:

Stock and Other Ownership Interests:

DS Hong: OncoResponse, Telperian, MolecularMatch, crossbridge Bio, Breakthrough Bio

DL. Bajor: Mirati Therapeutics, Revolution Medicines, Erasca, Inc

S Sharma: Beta Cat Pharmaceuticals, Salarius Pharmaceuticals, ConverGene

Stingray Therapeutics, Elevar Therapeutics, HLB, Barricade Therapeutics, Black Canyon Bio, Bonneville Bio

MJ Borad: ADC Therapeutics, Assertio Therapeutics, Homology Medicines, Abeona Therapeutics

J Teh, E Duperret, J Gong, E Zhi, and G Pouliot: Arvinas.

Advisory Board:

Consulting or advisory role:

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NJ Gandhi: CytomX Therapeutics

AI Spira: Incyte, Amgen, Novartis, AstraZeneca/MedImmune, Mirati Therapeutics, Gritstone Bio, Jazz Pharmaceuticals, Merck, Bristol-Myers Squibb, Takeda, Janssen Research & Development, Mersana, Blueprint Medicines, Gritstone Bio, Daiichi Sankyo/Astra Zeneca, Regeneron, Lilly, Black Diamond Therapeutics, Sanofi, ArriVent Biopharma, Synthekine, GlaxoSmithKline, crispr therapeutics, Revolution Medicines

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RD Kim: Taiho Oncology, Exelixis, SERVIER, Pfizer, Roche/ Genentech, AstraZeneca, Abbvie, Jazz Pharmaceuticals, Eisai, Bayer, Elevar Therapeutics, Takeda

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A Patnaik: Merck, Pfizer, Lilly, Plexxikon, Corvus Pharmaceuticals, Tesaro, Abbvie, Forty Seven, Five Prime Therapeutics, Infinity Pharmaceuticals, Pieris Pharmaceuticals, Surface Oncology, Livzon, Vigeo Therapeutics, Astellas Pharma, Klus Pharma, Symphogen, Syndax, Arcus Ventures, Fochon Pharmaceuticals, Upsher-Smith, Exelixis, Seagen, Bolt Biotherapeutics, Ionova, Daiichi Sankyo, Sanofi, Gilead Sciences, Daiichi Sankyo, Pionyr, Loxo@Lilly, Nektar, Alpine Immune Sciences, Amgen, Institut de Recherches Internationales Servier (IRIS), 1200 Pharma, Arcus Biosciences, Genentech, AADi, Prelude Therapeutics, KSQ Therapeutics, Carrick Therapeutics, Pyrotech Therapeutics, Quanta Therapeutics, BioTheryX, MOMA Therapeutics, IGM Biosciences, Loxo, Compugen, Scorpion Therapeutics, Olema Oncology, Moderna Therapeutics, Vividion Therapeutics, NiKang Therapeutics, Ensem Therapeutics, Roche, Ambrx, Arvinas, BioNTech, SERVIER, Ottimo Pharma

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S Sharma: Plexxikon, AADi, Syndax,

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DL Bajor: Apexigen, Tesaro, Rafael Pharmaceuticals, Calithera Biosciences, Bristol-Myers Squibb/Celgene, GlaxoSmithKline, Seagen, Abbvie, Astellas Pharma, Arvinas

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AI Spira: Leadership: Next Oncology

Honoraria: CytomX Therapeutics, AstraZeneca/MedImmune, Merck, Takeda, Amgen, Janssen Oncology, Novartis, Bristol-Myers Squibb, Bayer, Prelude Therapeutics, Abbvie, Astellas Pharma, Lilly.

A Patnaik: Speaker's bureau: Merck, San Antonio Pancreatic Cancer Symposium. Honoraria: Texas Society of Clinical Oncology (TxSCO).

DS Hong: Travel: Telperian, Medscape, ImmunoGenesis, AACR.

S Sharma: Honoraria: Array bioPharma. Travel: Project Cure CRC: Patents, Royalties, Other Intellectual Property: Provisional Application No. 62/961,930. Title: PepSeq as a platform to identify synthetic molecular binding agents, International PCT Application No. PCT/US20/13618 Title: BISPHOSPHONATE CONJUGATES AND USES THEREOF, Provisional application number: 62/818,037 Title: Trisubstituted Pyrazolo [1, 5-a] Pyrimidine Compounds and Methods of Use Thereof, Compositions and Methods for the Treatment of Coronavirus Infection. Provisional Application Serial No.: 63/ 005,780. Filing Date: 4/6/2020. TGen Ref No: 200401- 299PROV, Imidazolopyridazine Compounds and Methods of Use Thereof. Provisional Application No.: 63/079,951. Filing Date: 9/17/2020. TGen Ref No.: 200727-304PROV1. Seed Ref. No.: 910255.402P1, Imidazolopyrazine Compounds and Methods of Use Thereof. Provisional Application No.: 63/079,954. Filing Date: 9/17/2020. TGen Ref No.: 200727-304PROV2. Seed Ref. No.: 910255.403P1, Imidazolotriazine Compounds and Methods of Use Thereof. Provisional Application No.: 63/079,955. Filing Date: 9/17/2020. TGen Ref No.: 200727-304PROV3. Seed Ref. No.: 910255.404P1, Neoantigen-Informed Tumor-Infiltrating Lymphocyte Cancer Immunotherapy. WO 2021/222855. PCT/US2021/030331

Compositions and Methods for the Treatment of Cancer. Provisional Application Serial No. 63/270,005.

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Methods and Compounds for Neoantigen Vaccines Provisional Application Serial No.: 63/166,697.

Peptide Inhibitors Targeting the TBL1-Beta-Catenin Complex. Provisional Application Serial No.: 63/159,882.

SR Chandana: Speakers bureau for Natera Inc.

B O'Neil: Honoraria: Amgen.

DL Bajor: Travel: Cardinal Health

Honoraria: Agenus, Tempus.

L Wu: Honoraria: AstraZeneca, Partners Therapeutics.

RD Kim: Honoraria from Natera.

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8 **Oral**

Preliminary safety, pharmacokinetics, and efficacy of ERAS-0015: Results from the AURORAS-1 first-in-human trial

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Background: RAS GTPases are key to the MAPK pathway, known for their pivotal role in tumor cell proliferation and survival. Oncogenic mutations that shift RAS from a GDP- to GTP-bound state lead to prolonged pathway activation and tumorigenesis. ERAS-0015, a pan-RAS molecular glue designed to target mutant and wild-type GTP-bound KRAS, NRAS, and HRAS, showed potent nonclinical activity across a panel of cell-based and in vivo models with diverse RAS alterations. ERAS-0015 has higher binding affinity to cyclophilin A, greater cell-based potency, improved nonclinical pharmacokinetics (PK), and comparable tumor growth inhibition at lower doses in vivo vs RMC-6236, another pan-RAS molecular glue.

Material and methods: Safety, PK, and preliminary efficacy of ERAS-0015 are being evaluated in patients (pts) with advanced solid tumors with RAS alterations in an ongoing phase 1, first-in-human, open-label study (AURORAS-1, NCT06983743). Adults eligible for dose-escalation cohorts had locally advanced or metastatic (la/m) non-small cell lung cancer (NSCLC), cholangiocarcinoma, gallbladder carcinoma, or colorectal cancer with KRAS G12X or G13X mutations or la/m pancreatic ductal adenocarcinoma (PDAC) and received/declined standard-of-care therapy (or had none available). Exclusion criteria included prior RAS inhibitor therapy. Pts received once-daily oral ERAS-0015 in 3-wk cycles until progression or unacceptable toxicity; the primary objective was to establish the maximum tolerated dose (MTD) and recommend doses for expansion. Primary endpoints included safety/tolerability and PK. Secondary endpoints included objective response rate and duration of response. We present safety from the overall population and preliminary efficacy from KRAS G12X NSCLC and PDAC pts.

Results: As of May 25, 2026, 109 pts (median age, 65 y; male, 59.6%; PDAC, n = 66; NSCLC, n = 27) received ERAS-0015, with a median duration of exposure of 13.7 wk. During escalation (2-40 mg), ERAS-0015 exhibited linear PK with no observed dose-limiting toxicities or reaching MTD. Common (≥10%) any-grade treatment-related adverse events (TRAEs) were rash (dermatitis acneiform, rash, rash maculopapular, and erythema: 73.4%), diarrhea (31.2%), and nausea (23.9%); 14 pts (12.8%) reported grade ≥3 TRAEs. Of 15 pts receiving ERAS-0015 24-32 mg with KRAS G12X PDAC previously treated with chemotherapy, 6 (40.0%) had objective responses. Of 8 pts receiving ERAS-0015 8-32 mg with KRAS G12X NSCLC previously treated with an immune checkpoint inhibitor or platinum-based chemotherapy (without taxanes), 6 (75.0%) had objective responses. Updated data including additional pts and longer follow-up will be presented.

Conclusions: Preliminary safety, PK, and tumor response data suggest ERAS-0015 is safe and well tolerated, with linear PK and promising early clinical activity.

Conflict of interest:

Other Substantive Relationships:

Judy S. Wang: Travel, Accommodations, Expenses: NGM Biopharmaceuticals, Boehringer Ingelheim

Research Funding: AbbVie, Accutar Biotech, Adagene, Allorion Therapeutics, Alterome Therapeutics, Apollo, Artios, Astellas Pharma, BeiGene, Bicycle Therapeutics, BioNTech, BMS GmbH & Co. KG, Boehringer Ingelheim, C4 Therapeutics, Celgene/Bristol-Myers Squibb, Compass Therapeutics, Compugen, Cullinan Oncology, Conjupro Biotherapeutics, D3 Bio, Daiichi Sankyo/UCB Japan, DualityBio, Edgewood Oncology, Ellipses Pharma, Erasca, Inc., Genmab, Georgiamune, GlaxoSmithKline, Hotspot Therapeutics, Immunitas, Immunogen, Janssen, Jazz Pharmaceuticals, Kineta, Klus Pharma, Kumquat Biosciences, Kura Oncology, MacroGenics, MBQ Pharma, Merck KGaA, Mersana, Moderna Therapeutics, NGM Biopharmaceuticals, Novartis, Nurix, Olema Oncology, OnCusp Therapeutics, Pfizer, Pyxis, Quanta Therapeutics, Relay Therapeutics, Revolution Medicines, Sanofi, Step Pharma, Syndax, Tango Therapeutics, Vividion Therapeutics, Xencor, Zai Lab, Zymeworks, MediLink Therapeutics, Menarini, Circle Pharma, iTeos Therapeutics, Acrivon Therapeutics, Systimmune, Incyte, Accent Therapeutics, Halda Therapeutics, DAAN Biotherapeutics, Abdera Therapeutics, Genentech, Lilly, Loxo/Lilly, MabSpace Biosciences, Roche, Angiex, Axion Biosystems, Crescent, Day One Biopharmaceuticals, NiKang Therapeutics, Sutro Biopharma.

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Medicines, Regeneron, Alkermes, Revolution Medicines, Medikine, Black Diamond Therapeutics, Blueprint Oncology, Nalo Therapeutics, Scorpion Therapeutics, ArriVent Biopharma, Prelude Therapeutics, Lilly, Lepu Biopharma, Tango Therapeutics.

Yonina R. Murciano-Goroff: Travel, accommodation, and expenses: AstraZeneca and Loxo Oncology at Eli Lilly/ Eli Lilly and Company

Honoraria: Virology Education and Projects in Knowledge (CME program funded by an educational grant from Amgen)

Advisory board: Revolution Medicines

Consultant: AbbVie

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Erminia Massarelli: Consulting or Advisory Role: Sanofi, Bristol Myers Squibb Foundation, Gilead Sciences, Johnson & Johnson/ Janssen, AbbVie, Merck, Daiichi Sankyo/AstraZeneca, AstraZeneca

Travel, Accommodations, Expenses: Physicians' Education Resource, Johnson & Johnson/Janssen

Honoraria: AstraZeneca, Physicians' Education Resource.

Carrie Metcalf, Justine Lam, Gerri Lee, Dongyuan Xing, Les Brail, Shannon R. Morris: Erasca: Current Employment.

David S. Hong: Employment: MD Anderson Cancer Center

Consulting or Advisory Role: Amgen, AlphaSights, Boxer Capital, COR2ed, EcoR1 Capital, Gerson Lehrman Group, Guidepoint Pharmacy, ImmunoGenesis, Medscape, Pfizer, Revolution Medicines, T Knife Therapeutics, WebMD, Kestrel Therapeutics, Erasca, Inc., Acuta Capital Partners, Blueprint Medicines, PharmaResearch, AbbVie, Sequenom, BeiGene, ClearView Oncology, Morgan Stanley, Nextech Invest

Travel, Accommodations, Expenses: Telperian, Medscape, ImmunoGenesis, AACR

Stock and Other Ownership Interests: OncoResponse, Telperian, MolecularMatch, CrossBridge Bio, Breakthrough Bio

Research Funding: Genentech, Amgen, AbbVie, Bayer, Pfizer, Bristol-Myers Squibb, Deciphera, Merck Sharp & Dohme, Adlai Nortye, BeiGene, Lilly, Endeavor Biomedicines, Erasca, Inc., Roche, ImmunoGenesis, National Cancer Institute, Revolution Medicines, VM Pharma, BioBridge, Exelixis, Quanta Therapeutics, Alterome Therapeutics, Inhibrx, Kumquat Biosciences, Acendo, Adaptimmune, Arvinas, AstraZeneca, Kura Oncology, Novartis, STCube, Velavagio, Verastem.

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ORAL ABSTRACT SESSION

Plenary Session 7: Proffered Papers: Novel Agents and Targets

9 **Oral**

Interim results from the first-in-human phase 1 study of WEE1 inhibitor APR-1051 in patients with advanced solid tumors (ACESOT-1051)

T.A. Yap [1], S. Sen [2], D. Sommerhalder [3], A. Tolcher [3], C. Miller [4], D. Stenehjem [5], M. Carleton [4], P. Pultar [4], E. Kennedy [4]

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Background: WEE1 tyrosine kinase regulates cell cycle checkpoints (G1-S, G2-M) and DNA damage responses. Inhibiting WEE1 can force premature mitotic entry and subsequent apoptosis. APR-1051 is a highly potent WEE1 inhibitor (WEE1i) with initial clinical data demonstrating evidence of clinical activity. Low off-target inhibition of PLK kinases (PLK1, PLK2, PLK3) by APR-1051 differentiates it from other WEE1i's and may confer improved safety.

Methods: This open-label dose escalation and dose expansion study is evaluating APR-1051 monotherapy in a precision tumor marker driven fashion using an oral once-daily (QD) regimen. The intended study population is defined by uterine serous carcinoma, platinum resistant ovarian cancer overexpressing Cyclin-E by immunohistochemistry, genetic markers (CCNE1, CCNE2, FBXW7, PPP2R1A) regardless of tumor histology, HPV associated head and neck and gynecological cancers, and KRAS-$^{G12/G13}$ & TP53 colorectal cancer. The study is currently enrolling at multiple US sites (NCT06260514). Primary study objectives are characterization of initial safety, dose-limiting toxicity (DLT), maximum tolerated dose/ maximum administered dose, and recommended phase 2 dose of APR-1051. Secondary objectives include evaluating APR-1051 pharmacokinetic (PK) properties and preliminary efficacy (RECIST v1.1).

Results: As of May 6, 2026, 28 patients (median age 62 years [range: 40–86]; have been enrolled at dose levels up to 300 mg QD. The most common histologies enrolled are colorectal cancer (50%; 14/28) and uterine / endometrial cancer (29%; 8/28). The median prior lines of treatments was 3. Any grade adverse event (AE) was reported in 26 (93%) patients. Treatment-related AEs were reported in 15 (54%) patients; 13 (46%) patients had non-serious gastrointestinal events. Two patients (7%) had Grade 3 TRAEs: decreased lymphocyte count in one patient at 50 mg and increased AST /ALT in one patient at 50mg which met protocol-defined DLT criteria. PK data including patients dosed at 300mg continues to show dose proportional increases (AUC and Cmax), a Tmax average of 4 hours, and a half-life averaging 17 hours (C1D1) indicating relatively slow absorption and supporting once daily dosing. Evidence of clinical activity has been observed in patients dosed at 70 mg or greater (42%; 8/19). Two endometrial cancer patients with PPP2R1A mutations had partial responses (1 confirmed) per RECISTv1.1 and 6 patients had stable disease by the same standards.

Conclusions: In this ongoing trial, continuous daily oral dosing of APR-1051 QD has an encouraging preliminary safety profile with initial evidence of monotherapy clinical activity in patients with heavily pretreated advanced solid tumors. Updated data will be presented at the meeting.

Conflict of interest:

Corporate-sponsored Research:

This study is industry sponsored by Aprea Therapeutics

Other Substantive Relationships:

Crystal Miller, David Stenehjem, Mike Carleton, Philippe Pultar, Eugene Kennedy all have employment or consulting relationships with Aprea Therapeutics

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10 **Oral**

BBIT20, a first-in-class disruptor of BRCA1-BARD1 interaction, overcomes multidrug resistance in ovarian cancer

A.C. Matos [1,2], S.R. Moura [2,3], R. Moreira [4,5], A. Ciucci [6,7], S. Ricardo [8,9], M.I. Almeida [2,3], S. Mulhovo [10], C. Nero [11,12], S. Minuzzo [13], M. Alves [4], C. Sette [6,14], S. Indraccolo [13,15], M.J. Ferreira [16], L. Saraiva [1]

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Background: Therapeutic resistance drives relapse in > 70% of ovarian cancer (OC) patients, sustained by coordinated adaptations in DNA repair, transcriptional plasticity, mitochondrial metabolism and drug efflux. We investigated whether BBIT20, a first-in-class small-molecule disruptor of the BRCA1–BARD1 interaction, can collapse this resistance network.

Materials and methods: Dregamine 5-bromo-pyridin-2-ylhydrazone (BBIT20) was evaluated in BRCA-proficient and -mutated OC cell lines, MDR cells, six patient-derived organoids (PDOs), cell-derived (CDX) and patient-derived (PDX) xenograft mouse models. Activity was assessed alone or combined with paclitaxel (PTX), carboplatin (CB), and PARP inhibitors (PARPi). Mechanistic studies included DNA repair, apoptosis, epithelial–mesenchymal transition (EMT), drug efflux, mitochondrial imaging and integrated proteomic/ metabolomic analyses. In vivo efficacy and tolerability were assessed.

Results: BBIT20 induced BRCA status-independent cytotoxicity (IC50 3–6 μM) and impaired homologous recombination and non-homologous end joining, increasing DNA damage and apoptosis. Early BRCA1 depletion triggered RB–E2F and MYC-associated transcriptional collapse that precedes mitochondrial failure, establishing a temporally ordered vulnerability cascade linking nuclear dysfunction to bioenergetic collapse. This resulted in ATP limitation, suppression of ABCB1-mediated efflux and reversal of EMT.

Functionally, BBIT20 restored sensitivity to PTX (20-fold IC50 reduction), CB (~4-fold) and PARPi (up to 6-fold), with strong synergy (combination index 0.1-0.6) in wtBRCA and treatment-refractory models. In PDOs, including treatment-refractory models, BBIT20 robustly re-sensitized tumours to standard therapies.

In vivo, BBIT20 (2 mg/kg, i.p., 3×/week) reduced tumour burden (~60%, $p < 0.001$) and ascites (~75%, $p < 0.001$) and enhanced olaparib efficacy (65% vs 16% tumour growth inhibition, $p < 0.0001$). BBIT20 was well tolerated across i.p. and i.v. routes (0.1–2 mg/kg), with no significant alterations in hepatic or renal biomarkers and preserved organ histology, indicating absence of systemic toxicity at therapeutically active exposures.

Conclusions: Disruption of BRCA1–BARD1 by BBIT20 collapses a coordinated resistance network and restores sensitivity to standard therapies in OC, supporting its development as a first-in-class strategy for refractory OC.

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Conflict of interest

Ownership:

A patent protecting BBIT20 has been filed by S. Mulhovo, M.J. Ferreira, and L. Saraiva.

Other Substantive Relationships:

L. Saraiva and M.J. Ferreira are co-founders of BBIT-Therapeutics, Lda.

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11 **Oral**

Conditionally activated NKG2A-engaging tri-specific antibody remodels IO-resistant human tumor microenvironments with improved tumor killing and pharmacologic safety

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Background. Resistance to immune checkpoint blockade and chemoimmunotherapy remains a major challenge across solid tumors, highlighting the need for therapies that enhance anti-tumor immunity while limiting systemic toxicity. CAPTN-3 (IM1240) is a conditionally activated CD3x5T4xNKG2A trispecific antibody designed to engage NK- and T-cell cytotoxicity while reversing HLA-E/NKG2A-mediated immune suppression within the tumor microenvironment (TME). A protease-cleavable masking strategy restricts CD3 engagement to the TME, reducing peripheral immune activation and cytokine release while improving systemic exposure. We hypothesized that tumor-restricted IM1240 activation would induce NKG2A-dependent anti-tumor immunity in resistant patient-derived tumors while improving safety relative to an unmasked comparator.

Materials & Methods. Patient-derived biopsies and resections from IO- and chemo-resistant HNSCC, NSCLC, and bladder tumors were treated ex vivo with CAPTN-3 trispecifics to assess anti-tumor activity. Tumors were either dissociated for killing assays or maintained as patient-derived explants (PDEs) and analyzed using multiplex spatial imaging to characterize therapy-induced immune remodeling. Preliminary non-human primate toxicology and pharmacokinetic studies compared capped IM1240 with non-capped IM1222, including assessment of systemic exposure, clearance, cytokine induction, and peripheral immune activation.

Results. IM1240 induced potent anti-tumor activity in IO- and chemo-resistant HNSCC, NSCLC, and bladder tumors, including EV/pembrolizumab-resistant MIBC. In dissociated tumor cultures, IM1240 promoted robust tumor killing that required functional CD3 and NKG2A arms as well as 5T4 tumor expression, demonstrating coordinated dependence on tumor targeting and NKG2A blockade. In resistant NSCLC and HNSCC PDEs, IM1240 induced profound immune remodeling characterized by tertiary lymphoid structure (TLS) formation, increased CD8 T-cell and NK-cell infiltration, and reduced tumor and intratumoral Treg abundance. These effects were markedly reduced following NKG2A loss-of-function, supporting a central role for NKG2A blockade in reshaping anti-tumor immunity. In preliminary non-human primate studies, IM1240 demonstrated improved pharmacokinetic and safety profiles relative to IM1222, including increased systemic exposure, prolonged half-life, reduced clearance, and markedly lower cytokine induction despite higher dosing

Conclusions. IM1240 drives NKG2A-dependent anti-tumor immunity in resistant human tumors through coordinated tumor targeting, NK/T-cell engagement, and immune remodeling. Conditional CD3 masking improved safety while preserving potent anti-tumor activity, supporting an expanded therapeutic index for CAPTN-3 trispecific therapy. These findings support continued clinical development of IM1240 for treatment-resistant solid tumors.

Conflict of interest:

Ownership:

Hadas Reuveni, Avi Cohen, Michael Schickler and Yael Lahat Employee of Purple Biotech Ltd. holder of company stock/stock options.

Advisory Board: none

Board of Directors: none

Corporate-sponsored Research: Hadas Reuveni, Avi Cohen, Michael Schickler and Yael Lahat Employee of Purple Biotech Ltd

https://doi.org/10.1016/j.ejca.2026.117461

12 **Oral**

BMS-986500: A novel molecular glue degrader of Cyclin E1 with first-in-class potential for treating CCNE1-amplified cancers and overcoming CDK4/6 inhibitor resistance in HR+ breast cancer

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CCNE1 (Cyclin E1) is a historically undruggable oncogene that is frequently amplified and deregulated across solid tumors and is associated with resistance to standard-of-care therapies (SOC) such as CDK4/6 inhibitors. We report the discovery and preclinical characterization of BMS-986500, a potentially first-in-class CELMoD™ (Cereblon E3 Ligase Modulatory Drug) that directly targets Cyclin E1, a scaffolding protein and co-activator of cyclin-dependent kinases (CDKs) such as CDK2. BMS-986500 induced degradation of Cyclin E1 selectively across the proteome in a CRBN-dependent manner via a novel molecular glue mode of recruitment. In line with the target biology, BMS-986500 induced robust reactivation of the RB1 tumor suppressor, suppressed E2F transcription, and blocked G1/S cell cycle transition in *CCNE1*-dependent cancer cells. Consistent with genetic dependency, BMS-986500 selectively inhibited proliferation of *CCNE1*-amplified cancer cells (n = 13) across a large cancer cell line panel (n = 144), while sparing proliferation of *CCNE1*-wildtype cancer cells and human CD34+ bone marrow-derived normal cells. BMS-986500 was well tolerated in vivo and elicited robust and durable anti-tumor activity as a single agent across cell line derived xenograft (CDX) and patient derived xenograft (PDX) models with *CCNE1* gene amplification. Furthermore, treatment with BMS-986500 overcame resistance to CDK4/6 inhibitors in HR+ breast CDX and PDX models and elicited robust and sustained reduction of RB1 phosphorylation consistent with anti-tumor responses. Overall, BMS-986500 offers an innovative way to target Cyclin E1 through a mechanism that is well differentiated from CDK2 inhibitors, with the potential for reduced hematological toxicity risks, improved single agent efficacy, and ability to treat CDK4/6 inhibitor resistance. BMS-986500 is currently in Phase 1 clinical investigation in advanced solid tumors.

Conflict of interest:

Ownership: Authors are stockholders of Bristol Myers Squibb.

Corporate-sponsored Research: Research is sponsored by Bristol Myers Squibb.

Other Substantive Relationships: Authors are employees of Bristol Myers Squibb.

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13 **Oral**

Updated results from LuCa-MERIT-1, a Phase I trial evaluating BNT116, a fixed-antigen mRNA vaccine, alone and in combination with cemiplimab across distinct advanced NSCLC cohorts

R. Dziadziusko [1], D. Deme [2], A. Atmaca [3], B.B. Öven [4], E. Göker [5], J.L. Markman [6], C. Dalle Fratte [7], C.D. Hermann [8], V. Chen [9], M.K. Rout [10], N. Munshi [11], M. Wenger [12], T. Burkard [13], H. Weidenthaler [14], F. Seebach [15], I. Lowy [15], P. Brück [12], Ö. Türeci [16], U. Sahin [16], P. Forde [17]

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Background: Most patients (pts) with advanced NSCLC either show no response or only respond to anti-PD-(L)1-based therapies for a limited time. BNT116 is an intravenously administered investigational RNA-lipoplex therapeutic cancer vaccine comprising 6 mRNAs encoding tumor-associated antigens (TAAs) frequently expressed in NSCLC. Here, we report updated safety, clinical activity and biomarker data from three distinct cohorts of pts with advanced NSCLC receiving BNT116 or BNT116 + cemiplimab (cemi).

Methods: LuCa-MERIT-1 (NCT05142189) is an ongoing open-label Phase I trial evaluating BNT116 alone or in combination with cemi and/or other agents in advanced NSCLC. BNT116 is administered weekly for the first 6 doses and every 3 weeks thereafter. Cemi is administered every 3 weeks. In Cohort 1, heavily pretreated pts received BNT116 monotherapy (mono) with optional add-on cemi; all pts in Cohorts 2 (PD-L1-high NSCLC progressing on prior PD-1-based therapy) and 4 (frail pts ineligible for chemotherapy, irrespective of PD-L1 expression) received BNT116 + cemi. Endpoints include safety, tolerability, and preliminary clinical activity; blood samples were collected for biomarker analyses.

Results: Across the three cohorts, 70 pts have been treated (Cohort 1 mono n = 17, median age 63 yrs / add-on n = 13, median age 65 yrs; Cohort 2 n = 20, median age 61 yrs; Cohort 4 n = 20, median age 70 yrs). As of 15May2026, treatment-emergent AEs were manageable, as previously reported; no new safety signals were identified with longer follow-up (FU). Clinical activity was observed with BNT116 + cemi in all three cohorts (Table). Biomarker results indicate that BNT116 activates a type 1 interferon response and induces T cell TAA-specific responses in 78% (14/18) of pts with available samples, while circulating tumor DNA monitoring data align with the observed clinical activity.

Conclusions: In three distinct advanced NSCLC cohorts, BNT116 + cemi demonstrated antitumor activity, particularly in frail pts and those progressing on prior PD-1-based therapy. These findings support the potential of BNT116 + cemi to induce clinically meaningful responses and disease control and suggest that BNT116 may prevent or overcome resistance to PD-1 inhibition.

Table

	BNT116 mono N = 17	Cemi add-on N = 13	Progressing on PD-1-based therapy N = 20	Frail pts N = 20
ORR, n (%)	0	2 (15.4)	2 (10.0)	9 (45.0)
95% CI	0.0,19.5	1.9,45.4	1.2,31.7	23.1,68.5
DCR, n (%)	4 (23.5)	8 (61.5)	16 (80.0)	15 (75.0)
95% CI	6.8,49.9	31.6,86.1	56.3,94.3	50.9,91.3
Median duration of response, mos		NE	NE	10.5
95% CI		NE,NE	NE,NE	7.7,NE
Median OS, mos	5.8	23.8	25.4	29.1
95% CI	3.8,7.1	7.6,NE	21.4,NE	8.0,NE
Median PFS, mos	1.4	2.8	5.5	11.6
95% CI	1.3,1.7	1.4,NE	2.9,10.2	1.7,NE
Median FU time, mos	2.5	15.5	24.6	11.3
min–max	0.0–19.4	3.4–37.6	2.8–29.6	0.5–29.4
Median no. prior therapy lines	3	3	1	0
min–max	2–8	2–6	1–3	0–2

Conflict of interest:

Advisory Board:

Rafal Dziadziusk: consulting or advisory role for GlaxoSmithKline.

Akin Atmaca: advisory/consulting/speaker honoraria from BMS, MSD, Roche, Pfizer, AstraZeneca, BioNTech, Daiichi-Sankyo, BeiGene, FOMF, NeoConnect.

Patrick Forde: consultant for Ascendis, AstraZeneca, BioNTech, BMS, Curevac, Novartis, Regeneron, G1, Genelux, Genentech, Gritstone, Merck, Janssen, F Star, Sanofi, Amgen, Fosun, Teva, Synthekine, Flame, Iteos, Tavotek, Teva.

Corporate-sponsored Research:

Patrick Forde: research grants to his institution from AstraZeneca, BMS, Novartis, Regeneron, BioNTech.

Other Substantive Relationships:

Rafal Dziadziusk: travel, accommodations, expenses from Pfizer, GlaxoSmithKline

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Akin Atmaca: travel grants from MSD, Daiichi-Sankyo, Roche, BioNTech

Janet L Markman, Chiara Dalle Fratte, Chris D Hermann, Victoria Chen, Manas Kumar Rout, Neru Munshi, Michael Wenger, Tobias Burkard, Heinz Weidenthaler, Patrick Brück, Özlem Türeci, and Uğur Şahin are employees of BioNTech.

Frank Seeback and Israel Lowy are employees of Regeneron Pharmaceuticals, Inc.

Patrick Forde: DSMB membership for Polaris

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Posters in the Spotlight - Session 1

20 - PB-001 **Poster in the Spotlight**

Loss-of-function MTOR mutations genocopy the synergy between palbociclib and mTOR inhibition in KRAS-mutant lung cancer patients

G. Middleton [1,2], A. Finch [1], H. Robbins [1,2], J. Savage [3], J. De La Mata Chicharro [3], M. Mehmi [3], A. Greystoke [4], Y. Summers [5], D. Gilligan [6], P. Shaw [7], J. Cave [8], N. Steele [9], J. Spicer [10], A. Dangoor [11], M. Forster [12], S. Popat [13], D. Power [14], A.D. Beggs [15,16], L. Billingham [3]

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Background: We previously reported results of six genotype-matched cohorts treated with palbociclib in a large lung cancer platform trial (NCT02664935), in which outcomes numerically favoured the KRAS-mutant/STK11-proficient cohort. We report ctDNA analysis of KRAS-mutant patients to identify genomic drivers of prolonged disease control ($\geq$12 months) together with functional validation of the identified target.

Methods: ctDNA ($\geq$10 ng) was hybridised using the Illumina TSO500 ctDNA kit and sequenced to a median coverage of 50,000x. Downstream analysis was performed with the nf-core/oncoanalyser pipeline. H441 MTOR$^{WT/R1080C}$ and SKLU1 MTOR$^{WT/R1080C}$ cell lines were generated by Cyagen Biosciences. Cells were dosed with 0 - 1μM palbociclib. Colony forming assays were incubated for 14 days (H441) or 7 days (SKLU1), before staining with crystal violet and quantification using GelCount. Senescence was measured using β-galactosidase staining. pS6RP, p4EBP1 and peIF4E were assessed using western blotting. Ki67 and AKT pSer473 were quantified using Promega Lumit assay kits.

Results: Of 146 evaluable patients treated across six biomarker-selected cohorts, eight achieved disease control lasting > 12 months. Six of these patients harboured KRAS mutations, all of which were STK11 proficient. Three of the six long-term responders harboured concomitant MTOR mutations on ctDNA, all predicted to be pathogenic by both CADD and EVE. We engineered the heterozygous MTOR R1080C HEAT-domain mutation, found in the context of KRAS G12D, into the KRAS G12D LUAD cell line SKLU1 and, for context dependency, the KRAS G12V LUAD cell line H441. In both models, MTOR R1080C reduced phosphorylation of pS6RP, p4EBP1 and peIF4E and increased phosphorylation of Akt at pSer473, consistent with impaired mTORC1 signalling. R1080C increased colony formation in the KRAS G12D model and proliferation in the KRAS G12V model: senescence bypass was observed in both models. MTOR R1080C markedly increased sensitivity to the anti-proliferative effects of palbociclib compared with MTOR wild-type cells in both KRAS backgrounds. The common KDR Q472H polymorphism was enriched among patients with shortest durations of disease control, suggesting it may mediate resistance to palbociclib in KRAS-mutant lung cancer.

Conclusions: Clinical observations, supported by reverse-translational functional analyses, demonstrate that genetic loss of MTOR function genocopies the previously described pharmacological synergy between CDK4/6 and mTOR inhibition in KRAS-mutant lung cancer. KRAS-mutant LUAD harbouring loss-of-function MTOR mutations may therefore derive particular benefit from CDK4/6 inhibition. Further, pharmacological mTOR inhibition may similarly sensitise MTOR wild-type KRAS-mutant tumours, supporting prospective evaluation of combined CDK4/6 and mTOR inhibition in this population.

No conflict of interest

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21 - PB-002 **Poster in the Spotlight**

High-Throughput Screening Identifies NT-1 as a Dual JAK3/EGFR Inhibitor that Overcomes KRAS Inhibitor Resistance in Colorectal Cancer

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Background: KRAS ^{G12C} inhibitors (sotorasib, adagrasib) have transformed treatment of non-small cell lung cancer (NSCLC), but their efficacy in colorectal cancer (CRC) is limited by intrinsic resistance. The pan-RAS inhibitor daraxonrasib (RMC-6236) shows robust activity in pancreatic ductal adenocarcinoma (PDAC) yet only modest single-agent efficacy in KRAS-mutant CRC. This lineage-specific discrepancy suggests that colorectal tumors harbor feedback pathways that buffer against therapeutic stress. In CRC, KRAS blockade produces cytostatic arrest rather than cell death, implying that survival signals block apoptosis. We aimed to identify combinations that convert this cytostatic response into cytotoxicity.

Material and methods: We developed a high-throughput combinatorial screening platform using CRC cell lines with acquired KRAS inhibitor resistance and patient-derived organoids (PDOs) with fully annotated molecular profiles. Over 6,000 preclinical and clinical compounds were screened across parental and resistant lines.

Hits were validated in vitro and ex vivo in PDOs, and our top hit, NT-1, was validated *in vivo* using two KRAS inhibitor-resistant KRAS ^{G12D} CRC cell-line-derived xenograft (CDX) models (daraxonrasib- and MRTX1133-resistant). Target deconvolution used kinome profiling, and mechanism was interrogated by immunoblotting, small interfering RNA (siRNA) knockdown, and apoptosis assays.

Results: NT-1 emerged as the top sensitizer in both parental and resistant cells and organoids, and kinome profiling identified it as a dual JAK3/EGFR inhibitor. NT-1 showed significantly more potent synergy than the EGFR inhibitors osimertinib, erlotinib, and afatinib, achieving greater inhibition at lower doses. Combining NT-1 with KRAS-targeted agents (G12D-selective and pan-RAS) synergistically suppressed viability, triggered profound apoptosis in vitro, and drove tumor regression *in vivo*. Ex vivo, these combinations reproduced deep growth suppression and apoptosis in parental and resistant PDOs. Across emerging pan-KRAS inhibitors, NT-1 consistently outperformed approved EGFR inhibitors and cetuximab, producing deeper suppression of phospho-EGFR and phospho-ERK and stronger apoptotic induction. Mechanistically, JAK3 was upregulated under KRAS inhibitor monotherapy and, together with the known EGFR feedback loop, was associated with reactivation of downstream signaling that may limit the durability of KRAS blockade. SiRNA knockdown of JAK3 increased sensitivity to KRAS inhibition, supporting JAK3 as one functionally relevant component of the NT-1 response alongside EGFR inhibition. In both KRAS-resistant CDX models, NT-1 induced stronger anti-tumor effects, reducing tumor burden.

Conclusions: EGFR and JAK3 are pivotal drivers of KRAS inhibitor resistance in CRC. Dual JAK3/EGFR inhibition with NT-1 converts the cytostatic effect of KRAS inhibitors into a cytotoxic response and warrants clinical evaluation.

No conflict of interest

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22 - PB-003 **Poster in the Spotlight**

Patient-aligned 3D tumor models identify biomarker-enriched atebimetinib (IMM-1-104) combination strategies in pancreatic ductal adenocarcinoma

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Background: Pancreatic ductal adenocarcinoma (PDAC) remains among the deadliest solid tumors (5-year survival <13%) with limited therapeutic options. Near-universal KRAS mutations make the MAPK pathway the principal oncogenic driver, positioning MEK inhibition as a rational strategy; however, earlier MEK inhibitors showed limited clinical benefit owing to dose-limiting toxicities and adaptive resistance. Atebimetinib, an oral, once-daily agent achieving deep cyclic inhibition (DCI) of the MAPK pathway, is designed to deprive tumors of sustained oncogenic signaling while sparing normal cells via near-zero daily trough levels. In combination with gemcitabine/nab-paclitaxel (GnP), a regimen whose additive/synergistic activity was first predicted preclinically in the humanized 3D tumor growth assay (3D-TGA), atebimetinib showed encouraging first-line survival in a Phase 2a trial (ASCO 2026) and has advanced to the Phase 3 MAPKeeper 301 trial (NCT07562152), demonstrating the translational potential of this platform. Building on that validation and on atebimetinib's favorable clinical tolerability, we applied the same approach to identify rational vertical and orthogonal combination partners in PDAC.

Materials and Methods: PDAC tumor models were selected by patient alignment using databases including AACR GENIE. Pharmacogenomic data were integrated to build a model predictive of atebimetinib response and to identify biomarker-enriched subpopulations. Atebimetinib was evaluated across 20 PDAC cell lines in the 3D-TGA, including 8 tested in combination with KRAS inhibitors (mutation-specific and KRAS degrader) as vertical partners and 7 with PRMT5 or GSK-3β inhibitors as orthogonal partners.

Results: Co-targeting the RAS–MEK axis with atebimetinib plus KRAS inhibitors produced synergistic/additive tumor growth inhibition in all 8 PDAC models evaluated (TGI up to 100%). Atebimetinib plus PRMT5 inhibition showed enhanced activity in both MTAP-deleted models tested. Combination with GSK-3β inhibition produced effects consistent with known GSK-3β/MAPK crosstalk in 2 of 4 models evaluated.

Conclusions: Across the combination strategies explored, synergy was observed in models sharing defined genomic features, suggesting the degree of MAPK pathway utilization is a key determinant of combination depth. Orthogonal combinations showed more context-dependent activity, reflecting the nature of their MAPK cooperativity. Extending the same 3D-TGA platform that predicted the clinically validated GnP combination, these data support clinical investigation of multiple vertical and orthogonal combination strategies for atebimetinib in PDAC.

Conflict of interest

Ownership: Shareholders of Immuneering Corporation

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Posters in the Spotlight - Session 2

23 - PB-004 **Poster in the Spotlight**

The Cancer Perturbation Atlas: Mapping and reprogramming drug-induced cell states in patient-derived cancer organoids

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Background: Dynamic cell states enable tumour cells to adapt to therapeutic pressure and survive treatment, yet are rarely mapped systematically or linked to genotype, drug response and therapeutic escape. Single-cell drug perturbation screening can reveal the mechanisms shaping tumour cell transcriptional states, but has largely focused on cell lines. Extending this to patient-derived organoids is challenging, as they are laborious to culture, perturb and process at scale, yet they retain patient-specific biology and offer a substrate to identify therapy-induced escape states and train predictive models of drug response. As a first implementation of the Cancer Perturbation Atlas consortium, we developed HYDRA, a single-cell perturbation dataset in patient-derived colorectal cancer organoids.

Materials and methods: We established a platform for large-scale chemical perturbation screening in 3D patient-derived

organoids, spanning dissociation, plate seeding, in-plate treatment, pooling, fixation and split-pool barcoding single-cell RNA sequencing. Six colorectal cancer organoid models of distinct driver genotypes were exposed to 176 monotherapies and 122 combinations across three timepoints (6, 24, 48 h), yielding over 5,000 conditions and more than 7.5 million single cells. Data were integrated with a variational autoencoder, and perturbation effects quantified in latent space and by differential expression across donors and timepoints. Cell states were annotated de novo, and escape trajectories reconstructed using pseudotime.

Results: Perturbations resolved into interpretable transcriptional programmes capturing canonical drug responses and distinct routes of drug escape. Across compounds and targets, we identified two dominant escape modes. In adaptive reactivation, cells initially entered the expected drug-response state before progressing along a trajectory marked by reactivation of targeted or compensatory signalling. In selection of pre-existing refractory states, drug-tolerant subpopulations were present before treatment and enriched over time. These modes were separable by single-cell trajectory dynamics, and the mode, magnitude and timing of escape were strongly donor- and genotype-dependent, enabling perturbations to be classified by dynamic escape behaviour rather than endpoint viability alone.

Conclusions: HYDRA demonstrates that large-scale single-cell drug perturbation screening is feasible in patient-derived organoids and resolves clinically relevant escape states with donor- and genotype-specific structure. By distinguishing adaptive reactivation from selection of pre-existing refractory states, it provides a framework to nominate combination therapies and design strategies to reprogramme resistant states. More broadly, HYDRA establishes a foundation for the Cancer Perturbation Atlas and for predictive models of therapeutic response.

No conflict of interest

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24 - PB-005 **Poster in the Spotlight**

The Integrated Stress Response (ISR) promotes an immunosuppressive tumor microenvironment which is targetable with 2BAct

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Background: Environmental insults within the tumor microenvironment (TME) trigger the integrated stress response (ISR). By driving translational reprogramming via the eIF2α-ATF4 axis, the ISR is known to impair immune cell function and promote immunosuppressive myeloid polarization. In this study, we profiled the ISR across more than 300 patients with head and neck squamous cell carcinoma (HNSCC) and lung adenocarcinoma (LUAD) and investigated ISR inhibition in anti-tumor immunity using the eIF2B activator 2BAct.

Material and methods: Tumor biopsies from HNSCC (n = 239) and LUAD (n = 75) patients were profiled by scRNA-seq. Tensor decomposition was applied to HNSCC and LUAD cancer cells to identify tumor-intrinsic programs. Cells were annotated across T/NK, myeloid, stromal, and tumor compartments. ISR was scored per cell using a curated 95-gene signature. Differential composition was modeled by sccomp. Overall survival was modeled by Cox proportional hazards with HPV adjustment. C57BL/6 mice bearing multiple syngeneic tumors were treated with 2BAct with or without anti-PD-1.

Results: Our tensor-based model classified HPV status with AUC = 0.95. HPV+ cancer cells showed unfolded protein response (UPR), E2F activation, and glycolysis as the most enriched pathways consistent with viral stress. HPV- cancer cells showed epithelial-mesenchymal transition, collagen deposition, and NRF2/oxidative stress as the most enriched pathways (all FDR = 0). ISR showed a compartment-specific pattern: cancer cell ISR, driven by UPR (r = 0.64), was higher in HPV+ tumors (p = 2.4e-06), while immune cell ISR, driven by hypoxia (r = 0.90), was elevated in HPV- tumors across 11/12 T and NK subtypes (q < 0.05) and 6/8 myeloid subtypes (q < 0.003). SPP1+ tumor-associated macrophages (TAMs) had the highest ISR among myeloid subsets (q < 1e-9) and were enriched in HPV- tumors, while HPV+ tumors harbored more cDC1, cDC2, and CXCL10+ macrophages, alongside CXCL13+ tumor-reactive CD8 T cells. Independent of HPV status, high ISR in immune cells predicted worse overall survival (OS) across multiple lymphoid and myeloid compartments, including CD8 effector (adjusted HR = 2.08, p = 4e-4), CD8 exhausted (adjusted HR = 2.03, p = 0.003), and mregDC (adjusted HR = 2.18, p = 0.002). In an independent LUAD cohort, high ISR in CD8 T cells, fibroblasts, and cancer cells predicted worse OS. In syngeneic tumor models, 2BAct reduced ISR in immune cells resulting in increased CD8+ T cell stemness and less exhaustion, promoted macrophage maturation, decreased PD-L1 expression on myeloid and tumor cells, and enhanced anti-PD-1 efficacy.

Conclusions: ISR activation is a conserved feature of an immunosuppressive TME, linking stressors like hypoxia to immune-cell dysfunction. ISR inhibition with 2BAct reshapes the TME and potentiates checkpoint blockade, establishing ISR as a therapeutic target to enhance anti-tumor immunity.

Conflict of interest

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Poster Session: Antibody-drug conjugates

51 - PB-051 **Poster**

Translational validation of uPARAP (MRC2) as an antibody–drug conjugate target in osteosarcoma patient-derived xenograft models

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Background: Despite intensive multimodal therapy, outcomes for patients with relapsed or metastatic osteosarcoma remain poor, underscoring the need for novel targeted therapies. We previously identified uPARAP (MRC2) as a promising cell-surface antigen in osteosarcoma through comprehensive surfaceome profiling and demonstrated proof-of-concept activity of first-generation uPARAP-targeting antibody–drug conjugates (ADCs) (ADCE-003,010,011). We therefore evaluated a next-generation DXd-based ADC to independently validate the therapeutic potential of MRC2 in osteosarcoma patient-derived xenograft (PDX) models.

Methods: MRC2 transcript expression was evaluated in osteosarcoma PDX models using RNA sequencing, and protein expression was assessed by immunohistochemistry (IHC). Antitumor activity of the uPARAP-targeting DXd ADC, 2h9-DXd (ADCE-202), was evaluated in six independent osteosarcoma PDX models. Animals received vehicle (PBS), an isotype control DXd ADC ADCE-252, or the uPARAP-targeting ADC ADCE-202 at 3 or 10 mg/kg intravenously on days 1, 8, and 15. Tumor growth inhibition, tumor regression, and treatment tolerability were assessed weekly. Relative tumor volume (RTV), event-free survival (EFS), and objective response measures were analyzed.

Results: RNA sequencing demonstrated heterogeneous MRC2 expression across osteosarcoma PDX models, and MRC2 protein expression was confirmed by IHC. Compared with isotype control ADC, ADCE-202 induced substantial antitumor activity in multiple osteosarcoma models. All six PDX models treated with ADCE-202 at 10 mg/kg demonstrated significantly prolonged event-free survival compared with controls. Four of six PDX models showed significant sensitivity to treatment, with superior responses observed at 10 mg/kg compared with 3 mg/kg, demonstrating a dose-dependent therapeutic effect. Treatments were generally well tolerated, with no significant bodyweight loss or treatment-related toxicity observed. Ongoing analyses are evaluating the relationship between MRC2 protein expression and therapeutic response.

Conclusions: These findings provide additional translational evidence supporting uPARAP (MRC2) as a therapeutically actionable cell-surface target in osteosarcoma. In addition, the reproducible activity of the next-generation DXd-based ADC ADCE-202 across multiple osteosarcoma PDX models, together with confirmed target expression, supports further evaluation of MRC2 as a potential predictive biomarker for osteosarcoma.

No conflict of interest

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52 - PB-052 **Poster**

HMPL-A830, a novel EGFR-directed antibody-targeted therapy conjugate (ATTC) with a potent pan-KRAS inhibitor payload

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Background: Despite recent progress with RAS inhibitors, most patients eventually develop disease progression, largely driven by acquired resistance mechanisms, including activation or upregulation of RTKs and acquired KRAS alterations. Systemic co-inhibition of EGFR and KRAS enhances antitumor activity, but the associated toxicity limits clinical application. Leveraging anti-EGFR antibody-mediated tumor targeting to selectively deliver pan-KRAS inhibitors to tumor cells may enable simultaneous inhibition of both pathways. Moreover, selective targeting of KRAS while sparing HRAS and NRAS may further reduce potential toxicities.

Material and methods: EGFR binding was evaluated by FACS in EGFR positive cells and internalization was assessed using pHrodo labeling. Tumor cell growth inhibition and bystander effect were measured by CellTiter-Glo reagents. In vivo anti-tumor efficacy and EGFR/KRAS pathway inhibition were evaluated in multiple human xenograft tumor models in immunodeficient mice.

Results: The pan-KRAS inhibitor payload HM5043714 inhibited both the active (ON) and inactive (OFF) states of multiple KRAS alterations, including KRAS G12C, G12D, G12V, and wild-type. Through blockade of KRAS signaling, the payload induced potent inhibition of p-ERK and tumor cell proliferation with a sub-nanomolar median IC_{50}, while sparing HRAS and NRAS. HMPL-A830 was generated by conjugating the payload to an EGFR antibody via a proprietary linker. HMPL-A830 retained binding affinity and internalization properties comparable to the unconjugated antibody. It inhibited the growth of EGFR-positive tumor cells and induced death of EGFR-negative tumor cells through a bystander effect. In multiple KRAS-altered xenograft models, HMPL-A830 demonstrated potent, dose-dependent antitumor efficacy with favorable tolerability at 0.5-10 mg/kg via single intravenous administration, achieving superior tumor growth inhibition compared to the unconjugated antibody. Compared with daraxonrasib, HMPL-A830 exhibited comparable or superior activity with improved tolerability in CRC models. Compared with adagrasib, HMPL-A830 induced more durable tumor regression in NSCLC models. HMPL-A830 robustly suppressed the KRAS downstream marker p-RSK, with target inhibition increasing in parallel with elevated payload concentrations in tumor tissue.

Conclusions: HMPL-A830 demonstrates strong anti-tumor activity in preclinical models, supporting further clinical evaluation. Initiation of phase I human study is expected in the third quarter of 2026.

No conflict of interest

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53 - PB-053 **Poster**

Pre-clinical characterization of ARC-401, a first-in-class anti-Nectin-4 triple payload ADC

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Background: Araris' site-specific, one-step conjugation technology, AraLinQ™, enables the generation of stable, safe, and highly potent antibody-drug conjugates (ADCs) without requiring antibody engineering prior to payload conjugation. Here, we present ARC-401, a novel Nectin-4-targeting ADC carrying three distinct cytotoxic warheads. ARC-401 was designed to (1) overcome tumor heterogeneity and resistance by delivering multiple cytotoxic mechanisms to the same target cell, (2) minimize off-tumor toxicity through controlled bystander activity, and (3) maximize payload delivery while maintaining pharmacokinetics comparable to those of the unconjugated antibody through highly stable linker-payload coupling.

Material and methods: ARC-401 consists of a fully glycosylated anti-Nectin-4 antibody and a linker-payload containing MMAE and two different topoisomerase 1 inhibitors (TOP1i, DAR2 + 2 + 2), which was site-specifically conjugated to the glutamine 295 residue of the heavy chain using the AraLinQ™ technology, a one-step transglutaminase-mediated conjugation process. Stability under stressed conditions and in sera was evaluated *in vitro*, and stability in circulation was evaluated in pharmacokinetic experiments *in vivo*. *The* anti-tumor activity of ARC-401 was analyzed *in vivo* in various cell line-derived xenograft (CDX) and patient-derived xenograft (PDX) models from various indications.

Results: ARC-401 was obtained as a highly homogeneous DAR 6 ADC and exhibited excellent physicochemical stability without aggregation under stressed conditions. The ADC demonstrated potent target-dependent cytotoxicity in Nectin-4-positive tumor cell lines and showed high stability in mouse, cynomolgus monkey, and human serum, with no detectable linker-payload deconjugation or cleavage. In rodents, ARC-401 displayed pharmacokinetics comparable to the unconjugated parent antibody, consistent with its high *in vivo* stability. Controlled bystander activity was confirmed. In a rat dose-range finding study, ARC-401 was well tolerated with a highest non-severely toxic dose (HNSTD) exceeding 20 mg/kg, compared with 5 mg/kg for enfortumab vedotin. High tolerability was further confirmed in a non-GLP non-human primate study, with no significant skin or hematologic toxicities observed at high dose levels.

Conclusion: In conclusion, we present data on the proprietary ARC-401 ADC, a first-in-class Nectin-4-targeting triple-payload ADC, demonstrating robust anti-tumor efficacy in CDX and PDX models in mice and rats and superior tolerability in rats and non-human primates at high ADC doses compared with known ADCs. Further we show that combination of multiple payloads in one ADC can lead to improved anti-tumor efficacy compared to combination treatment.

No conflict of interest

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54 - PB-054 **Poster**

In vitro characterization of the mechanism of action of micvotabart pelidotin, an antibody-drug conjugate targeting extradomain-B of fibronectin

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Micvotabart pelidotin (MICVO) is a first-in-concept antibody–drug conjugate (ADC) targeting extradomain-B of fibronectin (EDB + FN), a non-cellular structural protein overexpressed in the extracellular matrix (ECM) of many solid tumors and largely absent in normal adult tissues. MICVO comprises a fully human IgG1 monoclonal antibody (mAb) with site-specific conjugation to a cleavable mcValCitPABC linker and an optimized auristatin payload. Unlike conventional cell-surface targeting and internalizing ADCs, MICVO binds to EDB + FN in the tumor ECM where extracellular proteases in the acidic environment cleave the linker to release the membrane-permeable payload. Here, the non-cell surface targeting mechanism of MICVO is further validated by extracellular protease-mediated linker cleavage resulting in cancer cell killing using conditioned media (CM) from diverse human cancer cell lines, as well as investigating the in vitro antibody-dependent cellular cytotoxicity (ADCC) property of MICVO.

CM harvested from a human cathepsin B (CTSB)-overexpressing cell line and multiple human cancer cell lines were incubated with MICVO at various pH conditions, and changes in drug-to-antibody ratio (DAR) were analyzed by hydrophobic interaction chromatography. Protease levels in CM were measured by ELISA kits. Functional free payload release was confirmed by treating an EDB + FN-negative cancer cell line with CM + MICVO mixtures in a cytotoxicity assay. ADCC characterization included Octet-based binding analysis of MICVO with human Fcγ receptors (hFcγRs) and cell-based functional ADCC assays.

The pH-dependent extracellular cleavage of MICVO's linker and reduction of DAR were observed with CM of a human CTSB-overexpressing cell line and various human cancer cell lines, which were associated with the protease levels in CM. In vitro, extracellularly released payload diffused into and killed EDB + FN-negative cancer cells that are insensitive to non-cleaved MICVO. Moreover, MICVO binding affinities to hFcγRs were comparable to cysteine-engineered MICVO-intermediate and wild-type anti-EDB IgG1 mAbs. Modest activity was observed in a cell-based ADCC assay for MICVO, indicating that Fc effector function may moderately contribute to MICVO's anti-tumor activity in vivo.

Extracellular proteases secreted by cancer cells can cleave MICVO's linker and release free payload without requiring ADC internalization, demonstrating MICVO's non-cellular associated antigen targeting in the tumor ECM is an effective mechanism to deliver a cytotoxic payload to cancer cells. ADCC may moderately contribute to the anti-tumor activity of MICVO, consistent with EDB + FN being a non-cellular target. These data support the rationale for investigating MICVO in patients with difficult-to-treat cancers in the ongoing clinical trials as a monotherapy (NCT05720117) and in combination with pembrolizumab (NCT06795412).

Conflict of interest

Ownership: All authors are employees of Pyxis Oncology and hold stock options in the company.

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55 - PB-055 **Poster**

Targeting PD-L1 Expressing Solid Tumors with CR-002, a Novel Topoisomerase 1-inhibitor (TOP1i) ADC Engineered for Increased Payload Delivery

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Background Programmed Death-Ligand 1 (PD-L1) expression is elevated in multiple solid tumors, making it an attractive target for antibody-drug conjugates (ADCs). CR-002 is a novel, fully human anti-PD-L1 antibody conjugated to the TOP1i payload DXd. Here, we report preclinical studies characterizing the internalization and cytotoxic payload delivery to target cells, the in vitro cytotoxic potency, and in vivo anti-tumor activity in PD-L1 expressing tumor models.

Materials and Methods In vitro testing focused on functional assays critical for ADC performance, including cytotoxicity and internalization. Antibodies were subject to binding to human PD-L1 via surface plasmon resonance.

Results A panel of antibodies with a range of affinities (K_D) towards human PD-L1 from ~100 pM to 10 nM were generated for screening as ADCs. These PD-L1 antibodies were conjugated to the drug linker deruxtecan (DXd) to form ADCs with a drug to antibody ratio (DAR) of 8. Cancer cells expressing PD-L1 were treated with our PD-L1 ADCs and measured for cellular cytotoxicity. Analysis of the cytotoxicity data of the panel of PD-L1 ADCs showed an inverse correlation between affinity of the binder and cytotoxicity (IC_{50}). CR-002 was selected among the PD-L1 clones with optimal cytotoxicity. Further cell-based assays confirmed CR-002 was able to efficiently internalize into PD-L1 expressing target cells. CR-002 demonstrated dose dependent anti-tumor activity against a panel of cancer cell line-derived xenograft (CDX) models in immunodeficient mice, as well as in a syngeneic mouse model engineered to express human PD-L1. Studies in cynomolgus monkeys demonstrate that CR-002 demonstrated a PK and safety profile consistent with other DXd ADCs.

Conclusion Together these findings suggest CR-002 has the potential to treat patients with PD-L1 positive solid tumors. A first-in-human clinical trial will begin in the second half of 2026.

Conflict of interest: Ownership: Some of the authors may have equity-based compensation and/or otherwise-acquired shares in the sponsor and/or their employer.

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Board of Directors: None.

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56 - PB-056 **Poster**

PF-08098488, A Novel CEACAM5-Targeting MMAE ADC with Optimized Engineered-Cysteine Sites Designed to Enhance Therapeutic Index, Demonstrates Potent Antitumor Activity in Preclinical Models

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Background: CEACAM5 is a clinically validated tumor-associated cell surface antigen expressed across multiple solid tumors including lung and pancreatic cancers, with limited normal tissue distribution, making it an attractive antibody–drug conjugate (ADC) target. PF-08098488 is a next-generation ADC which incorporates four engineered cysteine sites (EC4) within a novel CEACAM5-targeting antibody (mAb) backbone (SG-105.2E4) to achieve a homogeneous drug-to-antibody ratio (DAR) conjugation with an MMAE linker-payload. The EC sites were selected to promote a degree of maleimide–thiol instability, based on prior clinical experience with EC-vedotin ADCs showing ocular toxicity possibly driven by increased systemic exposure to conjugated drug. This design aims to improve the therapeutic index relative to conventional mixed DAR vedotin ADCs while maintaining potent antitumor activity.

Materials and Methods: EC conjugation site variants were assessed in nonclinical studies to characterize the relationship between linker plasma stability, systemic exposure, efficacy, and tolerability, enabling identification of an optimized EC configuration. The selected sites were then engineered into PF-08098488, which was comprehensively characterized for its binding properties, mechanism of action, and antitumor activity.

Results: EC4 variant ADCs demonstrated reduced hematologic toxicity in rats and cynomolgus monkeys, and comparable or improved ocular tolerability in rats, relative to more stable EC constructs. Despite improved tolerability, EC4 ADCs maintained antitumor activity comparable to mixed DAR4 vedotin ADCs in mouse xenograft models.

The SG-105.2E4 mAb exhibited high-affinity, specific binding to human CEACAM5 with no detectable cross-reactivity to related CEACAM family members, and robust, target-dependent internalization and endo-lysosomal trafficking. PF-08098488 demonstrated potent cytotoxic activity in CEACAM5-expressing cancer cell lines and patient-derived organoids. It induced significant tumor growth inhibition across multiple xenograft models, including those with heterogeneous CEACAM5 expression. PF-08098488 also demonstrated enhanced antitumor activity relative to tusamitamab ravtansine in preclinical models.

Conclusions: PF-08098488 is a novel, highly specific CEACAM5-targeting MMAE ADC that incorporates optimized EC technology to preserve efficacy while reducing toxicity, supporting an improved therapeutic index. Utilizing the well-characterized vedotin platform, its mechanism involves selective binding, internalization, and intracellular MMAE release. PF-08098488 demonstrates potent antitumor activity across CEACAM5-expressing preclinical models, supporting its clinical development for CEACAM5-positive solid tumors.

Conflict of interest: Corporate-sponsored Research:

We are employees (or former employees) of Seagen and Pfizer, and have stock ownership.

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57 - PB-057 **Poster**

BCG040, a Novel B7-H4-Targeting Biparatopic ADC, Demonstrates Superior Preclinical Efficacy in Heterogeneous Tumors

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B7-H4 (VTCN1) is overexpressed in many epithelial malignancies, particularly in ovarian, breast, biliary tract, and pancreatic cancers. These tumors are often resistant to both chemotherapy and immunotherapy, due to their aggressive nature and poor prognosis.

Here, we present BCG040, a novel first-in-class, fully human IgG1κ biparatopic B7-H4 ADC. BCG040 binds to two non-overlapping B7-H4 epitopes and is conjugated to the potent topoisomerase I (TOP1) inhibitor BCPT02 (DAR≈8) via a hydrophilic protease-cleavable linker. *In vitro*, BCG040 showed nanomolar affinity for B7-H4, superior to Hu2F7 and SGN-B7H4V benchmark analogs, with fully human/cynomolgus cross-reactivity and no off-target binding to other B7 family members. BCG040 exhibited stronger binding and more rapid internalization than the two analogs in breast and ovarian cancer cells. *In vivo*, a single low dose of BCG040 showed durable tumor regressions (~40 days) in breast cancer PDX models and significant efficacy in pancreatic cancer PDX models, outperforming other ADCs such as Hu2F7, SGN-B7H4V, or FPA150 (conjugated with MMAE or BCPT02). This potent efficacy was achieved without observable toxicity and was supported by a favorable pharmacokinetic (PK) profile. Furthermore, this drug demonstrates excellent developability.

The enhanced therapeutic activity of BCG040 is attributed to its unique biparatopic design, which promotes receptor clustering and accelerated intracellular trafficking, leading to enhanced delivery of payload. Notably, BCPT02-containing ADCs exhibited potent anti-tumor activity in heterogeneous PDX tumors, whereas MMAE-based conjugates were ineffective. These findings underscore the potential of BCG040 as a promising therapeutic candidate for the treatment of pancreatic, biliary tract, ovarian, and breast cancers.

No conflict of interest

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58 - PB-058 **Poster**

INA03, a MMAE-based ADC targeting the transferrin receptor CD71, demonstrates potent antitumor activity in breast cancer PDX models resistant to TOP1-ADCs

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Background: CD71 (transferrin receptor 1), encoded by *TFRC*, is overexpressed on proliferating tumour cells and represents an attractive target for antibody-drug conjugate (ADC) therapy. INA03 is a humanised anti-CD71 antibody (INA01) conjugated to monomethyl auristatin E (MMAE), which recently achieved its first-in-human clinical trial. Here we characterised *TFRC*/CD71 gene and protein expression across large cohorts of breast cancer (BC) patient samples and patient-derived xenografts (PDX) and investigated the antitumor activity of INA03 in BC PDX models.

Material and methods: *TFRC* mRNA expression was analysed by RT-PCR in 149 BC PDX and by transcriptomic analysis and RT-PCR in two independent BC patient cohorts (n = 143 and n = 514). CD71 protein expression was assessed by immunohistochemistry and mass spectrometry. *A*ntitumor efficacy of INA03 was evaluated in multiple PDX models of early-stage and metastatic BC resistant to standard therapies. GSEA performed on proteomic data (MsigDB Hallmark gene sets) identified biological programs associated with response and resistance to INA03.

Results: *TFRC* was significantly overexpressed in BC versus normal tissue, with highest levels in TNBC and HER2+ subtypes across two independent BC patient cohorts (n = 657), TCGA BC dataset and PDX. High *TFRC* expression was associated with adverse clinicopathological features and shorter metastasis-free survival in HR+/ERBB2– patients. *In vivo,* INA03 induced potent anti-tumour activity across PDX of metastatic BC, outperforming trastuzumab-deruxtecan (T-DXd) in an HR+/HER2-low model and sacituzumab govitecan in a TNBC PDX and retaining activity upon acquired T-DXd resistance. Activity was also observed in PDX resistant to chemotherapy, PARP inhibition and CDK4/6 inhibitor-based endocrine therapy. No correlation was observed between response and CD71 protein level (H-score and mass spectrometry-based quantification). GSEA identified Oxidative Phosphorylation and Fatty Acid Metabolism as top enriched hallmarks in sensitive models (FDR < 0.05), while E2F Targets and G2M Checkpoint were enriched in resistant models. Finally, preliminary data obtained *in vitro* with a dual-payload ADC (MMAE at DAR2 and Topo-I at DAR4) built on the same anti-CD71 antibody INA01 showed very encouraging results, with sustained activity compared to the single-payload ADC INA03 across multiple BC cell lines.

Conclusions: INA03 demonstrates potent anti-tumour activity across BC PDX models in settings of resistance to different standards of care, including TOP1-based ADCs. Up-regulation of mitochondria-dependent, iron-demanding metabolic programs, rather than CD71 protein level, correlated with INA03 response. These preclinical results provide a strong rationale for the clinical evaluation of INA03 in advanced BC, particularly after failure of TOP1-ADCs.

Conflict of interest: Ownership:Pierre Launey, Renato Monteiro, Emmanuel Gomez, Olivier Hermine

Corporate-sponsored Research: Elisabetta Marangoni

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59 - PB-059 **Poster**

A proliferative-luminal phenotype predicts trastuzumab deruxtecan sensitivity independent of HER2 expression in ER-positive breast cancer

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Background. Trastuzumab deruxtecan (T-DXd) is approved for HER2-positive and HER2-low metastatic breast cancer, yet predictive biomarkers of response and mechanisms of adaptive resistance remain poorly defined. We aimed to identify molecular determinants of T-DXd sensitivity and resistance in ER-positive breast cancer patient-derived xenograft (PDX) using an integrated multi-omics approach.

Methods. Thirty-five ER-positive PDX from metastatic (n = 27) or high grade early-stage breast cancers (n = 8) were treated with T-DXd and profiled by bulk RNA-seq and quantitative proteomics from FFPE tissues. Single cell RNA-sequencing was performed in one PDX across untreated, residual disease and relapse states.

Results. T-DXd induced complete or partial response in 16/35 (46%) PDX models. When available, patient responses were concordant with PDX responses. Neither HER2 expression by IHC nor HER2 protein abundance measured by quantitative proteomics was associated with T-DXd response. Baseline transcriptomic and proteomic analyses identified enrichment of E2F Targets, G2M Checkpoint, Mitotic Spindle, and Estrogen Response pathways in responder models, together with increased FOXA1 and GATA3 protein expression, defining a proliferative-luminal phenotype associated with sensitivity. Three independent proliferative-luminal classifiers (PAM50-derived, HER2DX-derived, and custom proteomic score) consistently predicted T-DXd response in transcriptomic and proteomic datasets (AUC 0.78–0.83, $p < 0.01$). In contrast, intrinsically resistant models showed elevated TNFα/NF-κB, EMT, Hypoxia and Interferon Alpha/Gamma pathway activity. Pharmacodynamic analyses performed on different responder and resistant models showed that treatment-induced suppression of E2F targets and G2M checkpoint genes, combined with induction of interferon-α/γ response pathways, was the transcriptional hallmark of T-DXd response. Estrogen response was also down-regulated in T-DXd-treated tumours independently of tumour response, with ER protein degradation confirmed by Western blot in multiple PDX through a mechanism currently under investigation. Single-cell RNA-seq revealed a two-phase adaptive program: persister cells displayed interferon/JAK-STAT signalling, stress-associated transcription factors (FOXO1/3, SMARCA4) and reduced metabolic activity consistent with dormancy; at relapse, HIF-2α/EPAS1-driven hypoxia, mTORC1 and OXPHOS were upregulated alongside a $KRT5^+$/$KRT72^+$ basal-like subpopulation, suggesting clonal evolution.

Conclusions. T-DXd sensitivity is driven by a proliferative-luminal molecular phenotype rather than HER2 expression alone. Tumour recurrence evolves through interferon-mediated dormancy, metabolic reprogramming and possibly basal-like expansion at relapse. These findings provide a biological rationale for future biomarker development and combination strategies with T-DXd.

No conflict of interest

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60 - PB-060 **Poster**

A novel dual-payload ADC platform that can offer synergistic antitumoral efficacy of MMAE while reducing undesired side effects

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MMAE-based microtubule-disrupting agents, particularly in vedotin platforms, represent one of the most clinically validated cytotoxic payload classes in antibody–drug conjugates (ADCs). However, MMAE-containing ADCs are often challenged by dose-limiting toxicities (DLTs) such as peripheral neuropathy, myelosuppression, and rash. Therefore, there remains a significant unmet need for strategies that can reduce MMAE-associated DLTs while preserving the clinically proven antitumor efficacy of MMAE.

We have developed a dual-payload ADC platform based on the combination of MMAE with Kinesin spindle protein (KSP) inhibitor payloads, which can offer synergistic antitumor efficacy while reducing side effects associated with MMAE.

KSP inhibitors revealed outstanding synergy with MMAE when we screened various drugs by measuring ZIP score in cytotoxicity assays. We then prepared DAR2 ADCs based on [2 + 2] dual-payload configuration targeting TROP2 and/or FRα, which showed comparable *in vitro* cytotoxicity to MMAE-only DAR4 ADCs across various cancer cell lines. CDX model studies using several different cancer cell lines also confirmed that the DAR2 dual-payload ADCs demonstrate robust *in vivo* efficacy comparable to DAR4 single-payload ADCs. The synergistic mechanism of this dual-payload approach was supported by increased G2/M accumulation and enhanced caspase 3/7 activation.

As we expected, the dual-payload ADCs revealed improved *in vitro* therapeutic window compared with vedotin-based DAR4 ADCs in normal cells such as HaCaT, Jurkat, and PBMC.

These findings support our novel dual-payload ADC strategy, in which KSP inhibitor payloads compensate for reduced MMAE loading through synergistic mitotic disruption. By maintaining antitumor efficacy while reducing undesired normal cell toxicities, this approach provides an improved therapeutic window compared with conventional MMAE-based single-payload ADCs. The dual-payload ADC platform targeting TROP2 and FRα is currently being advanced toward IND-enabling studies.

No conflict of interest

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61 - PB-061 **Poster**

A novel PLK1/BRD4-Targeting Antibody-Drug Conjugate (DAC) overcomes conventional payload resistance

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Background: Antibody-Drug Conjugates (ADCs) are cancer therapy mainstays, but limited response and emerging resistance, compounded by low payload diversity, remain major challenges. To address this, we identified PLK1 and BRD4 as synergistic targets for an innovative heterobifunctional degrader payload. PLK1 drives mitotic progression in aneuploid tumors, while BRD4 sustains the transcription of critical survival genes via super-enhancers. Their simultaneous degradation exploits a vulnerability in cancer cells that forces mitotic catastrophe. In patients, high PLK1 expression correlates with the presence of DNA repair deficiencies (e.g. *TP53* mutations) and poor survival.

Methods and Results: We generated a novel PLK1/BRD4 degrader payload exhibiting subnanomolar IC50s across a diverse *in vitro* cancer cell line panel. Crucially, the payload potently eliminated cells resistant or refractory to conventional payloads like DXd or MMAE. Mechanistically, our payload triggered mitotic catastrophe in tumor cells, most severely in *TP53*-mutant lines, leading to potent immunogenic cell death (ICD). The payload drives robust bystander killing within the tumor and is rapidly metabolized in systemic circulation to minimize off-tumor toxicity.

To conjugate our payload to clinically relevant antibodies with a high DAR, we developed a novel hydrophilic, protease-cleavable linker that can irreversibly react with an antibody. The resulting Degrader-Antibody Conjugates (DACs) showed native antibody-like hydrophilicity and excellent monomericity. The DACs demonstrated excellent pharmacokinetic profiles in mice, combined with minimal payload loss even at a drug-to-antibody ratio of 8 (DAR8).

***In Vivo* Validation:** As a proof-of-concept, we generated DACs using the clinically approved TROP2-targeting antibody sacituzumab. These DACs were highly active against TROP2+ cell lines that are refractory to clinically used ADCs. *In vivo*, the DACs induced potent tumor regression in a *TP53*-mutant breast cancer xenograft model (MDA-MB-468) without clinical signs of toxicity. Analysis of tumor samples confirmed the PLK1/BRD4 degrader mechanism.

Conclusion: Our PLK1/BRD4 degrader-based DAC platform is highly adaptable to various antibodies in different disease settings. It offers a promising therapeutic strategy for patients resistant or refractory to conventional ADC payloads.

Conflict of interest: Other Substantive Relationships: authors are employees of Crossfire Oncology B.V.

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62 - PB-062 **Poster**

In vivo efficacy and safety of a novel cMET-targeted miniaturized ADC for better solid tumour penetration and safety

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Background: Antibody Fragment Drug Conjugates (FDCs), represent an emerging class of smaller, "fast-in, fast-out" Antibody Drug Conjugate (ADC)-like therapeutics tailored for solid tumours. These promise many advantages over conventional ADCs including rapid, deeper and more homogeneous tumour penetration and faster and safer systemic clearance with reduced exposure to critical normal tissues. However, smaller formats have been technologically-challenging to apply in oncology. Our novel approach enables high Drug: Antibody Ratios (DARs) whilst retaining effective binding and other favourable biophysical properties.

Methods: To achieve this, single-chain Fvs and other recombinant antibody formats were selected using phage display of bespoke human antibody libraries built specifically by Antikor for bioconjugation stability and developability. Harmonious medicinal chemistry is employed to design and synthesize complex MMAE linker-payload chemical moieties that work with smaller formats, employing solubilization strategies. Lysine/NHS-ester based conjugation led to a DAR6 (equivalent to a DAR30 on a full IgG), which showed remarkable biophysical and plasma stability This platform technology has led to our lead product, ANT-045

Results: ANT-45 is a cMET-targeted FDC addressing a wide range of solid tumours. ANT-045 demonstrates superior tumour cure efficacy in cMET high (Hs746T), moderate (NUGC4) and low (NCIN87) gastric cancer CDX xenograft models at doses as low as 0.5mg/kg given weekly for 4 doses. Efficacy is also seen in gastric and pancreatic models where the cMET IHC score is ~100. ANT-045 is better tolerated compared to the leading competitor ADCs, notably telisotuzumab vedotin by body weight and safety biomarkers. Quantitative uptake studies showed that more MMAE-payload was delivered on a molar basis to the tumour at equivalent molar ADC/FDC dosing. In a non-GLP, non-human primate study, ANT-045 was well tolerated at doses as high as 2mg/kg (equivalent to 20mg/kg equivalent MMAE-containing ADC) with a predicted half-life in humans of around 12-14 hours supporting a viable clinical dosing strategy with a wide therapeutic window.

Conclusions: The "one size fits all" paradigm for ADCs is challenged by our smaller format approach showing that competitive drugs can be discovered and developed. Superior efficacy and safety provide motivation to bring such drugs to the market. Insights into how FDCs behave *in vivo* through quantitative uptake studies and toxicological parameters will be shared and how these have informed our follow-up products.

No conflict of interest

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63 - PB-063 **Poster**

TCX-201, an ADC targeting a highly specific tumor-associated carbohydrate antigen (TACA) shows excellent PK, safety profile, and preclinical efficacy in solid tumor models

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Tumor-associated carbohydrate antigens (TACAs) are defined oligosaccharide structures that are aberrantly expressed on the surface of cancer cells. They are derived from malignancy-associated changes in glycosylation pathways, which lead to overproduced or aberrant structures, providing the cancer cell with a survival advantage, and represent a still unexplored target class for cancer therapy.

We have generated specific antibodies against several of these difficult to target antigens and obtained a high affinity, fully humanized monoclonal antibody (mAb), TCX-201, against a TACA that is highly expressed across a broad range of solid tumor indications, including colon, pancreatic, and NSCLC. This mAb shows superior internalization (int50 ~0.5h in highly expressing cells), affinity, and specificity for the target compared to the available benchmark, as assessed by glycan array, flow cytometry, and immunohistochemistry. TCX-201 was conjugated via a cleavable linker to MMAE (DAR4) and was subsequently tested for potency and pharmacokinetic properties. *In vitro* studies showed effective killing of various pancreatic and colon cancer cell lines expressing different levels of the TACA (e.g. Colo-205 (IC50 of 0.013 nM), LS180 (IC50 of 4.7 nM), HuP-T4 (IC50 of 0.3 nM), Capan-2 (IC50 of 1.03 nM). Moreover, high efficacy was observed in different xenograft models with weekly iv administration: Capan-2 pancreatic cancer reaching T/C of 16% and 6% at 3 and 7 mg/kg MMAE (respectively), and Colo-205 colorectal cancer reaching T/C of 3% with 7 mg/kg MMAE. Moreover, a high accumulation of the MMAE payload at the tumor site above the *in vitro* IC90, according to LC-MS data, was observed. In addition to CDX models, high dose-dependent efficacy with complete remissions was observed in a PDAC (T/C of 52,5%, 10,7%, and 0% with 3, 5, and 10 mg/kg) and a CRC (met) (T/C of 36,1%, 4%, and 0% with 3, 5, and 10 mg/kg) PDX model. These results, coupled with a favorable PK and safety profile obtained in mice and Cynomolgus monkeys make this ADC a first-in-class molecule for the treatment of various solid tumors that express different levels of the target structure.

In conclusion, our antibody represents a new promising treatment option for different cancer indications and can be effectively employed as an ADC thanks to its fast internalization profile and long retention in circulation with high tolerability. Our approach demonstrates that we can produce targeted antibodies with high affinity against TACAs, which were previously considered undruggable, and they can be highly efficacious in the treatment of malignancies. The expansion of the target spectrum for cancers is a necessity, given the limited amount of available and druggable antigens. TACAs may represent a potential, powerful solution to increase the treatment options and overcome acquired resistance.

Conflict of interest: Ownership: The authors are all employed and hold shares of Tacalyx GmbH, a startup company focussed on generating anti-TACA antibodies

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64 - PB-064 **Poster**

Pre-clinical personalized antibody-drug conjugates using novel single payload ATR inhibitors

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Background: A novel approach to generate more effective and less toxic antibody-drug conjugates (ADCs) is to target surface antigens with payloads tailored to selected cancer mutations. DCx Biotherapeutics is using this approach to develop novel ADCs targeting TROP2+ve cancers with *ATM*, and *BRCA1/2* loss of function mutations using ataxia telangiectasia and Rad3-related kinase inhibitors (ATRi) as payloads. ATR stabilizes and restarts stressed replication forks, suppresses origin firing, activates the cell cycle checkpoint, and facilitates DNA repair, particularly in cells lacking ATM, BRCA1, BRCA2. There is strong overlap between cancers with ATRi sensitizing defects with those expressing high levels of TROP2 surface antigens including ovarian, breast, bladder and lung cancers. Our personalized ADC approach couples tumor surface targeting with increased tumor sensitivity to the delivered payload to improve the therapeutic index.

Materials and Methods: Cell lines expressing high levels of TROP2 were selected and isogenic models generated by knocking out *ATM* or mutating *TOP1*. Viability assays (Incucyte) were used to evaluate the potency of payloads and ADCs. Cell permeability in Caco-2 and human lysosomal and microsomal stability assays were conducted in standard assays. MDR1 and BCRP inhibition assays used verapamil and KO143 as inhibitors respectively. *In vivo* experiments were in NCG and SCID mice bearing sub-cutaneous tumors measured with calipers.

Results: Several proprietary and highly selective ATRi payloads with a linkable handle exhibit low nM potency in multiple cell lines lacking functional ATM or BRCA1/2 with a >10x selectivity compared to isogenic WT control cell lines. Lead payloads have desirable physical chemistry characteristics such as good stability and high clearance in human liver lysosomes and microsomes respectively. They have good hydrophobicity and excellent cell permeability with low cellular efflux. Datopotamab and sacituzumab- ATRi conjugates have low nM to pM potency with >1000x selectivity for mutation +ve cells vs WT, are not substrates of MDR1 or BCRP multidrug resistant pumps and have excellent human plasma stability. Furthermore, these ADCs maintain potency in a clinically relevant topoisomerase 1 mutated cell line indicating they can overcome deruxtecan resistance. In mouse models, single payload ADCs demonstrate tumor regressions and are well tolerated with no body weight loss or clinical signs. IgG control ADCs with the same linker-payload strategy show no activity suggesting a high degree of stability in circulation.

Conclusions: Our pre-clinical studies demonstrate excellent pre-clinical efficacy and tolerability for novel single payload ATRi ADCs in multiple models, highlighting the potential for a novel personalized ADC strategy for breast, bladder and lung cancers with *ATM* and HR-deficiency mutations.

Conflict of interest: Other Substantive Relationships: All authors are current or former employees of DCX Biotherapeutics Inc.

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65 - PB-065 **Poster**

Preclinical evaluation of IM-1617, a clinical-stage ADC for solid tumors

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Background: Antibody-drug conjugates (ADCs) have transformed the treatment landscape, but important limitations remain, including heterogeneous target expression, poor tumor penetration, and efflux-mediated resistance. IM-1617 is a clinical-stage, investigational ADC designed to address these challenges by targeting a broadly expressed novel tumor antigen and delivering HC74, a differentiated topoisomerase 1 (TOP1) inhibitor payload.

Methods: IM-1617 was evaluated in vitro and in vivo across multiple preclinical solid tumor models and compared with clinically relevant ADC benchmarks.

Results: The target of IM-1617 is expressed across multiple solid tumors, including non-small cell lung cancer, colorectal cancer, and breast cancer. IM-1617 leverages the HC74 payload, which has enhanced bystander activity and decreased susceptibility to efflux-mediated resistance. IM-1617 demonstrates robust preclinical efficacy in tumor models with target expression levels representative of greater than 70% of patient tumors across at least 7 solid tumor indications. Regressions in large, established tumors highlight IM-1617's ability to overcome challenges such as tumor penetration and payload diffusion, which have been shown to limit the efficacy of other TOP1 inhibitor-based ADCs. IM-1617 also shows activity in models with primary or acquired resistance to TROP2-directed ADCs and outperforms other emerging TOP1 inhibitor ADC benchmarks in patient-derived xenograft models of lung squamous, lung non-squamous, and colorectal cancer.

Conclusions: IM-1617 is a differentiated ADC that integrates a novel and broadly expressed target and the HC74 payload to address key limitations in the current solid tumor ADC landscape, including target heterogeneity, tumor diffusion, and resistance-associated biology. Robust activity was observed in models with patient-relevant target expression, where IM-1617 outperformed benchmark ADCs providing a rationale for the ongoing phase 1 clinical study and continued development across multiple solid tumor indications.

Conflict of interest: Ownership: All authors are current or former employees and shareholders of Immunome Inc.

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66 - PB-066 **Poster**

'CellPh-Linker Conjugation': An engineering-free Fab-site selective ADC conjugation technology

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Site-specific conjugation technology has attracted considerable interest in the ADC field, as it would offer improved CMC advantages and better control over undesirable side effects compared to traditional stochastic conjugation. Although many site-specific conjugation methods have been developed, they often require antibody engineering, enzyme assistance, or additional conjugation processes.

Herein, we disclose, for the first time, 'CellPh-Linker Conjugation', a novel engineering-free Fab-site selective conjugation platform which does not require any antibody engineering or enzymes in the conjugation process. The conjugation method using unique bifunctional linkers works by a convenient one-pot process, which can offer a great advantage of ADC manufacturing. Conjugation-site analyses based on LC/MS demonstrate that CellPh-Linker Conjugation occurs selectively at the Fab site by re-bridging the interchain disulfide bond between C_L and C_{H1} with approximately 90% DAR2-selective control. Notably, CellPh-Linker Conjugation generates over 90% intact bridged antibody, so that the half-antibody formation is minimized that is a key limitation of the known re-bridging-based conjugation technologies. CellPh-Linker Conjugation can be applied to various payloads such as MT inhibitors and TOP1 inhibitors with different linker types. CellPh-Linker ADCs maintain antigen-binding affinity, target-mediated internalization, and target-dependent cytotoxicity in cancer cell lines comparable to those of random-conjugated ADCs. CellPh-Linker ADCs demonstrate superior anti-tumor efficacy compared to randomly conjugated ADCs in in vivo CDX models, which may be rooted from enhanced plasma stability as shown in rodent PK studies.

With all the studies together, we claim that CellPh-Linker Conjugation can provide DAR-controlled ADCs that are crucial for managing ADC efficacy and undesired side effects. Moreover, CellPh-Linker Conjugation combined with various multi-payload ADC designs would offer a powerful option to reduce premature payload release that are a key consideration for administering different payload classes.

No conflict of interest

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67 - PB-067 **Poster**

Breaking through ADC resistance: Generating TOP1 mutation cancer model and evaluating next generation ADCs

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Antibody-drug conjugates (ADCs) have emerged as powerful oncology therapeutics in last decades by selectively delivering cytotoxic payloads to tumor antigen-expressing cells while minimizing damage to normal tissues. As a historic breakthrough in oncology therapy, Enhertu has become a new blockbuster due to its excellent performance in clinical trials compared with canonical antibody or chemotherapy-based approaches. However, acquired resistance remains a critical barrier to durable clinical efficacy. Therefore, it is critical to establish comprehensive and preclinical relevant ADC resistance models to investigate the resistance mechanism observed

in patients and to evaluate next generation ADCs designed to achieve more durable response.

TOP1 inhibitors such as camptothecin-based chemotherapies intercalate at the DNA/TOP1 interface to prevent the resolution of TOP1-induced single-strand breaks. The resulting stabilization of the TOP1 cleavage complex and then ultimately leads to double-strand DNA breaks and subsequent cell death. TOP1 inhibitors such as DxD, SN38, Exatecan are the most prevalent payloads used in ADCs. Emerging clinical evidence suggests that Top1 mutations such as R364H, G395E or W401C represents a major mechanism of acquired drug resistance to ADCs like Enhertu and Trodelvy. Therefore, we established clinically relevant TOP1 R364H-mutant ADC resistance models using HER2 and TROP2 positive HCC1954 breast cancer cells and NCI-N87 gastric cancer cells. TOP1 R364H mutant cells showed significant decreased sensitivity to TOP1 inhibitors and ADCs with TOP1 inhibitor payloads by cell killing assay. Consistently, xenograft tumor of TOP1 R364H-mutant cells displayed resistance to several HER2- or TROP2-targted ADCs carrying TOP1 inhibitor payloads, such as Enhertu and Trodelvy. To explore strategies to overcome the resistance, dual-payload ADCs have been developed in recent years. Therefore, we produced a HER2 targeted dual-payload ADC, Trastuzumab-DXD-MMAE. This dual-payload ADC exhibited improved anti-tumor effect and successfully overcome TOP1 R364H-mutation mediated resistance in vivo.

In summary, the established TOP1 mutation-driven cancer models provide a clinically relevant platform for investigating acquired ADC resistance mechanisms and evaluating next generation ADCs.

No conflict of interest

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68 - PB-068 **Poster**

Development of a Novel TAG-72 Targeting ADC with a proprietary pan-RAS(ON) molecular glue payload

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Background: Colorectal carcinoma (CRC) frequently exhibits oncogenic RAS mutations, driving aggressive tumor growth and resistance to conventional therapies. Despite advancements, direct therapeutic targeting of diverse RAS variants remains a significant challenge. Tumor-associated glycoprotein-72 (TAG-72) is a cell-surface mucin-like glycoprotein highly overexpressed in human adenocarcinomas, including up to 80% of CRC tissues, with minimal expression in normal tissues. This makes TAG-72 an attractive candidate for targeted drug delivery. To exploit this biology, we developed a novel antibody-drug conjugate (ADC) comprising a high-affinity anti-TAG-72 monoclonal antibody conjugated to a proprietary pan-Ras(on) inhibitor via a stable, cleavable linker. This study evaluates the pre-clinical efficacy, selectivity, and mechanism of action of this novel ADC in CRC models.

Material and Methods: The anti-TAG-72 antibody was conjugated to the proprietary pan-Ras(on) inhibitor as payload. Binding affinity and internalizing kinetics were analyzed via flow cytometry in a panel of human CRC cell lines expressing varying levels of TAG-72 and RAS mutation statuses. In vitro cytotoxicity and targeted inhibition of downstream signaling (pERK/pAKT) were measured by cell viability assays and Western blot analysis, respectively. In vivo therapeutic efficacy and tolerability were evaluated in TAG-72-positive, KRAS mutant or KRAS amplification cell line-derived xenograft (CDX) mouse models.

Results: The TAG-72 ADC demonstrated strong, specific binding to TAG-72-positive CRC cells and achieved efficient receptor-mediated internalization. Upon intracellular delivery and cleavable-linker degradation, the pan-Ras(on) inhibitor suppressed downstream MAPK/ERK signaling. Consequently, the ADC exhibited potent in vitro cytotoxicity against RAS-mutant CRC lines. In CRC mouse xenograft models, systemic administration of the ADC led to significant, dose-dependent tumor regression without notable body weight loss or adverse systemic signs, validating its favorable safety profile and robust therapeutic index.

Conclusions: Our novel TAG-72-targeted pan-Ras(on) inhibitor ADC successfully bridges precise tumor surface targeting with intracellular oncogene inhibition. By specifically delivering a pan-Ras (on) inhibitor directly into TAG-72-expressing malignant cells, this asset achieves profound anti-tumor efficacy in RAS-driven CRC carcinoma models while mitigating systemic off-target toxicities. These promising pre-clinical results support the further translational development and future clinical evaluation of this therapeutic candidate for patients suffering from advanced stage CRC and other tumor types with TAG-72 overexpression and RAS mutation.

No conflict of interest

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69 - PB-069 **Poster**

Association between human papillomavirus-driven tumor microenvironment biomarkers and anatomical subtypes in patients with recurrent or metastatic head and neck squamous cell carcinoma treated with CRB-701 (SYS6002) during a phase 1/2 study

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Background: Nectin-4, a cell-surface adhesion molecule, is overexpressed in multiple epithelial malignancies and is a clinically validated target for antibody–drug conjugates (ADCs). CRB-701 is a next-generation Nectin-4-targeting ADC with a stable linker and monomethyl auristatin E payload that has demonstrated preliminary clinical activity in cervical cancer, oropharyngeal squamous cell carcinoma (OPSCC) and metastatic urothelial carcinoma. Human papillomavirus (HPV) E6/E7-driven oncogenic signaling, together with an immune-inflamed tumor microenvironment, may contribute to a biologic context associated with Nectin-4 expression and therapeutic sensitivity in OPSCC. Here, we report exploratory biomarker analyses from the phase 1/2 CRB-701-01 study (NCT06265727) to investigate factors potentially associated with the clinical activity observed in OPSCC.

Materials and methods: Patients with recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) previously treated with ≥ 1 systemic therapy received CRB-701 (1.8–3.6 mg/kg every 3 weeks). Archival and/or pretreatment formalin-fixed, paraffin-embedded tumor specimens collected < 5 years before cycle 1 day 1 were centrally evaluated for Nectin-4 expression by immunohistochemistry (IHC) and quantified by a combined membranous and cytoplasmic H-score (low, 0–99; medium, 100–199; high, 200–300). Programmed death-ligand 1 (PD-L1) expression, $CD8^+$ tumor-infiltrating lymphocyte density and HPV status (p16 IHC and/or HPV genomic testing per investigator) were assessed. Exploratory analyses evaluated associations between biomarkers and HNSCC anatomical subtypes.

Results: A greater proportion of patients with OPSCC were HPV-positive than those with non-OPSCC (85.4% vs 23.5%). Nectin-4 H scores were heterogenous (range, 10–285), with enrichment of medium-to-high Nectin-4 expression observed in OPSCC versus non-OPSCC tumors. OPSCC tumors also exhibited higher intratumoral $CD8^+$ T-cell density and increased PD-L1 positivity than non-OPSCC tumors.

Conclusions: OPSCC tumors were enriched for HPV positivity, higher Nectin-4 staining intensity, increased $CD8^+$ T-cell infiltration and PD-L1 positivity, consistent with the immune-inflamed biology of HPV-driven disease. These findings align with previous reports linking persistent HPV E6/E7 activity to enhanced immune infiltration in OPSCC tumors and suggest that medium-to-high Nectin-4 expression is more common within this HPV-associated immune-inflamed tumor microenvironment. Together, these data support a mechanistic hypothesis whereby HPV E6/E7-driven oncogenic signaling and an activated immune microenvironment may promote Nectin-4 expression, potentially enhancing susceptibility to Nectin-4-directed ADC therapy.

Conflict of interest

Corporate-sponsored Research: This study was funded by Corbus Pharmaceuticals Inc.

Other Substantive Relationships: Vaishali Shinde and Ian Hodgson are employees of Corbus Pharmaceuticals Inc. and have stock/stock options. Danish Memon is an independent consultant for Corbus Pharmaceuticals Inc.

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70 - PB-070 **Poster**

Evaluation of Nectin-4 protein expression and gene amplification in patients with recurrent or metastatic head and neck squamous cell carcinoma treated with CRB-701 (SYS6002) during a phase 1/2 study

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Background: Nectin-4 is a validated antibody–drug conjugate (ADC) target that is overexpressed in many epithelial malignancies. CRB-701 is a next-generation Nectin-4-targeted ADC that has demonstrated preliminary efficacy in bladder cancer, cervical cancer, and head and neck squamous cell carcinoma (HNSCC), which are tumor types identified as having high Nectin-4 expression in prior The Cancer Genome Atlas bulk RNA sequencing and tissue microarray-based immunohistochemistry (IHC) analyses. We evaluated Nectin-4 protein expression (tumor) and blood-based *NECTIN4* gene amplification as potential predictive biomarkers of response in patients with recurrent/metastatic (R/M) HNSCC enrolled in a phase 1/2 study (NCT06265727).

Materials and methods: Patients with R/M HNSCC previously treated with ≥ 1 systemic therapy received CRB-701 (1.8–3.6 mg/kg every 3 weeks). Archival and/or pretreatment formalin-fixed, paraffin-embedded tumor specimens collected < 5 years before cycle 1 day 1 (C1D1) were centrally evaluated for Nectin-4 expression by IHC and quantified by H-score (low, 0–99; medium, 100–199; high, 200–300). *NECTIN4* gene amplification was assessed using a novel proprietary droplet digital polymerase chain reaction (ddPCR) assay in blood plasma samples collected pre-dose on C1D1. Exploratory analysis evaluated associations between these biomarkers and clinical outcomes in oropharyngeal squamous cell carcinoma (OPSCC) and non-OPSCC HNSCC.

Results: As of April 2026, biomarker data were available for 79 patients (43 OPSCC, 36 non-OPSCC). Nectin-4 H scores were heterogeneous (range, 10–285), with enrichment of medium-to-high Nectin-4 expression observed in OPSCC versus non-OPSCC tumors. The *NECTIN4* gene amplification assay demonstrated sensitive detection of copy number gains. *NECTIN4* gene amplification status and protein expression were positively associated; patients with higher blood copy number generally had greater tumor staining intensity. Patients with OPSCC who responded to CRB-701 treatment had higher Nectin-4 staining intensity and higher gene copy number than those who did not respond to CRB-701.

Conclusions: These exploratory analyses indicate that higher Nectin-4 protein expression and gene amplification measured by IHC and ddPCR may be associated with improved clinical outcomes following CRB-701 treatment, particularly in patients with OPSCC, suggesting that the enrichment of high-intensity Nectin-4 expression and gene amplification may contribute to the enhanced activity of CRB-701. The lack of direct correlation between overall Nectin-4 expression in archival tissue and clinical outcomes may reflect temporal and spatial differences between archived samples and current disease biology. Baseline blood-based *NECTIN4* gene amplification is a promising non-invasive biomarker that warrants further evaluation as a predictor of response to CRB-701.

Conflict of interest

Corporate-sponsored Research: This study was funded by Corbus Pharmaceuticals Inc.

Other Substantive Relationships: Vaishali Shinde and Ian Hodgson are employees of Corbus Pharmaceuticals Inc. and have stock/stock options. Danish Memon is an independent consultant for Corbus Pharmaceuticals, Inc.

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71 - PB-071 **Poster**

Baseline tumor genomic features associated with efficacy outcomes of farletuzumab ecteribulin (FZEC) antibody-drug conjugate (ADC) therapy

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Background: Platinum-resistant ovarian cancer (OC)/endometrial cancer (EC) have limited treatment options. Study 201 (phase 1/2; NCT04300556) is ongoing to evaluate safety/efficacy of FZEC (previously MORAb-202), a folate receptor α targeting ADC, in patients (pts) with various tumors (eg, OC/EC). Here, we analyzed baseline tumor genomic features associated with clinical outcomes following FZEC therapy in Study 201 in pts with OC/EC.

Material and methods: Pts from Dose Escalation (0.9mg/kg and 1.2mg/kg IV Q3W)/Dose Confirmation (25mg/m^2 and 33mg/m^2 IV Q3W)/Dose Optimization part A (8mg/m^2 day [D]1/D8/D15 IV, 12mg/m^2 D1/D8 IV, and 25mg/m^2 D1 IV + oral steroid D8/D9/D10; 21D cycle) phases of Study 201 were considered for analysis. Of the 89 pts from these phases, 71 had tumor tissue samples available and underwent genomic analysis. As only 1 pt with available samples had non-small-cell lung cancer, this pt was excluded; 70 pts with

OC/EC were included herein. Baseline tumor whole-exome sequencing was performed, and oncogenic alterations were annotated using OncoKB. *TP53* mutations were classified as gain-of-function (GOF)/loss-of-function (LOF). Associations between genomic features and efficacy (clinical benefit [complete/partial response or stable disease for ≥23 wks], OS, and PFS) were evaluated per ANCOVA, logistic regression, and Cox models (HR.*p*); gene mutation analyses were adjusted for multiple covariates.

Results: Of 70 pts, 41 had OC and 29 had EC. Mutated *TP53* was associated with favorable OS in the OC (HR = 0.20; 95%CI 0.06-0.73; HR.*p* = 0.015) and EC (HR = 0.15; 95%CI 0.03-0.75; HR.*p* = 0.021) cohorts. In OC, both GOF (HR = 0.23; 95%CI 0.06-0.95; HR.*p* = 0.043) and LOF (HR = 0.18; 95%CI 0.05-0.73; HR.*p* = 0.016) *TP53* mutations were associated with improved OS; in EC, LOF *TP53* mutations were associated with longer OS (HR = 0.14; 95%CI 0.02-0.90; HR.*p* = 0.039). Higher tumor mutation burden (TMB) was associated with clinical benefit (Cohen's D = 1.02; ANCOVA *p* = 0.007) and favorable PFS (HR = 0.58; 95%CI 0.34-0.99; HR.*p* = 0.045) in EC. Additional factors (eg, microsatellite instability [MSI]/selected gene mutations) and their associations with efficacy are shown (**Table**).

Conclusions: Baseline genomic features were associated with clinical outcomes following FZEC, with distinct biomarker patterns observed between OC and EC. These results support further evaluation of baseline genomic markers for pt stratification and hypothesis generation in the clinical development of FRα-targeting ADCs.

Data set	Marker	Clinical benefit	Endpoint OS	PFS
OC	TMB			
	MSI status			
	PIK3CA[a]			
	TP53[a]		X	
	TP53 GOF		X	
	TP53 LOF		X	
EC	TMB	X		X
	MSI status			
	ARID1A[a]			
	FBXW7[a]			
	KRAS[a]			
	PIK3CA[a]			
	PPP2R1A[a]			
	PTEN[a]			
	TP53[a]		X	
	TP53 GOF			
	TP53 LOF		X	

[a]Frequently altered genes (mutated in >5% of pts with tissues available and in >5% of the respective OC or EC cohort)

X denotes statistically significant associations (<0.05 by ANCOVA or HR.*p*).

Conflict of interest:

Advisory Board: Isabelle Ray-Coquard and Vicky Makker report receiving advisory/consultation fees from Eisai.

Corporate-sponsored Research: Vicky Makker reports receiving research funding from Eisai.

Other Substantive Relationships: Rachael Scott, Yuanqing Ye, Yan Zhang, and Pallavi Sachdev are employees of Eisai. Vicky Makker reports receiving travel reimbursement from Eisai.

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72 - PB-072 **Poster**

RVU602: A Non-TOP1/Non-Tubulin Cytotoxic and Immunomodulatory Payload for Next-Generation ADCs

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Background: Antibody-drug conjugates (ADCs) have transformed oncology but rely on few payload classes: microtubule inhibitors and topoisomerase I (TOP1) inhibitors — driving limited therapeutic windows, convergent toxicities, and emerging cross-resistance (>150 programs discontinued by 2024). To address these challenges, the Ryvu platform integrates patient-derived models and high-throughput phenotypic screening to discover and validate novel payloads with distinct mechanisms of action. Here we present RVU602, a proprietary non-TOP1/non-tubulin payload, and confirm its activity across multiple antibodies and in TOP1 inhibitor-resistant settings.

Materials and methods: RVU602 was profiled across a panel of diverse cancer cell lines. ADCs were generated by stochastic cysteine conjugation of RVU602 to Sacituzumab (anti-TROP2), Cetuximab (anti-EGFR), Telisotuzumab (anti-c-MET) and Trastuzumab (anti-HER2) at DAR 5-8, and their effect on viability was measured by 5-day CTG assay. Immunogenic cell death (ICD) was assessed by extracellular ATP (exATP) release. In vivo efficacy was evaluated in a TROP2-positive model (HCC70) using the Sacituzumab-RVU602 ADC.

Results: RVU602 payload disrupts an essential intracellular survival process, has broad activity across cancer-cell states, including those less responsive to classical payloads. RVU602 shows higher potency in a subset of cell lines than DXd (mean EC50 34 vs 45 nM). RVU602 formed active ADCs across all antibodies tested (anti-TROP2, anti-EGFR, anti-c-MET, anti-HER2), reaching sub- to low-nanomolar potencies (TROP2 responders EC50 0.22-14 nM) with 3-23-fold shifts versus free payload. In TROP2 models, the Sacituzumab-RVU602 ADC matched or exceeded Datopotamab-DXd; the Cetuximab-RVU602 ADC was on par with Cetuximab-MMAE. Ryvu Sacituzumab-based ADC using RVU602 payload was efficacious and well tolerated in an in vivo mouse xenograft efficacy study. The payload was also shown to induce exATP release, an important hallmark of immunogenic cell death, exceeding the effect of a topoisomerase inhibitor. Validation of tolerability and therapeutic window is ongoing.

Conclusions: These data demonstrate the platform's ability to deliver market-relevant innovation, which identified a new class of payload and validated in models resistant to topoisomerase I inhibitors. The payload exhibits broad cytotoxic activity, confirmed target engagement, and superior efficacy compared to established competitors in resistant tumor models.

Conflict of interest:

Ownership: Stock ownership: applies to all listed authors

Board of Directors: Krzysztof Brzozka

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73 - PB-073 **Poster**

Insights into resistance mechanisms against antibody-drug conjugates using large cancer cell panel profiling

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Antibody-drug conjugates (ADCs) are targeted cancer therapies that deliver cytotoxic drugs directly to tumors by binding to receptors overexpressed on cancer cells. Following receptor binding, the receptor-bound ADC is internalized and the drug is released, triggering cell death. The occurrence of resistance at different stages of ADC mechanism of action remains a challenge for ADC development. Profiling ADCs and their respective payloads on a large cancer cell line panel may reveal resistant cell lines that can give insight into resistance mechanisms at different stages of ADC mechanism of action.

In this study, a framework was developed to efficiently gain insights into the resistance mechanism of ADC resistant cell lines. This framework uses cell line sensitivity to ADC and their respective payload as well as ADC characteristics to classify cell lines for dedicated resistance identification. The latter includes bioinformatics analyses with cell line characteristics, including basal gene or protein expression levels as well as genomic alterations. The framework was benchmarked using cell viability profiling results of datopotamab deruxtecan (Dato-DXd) and DXd, which were profiled on 270 cancer cell lines. It was then extended to six other ADCs and their respective payloads. Cells were incubated with a 9-points dose range of ADC or payload for 120 hours after which viability was determined by intracellular ATP measurement. Drug response metrics, such as half-maximum inhibitory concentrations (IC_{50}s), were derived and used as input for the framework.

Cell panel profiling of Dato-DXd and its respective payload DXd showed a highly selective IC_{50} profile for Dato-DXd, whereas DXd was active in nearly all cell lines. Basal expression of the TROP2-encoding gene *TACSTD2* was significantly correlated with cell line sensitivity to Dato-DXd. However, TROP2 gene expression was not a uniform predictor for response to Dato-DXd, since a significant number of TROP2-high cell lines were resistant against Dato-DXd (IC_{50} > 10,000 ng/mL). Analyzing the TROP2-high Dato-DXd-resistant cell lines using the developed framework revealed cell lines with different resistance mechanisms, including drug efflux transporter-mediated payload resistance. The framework was applied to cell panel profiling results of additional ADCs identifying other mechanisms of resistance.

This study presents a framework to efficiently gain insights into resistance mechanisms using large cancer cell panel profiling of an ADC and its respective payload in combination with cancer cell line characteristics. The identified cell lines may be valuable models for next-generation ADC development, such as novel payloads that overcome intrinsic resistance to current payloads, or different linker chemistry.

No conflict of interest

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74 - PB-074 **Poster**

Preclinical characterization of LY4402289, a novel DLL3-targeting antibody drug conjugate (ADC) delivering a NAMPT inhibitor payload

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Background: DLL3 (Delta-like ligand 3) is an inhibitory Notch ligand expressed on the cell surface of small cell lung cancer (SCLC) and other high-grade neuroendocrine tumors (NETs), with minimal expression in normal tissue. DLL3-expressing tumors also express low levels of nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting NAD^+ salvage enzyme, creating a targetable metabolic vulnerability. We have developed LY4402289, an Fc-silenced anti-DLL3 ADC conjugated to a novel NAMPT inhibitor via a hydrophilic polysarcosine (PSAR) linker, that induces tumor cell death via targeted NAD^+ depletion.

Material and Methods: A DLL3-specific antibody was selected based on *in vivo* efficacy, specificity, biophysical properties, and low immunogenicity risk. A novel and highly potent NAMPT inhibitor payload with properties optimized for ADC delivery was conjugated to the antibody via native cystine maleimide conjugation to a hydrophilic linker combining a cleavable Val-Ala dipeptide with a PSAR hydrophobicity-masking spacer at a stable drug-to-antibody ratio (DAR) of 8. Specificity, internalization, cytotoxicity, and bystander activity were assessed in tumor cells with varying DLL3 expression levels. *In vivo* efficacy was assessed in CDX and PDX xenograft models. PD was evaluated by monitoring NAD^+ depletion in tumors and normal tissues. DLL3 and NAMPT were profiled by immunohistochemistry (IHC) in patient tumors and xenograft models; PK and tolerability were evaluated in mice, rats, and monkeys.

Results: LY4402289 bound specifically to DLL3 at a unique epitope distinct from that of tarlatamab (non-competing) and was rapidly internalized. Potent cytotoxicity was observed across SCLC lines expressing high to low levels of DLL3 along with bystander killing of DLL3-negative cells co-cultured with DLL3-positive cells. The payload was highly potent across SCLC lines (IC_{50} <1 nM) and

retained activity in lines resistant to MMAE and Topo-I payloads. As a single agent, LY4402289 induced durable tumor regression in DLL3-positive SCLC xenograft models with minimal activity in DLL3-negative models. Activity correlated with tumor NAD^+ depletion, and tumor payload concentration was high relative to healthy tissues. PK was similar to that of unconjugated antibody with low systemic payload exposure. LY4402289 was well tolerated, with a mouse MTD $\geq$200 mg/kg. IHC confirmed a DLL3-high/NAMPT-low profile in SCLC.

Conclusions: LY4402289 is a novel, mechanistically differentiated therapeutic candidate for DLL3-positive tumors, including ES-SCLC and other NETs. High potency of the payload in Topo-I–resistant models suggests that LY4402289 retains activity following Topo-I–based therapies. LY's favorable tolerability, together with the DLL3-high/NAMPT-low profile observed in SCLC, supports clinical evaluation of LY4402289 in this setting. An IND submission is planned for 2027.

Conflict of interest:

Ownership: Shareholder: Eli Lilly: Jorge Peiró, Michael Topper, Miguel Garzón Sanz, Stephanie M. Chambless, Kristina A. Coleman, Bo Liu, Cristina Ricardo Carter, Benjamin M. Whitlock, Mandy Jiang, Carlos Marugán, Sachin Shivatare, Gregg Czerwieniec, Andrew Cooke, Wailin Wong, Loredana Puca, Wenjuan Wu, Timil Patel, Rikke B. Holmgaard, Steven W. Andrews, Kristin Bedard

Other Substantive Relationships:

Employment: Eli Lilly: Jorge Peiró, Michael Topper, Miguel Garzón Sanz, Stephanie M. Chambless, Kristina A. Coleman, Bo Liu, Cristina Ricardo Carter, Benjamin M. Whitlock, Mandy Jiang, Carlos Marugán, Sachin Shivatare, Gregg Czerwieniec, Andrew Cooke, Wailin Wong, Loredana Puca, Wenjuan Wu, Timil Patel, Rikke B. Holmgaard, Steven W. Andrews, Kristin Bedard

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75 - PB-075 **Poster**

Preclinical evaluation of BNT329, a novel antibody-drug-conjugate targeting the sialyl Lewis A antigen CA19-9

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Background: The tumor marker CA19-9 is expressed in various tumor types (most prominently pancreatic ductal adenocarcinoma, PDAC) and is associated with tumor progression and metastasis, but antigen shedding and limited specificity for malignant conditions challenge its use as a therapeutic target. Building on our clinical experience with BNT321, a fully human monoclonal antibody targeting CA19-9, we developed BNT329, an antibody–drug-conjugate (ADC) against the same epitope. BNT329 is an ADC with a topoisomerase inhibitor payload, engineered to improve therapeutic efficacy against CA19-9-positive tumors. Here, we present its preclinical characterization.

Material and Methods: The specificity, cytotoxicity and bystander effect of BNT329 were characterized *in vitro*. Antitumor activity was investigated in two cell line-derived and one patient-derived PDAC xenograft mouse models *in vivo*. Preclinical toxicity was evaluated in cynomolgus monkeys with clinical and laboratory endpoints. In addition, blood from healthy human donors was tested for release of cytokines upon incubation with BNT329.

Results: *In vitro*, BNT329 displayed specific, low nanomolar affinity binding to CA19-9, as well as target expression-dependent internalization and killing of target-expressing tumor cells at EC50s in the picomolar to low nanomolar range. Co-culture experiments confirmed a bystander killing effect in CA19-9-negative cells. *In vivo*, BNT329 significantly reduced tumor growth and improved overall survival in a dose-dependent fashion. No clinical signs of toxicity or body weight decreases were observed.

Treatment-related adverse events in cynomolgus monkeys included reversible regenerative/degenerative hyperplasia of the small intestine at higher doses and non-severe decreased lymphoid cellularity/increased lymphocyte apoptosis in thymus and lymphoid organs. There were no treatment-related effects on ophthalmology, electrocardiogram, neurobehavioral observation, body temperature, respiratory rate, coagulation, clinical chemistry, cytokine release, or urine analysis. Incubation of BNT329 with human blood did not induce measurable cytokine secretion at high doses.

Conclusions: A novel ADC, targeting CA19-9 with low nanomolar binding affinity and picomolar *in vitro* cytotoxicity, showed robust, dose-dependent antitumor activity in various murine models. Treatment-related adverse events in cynomolgus monkeys were reversible, and incubation of human blood with BNT329 did not cause cytokine release. Based on these results, a phase I clinical study has been initiated, which is currently recruiting (NCT07186842).

Conflict of interest: Other Substantive Relationships: All authors are employees of BioNTech SE (Mainz, Germany) or BioNTech US (Cambridge, MA, USA) and may hold stocks or stock options from BioNTech. U. Sahin is a cofounder and management board member of BioNTech. K. Roesch, U. Ellinghaus, Y. Hu and U. Sahin are inventors on patents and patent applications related to this study.

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76 - PB-076 **Poster**

JAB-BX610, a First-in-Class Tissue Factor-Directed Antibody Drug Conjugate Delivering a Novel KRAS G12D Inhibitor

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Background: KRAS G12D is a prevalent oncogenic driver, occurring in approximately 40% of pancreatic ductal adenocarcinoma (PDAC) cases. Although KRAS G12D inhibitors have demonstrated encouraging efficacy in PDAC patients, there remains considerable room for improvement. Leveraging the antibody–drug conjugate (ADC) modality to achieve tumor-specific delivery of KRAS G12D inhibitors represents a promising strategy to address this unmet medical need. Tissue Factor (TF) is a clinically validated target for ADC, which is highly expressed in various solid tumors, particularly PDAC. Therefore, we developed JAB-BX610, a TF-directed ADC designed for the tumor-specific delivery of a novel, highly potent KRAS G12D inhibitor with bystander activity.

Method: The KRAS G12D inhibitor, JAB-22G82, was used as the ADC payload. The internalization efficacy of JAB-BX610 was evaluated by flow cytometry. The inhibitory effect of JAB-BX610 and JAB-22G82 on cell viability was evaluated by a luminescence-based assay. The plasma stability of JAB-BX610 across different species was analyzed by LC-MS/MS, and its *in vivo* antitumor efficacy was validated in cell line-derived xenograft (CDX) models. The pharmacokinetic (PK) profile of JAB-BX610 in cynomolgus monkeys was also characterized.

Results: The KRAS G12D inhibitor JAB-22G82 demonstrated high potency in reducing tumor cell viability, with sub-nanomolar IC_{50} values across most KRAS G12D mutant tumor cells tested. As an ADC, JAB-BX610 showed high binding activity and efficient internalization in tumor cells, as well as potency in inhibiting tumor cell viability with IC_{50} values at the 10 pM level. In multiple PDAC animal models, a single dose of JAB-BX610 at 3 mg/kg induced durable tumor regression. Furthermore, JAB-BX610 displayed a favorable pharmacokinetic (PK) profile in cynomolgus monkeys.

Conclusions: JAB-BX610 demonstrates robust antitumor efficacy across KRAS G12D-mutant tumor models with a favorable preclinical safety profile, which strongly supports the clinical evaluation of JAB-BX610 as a promising therapeutic strategy for KRAS G12D-driven cancers, particularly pancreatic ductal adenocarcinoma (PDAC).

Conflict of interest: Other Substantive Relationships: All authors are employees of Jacobio Pharmaceuticals or Jacobio (US) Pharmaceuticals. Amin Li, Andrea Wang-Gillam, Xin Sun, and Yanping Wang are Jacobio Pharmaceuticals stockholders.

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77 - PB-077 **Poster**

Nectin-4 as a therapeutic target in vulvar squamous cell carcinoma and other gynecologic cancers

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Background: Nectin-4 is a transmembrane protein and a target for antibody-drug conjugates (ADCs). Prior studies demonstrated Nectin-4 expression by immunohistochemistry (IHC) in gynecologic cancers including ovarian, uterine, and cervical cancer and vulvar squamous cell cancer (SCC).

Material and methods: We generated a dataset of targeted DNA sequencing, HPV status, clinical data, and Nectin-4 IHC in an institutional cohort of 69 patients with vulvar SCC. Thirty-three patients (Cohort A) were sequenced using Oncopanel targeted sequencing assay. p16 IHC and HPV PCR were used to classify 18 samples as HPV-negative and 15 as HPV-positive, and we compared genomic features in these two subgroups. We developed a classifier model using the statistically significant genomic features distinguishing HPV-positive and -negative groups. The classifier was validated in Cohort B (36 additional vulvar SCC patient samples with Oncopanel data, 22 of these with HPV status). We analyzed clinical and genomic correlations in a combined dataset of Cohort A and B. Finally, we investigated the frequency of amplifications of *NECTIN4* across gynecologic cancers using Oncopanel data.

Results: *CDKN2A* and *TP53* were significantly more frequently mutated in HPV-negative patients (padj = 0.03). Copy number gain of *NECTIN4* was present in 73% of HPV-positive patients and was significantly more frequent in HPV-positive patients (padj = 0.007). A classifier model based on *TP53* and *CDKN2A* mutation status and *NECTIN4* copy number status predicted HPV status in 19/22 patients in the validation cohort (AUC 0.89). In clinical-genomic analysis of the combined cohort, lichen sclerosus was associated with HPV-negative status (and with genomic features of HPV-negative vulvar cancers). Usual-type vulvar intraepithelial neoplasia (VIN) was more prevalent in HPV-positive samples, whereas differentiated VIN was predominant in HPV-negative samples. HPV-positive patients had significantly better survival outcomes compared to HPV-negative patients, as previously reported. Nectin-4 IHC was available in 26 patients with invasive vulvar SCC, with H-scores ranging from 30-245; 10 patients had an H-score of ≥ 150. Given that *NECTIN4* gene amplification may be associated with Nectin-4 ADC response, we examined *NECTIN4* amplification frequency in gynecologic cancers in our institutional data, revealing 5% frequency in cervical cancer and 1-2.5% in ovarian, uterine, and vaginal/vulvar cancers.

Conclusions: *NECTIN4* copy number gain is frequent in HPV-positive vulvar SCC, and most patients with vulvar SCC show Nectin-4 expression by IHC. Nectin-4 may be a therapeutic target in vulvar SCC and in a subset of other gynecologic cancers.

No conflict of interest

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78 - PB-078 **Poster**

A novel HER2-targeting antibody–drug conjugate with a BRD4 molecular glue degrader as payload overcomes trastuzumab deruxtecan resistance in HER2-positive cancers

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Background: Trastuzumab deruxtecan (T-DXd) has transformed the treatment of HER2-positive cancers, but its clinical benefit is frequently limited by acquired resistance driven by impaired payload activity, altered internalization, or drug efflux. To address these challenges, we developed a next-generation molecular glue degrader antibody conjugate (GLUE-DAC), trastuzumab–F741 (T- F741).

Material and Methods: T-F741 was generated using site-specific glyco-engineering through a cleavable linker, yielding a homogenous conjugate with a drug-to-antibody ratio (DAR) of approximately 4. This antibody conjugate was tested in pharmacologically relevant in vitro and in vivo models to assess its nonclinical efficacy and safety. To determine whether T-F741 could overcome TOP1 resistance mechanisms, we engineered HER2-positive cancer cells with the clinically relevant TOP1 R364H mutation, attenuating cytotoxicity to TOP1 inhibitors and conferring T-DXd resistance.

Results: The BRD4 molecular glue degrader payload by itself exhibits single-digit nanomolar to sub-nanomolar potency across diverse HER2-positive cancer models, while the next-generation GLUE-DAC T-F741 retained robust cytotoxicity, consistently demonstrating superior activity to T-DXd in multiple HER2-positive in vitro and in vivo models, including T-DXd-insensitive xenografts. T-F741 also maintained potent cytotoxicity in TOP1 inhibitor–resistant cells. In a cynomolgus monkey study, T-F741 was well tolerated, supporting further nonclinical development of this novel GLUE-DAC.

Conclusions: These findings establish T-F741 as a mechanistically distinct HER2-targeted therapeutic capable of overcoming T-DXd resistance. By combining targeted delivery with potent BRD4 degradation, T-F741 demonstrates superior preclinical efficacy and highlights selective BRD4 molecular glue degraders as promising payloads for next-generation ADCs in patients to overcome resistance from topoisomerase inhibitor-based ADCs.

Conflict of interest: Ownership: Xin Yu, Shuting Zhang, Bin Yang, Wendi Ni, Jin Wang, Haibo Liu and Jan Theunissen are equity holders of Fortitude Biomedicines.

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79 - PB-079 **Poster**

Micvotabart pelidotin in combination with EGFR-targeted therapy improves duration of response in HNSCC PDX models

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Head and neck squamous cell carcinoma (HNSCC) patients with recurrent and metastatic (R/M) disease have limited therapeutic options. Cetuximab (cetux) is the only FDA-approved EGFR-targeted therapy for HNSCC, and several next-generation EGFR-targeted therapies are in clinical development. Micvotabart pelidotin (MICVO) is a first-in-concept antibody-drug conjugate (ADC) targeting the extradomain-B of fibronectin (EDB + FN), a non-cellular structural protein in the tumor extracellular matrix. In vivo, MICVO demonstrated broad anti-tumor activity in HNSCC patient-derived xenograft (PDX) models and sensitized an immunotherapy refractory syngeneic HNSCC model to anti-PD-1 treatment, supporting the ongoing clinical development of MICVO as monotherapy (mono) (NCT05720117) and in combination (combo) with pembrolizumab (NCT06795412) in R/M HNSCC patients. Here, the combinatorial potential of MICVO with cetux was assessed in HNSCC PDX models. MICVO anti-tumor activity was assessed across HNSCC PDX models and baseline tumors were collected for histological analyses. MICVO-responsive HNSCC PDX models were selected to test a suboptimal dose of MICVO in combo with cetux (Q4Dx4). Tumor volume (TV) and body weight (BW) were monitored twice weekly. Tumor regression was defined as reduction in TV below the average baseline TV for at least two consecutive measurements. Following regression, tumor relapse was defined as an increase in TV above the average baseline TV. Immunohistochemistry analysis demonstrated robust EDB + FN expression in baseline tumors and no correlation was observed between the level of EDB + FN expression and MICVO response. The combo of MICVO and cetux demonstrated improved anti-tumor activity compared to either mono treatment in two selected HNSCC PDX models. In one model, the combo resulted in an increased number of tumor regressions (10/10 mice) compared to cetux alone (5/9 mice) or MICVO alone (5/10 mice). Furthermore, only 4/10 mice with tumor regressions in the combo group later demonstrated relapse, while 5/5 and 4/5 relapsed in the cetux and MICVO mono groups respectively. The average day of relapse was later in the combo group indicating delayed tumor regrowth after treatment compared to mono. In a second HNSCC model, both mono and combo resulted in strong tumor regressions, but the combo group had no relapse (0/9) while the cetux and MICVO groups had 3/9 and 6/9 mice relapse, respectively. In these models, BW was normal across treatment groups. These results demonstrate the level of EDB + FN expression does not correlate with MICVO anti-tumor activity in PDX models of HNSCC. Additionally, the combo of MICVO and cetux improved duration of response in two HNSCC PDX models compared to either mono treatment and was well tolerated. These findings indicate the potential of MICVO to combine with EGFR-targeted therapies for patients with R/M HNSCC.

Conflict of interest: Ownership: All authors are employees of Pyxis Oncology and hold stock options in the company

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80 - PB-080 **Poster**

IPH4502, a differentiated Nectin-4 exatecan antibody-drug conjugate with best-in-class potential

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Background: Nectin-4 is a clinically validated tumor antigen overexpressed in a broad range of solid tumors and associated with poor prognosis. Targeting Nectin-4 with enfortumab vedotin (EV), an antibody-drug conjugate (ADC) carrying a monomethyl auristatin E (MMAE) payload, has demonstrated significant clinical benefit and has become a standard of care in urothelial carcinoma (UC). However, a significant unmet medical need remains for patients with UC who are ineligible for EV, relapse, or develop resistance. Beyond UC, Nectin-4 expression has been reported across multiple other solid tumor types, often at lower levels or with greater heterogeneity. To address these unmet therapeutic needs, we developed IPH4502, a novel ADC targeting Nectin-4, conjugated via a cleavable linker to exatecan, a potent topoisomerase I inhibitor with a high drug-to-antibody ratio (DAR = 8). IPH4502 is designed to overcome MMAE resistance mechanisms and to be effective in tumors with low or heterogeneous Nectin-4 expression.

Material and methods: Epitope mapping of Nectin-4 was performed by assessing the binding of IPH4502, EV and analogs of other clinical-stage Nectin-4 ADCs to a panel of Nectin-4 mutants and domain-deleted constructs. Their respective internalization efficiency was evaluated *in vitro*. Linker sensitivity to enzymatic cleavage was evaluated and compared with benchmarks, and DAR plasma stability was monitored *in vitro*. The *in vivo* anti-tumor activity of IPH4502 was evaluated in a head-to-head comparison with an SHR-A2102 analog (rezetecan-based ADC with a DAR of 4) in two cell line-derived xenograft (CDX) models expressing different levels of Nectin-4.

Results: Epitope mapping revealed that IPH4502 recognizes a distinct epitope at the hinge between the V and distal C2 domains of Nectin-4, whereas other clinical-stage ADCs bind the V-domain. In vitro, IPH4502 displayed comparable or superior internalization efficiency relative to other binders of clinical stage ADCs.

The IPH4502 linker demonstrated superior stability against neutrophil elastase-mediated cleavage compared with the EV linker, and maintained *in vitro* DAR stability over time in plasma, suggesting a minimized risk of systemic payload release in patients.

Finally, IPH4502 demonstrated significantly stronger *in vivo* anti-tumor activity compared to SHR-A2102 analog in both CDX models.

Conclusion: IPH4502 has a highly differentiated pharmacological profile, driven by a unique epitope binding, strong

internalization, high linker stability, and a potent exatecan payload, which collectively translate into robust preclinical anti-tumor efficacy. These compelling data provide a strong rationale for the ongoing Phase 1 clinical evaluation of IPH4502 (NCT06781983) in patients with advanced Nectin-4-expressing solid tumors.

Conflict of interest: Other Substantive Relationships: All co-authors are shareolders of Innate Pharma

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81 - PB-081 **Poster**

Preliminary phase 1 results from AVENTINE-1, a phase 1/2 study of AVZO-1418, an EGFR-HER3 bispecific antibody-drug conjugate (BsADC) for the treatment of patients with locally advanced or metastatic solid tumors

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Background: AVZO-1418 is a novel epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 3 (HER3) BsADC, with a topoisomerase I inhibitor payload that has shown high internalization in EGFR/HER3 co-expressing or mono-expressing tumor cells. In xenograft models, AVZO-1418 has shown significant anti-tumor activity across various tumor types.

Methods: The ongoing phase 1/2 AVZO-1418-1001 study (NCT07038343) investigates the safety, tolerability, efficacy, and pharmacokinetics of AVZO-1418 as a monotherapy (Part A) or in combination with standard-of-care therapies (Part B). Phase 1 Part A utilizes a BOIN dose escalation design and backfill to identify the preliminary recommended Phase 2 dose (RP2D) and maximum tolerated dose (MTD) of AVZO-1418 monotherapy. Eligible patients for Phase 1 Part A dose escalation have locally advanced/metastatic solid tumors expressing EGFR and HER3 (e.g., lung cancer, squamous cell carcinoma of the head and neck [HNSCC], nasopharyngeal carcinoma [NPC], triple-negative breast cancer [TNBC], urothelial cancer [UC]) and received ≤ 3 prior lines of systemic cytotoxic chemotherapy (including ADCs). Backfill in Phase 1 Part A includes patients with NSCLC and ≤ 2 prior lines of chemotherapy. Efficacy-evaluable population includes patients with baseline measurable disease with ≥ 1 evaluable post-baseline scan.

Results: Enrollment into Phase 1 Part A is ongoing to identify preliminary monotherapy RP2D/MTD. As of May 13, 2026, 32 patients have been treated in Phase 1 Part A at 2, 4, 4.5, and 6 mg/kg Q2W and 6 mg/kg Q3W intravenously. The median age was 63.5 years, 50% were female, and 59% had NSCLC with EGFRm or with no AGA. Patients had a median of 2 prior lines of therapy in the metastatic setting. AVZO-1418 has been generally well tolerated at doses up to 4.5 mg/kg with the most common ($\geq 20\%$) treatment-emergent adverse events being alopecia, nausea, fatigue, and decreased appetite. Doses of 6 mg/kg Q2W ($N = 7$) and 6 mg/kg Q3W ($N = 5$) exceeded MTD with 2 patients experiencing dose-limiting toxicities at each schedule.

Of 18 efficacy evaluable patients, 9 (50%) remained on treatment, including 5 partial responses (2 confirmed, 3 unconfirmed awaiting confirmatory scans). Responses were seen across multiple tumor types and dose levels. In the subset of the 10 efficacy-evaluable patients with NSCLC, 9 had tumor reduction, including 4 (40%) with a partial response (2 confirmed; 2 unconfirmed awaiting confirmatory scans). Monotherapy dose finding is ongoing and additional safety and efficacy results are planned for presentation.

Conclusions: AVZO-1418 is a novel EGFR-HER3 bispecific ADC that demonstrates a favorable tolerability profile with responses across multiple tumor types and dose levels. Monotherapy dose levels are continuing and initiation of combinations are planned.

Conflict of interest: Board of Directors: NEXT Oncology Virginia
Corporate-sponsored Research: Avenzo Therapeutics, Duality Biologics
Other Substantive Relationships: Employment by Avenzo Therapeutics

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82 - PB-082 **Poster**

Development and Preclinical Characterization of a First-in-Class Nectin-4/HER2 Bispecific Antibody-Drug Conjugate with a Topoisomerase I Inhibitor Payload for Solid Tumors

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Background: Nectin-4 and HER2 are frequently co-expressed in multiple solid tumors, including urothelial, breast, lung, esophageal, and pancreatic cancers, while showing limited expression in normal adult tissues. Dual-antigen co-expression reaches approximately 64% in upper tract urothelial carcinoma (UTUC), supporting the development of bispecific antibody-drug conjugates (bsADCs). Although approved Nectin-4- or HER2-targeting ADCs have demonstrated clinical benefit, avidity-driven dual-antigen targeting may improve tumor selectivity and the therapeutic window, while a topoisomerase I inhibitor payload may provide an effective treatment option following MMAE-based ADC therapy.

Materials and methods: A panel of Nectin-4/HER2 bispecific antibodies (bsAbs) was engineered with moderate monovalent affinity to enable avidity-driven selective binding to dual-positive tumor cells. Lead bsAbs were conjugated with different payloads to generate bsADCs. Binding, internalization, and cytotoxicity were evaluated in vitro. Antitumor efficacy was assessed in cell line-derived xenograft (CDX) models with varying Nectin-4/HER2 expression. Plasma stability, pharmacokinetics, and repeat-dose non-GLP toxicology were evaluated in cynomolgus monkeys.

Results: Lead optimization identified the anti-Nectin-4 Ig-like V-type domain NE4(V), which bound human, cynomolgus monkey, and rat Nectin-4 with balanced affinity and showed no detectable

cross-reactivity with other Nectin family members. The optimized bsAb demonstrated enhanced cell-surface binding and internalization compared with monospecific anti-Nectin-4 or anti-HER2 antibodies in dual-positive tumor cells. The lead candidate, bsADC1, incorporates a topoisomerase I inhibitor payload, providing a mechanistically distinct alternative to MMAE-based ADCs. In multiple CDX models with heterogeneous Nectin-4/HER2 expression, bsADC1 produced greater tumor regression than enfortumab vedotin, trastuzumab deruxtecan (DS-8201), and Disitamab Vedotin at equivalent or lower doses (1–10 mg/kg). In repeat-dose non-GLP studies in cynomolgus monkeys (20 mg/kg, Q3W $\times 3$), bsADC1 was well tolerated, with a high no-observed significant toxic dose (HNSTD ≥ 20 mg/kg), minimal anti-drug antibody (ADA) effects on systemic exposure, and a terminal half-life of 3–5 days.

Conclusions: bsADC1 is a first-in-class Nectin-4/HER2 bispecific ADC combining avidity-driven dual-antigen targeting, enhanced tumor-cell internalization, potent preclinical antitumor activity, and a favorable safety profile. Its topoisomerase I inhibitor payload may provide advantages over MMAE-based ADCs, particularly in tumors with heterogeneous Nectin-4/HER2 expression or acquired MMAE resistance. These findings support further clinical development of bsADC1 for urothelial carcinoma and other Nectin-4/HER2 co-expressing solid tumors.

No conflict of interest

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83 - PB-083 **Poster**

Engineering and development of a novel bispecific ADC targeting EGFR and FGFR2b

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Background: Epidermal growth factor receptor (EGFR) is a clinically validated oncogenic driver frequently overexpressed in gastric cancer (GC). Fibroblast growth factor receptor 2b (FGFR2b) is overexpressed in approximately 30% of GC/gastroesophageal junction (GEJ) cancers and is associated with poor prognosis. Co-expression of EGFR and FGFR2b in subsets of gastric tumors suggests cooperative signaling that may promote tumor progression and therapeutic resistance. Although FGFR2b-directed antibodies such as bemarituzumab have shown clinical activity in FGFR2b-positive GC/GEJ cancer, corneal adverse events highlight the need for safer, tumor-selective approaches.

Material and methods: We engineered a bispecific antibody (bsAb) targeting EGFR and FGFR2b and generated antibody-drug conjugates (bsADCs) using multiple cytotoxic payloads. Binding, internalization, and ligand-induced FGFR2b signaling were evaluated in EGFR/FGFR2b co-expressing cancer cell lines and compared with analogs of bemarituzumab, BG-C137/BGAh9179, and MRG003. Antitumor efficacy of lead bsADC candidates was assessed in an SNU16 cell-derived xenograft (CDX) model.

Results: The EGFR $\times$ FGFR2b bsAb showed enhanced cell binding and more efficient internalization than FGFR2b monospecific comparator antibodies in EGFR/FGFR2b co-expressing cells. In contrast to potent FGFR2b pathway blockade by FGFR2b antibodies, the bsAb only weakly inhibited FGF7/FGF10-driven FGFR2b signaling, suggesting the potential to reduce on-target, off-tumor effects related to FGFR2b signaling inhibition in normal corneal epithelium. Among the generated bsADCs, the lead candidate demonstrated superior antitumor activity in SNU16 xenografts compared with analogs of the anti-EGFR ADC MRG003 and the clinical-stage anti-FGFR2b ADC BG-C137, supporting the benefit of dual target engagement and enhanced payload delivery.

Conclusions: A dual EGFR $\times$ FGFR2b bsADC may exploit receptor co-expression in gastric cancer to improve tumor-selective internalization and antitumor efficacy while minimizing FGFR2b ligand-pathway inhibition associated with corneal toxicity. These data support further development of the lead EGFR $\times$ FGFR2b bsADC as a differentiated therapeutic candidate for EGFR/FGFR2b co-expressing GC/GEJ cancer.

No conflict of interest

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84 - PB-084 **Poster**

An AI-Guided Biparatopic B7H3-Targeting ADC Demonstrates Enhanced Preclinical Efficacy

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Purpose: B7H3 (CD276) is an immune checkpoint molecule aberrantly overexpressed in a wide range of solid tumors—including lung, gastrointestinal, and prostate cancers—while exhibiting restricted expression in normal tissues. High B7H3 expression correlates with tumor progression, metastasis, drug resistance, and poor clinical outcomes. To overcome the limitations of conventional B7H3-targeting therapies, we utilized an AI-guided design platform to engineer HXN-2013, a novel biparatopic antibody-drug conjugate (ADC) tailored for superior receptor internalization, enhanced cytotoxicity, and optimized developability.

Methods: Leveraging our AI platform for structural modeling and non-overlapping distal epitope selection, we generated a biparatopic anti-B7H3 antibody. This antibody was conjugated to novel cytotoxic payloads via cleavable linkers. *In vitro* binding affinity, internalization kinetics, and cytotoxicity were profiled across a panel of B7H3-expressing cancer cell lines. *In vivo* anti-tumor efficacy and preliminary safety were evaluated in multiple cell line-derived xenograft (CDX) mouse models.

Results The AI-optimized biparatopic antibody demonstrated significantly enhanced cell binding and receptor-mediated internalization compared to its parental monoclonal counterparts. *In vitro*, HXN-2013 exhibited potent, antigen-dependent cytotoxicity with IC_{50} values in the nanomolar (nM) range, alongside a robust bystander killing effect capable of overcoming tumor heterogeneity. *In vivo*, low-dose administration of HXN-2013 induced robust, dose-dependent tumor regression across multiple CDX models, while maintaining an excellent preliminary safety and tolerability profile in rodents.

Conclusion HXN-2013 represents a promising next-generation ADC that effectively exploits AI-driven epitope selection to trigger rapid target internalization and potent cytotoxicity. Supported by its strong preclinical efficacy and favorable initial safety window, further IND-enabling evaluation of HXN-2013 is warranted to accelerate its clinical translation for B7-H3-overexpressing malignancies.

No conflict of interest

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85 - PB-085 **Poster**

An AI-Guided Biparatopic DLL3-Targeting ADC Demonstrates Enhanced Preclinical Efficacy

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Purpose: Delta-like ligand 3 (DLL3) is a highly selective therapeutic target overexpressed in ~80% of small cell lung cancer (SCLC) and neuroendocrine carcinomas (NEC), with minimal expression in normal adult tissues. To overcome the clinical limitations and resistance mechanisms of first-generation DLL3-directed therapies, we utilized an AI-guided platform to engineer HXN-2010, a novel biparatopic dual-payload antibody-drug conjugate (dpADC) designed for increased internalization, enhanced cytotoxicity, and optimized developability.

Methods: Leveraging our AI-guided platform for distal epitope selection and structural modeling, we engineered a biparatopic anti-DLL3 antibody targeting non-overlapping epitopes. The antibody was conjugated to two distinct cytotoxic payloads with complementary mechanisms of action via stable, hydrophilic cleavable linkers. *In vitro* binding affinity, internalization kinetics, and cytotoxicity were profiled across a panel of DLL3-expressing SCLC cell lines. *In vivo* anti-tumor efficacy and preliminary safety were evaluated in multiple cell line-derived xenograft (CDX) mouse models.

Results: The AI-optimized biparatopic antibody demonstrated significantly accelerated receptor-mediated internalization efficiency and superior payload delivery capability compared to its monoclonal counterparts. Notably, the dual-payload design conferred superior *in vitro* antitumor activity compared with single-payload ADC counterpart and produced a robust bystander killing effect, highlighting its potential to overcome intratumoral antigen heterogeneity. In addition, HXN-2010 retained strong cytotoxic activity in tumor cells resistant to a single payload, supporting the ability of the dual-payload strategy to address payload-specific resistance. *In vivo,* low-dose administration of HXN-2010 induced robust and dose-dependent tumor regression across multiple SCLC CDX models, while maintaining a favorable preliminary safety and tolerability profile in rodents. Importantly, HXN-2010 also demonstrated sustained anti-tumor efficacy in an Top1i ADC-resistant tumor model, further supporting the therapeutic advantage of combining a biparatopic antibody format with a dual-payload ADC strategy.

Conclusion: HXN-2010 is a next-generation biparatopic, dual-payload ADC designed to enhance antitumor potency and overcome payload-specific resistance. Together with its robust preclinical efficacy and promising therapeutic window, these findings support the strong clinical potential of HXN-2010 for SCLC and other DLL3-positive malignancies and warrant its advancement into IND-enabling studies.

No conflict of interest

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86 - PB-086 **Poster**

A Novel Bispecific TROP2/PD-L1 Antibody-Drug Conjugate Demonstrates Potent Synergistic Antitumor Activity and a Favorable Safety Profile

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Purpose: This study aimed to develop and characterize a novel bispecific antibody-drug conjugate (ADC) targeting both TROP2 and PD-L1 to overcome the limitations of current single-target therapies and combat treatment resistance in advanced cancers.

Methods: We engineered a bispecific antibody (bsAb) simultaneously targeting TROP2 and PD-L1 (α-TROP2/PD-L1), which was subsequently conjugated to a novel topoisomerase I inhibitor (TOP1i) payload via an optimized cleavable linker (designated as HXN-2006). Comprehensive *in vitro* characterization encompassed binding affinity, internalization efficiency, bystander killing, and PD-L1 degradation assays. *In vivo* efficacy was evaluated in multiple cell line-derived xenograft (CDX) models and a syngeneic MC38-huTROP2/PD-L1 model. Safety, tolerability, and toxicokinetics (TK) were thoroughly assessed in cynomolgus monkeys via a repeat-dose toxicity pre-study.

Results: The α-TROP2/PD-L1 bsAb demonstrated potent dual-binding activity, rapid internalization, and effectively induced PDL1 target degradation. Intriguingly, while TOP1i payload-mediated DNA damage upregulated compensatory tumor PD-L1 expression, the bispecific antibody backbone successfully internalized and cleared this induced PD-L1. This achieved a self-reinforcing synergistic effect with immuno-oncology (IO) pathways, yielding marked tumor regression and durable responses in the syngeneic MC38-huTROP2/PD-L1 model. The fully conjugated ADC, HXN-2006, exhibited robust cytotoxicity across multiple TROP2/PD-L1-expressing cell lines alongside strong bystander killing effects. A repeat-dose safety evaluation in cynomolgus monkeys demonstrated that HXN-2006 was well tolerated at intravenous doses up to 40 mg/kg administered biweekly (three total infusions), without eliciting significant adverse toxicological findings. Toxicokinetic analysis also demonstrated excellent systemic stability of HXN-2006; intact ADC and total antibody displayed similar clearance rates and matching exposure profiles, while maintaining low levels of leaked free payload in the systemic circulation.

Conclusion: HXN-2006 represents a highly promising, next-generation therapeutic strategy. By elegantly integrating PD-1/PD-L1 axis blockade, target degradation, and TROP2-directed cytotoxic payload delivery, it achieves potent synergistic antitumor efficacy while maintaining a superior safety margin and stable PK profile in non-human primates, strongly supporting its advancement into clinical development.

No conflict of interest

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87 - PB-087 **Poster**

Population pharmacokinetics (popPK) and exposure-response analyses of sacituzumab tirumotecan (sac-TMT) antibody-drug conjugate (ADC) in participants (pts) with advanced solid tumors

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Background: Sac-TMT, a TROP2-directed ADC with a unique, bifunctional linker that maximizes payload delivery to tumor cells, has antitumor activity with manageable safety in unresectable, locally advanced or metastatic solid tumors. Based on the totality of data, sac-TMT 4 mg/kg Q2W and 5 mg/kg Q2W are being further evaluated. We characterized the popPK of sac-TMT, free payload, and total antibody (TAb) and assessed the correlation between exposure and clinical outcomes.

Materials and Methods: A semi-mechanistic popPK model was developed with data from 2082 pts with unresectable, locally advanced or metastatic solid tumors from 4 studies: 2870-001 (NCT04152499), 2870-002 (NCT05642780), 2870-003 (NCT05816252), and 2870-017 (NCT05631262) in which pts received sac-TMT at doses of 2 mg/kg (n = 4), 4 mg/kg (n = 1068), 5 mg/kg (n = 678), 5.5 mg/kg (n = 5), and 6 mg/kg (n = 7) Q2W. The popPK model was developed sequentially with the combined ADC-TAb model including 10 DAR species (DAR0–DAR9), each represented by a 2-compartment model linked to a 2-compartment model for payload. The model was used to estimate ADC post hoc exposures (C_{max}, AUC, and C_{trough}) of sac-TMT doses, including for a simulated dose of 3 mg/kg Q2W. Exposure-response was analyzed by logistic regression using data from 1410 pts who received sac-TMT in study 2870-001.

Results: The popPK model assumed gradual DAR degradation; average sac-TMT DAR, 7.6. Typical parameter estimates for clearance and central volume of distribution were 0.0408 L/h and 2.98 L for ADC-TAb and 9.99 L/h and 12.1 L for payload. Sac-TMT had linear PK. Estimated cycle 1 exposure was greater with sac-TMT 5 mg/kg vs 4 mg/kg with overlapping ranges: median (range) C_{max} was 99.9 (56.9–149.0) μg/mL vs 80.5 (39.7–124.0) μg/mL, AUC was 5030 (2230–8480) μg*h/mL vs 4000 (1570–6190) μg*h/mL, and C_{trough} was 224 (42.8–616.0) ng/mL vs 188 (13.8–716.0) ng/mL. Simulated median (range) C_{max}, AUC, and C_{trough} for sac-TMT 3 mg/kg was comparatively lower at 60.5 (36.7–100.0) μg/mL, 2970 (1570–5910) μg*h/mL, and 127 (25.0–340.0) ng/mL, respectively. Exposure-response analyses showed a positive correlation of higher ADC sac-TMT exposures with confirmed ORR and DCR and a negative correlation with PD, and an association between increased sac-TMT C_{max} and higher probability of grade ≥3 AEs and treatment-related AEs leading to dose modification or interruption or treatment discontinuation. AEs were mostly hematologic and stomatitis events, and were manageable with protocol-recommended dose modification and interruption; incidence of AEs leading to treatment discontinuation was low. Exposure-response relationships were comparable across tumor types.

Conclusions: These findings suggest a favorable benefit/risk profile of sac-TMT 4 mg/kg and 5 mg/kg Q2W, while lower sac-TMT doses may not provide sufficient efficacy for pts with advanced solid tumors.

Conflict of interest:

Other Substantive Relationships: Jordi Rodon: reports non-financial support and reasonable reimbursement for travel from European Society for Medical Oncology, American Society of Medical Oncology, National Taiwan University Cancer Center, 280-Biotech, Dava Oncology, and STOP Cancer

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Yezhe Cheng, Lin Zhu, Yaling Li, Xin Li, Junyou Ge: employees of Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

Carolina De Miranda Silva, Anne Chain, Tanya Keenan, Azher Hussain: employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA.

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88 - PB-088 **Poster**

In vivo pharmacokinetics (PK) of the TROP2-directed antibody drug conjugate (ADC) sacituzumab tirumotecan (sac-TMT) and effects on the immune system

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Background: Sac-TMT, a TROP2-directed ADC with a unique, bifunctional linker that provides stability in circulation and maximizes payload delivery to tumor cells, has shown antitumor activity with manageable safety across a range of tumor types in clinical studies. We investigated PK and immune-related effects of sac-TMT in cancer mouse models.

Material and Methods: To evaluate PK of sac-TMT, 70 BALB/c nude mice inoculated with HCC1806 cells (breast cancer) were split into 2 equal groups and administered 1 dose of sac-TMT 1 mg/kg or 10 mg/kg; blood and tumor samples were collected pre-dose and 1,

4, 8, 24, 72, 168, and 336 h post-dose. To evaluate immune reconstitution, 25 immunodeficient NCG mice inoculated with HCC827 cells (NSCLC) and human peripheral blood mononuclear cells (hPBMCs) were split into 5 equal groups and administered sac-TMT 0.3 or 1 mg/kg twice weekly (BIW) for 2 wks starting day 1 post inoculation, hIgG BIW for 2 wks starting day 1, or sac-TMT 0.3 or 1 mg/kg BIW for 1 wk starting day 8; immune cells were measured in peripheral blood and tumor samples on day 17.

Results: In the HCC1806 mouse model, sac-TMT payload exposures were greater with sac-TMT 10 mg/kg vs 1 mg/kg in tumor (C_{max}: 8.78 ng/g and 0.664 ng/g) and in serum (C_{max}: 11.8 ng/mL and 1.12 ng/mL); sac-TMT payload AUC exposures were greater in tumor ($AUC_{0-\infty}$: 1570 h·ng/g and 151 h·ng/g) vs serum ($AUC_{0-\infty}$: 344 h·ng/mL and 30 h·ng/mL). Serum exposures of sac-TMT ADC were dose-dependent (C_{max}: 146 µg/mL and 13.5 µg/mL; $AUC_{0-\infty}$: 5280 h·µg/mL and 607 h·µg/mL), and similar with sac-TMT monoclonal antibody (C_{max}: 170 µg/mL and 12.6 µg/mL; $AUC_{0-\infty}$: 10500 h·µg/mL and 664 h·µg/mL). In the HCC827 mouse model, the proportion of $hCD45^+$ hPBMCs, $hCD45^+CD3^+$ T cells, $hCD45^+CD3^+CD4^+$ Th cells, and $hCD45^+CD3^+CD8^+$ Tc cells in peripheral blood were significantly greater with sac-TMT 0.3 mg/kg administered starting on day 8 ($P<0.05$ vs hIgG); there were no significant increases in the proportion of these cells in other dose groups. The proportions of these cells in tumors were increased in both sac-TMT 0.3 mg/kg dose groups and the proportion of $hCD45^+CD3^+CD8^+$ Tc cells in the group administrated sac-TMT 0.3 mg/kg starting day 8 post inoculation was significantly increased ($P<0.05$ vs hIgG).

Conclusions: In an in vivo mouse model of breast cancer, the sac-TMT payload was detected at AUC exposures 5 times higher in tumor than serum, indicating stability in circulation and enhanced payload delivery to tumors. Sac-TMT promoted immune reconstitution and immune cell infiltration of tumor cells in an in vivo HCC827 human immune reconstitution model. These findings suggest that sac-TMT may optimize tumor targeting and induce immunogenic cell death through reinvigoration of antitumor immunity; thus, supporting combination therapy with immune checkpoint inhibitors such as pembrolizumab.

Conflict of interest: Other Substantive Relationships: Xiaoxi Yuan, Yuzhi Pu, Jia Xie, and Junyou Ge: employees of Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

Ian Knemeyer and Yanyan Zheng: employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA.

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89 - PB-089 **Poster**

First Results from a First-in-Human Phase 1, Open-label, Multicenter Study of the Safety, Tolerability, and Efficacy of IPH4502, an anti-Nectin-4 ADC, as a Single Agent in Advanced Solid Tumors

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Background: IPH4502 is a novel, differentiated Nectin-4-targeting antibody-drug conjugate (ADC) with topoisomerase I inhibitor exatecan as payload. IPH4502 has been developed to address the unmet medical need in patients with urothelial cancer (UC) who have progressed after enfortumab vedotin (EV) or do not tolerate EV, and has the potential to treat other tumors, including those with moderate to low or heterogeneous Nectin-4 expression, such as head and neck squamous cell carcinoma and non-small cell lung cancer.

Material and Methods: IPH4502-101 is a first-in-human, open-label, multicenter, dose escalation guided by Backfilling Bayesian optimal interval (BF-BOIN) design, followed by dose optimization. The study aims to evaluate the safety and tolerability of IPH4502, to determine the maximum tolerated dose (MTD), and assess preliminary efficacy. Adults with histologically confirmed, unresectable, locally advanced, or metastatic solid tumors in selected indications known to express Nectin-4 were eligible for the dose escalation phase. The expression of Nectin-4 was evaluated retrospectively. IPH4502 was administered Q3W at doses ranging from 0.6 to 3.6 mg/kg.

Results: IPH4502-101 study is currently in the dose escalation phase and has completed enrollment with 76 patients. MTD declaration is outstanding at the time of abstract submission. To date, IPH4502 shows a favorable safety profile with grade 3 oral mucositis as a characteristic dose-limiting toxicity at 3.6 mg/kg, and low bone marrow and skin toxicity. IPH4502 demonstrated clinical activity in patients with UC previously treated with EV, as well as in additional tumor types. Preliminary pharmacokinetic analyses support Q3W dosing of IPH4502.

Conclusions: Preliminary findings suggest that IPH4502 is well tolerated and shows encouraging efficacy within its therapeutic window in patients with UC previously treated with EV, as well as in other solid tumors.

Clinical trial identification
NCT06781983

Conflict of interest: Other Substantive Relationships: Markus Jensen, A.J. Leyco, David Magrez, and Sonia Quaratino are employees and shareholders of Innate Pharma.

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Poster Session: Artificial Intelligence

90 - PB-090 **Poster**

A Data-Driven Landscape Analysis of Novel Targets for CAR-T Cell Therapy in Acute Myeloid Leukemia

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Background: While Chimeric Antigen Receptor (CAR)-T cell therapy has demonstrated remarkable success in certain hematological malignancies, treating Acute Myeloid Leukemia (AML) remains a significant clinical hurdle. To drive therapeutic innovation for a confidential biopharmaceutical partner, BioLizard – a specialized bioinformatics, AI, and data science consultancy – quantified the potential of CAR-T cell therapy in AML. The primary objective was to systematically identify relevant markers to inform both future research directions and business value.

Material and Methods: Leveraging deep expertise in biological data analytics, BioLizard executed a comprehensive, three-tracks landscaping strategy to evaluate the target space:

- Literature Mining: An overview of the published state of the art was conducted to search for currently researched targets and potential disease mechanisms. This analysis was augmented by the possibility to further mine scientific literature for targets using BioReflect, BioLizard's proprietary literature mining and data visualization tool.
- Patent Exploration: The intellectual property landscape was mapped by exploring Google Patents and the European Patent Office for relevant AML targets.
- Clinical Trial Analysis: Translational pipelines were investigated by evaluating the EU Clinical Trials Register, ICTRP, and ClinicalTrials.gov to uncover clinical-stage targets for CAR-T therapy in AML.

Results: By integrating these multi-dimensional datasets, we successfully mapped the CAR-T target ecosystem. The analysis differentiated established, "usual" targets – such as CD33, CLL-1, CD123, and FLT3 – from an extensive array of novel/additional targets, including IL-1RAP, TIM-3, ADGRE2, and Siglec-6. The study also elucidated critical AML-specific mechanisms of initiation and progression, highlighting pathways involving TP53 mutations, CD47 upregulation, and mutated NPM1c. Importantly, the landscape review emphasized that AML possesses few driver mutations, making it inherently harder to treat with traditional CAR-T approaches.

Conclusion: Through rigorous, tech-enabled data science, BioLizard provided the partner with highly actionable, prioritized intelligence for their oncology pipeline. To overcome the inherent lack of traditional driver mutations in AML, the study concluded that rare fusions might yield efficient targets, alongside a strong potential for targeting neo-epitopes. Furthermore, the investigation identified that attractive future targets will likely involve mRNA splicing, genetic and epigenetic alterations, and splice-variants of cell surface proteins. Ultimately, to reduce toxicity, enhance CAR-T safety, and prevent on/off-target effects, BioLizard highlights the necessity of utilizing novel technologies, such as proteogenomics and spatial transcriptomics, to uncover the next generation of highly specific AML antigens.

No conflict of interest

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91 - PB-091 **Poster**

Systematic Prioritization of Oncology Targets (SPOT): A Multi-Agent Artificial Intelligence Platform for Evidence-Based Drug Target Prioritization

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Background: Target selection in oncology requires simultaneously weighing tractability, tumor biology, functional essentiality, competitive landscape, and safety—a task rapidly outpacing manual review. High-throughput initiatives including The Cancer Genome Atlas (TCGA), Clinical Proteomic Tumor Analysis Consortium (CPTAC), and Cancer Dependency Map (DepMap) have generated unprecedented multi-omic profiling of tumors and cancer cell lines, while mounting clinical trial data illuminate each target's competitive landscape and observed outcomes. The convergence of these resources with modern large language models creates a unique opportunity to build artificial intelligence (AI)-guided systems for rational, genome-wide target prioritization.

Material and methods: We developed SPOT (Systematic Prioritization of Oncology Targets), a three-layer platform. A curated database integrates open-source and proprietary data across eight evidence modules, spanning tractability, patient stratification biomarkers, immuno-oncology functional CRISPR screens, cancer cell line dependency, competitive landscape, biological characterization, safety liabilities, and preclinical translatability. Module-specific algorithms produce normalized scores (0–1) combined into an adjustable weighted composite for genome-wide ranking. The intelligence layer is a multi-agent AI system in which a primary SPOT Agent orchestrates different specialized subagents—DepMap, Omics, Mechanism, Safety, and Preclinical Validation—with live access to external databases and clinical trial registries, enabling natural-language target evaluation.

Results: SPOT enables reproducible, genome-wide target prioritization grounded in convergent evidence. To validate the scoring framework, we assessed 12 clinically established oncology targets—BRAF, EGFR, BTK, KRAS, and others—across the full scored portfolio. By applying equal weights to seven modules—and excluding competitive landscape which by design penalizes established drug programs—the validated targets achieved an average rank in the 93rd percentile. Specifically, out of a 2,665 gene set, EGFR ranked 7th, KRAS 8th, and BRAF 36th, with 11 of the 12 targets finishing in the top quartile. The multi-agent AI layer synthesizes evidence into source-attributed target assessments, surfaces therapeutic hypotheses, and explicitly flags conflicting signals across data modalities. Scientists interact conversationally with SPOT's agentic infrastructure to receive integrated evaluations spanning each SPOT module, reason over biological nuances, and refine therapeutic hypotheses.

Conclusions: SPOT demonstrates that principled integration of multi-omic, functional, and clinical evidence—augmented by multi-agent AI reasoning—has the potential to accelerate and rationalize therapeutic target identification in oncology.

Conflict of interest: Other Substantive Relationships: All co-authors are full-time Calico employees.

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92 - PB-092 **Poster**

Multi-modal Digital Twin Model Outperforms Conventional Biomarker Stratification in Pancreatic Cancer

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Background: Better patient selection is critical for improving outcomes in advanced pancreatic ductal adenocarcinoma (PDAC), particularly for the aggressive Basal-like subtype which currently lacks effective predictive biomarkers for chemotherapy response. This study evaluates the potential of the FarrSight® Bayesian digital twin model to predict individual patient responses to chemotherapy compared to conventional biomarker stratification.

Material and Methods: Using data from the COMPASS clinical trial (NCT02750657) involving 206 patients treated with mFOLFIRINOX or gemcitabine + nab-paclitaxel, we generated molecular digital twins using the FarrSight® foundation model. These predictions were compared to conventional biomarker stratification

derived via ElasticNet on transcriptomic gene expression data. The primary endpoint was Disease Control (DC), defined by RECIST criteria.

Results: In the Basal-like cohort (n = 38), the FarrSight®-derived biomarker significantly outperformed the conventional model, achieving an AUC of 72.3% compared to 44.8%, overall accuracy of 65.8% versus 47.4%, positive predictive value (PPV) of 60% versus 40%, and negative predictive value (NPV) of 72.2% versus 52.2%. FarrSight® correctly classified all partial responders in this subgroup, whereas the conventional approach misclassified two. Additionally, FarrSight®-derived stratification was associated with significantly improved overall survival (log-rank p = 0.04). Performance in the Classical subtype (n = 168) was comparable between the two methods.

Conclusions: The FarrSight® digital twin model demonstrates superior predictive performance over conventional methods in stratifying the Basal-like PDAC subtype. These findings highlight the potential of Bayesian *in silico* simulations to move beyond rigid biomarker paradigms, supporting enhanced precision medicine and optimized therapeutic decision-making for patients with severe malignancies.

Conflict of interest: Ownership: Matthew Griffiths, Irina Babina have financial interests in Concr

Board of Directors: Andrew Biankin is a Non-Executive Director at Concr.

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93 - PB-093 **Poster**

Multimodal Digital Twins Predict Chemotherapy Backbone Response to Uncover Immunotherapy Benefit in TNBC

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Background: Heterogeneous patient responses to immunotherapy in triple-negative breast cancer (TNBC) often obscure subgroup effects during standard cohort-level analyses, presenting a major bottleneck in early small-cohort drug development. Predicting individual-level responses to standard-of-care backbones could optimise combination therapy selection and patient stratification.

Methods: Retrospective data from the VISION trial (NCT06409221; chemotherapy ± pembrolizumab) was analysed. Digital Twins were generated using FarrSight®-Twin, a multimodal AI model that integrates patient-specific genomic variants (WES) and transcriptomic expression profiles (RNAseq) with baseline clinical data. By mapping these multi-modal omics-centred features onto deep biological interaction networks, the model simulates individual pathological complete response (pCR) probabilities to the chemotherapy backbone alone. Patients were subsequently stratified into high- versus low-probability chemotherapy responders.

Results: At the overall cohort level, the addition of pembrolizumab did not yield a statistically significant pCR improvement over chemotherapy alone (53.3% vs. 30.8%; p = 0.12). The digital twin model accurately predicted observed pCR to the chemotherapy backbone in participants that received chemotherapy only (AUC = 76.3%; calibration error = 6.7%), stratifying the cohort into high- and low-probability groups (n = 37, n = 49, respectively). High-probability responders derived no additional benefit from pembrolizumab. Conversely, in the low-probability chemotherapy subgroup, the addition of pembrolizumab (n = 13) yielded a highly significant, clinically meaningful pCR improvement over chemotherapy alone (53.8% vs. 20.0%; p = 0.03; log odds ratio = 2.9, 95% CI: 1.2–4.6).

Conclusions: Using assays available at clinical grade, FarrSight®-Twin multimodal platform successfully resolved clinical trial response heterogeneity, uncovering a significant immunotherapy benefit that conventional analysis failed to detect. By isolating and modelling the comparator backbone, this mechanism-agnostic approach empowers robust evidence generation from small cohorts and real-world data, directly supporting regulatory model-informed drug development and market access.

Conflict of interest: Ownership: Matthew Griffiths, Irina Babina have financial interests in Concr

Advisory Board: Uzma Asghar is a Medical Advisor for Concr

Board of Directors: Andrew Biankin is a Non-Executive Director at Concr

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Poster Session: Biomarkers Assays

94 - PB-094 **Poster**

Exploring the Interplay Between EBV and Autophagy-Related Gene Expression Patterns in Nasopharyngeal Carcinoma

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Background: While components of the autophagy pathway have been linked to cancer prognosis, their relationship with clinical outcomes remains unclear. This study investigates the expression levels of autophagy-related genes (ATGs) at both mRNA and protein levels in nasopharyngeal carcinoma (NPC) and their association with Epstein-Barr virus (EBV) infection, clinicopathological characteristics, and clinical outcomes.

Material and Methods: Thirty-five formalin-fixed, paraffin-embedded (FFPE) tissue specimens from NPC patients and five non-cancerous nasopharyngeal mucosa control samples were analyzed. Quantitative PCR (qPCR) was used to assess the mRNA levels of nine ATGs, while protein expression was evaluated by immunohistochemistry.

Results: The results showed that ATG3, ATG4D, ATG4C, ATG4A, ATG2B, and ATG5 expression were significantly higher in EBV-positive NPC, suggesting a notable role of EBV in modulating these genes. Expression of ATG3 and ATG4C proteins was significantly more frequent in EBV-positive NPC patients compared to EBV-negative patients, with a strong correlation between expression of ATG3 or ATG4C and EBV positivity (P = 0.002 for both proteins). Elevated ATG4B and ATG4D expression was significantly associated with reduced distant metastasis in NPC patients (P = 0.019) and within the EBV-positive subgroup (P = 0.014). Reduced ATG4D mRNA levels were also correlated with higher metastasis rates and shorter distant metastasis-free survival (DMFS), highlighting a potential association of ATG4D with DMFS.

Conclusions: Overall, these findings emphasize the importance of assessing autophagy-related gene expression as a valuable tool for predicting clinical outcomes in NPC and underscore the need for further research to validate these results and explore therapeutic implications.

No conflict of interest

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95 - PB-095 **Poster**

Detection of prostate cancer-associated structural biomarkers in nail samples using X-Ray diffraction

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Background: Prostate cancer induces systemic biological changes that may influence the structural organisation of tissues distant from the primary tumour. In a joint project with Matur and EosDx UK, we investigated whether prostate cancer-associated structural biomarkers could be detected in murine nail samples using X-ray diffraction (XRD).

Material and methods: Nails were collected from C57BL/6 mice following orthotopic implantation of RM-1 prostate cancer cells and from healthy controls. Small-angle X-ray scattering (SAXS) and wide-angle X-ray scattering (WAXS) profiles were acquired at multiple time points between 6 and 384 hours post-inoculation and in the control group.

Results: Diffraction data were analysed using Fourier transform preprocessing, principal component analysis (PCA), and logistic regression to evaluate structural changes with tumour progression. Preliminary analysis of samples collected up to 120 hours post-inoculation revealed that WAXS profiles retained keratin scattering pattern across all time points, with increasing divergence in scattering intensity observed at later stages of disease progression. Although substantial overlap was present among the diffraction profiles, machine learning analysis identified progressively stronger cancer-associated signatures over time. Classification performance achieved 0.88 and 0.92 ROC-AUC values at 96 and 120 hours, respectively. PCA revealed a continuous progression trajectory rather than distinct clustering, suggesting gradual evolution of tumour-associated structural changes in the nail. These findings demonstrate that XRD can detect structural alterations in the nail associated with prostate cancer.

Conclusion: The results support the presence of detectable cancer-associated structural biomarkers in remote tissues and highlight the potential of combining nail-based XRD with machine learning cancer detection.

No conflict of interest

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96 - PB-096 **Poster**

Evaluation of MAGE (melibiose-derived advanced glycation end-product) and HER2 in Peritoneal Lavage Fluid and Blood as Potential Biomarkers of Treatment Response in Gastric Cancer

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Background: Peritoneal dissemination remains the most common pattern of recurrence and the leading cause of mortality in patients with gastric cancer (GC), despite advances in treatment. Conventional diagnostic strategies have limited sensitivity for detecting minimal residual disease and early treatment response, particularly within the peritoneal cavity. Novel biomarkers measured in peritoneal lavage fluid (PLF) may provide a more direct assessment of the local tumour microenvironment and residual disease burden, while complementary serum biomarkers may reflect systemic treatment effects. Melibiose-derived advanced glycation-end products (MAGE) have been identified in metastatic adenocarcinoma. We aimed to evaluate the clinical utility of MAGE and HER2 as biomarkers to be quantified in peritoneal lavage and serum from GC patients as potential indicators of treatment effectiveness and disease response. *In vitro* models for development of novel MAGE-targeting strategies were investigated.

Materials and Methods: This prospective study included 31 patients with GC undergoing surgical treatment. Peritoneal lavage fluid (PLF) and peripheral blood serum (S) were collected during diagnostic laparoscopy (before treatment) and gastrectomy (post treatment). MAGE concentrations were quantified using the enzyme-linked immunosorbent assay (ELISA) with anti-MAGE mAb. HER2 was determined using the previously developed and validated sandwich ELISA. Biomarker levels in PFL and S were analysed along with the cytological assessment of peritoneal material and immunofluorescent staining for CK8. Biomarker levels in S and PLF were correlated pre- and post- gastrectomy to assess their potential as indicators of treatment effectiveness. NCI-N87 cells were *in vitro* exposed to model MAGE-FITC and observed under confocal microscope.

Results: MAGE concentrations were significantly higher in S than in PFL group. Serum levels of MAGE decreased significantly following gastrectomy. Post-gastrectomy S and PFL showed a strong positive correlation of MAGE levels. HER2 was also detected at significantly higher concentrations in serum than in peritoneal lavage fluid before and post-gastrectomy. Like for MAGE, serum levels of HER2 were lower after gastrectomy. Cytological analysis demonstrated variable cellularity in peritoneal lavage specimens, with most recovered cells exhibiting a non-epithelial phenotype. *In vitro*, MAGE was shown to accumulate inside NCI-N87 cells.

Conclusions: MAGE and HER2 are detectable at quantifiable levels in S and PFL collected during diagnostic laparoscopy. Reduced MAGE and HER2 R2 levels after gastrectomy are associated with treatment and may serve as indicators of therapeutic effectiveness. NCI-N87 cells exposed to MAGE *in vitro* accumulate the compound, supporting their use as a model for developing novel diagnostic strategies targeting gastric cancer cells.

Conflict of interest: Ownership: Magdalena Staniszewska - SDS Optic

Board of Directors: Magdalena Staniszewska - SDS Optic

Other Substantive Relationships: Dariusz Lenart - SDS Optic financial support

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98 - PB-098 **Poster**

Biomarker-signature determinants of BTM-class OMA1-activator sensitivity in solid tumor cell lines, with prevalence mapped in 9,850 human tumors

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Background: BTM-3566 is an orally bioavailable, clinical-stage activator of OMA1, a mitochondrial inner-membrane protease governing OPA1 processing and apoptotic priming. BTM-3528, a related analog, was profiled to define its in vitro activity, molecular determinants, and biomarker prevalence in human tumors.

Methods: BTM-3528 was screened against 332 solid tumor cell lines (IC50, percent inhibition, AUC; sensitivity pre-defined as IC50 < 1 μM and inhibition >70%). Models were matched to DepMap 24Q4 (300/332) for mutation, copy-number, transcriptomic, CRISPR-dependency and proteomic (CCLE) analyses, with FDR correction; multi-marker classifiers were evaluated by nested cross-validation. Signature prevalence was estimated in 9,850 TCGA solid tumors (30 types) co-measuring all three markers. Pharmacodynamics were profiled by RNA-seq in a synchronized HCT-116 time-course (0.1–10 μM, 1–8 h, vs time-matched controls).

Results: Sensitivity occurred in 52 of 332 lines (15.7%) across lineages (nominally higher in uterine, biliary, lung and CNS), with no lineage, mutation or copy-number alteration surviving FDR correction. Transcriptome-wide, low MIMS2 (formerly FAM210B) was the strongest correlate of sensitivity (rank 1/19,152; $\rho = -0.40$; FDR ≈ 0), confirmed at the protein level ($\rho = -0.42$; n = 124). A three-marker signature (low MIMS2, low BCL-XL, high PHB2) reached AUROC 0.74 with ~2-fold enrichment of sensitive models. In TCGA, the signature was present in ~15% of solid tumors at median cutoffs (per-type 4.6–22%) and ~5% at tertile cutoffs, matching the cell-line estimate (13.2%/4.2%). Prevalence was highest in colorectal, cervical, squamous-lung, gastroesophageal and bladder tumors and lowest in clear-cell renal, glioblastoma and pancreatic tumors. BTM-3528 produced dose- and time-dependent ATF4/integrated stress response induction (ASNS, CHOP, ATF4; FDR ≈ 0), supporting tumor-derived ATF4/ISR transcripts as candidate pharmacodynamic markers.

Conclusions: BTM-class activity is lineage-agnostic and engages a mitochondrial inner-membrane stress and proteostasis-dependency state, confirmed by on-treatment ATF4/ISR induction. A MIMS2-low/BCL-XL-low/PHB2-high signature enriches sensitivity and is present in ~1 in 7 human solid tumors (~1 in 20 stringent). Signature-positivity reflects prevalence, not response: the highest-prevalence lineages were not uniformly the most sensitive. Prevalence and sensitivity converged in lung, gastroesophageal, bladder and uterine models, nominating these as priority biomarker-defined populations for development of the BTM OMA1-activator class.

Conflict of interest: Ownership: GJW, MJK, TH, MS Bantam Pharmaceutical

Board of Directors: MS: Bantam Pharmaceutical

Corporate-sponsored Research: GJW, MJK, and LM: Bantam Pharmaceutical

Other Substantive Relationships: GJW, MJK, LM, TH, and MS: consulting fees from Bantam Pharmaceutical. MJK: Bantam Pharmaceutical patents

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99 - PB-099 **Poster**

Neuroblastoma differentiation is accompanied by dynamic nucleolin redistribution

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Background: Neuroblastoma (NB) is the most common extracranial solid tumor of childhood and accounts for approximately 15% of pediatric cancer-related deaths. Nucleolin (NCL) is a multifunctional nucleolar protein ubiquitously expressed in normal cells, whereas in cancer it is also detected within the cytoplasm and at the cell surface, where it has emerged as a promising therapeutic target. Although we previously identified cell surface NCL in NB, whether its subcellular localization is dynamically regulated during tumor differentiation remains unknown.

Materials and Methods: NCL expression and subcellular localization were investigated by immunohistochemistry (IHC) in a large cohort of primary neuroblastic tumors representing different stages of differentiation, including poorly differentiated NB, differentiating NB, nodular ganglioneuroblastoma, intermixed ganglioneuroblastoma, and ganglioneuroma. In parallel, NB cell lines were differentiated with 13-cis retinoic acid and analyzed for cell surface NCL localization by Imaging Flow Cytometry (IFC) and immunofluorescence (IF).

Results: IHC analysis revealed a differentiation-dependent redistribution of NCL. In poorly differentiated tumors, NCL was predominantly confined to the nucleus, whereas progressive tumor differentiation was associated with a gradual redistribution of NCL toward the cytoplasmic and plasma membrane compartments. Consistently, differentiation of NB cell lines induced by 13-cis retinoic acid resulted in increased NCL localization at the cell surface compared with untreated cells, confirming that NCL compartmentalization is dynamically regulated during the differentiation process.

Conclusions: Our findings demonstrate that NB differentiation is accompanied by a marked redistribution of NCL from its canonical nuclear localization toward the cytoplasmic and plasma membrane compartments. These findings identify NCL subcellular localization as a dynamic feature associated with tumor differentiation and provide a biological rationale for exploiting cell surface NCL as a therapeutic target in differentiated neuroblastic tumors.

No conflict of interest

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100 - PB-100 **Poster**

Flexible detection and characterisation of fusion isoforms with a targeted RNA enrichment platform

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Fusion genes are chimeras formed when two genomic loci are aberrantly joined. They are among the most actionable mutations in oncology, but also among the hardest to detect reliably. Many fusion mutations are rare, and poor detection sensitivity further limits addressable populations, unnecessarily hampering the development and commercial viability of targeted therapies. Furthermore, fusions

are often unstable, with variable breakpoints, partner genes, and alternative splicing patterns, confounding detection with current approaches. While fusions have been studied for decades, relatively little attention has been paid to fusion isoform variation. Characterising fusion isoforms from full length RNA presents an opportunity for highly sensitive detection of fusions that are actively involved in tumour biology.

We applied ATLUS, a flexible targeted enrichment platform, to amplify full-length fusion transcripts. ATLUS enriches full-length molecules irrespective of their specific breakpoint and isoform structure, providing a more sensitive way to detect fusion genes. To benchmark its performance, we conducted an analytical characterisation study using spike-in RNA variants. From this we calculated limit of detection and limit of blank. We then applied the platform to samples from breast cancer patients, targeting clinically actionable fusions including ESR1-CCDC170, a known breast cancer driver.

We demonstrate ATLUS' analytical profile, with estimated limit of detection below 0.05 parts per million RNA molecules and limit of blank of effectively zero. We achieve order-of-magnitude enrichment of clinically actionable fusions in breast cancer tissue samples, enabling isoform and breakpoint characterisation of fusions to uncover previously unseen fusion gene complexity. We show the presence of variable breakpoints that can result in false negatives from conventional fusion detection. We also identify alternatively spliced fusion transcripts with therapeutically relevant impacts on the translated protein, a level of granular information only available from full-length RNA sequencing.

Patients with fusions are underserved by current therapy, despite their highly actionable mutations. Poor sensitivity from ctDNA and issues with solid tumour biopsies limit the identification of addressable target populations. We have developed a targeted RNA enrichment platform to improve the sensitivity and information content of fusion gene detection. Working with full-length RNA confers clear benefits, including improved sensitivity and extremely high specificity relative to existing DNA and panel-based methodologies. Furthermore, fusions show heightened alternative splicing in their biologically active components, suggesting that isoform characterisation is beneficial for identifying responders to fusion gene therapies.

Conflict of interest: Ownership: RK sits on the board of Wobble Genomics, owns shares in Wobble Genomics, and is named on patents associated with Wobble Genomics.

Corporate-sponsored Research: JMD received research funding from Wobble Genomics.

Other Substantive Relationships: JB, MB, TB, SM, AG, II, CB, JD, are employees of Wobble Genomics.

AT received Honoraria from Eli Lily.

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101 - PB-101 **Poster**

RAS-BIO: ctDNA dynamics of KRAS mutation during immune checkpoint inhibition of advanced NSCLC

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Background: Acquired treatment resistance remains a major challenge in oncogene-driven NSCLC, while digital PCR (dPCR) offers the potential to detect and monitor tumour mutations in circulating tumour DNA (ctDNA) with unparalleled levels of resolution. We undertook an analysis of retrospective plasma samples from patients affected by oncogene-driven non-small cell lung cancer (NSCLC), aiming to i) assess dPCR sensitivity for longitudinal ctDNA detection relative to Next Generation Sequencing techniques, and ii) further inform KRAS- and EGFR-mutant biology during targeted treatments.

Materials and Methods: Longitudinal blood samples were collected from advanced NSCLC patients with known actionable mutations in *EGFR* and *KRAS*, confirmed by UK NHS standard molecular testing. Blood samples were prepared into double-spun plasma from which circulating tumour DNA (ctDNA) was extracted using QIAamp MinElute ccfDNA kit. Digital PCR was then performed using the QIAcuityDx instrument and dPCR LNA Mutation Assays (QIAGEN). Clinical review of diagnostic, prognostic, treatment and survival outcomes was undertaken.

Results: Patients are being recruited to four cohorts: (A) KRAS-mutant cancers receiving immune checkpoint inhibitors, (B) KRAS-mutant cancers receiving KRAS inhibitors, (C) EGFR-mutant cancers receiving osimertinib monotherapy, and (D) EGFR-mutant cancers receiving osimertinib-chemotherapy. In this interim analysis, dPCR analysis and correlative clinical outcomes were completed for 17 patients. In cohort A, 10/12 KRAS-mutant patients had detectable ctDNA at baseline. Of KRAS-mutant patients treated with immune checkpoint blockade who had at least one baseline and one on-treatment sample, 4/10 cases showed early ctDNA clearance (>90% VAF reduction), 2/10 showed moderate reduction in ctDNA VAF, and 4/10 cases showed early ctDNA VAF increases. Early molecular response in 6/10 cases suggest that their driver KRAS mutant clone was immunologically visible. Of seven cases with response and detectable VAF longitudinally, the same diagnostic KRAS-mutant clone increased in four patients at point of radiological progression. In four cases showing early (C2D1) increases in VAF, all patients best response as per RECIST 1.1 was progressive disease.

Conclusions: We confirmed dPCR is highly sensitive for longitudinal ctDNA detection. Early ctDNA clearance on treatment suggests immune visibility of driver KRAS-mutant clones in many cases, while regrowth of the same clone provides evidence for adaptive immune escape. Recruitment is ongoing in all four cohorts.

Conflict of interest: Advisory Board: Qiagen

Corporate-sponsored Research: Institutional research funding from Qiagen

Other Substantive Relationships: All unrelated to this study. Institutional Research funding from BI and Revolution Medicines. Advisor/education from Revolution Medicines, Eli Lilly and Merck.

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103 - PB-103 **Poster**

Single-cell functional assessment of Homologous Recombination Proficiency via direct detection of RAD51 at double-strand DNA breaks using dSTRIDE-HR

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Background: Evaluating Homologous Recombination (HR) status is critical to optimize patient selection for PARP and DNA Damage Response (DDR) inhibitors. Genomic scarring assays provide a static historical log of genomic instability but fail to reflect

real-time functional repair or emerging resistance. We assessed the feasibility and analytical characteristics of dSTRIDE-HR™, an innovative in situ assay providing sensitive, direct detection of RAD51 actively recruited to physical double-strand DNA breaks (DSBs), to establish readiness for a formal analytical and clinical validation (AV/CV) program.

Material and Methods: The dSTRIDE-HR™ assay was characterized across multiple cellular models and formalin-fixed paraffin-embedded (FFPE) matrices, demonstrating compatibility with standard clinical FFPE histopathology workflows. Positive controls tracked repair kinetics after DNA damage induction by ionizing radiation (IR), chemotherapies, topoisomerase inhibitors, a PARP inhibitor, and a novel DDR inhibitor across various human tumor and non-tumor cell lines. Specificity was tested via biological negative controls, including siRNA knockdown and small-molecule inhibition, alongside technical and isotype controls in patient-derived xenograft (PDX) tissue. Analytical precision, repeatability, and section stability were evaluated using archival cancer patient samples. Feasibility for automation on clinical-grade Roche and Leica autostainers was also demonstrated, supporting scalable deployment in clinical laboratory settings.

Results: IR exposure significantly increased dSTRIDE-HR™ foci, appearing as discrete, countable nuclear signals suitable for pathologist review. Chemotherapies and DDR/PARP inhibition similarly induced strong foci accumulation, while siRNA transfection abolished recruitment. Technical and isotype controls showed minimal background. Repeatability and stability testing confirmed consistent performance, with low within-run coefficients of variation and robust storage stability. The assay effectively stratified functional repair status in baseline patient biopsies, clearly differentiating BRCA-mutated sections from wild-type controls.

Conclusions: The dSTRIDE-HR™ platform is a highly specific, robust, rapid functional assay capable of identifying active repair complexes at single-cell resolution directly at DNA break sites within standard clinical FFPE histopathology. Paired with CABLES, intoDNA's proprietary AI/ML-backed image analysis platform, the assay delivers a pathologist-interpretable, objectively quantified readout of active HR repair dynamics. Together, these capabilities, including resolution of HR status at the single-cell level within the tumor microenvironment, demonstrate significant clinical utility as a predictive biomarker to guide patient stratification and longitudinal monitoring for PARP and DDR inhibitor treatment.

Conflict of interest: Ownership: Kamil Solarczyk and Magdalena Kordon-Kiszala are co-founders and shareholders of intoDNA.

Board of Directors: Kamil Solarczyk and Magdalena Kordon-Kiszala are members of the Board of Directors for intoDNA.

Other Substantive Relationships: Other co-authors: Olga Wójcikowska, Kamila Schirmeisen, Julita Imioło, Agnieska Waligórska, Zsombor Prucsi are intoDNA employees.

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104 - PB-104 **Poster**

Genome-wide scoring and prediction of the CpG island methylator phenotype in colorectal cancer

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Background: The CpG island methylator phenotype (CIMP) is an increasingly recognised marker of epigenetic reprogramming in colorectal cancers, present in approximately 20% of cases, and characteristically proximal, microsatellite-unstable, and *BRAF*^{V600E} mutant. However, identification and clinical interpretation of CIMP remain inconsistent. CIMP-high calls depend on the panel or clustering method used, are confounded by assay type, cohort differences, and tumour purity. To address these limitations, we have developed a continuous, genome-wide, probe-weighted CIMP score that replicates across cohorts. This score can be accurately inferred from other omics or clinical variables, enabling CIMP assessment even in the absence of methylome profiling data, which remain scarce.

Material and methods: In the Cancer Genome Atlas Colon and Rectal Adenocarcinoma cohorts (n = 235), after stringent quality control and tumour purity correction, we derived a continuous, genome-wide score by mixture modelling of per-probe methylation, and classified tumours as CIMP-high by optimal partitioning of the score. We compared common unsupervised clustering methods to test the stability of the canonical CIMP-calling approach, and benchmarked statistical and machine-learning algorithms for both the CIMP-high call and the CIMP score. We cross-validated (CV) predictive performance using multivariable models based on RNA expression, clinical variables, mutation status, or consensus molecular subtypes (CMS), and characterised CIMP using gene set and interaction network analyses.

Results: CIMP status can be reliably inferred from transcriptomic and clinical data alone. The score is built from tens of thousands of CpG sites, indicating that CIMP reflects a genome-wide, coordinated epigenetic programme. In 5-fold CV, a model based on RNA expression distinguished CIMP-high tumours with an AUROC of 0.98 (95% CI [0.97, 1.00]) and explained 80% of the CIMP score (R^2 = 0.80). A separate model on clinical variables achieved an AUROC of 0.80 (95% CI [0.72, 0.88]), which increased to 0.84 (95% CI [0.74, 0.93]) with *BRAF* mutation status and CMS. Unsupervised clustering methods showed low concordance in CIMP assignment, whereas the quantitative measure recovered the canonical CIMP-high call and captured additional inter-tumour variability. Across independent methylation cohorts, the score preserved the ordering of methylation-defined clusters (Spearman $|\rho|$ = 0.72-0.85, $p < 0.0001$). Tumours classified as CIMP-high were enriched for pathways such as interferon signalling, consistent with CMS1 (adjusted $p < 0.0001$).

Conclusions: By modelling CIMP as a continuous score, we establish a reproducible and cross-cohort definition that can be derived from clinical or other omics data in the absence of methylation data, providing a common measure for its biological and clinical characterisation.

No conflict of interest

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Poster Session: Cellular Therapies

106 - PB-106 **Poster**

Development and validation of a simple functional assay to detect neutralizing antibodies in primate sera for AAV gene therapy stratification

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Gene therapy using viral vectors is becoming increasingly important for the treatment of a wide range of diseases, including cancer.

A key determinant of therapeutic success is the absence of pre-existing neutralizing antibodies against the viral serotype used, as these antibodies—arising from natural exposure—can neutralize the vector and compromise treatment efficacy. This issue is particularly significant for adeno-associated virus (AAV)-based therapies, given the high prevalence of immunity against multiple AAV serotypes in both humans and non-human primates.In this study, we describe the development and validation of a simple and robust functional assay for the detection of neutralizing antibodies in primate sera. The method is based on transduction of a human cell line using AAV vectors of different serotypes encoding Gaussia luciferase as a reporter. Furthermore, the assay is being bridged to an established, but more labor-intensive, detection method based on transgene expression measured by MSD technology, as previously reported[1]. This methodology enables efficient stratification of primates and patients based on the presence of neutralizing antibodies prior to initiation of AAV-based therapies. In addition, the assay may be adaptable to other viral vector platforms, broadening its applicability to diverse gene therapy strategies.

[1] Pajaziti et al.; Human Gene Therapy; 2025

No conflict of interest

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Poster Session: Drug Resistance and Modifiers

107 - PB-107 **Poster**

Repurposing of HTS-10 to Overcome C797S-Mediated Osimertinib Resistance in EGFR-Mutant Lung Adenocarcinoma

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Rationale: Acquired resistance to osimertinib mediated by the EGFR C797S mutation remains a major therapeutic challenge in EGFR-mutant non–small cell lung cancer (NSCLC), with limited effective treatment options.

Objectives: To determine whether HTS-10, an FDA-approved CDK4/6 inhibitor, can overcome C797S-mediated osimertinib resistance in EGFR-mutant NSCLC.

Methods: A high-throughput screen of approximately 125,000 compounds was performed using Ba/F3 cells expressing EGFR triple mutations (L858R/T790M/C797S and Del19/T790M/C797S). The activity of HTS-10 was evaluated using biochemical assays, cellular thermal shift assays (CETSA), molecular docking analyses, CRISPR-engineered isogenic models, xenografts, and patient-derived xenograft (PDX) models.

Measurements and Main Results: HTS-10 was identified as a potent inhibitor of EGFR triple-mutant cell growth and exhibited preferential activity toward mutant EGFR-dependent models. IL-3 rescue assays demonstrated that its antiproliferative effects were dependent on suppression of oncogenic EGFR signaling. HTS-10 inhibited mutant EGFR kinase activity, reduced EGFR phosphorylation, and induced apoptotic cell death in osimertinib-resistant models while exhibiting substantially weaker activity toward wild-type EGFR. CETSA and molecular docking analyses supported direct engagement of mutant EGFR by HTS-10. Importantly, HTS-10 significantly suppressed tumor growth in CRISPR-engineered isogenic xenografts and PDX models harboring EGFR C797S-mediated osimertinib resistance.

Conclusions: HTS-10 selectively suppresses C797S-mutant EGFR signaling and demonstrates robust antitumor activity in preclinical models of osimertinib-resistant EGFR-mutant NSCLC. These findings support the therapeutic repurposing of HTS-10 as a potential treatment strategy for EGFR C797S-mediated resistance and provide a translational strategy for overcoming resistance-associated EGFR alterations using clinically available targeted agents.

No conflict of interest

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108 - PB-108 **Poster**

TROP2 Predicts Response to TUSC2 Gene Therapy (Quaratusugene Ozeplasmid) and Its Modulation Sensitizes Non-Small Cell Lung Cancer to Treatment

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The tumor suppressor gene TUSC2 is downregulated or absent in more than 80% of NSCLC and nearly all small cell lung cancers. TUSC2 gene therapy has shown antitumor activity by overcoming resistance to targeted therapies and enhancing immune checkpoint blockades in immunotherapy-resistant KRAS/LKB1-mutant NSCLC models. These effects are mediated by inhibiting MAPK and mTOR signaling, inducing cell-cycle arrest and apoptosis, and activating antitumor immune responses. To identify biomarkers of resistance to TUSC2 gene therapy, we established models of primary and acquired resistance (AR) using NSCLC cell lines, patient-derived xenografts (PDXs), and PDX-derived organoids (PDXOs). Screening of 10 cell lines revealed primary resistance in approximately 50%, as determined by Annexin V staining and colony formation assays. Similarly, ATP-based viability assays showed that 50% of 12 PDXOs were resistant to TUSC2. We developed TC314AR (sotorasib-AR) PDX and xenografts (A549, H1299, H23AR) in NSG mice and treated them with TUSC2 gene therapy. In each model, approximately 20–30% of tumors failed to respond to TUSC2, showing no significant reduction in tumor growth compared with vector-treated controls. RPPA analysis of approximately 500 proteins identified distinct protein expression signatures associated with resistance. Although resistant tumors displayed model-specific protein alterations, comparative analyses across cell lines, PDXOs, and PDXs consistently identified low TROP2 expression as a biomarker of primary resistance. This association was independently confirmed by IHC of pretreatment tumor biopsies from patients enrolled in a clinical trial with quaratusugene ozeplasmid.

To determine whether TROP2 directly influences therapeutic response, TROP2 expression was genetically manipulated in NSCLC cell lines. We took NSCLC cells that did not express TROP2 and created overexpressing TROP2 cells. These stable TROP2-

overexpressing derivatives (H1299-TROP2++ and H460-TROP2++) exhibited significantly greater TUSC2-induced apoptosis than their parental counterparts and had levels of apoptosis similar to NSCLC cells endogenously overexpressing TROP2. Conversely, in TROP2-high H358 and H322 cells, transient TROP2 knockdown by shRNA significantly enhanced apoptosis by TUSC2. Similarly, CRISPR/Cas9-generated TROP2-knockout H358 and H322 cells displayed significantly greater sensitivity to TUSC2 than parental cells, suggesting that TUSC2 exploits disruption of TROP2-dependent signaling. Studies investigating the molecular mechanisms underlying these context-dependent effects are ongoing. Collectively, these findings identify TROP2 as a predictive biomarker for response to quaratusugene ozeplasmid gene therapy and suggest that modulation of TROP2 signaling may represent a novel strategy to enhance the therapeutic efficacy of TUSC2 gene therapy in NSCLC.

Conflict of interest: Ownership: Jack A. Roth is a consultant and stock owner (including pending patents) in Genprex, Inc. All other authors have declared that no competing interests exist.

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109 - PB-109 **Poster**

Unfolded Protein Response as a Driver of Carboplatin-Paclitaxel Resistance in Ovarian Cancer Patient-Derived Xenografts

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Background: Platinum resistance remains the primary obstacle to long-term survival in ovarian cancer (OC). Identifying mechanistic drivers of chemoresistance is critical for the development of novel therapeutic strategies. To identify actionable therapeutic targets in the chemoresistance setting, we established a panel of patient-derived xenografts (PDX) from patients with OC including different chemo-resistant cases.

Materials and Methods: Forty OC patient-derived xenograft (PDX) models were established, including different histological subtypes (high-grade serous, clear cell, mucinous and carcinosarcoma). They were molecularly characterized by RNA sequencing, FFPE-based Data-Independent Analysis by Trapped Ion Mobility and Mass Spectrometry (DIA TIMS MS), targeted NGS (570 genes), and shallow whole-genome sequencing for HRD assessment. Sixteen PDX models were treated *in vivo* with carboplatin-paclitaxel. Matched PDX-derived organoids (PDXO) were established from chemo-resistant PDX. GSEA was performed with MSigDB Hallmarks. The PERK (protein kinase R-like endoplasmic reticulum kinase) inhibitor GSK2606414 and the mTOR inhibitor everolimus were tested in monotherapy and in combination with carboplatin-paclitaxel in matched chemo-resistant PDXO and PDX.

Results: Of the 16 PDX treated with carboplatin-paclitaxel, 6 responded with complete or partial response, 5 had stable disease, and 5 had progressive disease. The response correlated with matched patient clinical outcomes. HRD status did not correlate with response to chemotherapy. GSEA of RNAseq data identified significant enrichment of the Hallmark Unfolded Protein Response (UPR) and MTORC1 Signalling in resistant PDX. Proteomic GSEA identified enrichment of the UPR downstream protein secretion machinery and overexpression of some UPR effector proteins in resistant models, with a significant correlation between UPR protein score and best tumour response. Pharmacologic inhibition of the PERK-ATF4 branch of UPR decreased chemotherapy resistance both *in vitro* in PDXO and *in vivo* in PDX, implicating UPR activation in the resistance mechanism. In contrast, the mTOR inhibitor everolimus exhibited potent single-agent anti-tumour activity but did not sensitize tumours to carboplatin-paclitaxel when used in combination. Additionally, one of the PDX models responding to the GSK2606414-chemotherapy combination also showed resistance to the antibody-drug conjugate mirvetuximab soravtansine.

Conclusions: In summary, we established matched organoids and PDX of OC and found that the UPR, and specifically the PERK-eIF2α axis, is a mechanistic driver of carboplatin-paclitaxel resistance. These findings support the clinical development of PERK inhibitors in platinum-resistant OC.

No conflict of interest

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110 - PB-110 **Poster**

Developing Different Preclinical RAS Inhibitor Resistant Xenograft Models for Next-Generation Therapeutic Evaluation

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Background: Despite the clinical success of KRASG12C inhibitors, AMG510 and MRTX849, KRASG12C mutation accounts for ~15% of KRAS-mutant cancers, leaving most patients, including those with common alterations such as G12D, G12V, and G12R, without approved targeted therapies. Moreover, acquired resistance frequently emerges under selective pressure from KRASG12C inhibition through secondary KRAS alterations at codons 95 and 96. Although KRASG12D inhibitors and pan-RAS inhibitors may broaden the therapeutic landscape beyond KRASG12C mutant tumors, emerging clinical data indicates that acquired resistance can also develop to these agents. To support the development of strategies to overcome resistance, we established a panel of xenograft models resistant to KRASG12C inhibitors, KRASG12D inhibitors, or pan-RAS inhibitors.

Materials and Method: Secondary KRAS mutations, including Y96D/C/S and H95D/Q/R, were introduced into a pancreatic cancer cell line, MIA PaCa-2, which harbors a homozygous KRASG12C mutation. Subcutaneous MIA PaCa-2, MIA PaCa-2 KRASY96D/C/S and MIA PaCa-2 KRASH95D/Q/R models were treated with AMG510 (50 mg/kg, QD), MRTX849 (50 mg/kg, QD), RMC-7977 (pan-RAS inhibitor, 10 mg/kg, QD). In parallel, subcutaneous Capan-1 (KRASG12V) and PSN-1 (KRASG12R) models were treated with RMC-6236 (Daraxonrasib pan-RAS inhibitor, 25 mg/kg, QD). Additionally, two subcutaneous patient-derived xenograft (PDX) KRASG12D mutated models, CR9821 and PA2410, were treated daily with KRASG12D inhibitor, RMC-9805 (Zoldonrasib), at 100

mg/kg. The fastest growing treated tumor was serially passaged in naïve mice until no significant response was observed. Tumor growth and body weight changes were measured twice per week. Statistical analyses were performed using Conover's test.

Results: Following confirmation of homozygous KRAS secondary mutations, MIA PaCa-2 tumors bearing KRASY96D/C/S mutations showed marked resistance to single treatment of AMG510 or MRTX849 in vivo, compared to the parental model. Interestingly, secondary KRASH95D/Q/R mutations only conferred resistance to MRTX849, not AMG510. Notably, RMC-7977 overcame the resistance with TGI of ~100%, respectively, in all these models ($p < 0.001$). Moreover, RMC-6236 induced complete tumor regression in PSN-1 models bearing KRASG12R mutation and Capan-1 models with KRASG12V mutation. However, tumor relapse was also observed after prolonged treatment. Similarly, RMC-9805 significantly inhibited tumor growth in CR9821 with TGI of 66% and PA2410 with TGI of 70%, whereas resistance emerged in both models after prolonged treatment (TGI < 30%). The underlying resistance mechanisms remain under investigation.

Conclusions: We have successfully developed a panel of preclinical xenograft models for investigating therapeutic strategies to overcome acquired resistance to KRASG12C inhibitors, KRASG12D inhibitors and pan-RAS inhibitors.

No conflict of interest

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111 - PB-111 **Poster**

Selective targeting of AXL overcomes inherent resistance to RAS targeting therapies

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Background: High levels of AXL correlate with poor prognosis in cancer patients and mediate lack of response to multiple therapies, including RAS inhibition. While RAS inhibitors (RASi) have greatly improved patient outcomes, the treatment is not curative. AXL inhibition by AB801, a potent and selective small molecule AXL inhibitor, in combination with adagrasib, RMC-6236 (daraxonrasib) or RMC-9805 (zoldonrasib), results in significantly improved tumor control relative to single agent treatments. These data support that AXL inhibition can overcome inherent resistance to RAS targeted therapies

Materials & Methods: Expression of AXL and GAS6 was evaluated in tumors by KRAS mutation status (TCGA) and after KRAS inhibitor treatment (publicly available data). Protein expression of AXL and Gas6 was evaluated by IHC in PDAC biopsies. Cell lines were treated with adagrasib, RMC-6236 or RMC-9805 (RASi; OFF, ON, multi- or mutant-selective) alone or in combination with AB801. DUSP6, SPRY4 and GAS6 expression were evaluated by qPCR. YAP subcellular localization was assessed by immunofluorescence. Phospho-ERK1/2 (pERK), phospho-AKT (pAKT), and phospho-S6 (pS6), were measured by Western blot. *In vitro* efficacy was evaluated by confluency and colony formation assays. *In vivo* tumor growth inhibition (TGI) was assessed following administration of adagrasib or RMC-6236 alone or in combination with AB801

Results: KRAS mutations are present in a large percentage of PDAC, NSCLC, and CRC tumors, which also express high levels of both AXL & GAS6. AXL protein was detected in 78% of PDAC biopsies, 94% of which co-expressed Gas6. In tumor biopsies of patients treated with adagrasib or sotorasib, KRAS inhibition resulted in rapid and sustained upregulation of both AXL and Gas6. Treatment with RASi in AXL^+ KRASmut cancer cell lines consistently increased YAP nuclear localization and GAS6 transcription, while decreasing SPRY4 transcription, indicating cancer cells' adaptive response to RASi is primed for AXL activation. Combined treatment with AB801& RASi, resulted in enhanced inhibition of RAS pathway signaling vs. single agent RAS inhibition, evidenced by reduced pERK, pAKT, and pS6. AB801 increased cancer cell sensitivity to RASi, shown by both reduced confluency & colony formation in multiple cell lines. In H1373 $KRAS^{G12C}$ human NSCLC xenografts, TGI was significantly enhanced by combining AB801 with either adagrasib or RMC-6236. Significantly greater TGI was also observed in the KPC $KRAS^{G12D}$ syngeneic model when AB801 was combined with RMC-6236. Notably, complete tumor regression was achieved in 10 of 10 mice receiving combination treatment

Conclusions: These data provide strong rationale for combining AB801 with RAS inhibitors to achieve deeper and more durable responses by overcoming intrinsic AXL-mediated resistance often observed as a consequence of RAS inhibitor monotherapy

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Corporate-sponsored Research: Arcus Biosciences

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112 - PB-112 **Poster**

A super glue to trap wild-type and mutant variants of the ARAF: MEK1 complex

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Background: Resistance to targeted therapies in the RAS–MAPK pathway frequently arises through mutations that disrupt protein interactions or restore downstream signaling. Molecular glues that stabilize native protein complexes offer a promising strategy to overcome these resistance mechanisms. We hypothesized that highly cooperative "super glues" could chemically rescue destabilized protein complexes by enhancing ternary complex formation.

Methods: We developed a series of molecular glue analogs designed to target the ARAF:MEK1 interface. Live-cell target engagement assays, biochemical characterization, endogenous co-immunoprecipitation, intact mass spectrometry, X-ray crystallography, and functional studies in KRAS-mutant cancer models were used to evaluate compound activity, cooperativity, structural mechanism, and therapeutic potential.

Results: We identified trametivalent, a molecular glue that selectively stabilizes the native ARAF complex through ternary complex formation with MEK1. Live-cell target engagement demonstrated exceptionally high cooperativity, enabling robust ternary complex formation while overcoming engineered interface mutations and clinically observed resistance-associated mutations in both ARAF and MEK1. Unlike clinical MEK inhibitors or previously reported RAF glues, trametivalent produced marked enrichment of

endogenous ARAF complexes across multiple cancer cell lines while maintaining paralog selectivity over BRAF and CRAF. Structural analysis revealed an unique interfacial pocket and demonstrated that trametivalent accommodates multiple conformational states of the ARAF:MEK1 complex, providing a structural basis for its unusually high cooperativity. In KRAS-mutant models, trametivalent disrupted ARAF–KRAS interactions by trapping ARAF with MEK1 and, when combined with the RAS inhibitor daraxonrasib, further displaced RAF effector interactions, suppressed ERK signaling, and enhanced inhibition of clonogenic growth compared with single agent treatment.

Conclusions: We describe an ARAF:MEK1 super glue that selectively stabilizes the wild-type and mutant forms of this signaling complex. By chemically rescuing disease-associated and resistance-associated mutations through highly cooperative ternary complex formation, trametivalent establishes a new strategy for targeting adaptive resistance within the RAS–MAPK pathway. These findings demonstrate that exploiting native protein interfaces with high cooperativity molecular glues represents a broadly applicable therapeutic approach for overcoming resistance to targeted cancer therapies.

No conflict of interest

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113 - PB-113 **Poster**

Development of a DAPA-derived platinum platform for targeted therapy of platinum-resistant malignancies

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Background: The clinical utility of platinum-based chemotherapy is constrained by acquired resistance and treatment-associated toxicity. To address these challenges, we are developing a DAPA-derived platinum platform designed to enhance intracellular platinum accumulation and improve activity in resistant tumors.

Materials and Methods: The DAPA-derived platinum complexes PMX114 and PMX118 are being evaluated using an integrated preclinical workflow comprising in vitro characterization, in vivo pharmacokinetic and antitumor efficacy studies, and mechanistic investigations. Anticancer activity and platinum accumulation were assessed across cancer cell models differing in SMVT expression. Pharmacokinetic, efficacy, and hematological toxicity studies were performed in mice. SMVT-associated uptake was examined through biotin-competition assays, and cytotoxicity toward non-malignant WJMSCs was also assessed.

Results: PMX-complexes retained activity in both cisplatin-naïve and cisplatin-resistant ovarian cancer models, whereas cisplatin exhibited a 4.6-fold reduction in activity in the resistant line. Mass cytometry demonstrated substantially greater intracellular platinum accumulation for PMX114 and PMX118 compared with carboplatin across selected cancer cell models. Based on combined efficacy and uptake profiles, PMX114 was advanced to pharmacokinetic and in vivo studies. Following intraperitoneal administration, PMX114 achieved systemic exposure, supporting subsequent in vivo efficacy evaluation. In xenograft models, PMX114 demonstrated antitumor activity comparable to carboplatin, with numerically greater tumor inhibition at equimolar doses. Biotin-competition studies showed an approximately 3-fold increase in PMX114 IC_{50} and reduced intracellular platinum accumulation, whereas carboplatin activity remained unchanged, supporting SMVT-associated uptake. PMX114 also exhibited markedly reduced cytotoxicity toward WJMSCs, with no measurable IC_{50} at concentrations exceeding 300 μM, compared with cisplatin and carboplatin. To further assess their safety profile, an optimized in vivo hematological toxicity model was developed for comparative evaluation of the molecules against carboplatin.

Conclusions: The DAPA-derived platinum platform represents a promising next-generation strategy for platinum chemotherapy. The observed pharmacological profile supports further investigation of SMVT-associated targeting as a means to improve platinum delivery and overcome resistance. Ongoing studies are expanding this approach to additional tumor models, including pancreatic cancer, and examining its potential to reduce platinum-associated hypersensitivity.

Conflict of interest: Other Substantive Relationships: Walter H. Moos, Robert J. Zamboni, Kosta Steliou, and Constantin Tamvakopoulos are inventors on a European patent related to the compounds described in this abstract. The patent is assigned to the Biomedical Research Foundation of the Academy of Athens. All other authors declare no competing financial interest.

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114 - PB-114 **Poster**

Divergent mechanisms of acquired resistance to the RAS(ON) multi-selective inhibitor daraxonrasib in KRAS mutant cancer

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Daraxonrasib (RMC-6236) represents a paradigm shift in targeting the “Undruggable” RAS oncogene, achieving a landmark clinical breakthrough for pancreatic cancer. As a first-in-class, oral pan-RAS (ON) inhibitor that function as a molecular glue, it recruits the chaperone protein cyclophilin A (CYPA) and bind to the active, GTP-bound state of RAS to form a Tri-complex that blocks oncogenic signaling. This innovative mechanism enables broad-spectrum activity across multiple RAS mutations (including G12C, G12D, G12V, and G13X) and wild-type RAS. Although daraxonrasib has shown compelling preclinical efficacy across a broad spectrum of KRAS-mutant tumor models and demonstrated clinical activity in patients with RAS mutant PDAC & NSCLC, the clinical durability of RAS-targeted therapies is threatened by the inevitable emergence of resistance, and the underlying mechanisms remain poorly defined.

Robust preclinical resistant models are therefore essential to dissect these mechanisms and to guide the development of rational therapeutic strategies.

Here, we simulated prolonged *in vitro* exposure to daraxonrasib to determine whether cells adapt to continuous treatment and to establish drug-resistant cell lines. We successfully generated multiple daraxonrasib-resistant cell lines individually harboring diverse KRAS mutations, and further characterized their resistance phenotypes and underlying mechanisms. These resistant cells maintain stable resistance phenotypes to daraxonrasib both *in vitro* and *in vivo*. Preliminary mechanistic studies uncovered multiple, non-mutually exclusive resistance mechanisms, including secondary KRAS mutations, KRAS overexpression, activation of RTK bypass signaling, and upregulation of drug efflux pumps. Notably, these resistant cells exhibited distinct cross-resistance profiles and divergent resistance mechanisms across models. Collectively, our daraxonrasib resistant models will address the urgent need for robust preclinical systems that recapitulate acquired resistance, guide the development of next-generation RAS-targeting strategies and inform biomarker-driven clinical trial designs.

No conflict of interest

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115 - PB-115 **Poster**

Characterization and targeting of adaptive KRASG12C inhibitor resistance through large-scale drug combination screening

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The glycine-to-cysteine mutation in KRAS at position 12 ($KRAS^{G12C}$) is the most frequent oncogenic driver in non-small cell lung cancer (NSCLC). First-generation $KRAS^{G12C}$ inhibitors sotorasib (AMG 510) and adagrasib (MRTX849) inhibit oncogenic signaling by locking KRAS in the GDP-bound state. Although initially promising, their clinical benefit is limited by the rapid emergence of drug resistance. Next-generation $KRAS^{G12C}$ inhibitors, such as divarasib (GDC-6036), that inhibit KRAS in a similar manner show improved selectivity and potency but are expected to encounter similar resistance limitations. Understanding the drug resistance mechanisms and effective therapy combinations is essential to optimize the clinical use of these emerging agents.

$KRAS^{G12C}$ inhibitor-resistant NSCLC cell line models were generated by prolonged exposure to the inhibitor. Resistance mechanisms were characterized through sequencing analyses, determination of RTK and MAPK pathway phosphorylation, and broad therapeutic and combination profiling. A large panel of therapeutics, including targeted agents, chemotherapeutics, and ADCs, was profiled in duplicate 9-point dose ranges in cell viability assays using ATPlite™ as indirect readout after 72 or 120 hour incubation. All therapeutics were also profiled in combination with divarasib in quadruplicate 6-by-6 matrices and synergy was determined using the Bliss independence model.

The generated $KRAS^{G12C}$ inhibitor-resistant NSCLC models showed cross-resistance to other $KRAS^{G12C}$ inhibitors, as well as the pan-RAS inhibitor RMC-7977 (serving as a tool compound for daraxonrasib). Resistance was primarily reflected by reduction in inhibitor efficacy, rather than potency. Whole-exome sequencing did not identify acquired mutations that could explain the resistance. Furthermore, profiling against a broad panel of therapeutics did not reveal novel dependencies in the resistant cell lines. In contrast, combination studies of divarasib and the same compound panel identified inhibitors targeting RTKs and RAS signaling nodes, such as SOS1 and SHP2, as strong synergistic partners. Subsequent protein expression analysis was performed to confirm increased activation upstream of KRAS. These findings suggest persistence of an on-target effect despite reduced dependence on $KRAS^{G12C}$ signaling and are consistent with an adaptive resistance mechanism involving upstream pathway reactivation.

$KRAS^{G12C}$ inhibitor-resistant cell lines were successfully generated and characterized. The observed sensitivity to combinations targeting upstream signaling components suggests potential therapeutic strategies to overcome resistance. These resistant cell line models represent valuable systems for evaluating next-generation KRAS inhibitors and identifying new drug combinations to optimize the clinical benefit of $KRAS^{G12C}$ inhibitors.

No conflict of interest

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116 - PB-116 **Poster**

Characterization and Overcoming of KRAS-Targeted Therapy Resistance in Resistant Cancer Cell Lines

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Background: KRAS mutations are dominant oncogenic drivers in many solid tumors. Despite the clinical promise of KRAS G12C inhibitors and pan-RAS targeted agents, intrinsic and acquired resistance remains a major challenge. This study aimed to establish a robust preclinical platform to investigate resistance mechanisms and identify strategies to overcome RAS-driven resistance.

Methods: We established a well-validated panel of cancer cell lines with acquired resistance to KRAS G12C/G12D inhibitors, pan-RAS molecular glues, and pan-RAS inhibitors through in vitro drug induction. These resistant models underwent multi-omics characterization, including genomic and transcriptomic analyses, to define key resistance features such as copy number alterations and secondary KRAS mutations. We also performed cross-resistance profiling and evaluated diverse combination strategies using high-throughput screening and dose-response matrix assays to identify synergistic partners capable of overcoming resistance.

Results: Our resistant cell line platform successfully models various resistance scenarios. Multi-omics analysis revealed distinct resistance patterns and elucidated underlying mechanisms, including the activation of bypass signaling pathways. Cross-resistance profiling highlighted unique patterns across different KRAS mutational backgrounds. High-throughput screening in resistant cells identified several hit compounds. Furthermore, we demonstrated that specific combination strategies, such as pairing a KRAS inhibitor with other targeted agents, could effectively restore sensitivity and overcome resistance, as confirmed by significant synergy scores in dose-matrix experiments.

Conclusion: We have successfully established a comprehensive preclinical platform of KRAS inhibitor-resistant cell lines. This

platform provides valuable insights into the mechanisms of resistance to RAS-targeted therapies and serves as a powerful tool for evaluating next-generation therapeutic strategies. Our findings support the development of rational combination therapies to overcome resistance and improve outcomes for patients with KRAS-mutant cancers.

No conflict of interest

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117 - PB-117 **Poster**

Comparison of CRISPR screens in two- and three-dimensional ovarian cancer models to identify architecture-dependent mechanisms of resistance to CHEK1 inhibition

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Background: Therapeutic resistance remains the primary cause of treatment failure in ovarian cancer (OvCa), leading to poor patient outcomes. Although the CHEK1 inhibitor prexasertib (PRX) has shown clinical activity in platinum-resistant OvCa, PRX resistance limits the therapeutic benefit. Prior genome-wide CRISPR screens have identified OvCa drug resistance mechanisms, however, their reliance on two-dimensional (2D) cultures fails to recapitulate the three-dimensional (3D) architecture of advanced disease. Since OvCa disseminates as multicellular spheroids within the peritoneal cavity, we developed parallel CRISPR screening approaches in 2D monolayers and 3D spheroids to identify conserved and architecture-dependent mechanisms of PRX resistance.

Material and methods: Cas9-expressing OVCAR8 cells transduced with a genome-wide CRISPR knockout library were treated with PRX in 2D culture. Surviving cells were collected and sgRNA abundance was quantified by next-generation sequencing. Candidate resistance and microenvironmental genes were prioritized and validated, and 131 genes, filtered at high confidence, were systematically selected to generate a targeted sgRNA library for parallel CRISPR screens in matched 2D and 3D cultures. Ongoing sequencing analysis will identify conserved and context-dependent genes and pathways associated with PRX resistance across culture formats, followed by orthogonal functional validation.

Results: Genome-wide CRISPR screening identified candidate mediators of PRX resistance, including DNA damage response regulators and drug efflux transporters, several of which were functionally validated. Consistent with clinical observations, OvCa cells exhibited greater resistance to PRX in 3D spheroids than in 2D monolayers, supporting a role for tumor architecture in shaping therapeutic response. Parallel 2D and 3D CRISPR screens were completed with robust sgRNA library representation maintained throughout spheroid culture and drug selection. Integrated sequencing analysis will identify the essential and architecture-dependent determinants of PRX response for subsequent validation in OvCa spheroids.

Conclusions: We established a scalable CRISPR screening platform to interrogate therapeutic resistance in physiologically relevant OvCa models. Comparative screening in matched 2D and 3D systems enables systematic identification of context-dependent vulnerabilities that may inform predictive biomarkers and rational combination therapies to improve CHEK1 inhibitor efficacy. This approach can be extended to patient-derived organoids that recapitulate clinical tumor heterogeneity and drug response profiles. Furthermore, this can be adapted to other cancer models and drug classes to identify clinically relevant resistance mechanisms across diverse therapeutic contexts.

No conflict of interest

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118 - PB-118 **Poster**

Clinical emergence of on-target WRN mutations during Werner helicase inhibitor therapy in MSI colorectal cancer

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Background: Werner helicase (WRN) inhibitors (WRNi) are in clinical development for microsatellite instability (MSI) cancers. Preclinical studies, including our resistance modelling, indicate that on-target WRN mutations can emerge under WRNi selective pressure, but clinical evidence from treated patients remains limited. We established an integrated preclinical-clinical programme to model WRNi resistance, analyse emerging clinical resistance, and evaluate whether preclinical resistance profiles can inform therapeutic adaptation.

Material and methods: WRNi resistance was investigated using complementary functional-genomic, mutagenesis, long-term drug-selection, organoid, xenograft and cross-resistance studies in MSI cancer models exposed to clinically relevant WRNi. Clinical, radiographic, biomarker and circulating tumour DNA (ctDNA) data were analysed from WRNi-treated patients.

Results: Preclinical resistance modelling converged on recurrent on-target WRN mutations as candidate mediators of reduced WRNi sensitivity, rather than robust genetic bypass of WRN dependency. These included substitutions in functional WRN domains, such as I852F in the helicase domain, which showed distinct inhibitor-specific and cross-resistant profiles in preclinical models. Clinical evidence of emerging on-target resistance was obtained from a 74-year-old man with metastatic MSI-H/dMMR small bowel adenocarcinoma received the WRN inhibitor VVD-133214 as monotherapy. He experienced clinical benefit, with RECIST v1.1-defined stable disease until progression at month 11. At progression, ctDNA analysis identified WRN E846D at a variant allele frequency of 2.75%; this variant was not detected at baseline. E846D localises to the WRN helicase domain, six residues from I852F, providing convergent preclinical and clinical evidence that on-target WRN mutations can arise during WRNi therapy.

Conclusions: This study provides clinical evidence that on-target WRN mutations can emerge at progression during WRNi therapy in MSI cancer. The detection of WRN E846D at progression, adjacent to the I852F resistance hotspot identified by preclinical modelling, supports longitudinal ctDNA monitoring in WRNi trials. Preclinical resistance maps may help guide mutation-informed therapeutic adaptation, including rational combinations and potential switching between WRNi with non-overlapping resistance profiles.

Conflict of interest: Other Substantive Relationships: M.J.G. is a consultant for Bristol Meyers Squibb. M.J.G. is a founder and advisor at Mosaic Therapeutics, and GP is a consultant for Mosaic Therapeutics. M.F. reports personal fees from Takeda Pharmaceuticals, personal fees from Eikon, personal fees from Intera Oncology, Inc., personal fees from Pentec Health, Inc, personal fees from D.E. Shaw.

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119 - PB-119 **Poster**

Dissecting tumour microenvironment signatures associated with chemoresistance in triple negative breast cancer

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Background: Despite identical chemotherapy regimens, triple negative breast cancer (TNBC) patients show dramatically different treatment responses, suggesting that intrinsic tumour microenvironment (TME) features influence therapeutic outcome. TME plays a major role in chemoresistance, acting through physical barriers, soluble factors and recruitment of supportive cells. Stromal cells like cancer-associated fibroblasts (CAFs) can promote resistance by secreting growth factors and extracellular matrix components, while immune cells can adopt immunosuppressive phenotypes that further limit treatment efficacy. Understanding how the TME shapes treatment outcome in TNBC is crucial for developing more effective therapies and predictive biomarkers.

Material and method: We investigated the TME features at the point of resistance onset using the AT3 murine TNBC model. Tumour-bearing mice were treated with standard-of-care chemotherapy consisting of doxorubicin (2 mg/kg) and cyclophosphamide (50 mg/kg), administered weekly for three cycles. Tumours were harvested one week after the final dose and analysed by flow cytometry. In parallel, multiplex immunofluorescence (mIF) was performed in formalin-fixed tumours using a panel targeting CD8 and CAF markers. For transcriptomic profiling, samples were processed for scRNAseq analysis using the 10X Genomics Flex kit.

Results and discussion: Despite receiving identical treatment, tumours from genetically identical mice displayed varying responses and were classified as chemosensitive or chemoresistant based on tumour size and growth kinetics. Flow cytometry revealed that chemoresistant tumours contained fewer effector CD8+ T cells and increased PDPN+ CAF abundance. Immunofluorescence further demonstrated a distinct immune–stromal organisation in resistant tumours, with higher proportions of $PDPN^+$ and FAP^+ CAFs. In these tumours, proximity analysis showed that CD8+ T cells were closer to PDPN+ FAP+ double-positive CAFs, while no differences were seen with single-positive populations, suggesting a specific role for this CAF subset. scRNAseq analysis further showed that the lymphocyte compartment of resistant tumours was enriched for naïve-like T cells, while sensitive tumours contained a higher proportion of cytotoxic $CD8^+$ T cells. Together, these findings indicate that chemoresistance is associated with an immune microenvironment characterised by reduced T-cell activation and impaired cytotoxic function. Ongoing studies are investigating the functional impact of $PDPN^+FAP^+$ CAF–T-cell interactions in shaping this immune phenotype.

Conclusion: Our findings highlight the existence of divergent TME configurations that correlate with chemotherapy response, even within a group of isogenic mice. These TME features could serve as predictive biomarkers or therapeutic targets to overcome resistance.

No conflict of interest

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Poster Session: Epigenetic modulators (HDAC Bromodomain modulators, EZH2)

120 - PB-120 **Poster**

Selective degradation of KAT6A suppresses ERα signaling and tumor growth in ER^+ breast cancer models

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KAT6 paralogs KAT6A (MOZ; MYST3) and KAT6B (MORF; MOZ2; MYST4) are histone acetyltransferases that regulate gene transcription through acetylation of histone H3 and modulation of chromatin structure. Dysregulation of KAT6 activity, including amplification and overexpression, is observed across multiple tumor types. In breast cancer, KAT6A is frequently amplified within the 8p11–p12 locus and/or overexpressed in approximately 15% of tumors, with elevated expression associated with poorer clinical outcomes in $ER^+/HER2^-$ disease.

The dual catalytic and scaffolding functions of KAT6A motivated us to investigate targeted protein degradation as a strategy to suppress completely KAT6A-dependent transcription as well as other functions of KAT6A.

We describe a series of KAT6A-selective OP degraders that induce rapid and sustained degradation of KAT6A, with selectivity over KAT6B, in cellular models. In the ER^+ ZR-75-1 breast cancer cell line, KAT6A degradation is associated with robust target engagement, including modulation of histone H3 acetylation and suppression of ERα expression, consistent with disruption of ERα-dependent signaling. In ER^+ breast cancer cell lines, including ZR-75-1 and T47D, KAT6A degradation results in potent antiproliferative effects.

Representative lead degraders have pharmacokinetic properties supportive of oral dosing across species leading to sustained target suppression in tumor tissue. In vivo, treatment induces significant tumor growth inhibition and regression in multiple ER^+ breast cancer xenograft models, including T47D and MCF7, as well as the endocrine-resistant ST941c model. Collectively, these findings support a nonredundant role for KAT6A in sustaining ERα-driven tumor growth and establish selective KAT6A degradation as a promising therapeutic strategy for ER^+ breast cancer.

Conflict of interest: Ownership: R. Ng, S. Barratt, C. Hope, G. Palanisamy, D. Yeghikyan, G. Pena, S. Jayaraman, D. Heerding, and

D.C. Myles are employees of Olema Oncology and have a financial interest in the company in the form of stock and/or stock options.

Corporate-sponsored Research: This work was conducted in part under a research collaboration agreement between Olema Oncology and Aurigene Oncology Limited.

Other Substantive Relationships: C. Venkateshappa, M. Goyal, L. Khare, D. Achuthankutty, S.S. Dodheri, S. Gore, V.S.R. Nagireddy, S. Sumajdar, and M. Ramachandra are employees of Aurigene Oncology Limited, which has a research collaboration agreement with Olema Oncology.

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121 - PB-121 **Poster**

TQB3306: A second-generation menin-MLL inhibitor overcoming acquired MEN1 resistance with superior efficacy in acute leukemia models

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Background: The menin-MLL interaction is a validated therapeutic target in acute leukemias driven by KMT2A rearrangements (KMT2A-r) or NPM1 mutations (NPM1m). Although first-generation menin inhibitors (revumenib, ziftomenib) have demonstrated clinical benefit, acquired MEN1 resistance mutations emerge in ~40% of patients, limiting durable responses. Here we report TQB3306, a novel, orally bioavailable second-generation menin-MLL inhibitor designed to overcome these clinically observed resistance mutations.

Methods: Menin binding was evaluated using fluorescence polarization (FP) assays against wild-type menin and five clinically relevant mutant proteins. Anti-proliferative activity was assessed in cells harboring KMT2A-r (MV4-11, MOLM-13), NPM1m (OCI-AML3), and wild-type MLL leukemia cells. *In vivo* efficacy was evaluated in MV4-11 xenograft models expressing menin M327I, G331R, and T349M.

Results: TQB3306 potently disrupted the menin-MLL interaction with an IC_{50} of 4.8 nM against wild-type menin and maintained strong activity against resistance mutants M327I, T349M, G331R, M327V, and G331D, demonstrating 7- to 70-fold improved potency over SNDX-5613 (revumenib), which showed markedly reduced activity against these mutants (IC_{50}: 79.6 to 1559 nM). TQB3306 exhibited potent anti-proliferative activity in KMT2A-r (MV4-11: IC_{50} 0.9 nM; MOLM-13: 2.6 nM) and NPM1m (OCI-AML3: 15 nM) cells, displaying 15-27-fold greater potency than SNDX-5613, while showing no cytotoxicity in wild-type MLL cells. TQB3306 potently suppressed *MEIS1* and *HOXA9* expression, and induced the differentiation marker CD11b, confirming on-target engagement. *In vivo*, oral administration of TQB3306 achieved tumor growth inhibition of 90.6%–98.6% at 15–25 mg/kg in MV4-11 wild-type xenografts, superior to SNDX-5613, DSP-5336, and BN-104. Notably, in MV4-11 menin-M327I mutant xenografts where SNDX-5613 was ineffective (TGI: −24.1%), TQB3306 demonstrated dose-dependent efficacy with tumor regression, including complete regression at the high dose. TQB3306 also achieved tumor shrinkage in all animals bearing menin G331R and T349M mutant xenografts, whereas SNDX-5613 showed minimal or no activity in these models. TQB3306 showed no cytotoxicity in normal human cell panels and was well tolerated in exploratory toxicology studies.

Conclusions: TQB3306 is a potent, orally available second-generation menin-MLL inhibitor with broad-spectrum activity against clinically relevant *MEN1* resistance mutations and superior preclinical efficacy across multiple leukemia models. These results support its further development as a promising therapeutic strategy for KMT2A-r and NPM1m acute leukemias. IND-enabling studies are ongoing to support clinical trial initiation in 2026.

Conflict of interest: Ownership: Hongjiang Xu, Fei Liu, Wei Zhao, Xiquan Zhang are current employees of Chia Tai Tianqing Pharmaceutical Group and hold stock or stock options in the company

Corporate-sponsored Research: The study was supported by Chia Tai Tianqing Pharmaceutical Group

Other Substantive Relationships: All authors are employees of Chia Tai Tianqing Pharmaceutical Group

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122 - PB-122 **Poster**

OTR-8100, a potent and selective EED inhibitor, demonstrates synergistic antitumor activity with targeted therapies in solid tumors

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OTR-8100 is a potent, selective EED inhibitor designed to suppress PRC2-mediated oncogenic transcriptional programs. In a first-in-human Phase 1 study in patients with hematologic malignancies and other advanced tumors, it has demonstrated preliminary efficacy with favorable safety and pharmacokinetic/pharmacodynamic (PK/PD) profiles, supporting further development in other indications as mono- or combination therapy. To expand its therapeutic potential into solid tumors, we conducted a series of preclinical translational studies evaluating OTR-8100 both as a single agent and in combination with other targeted therapies. Across multiple solid tumor models, OTR-8100 demonstrated synergistic anti-tumor effects with clinically validated agents, particularly androgen receptor antagonists in prostate cancer and pan-KRAS inhibitors across various solid tumors. These findings support the biological rationale for targeting PRC2/EED-dependent epigenetic regulation in molecularly defined solid tumors and provide a translational foundation for clinical combination strategies. Based on these data, OTR-8100 is currently being evaluated in a Phase 1 clinical study in combination with androgen receptor antagonists in patients with prostate cancer. Together, these preclinical and early clinical data support further development of OTR-8100 as a promising epigenetic-targeting therapy with broad potential for combination treatment in multiple solid tumors.

No conflict of interest

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123 - PB-123 **Poster**

Histone deacetylase activity limits the response to EZH2 inhibition-based therapy in epithelioid sarcoma and is targetable by epigenetic combination

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Background: Epithelioid sarcoma (EpS) is an aggressive and ultra-rare soft tissue sarcoma (STS) driven by INI1 loss, which triggers hyperactivation of the chromatin-modifying enzyme EZH2. However, objective responses to the EZH2 inhibitor (EZH2i) tazemetostat (TZM) remain limited to approximately 15% of patients. Combination strategies incorporating EZH2i with doxorubicin (DOX), the first-line standard for advanced STSs, may enhance the activity of either agent alone, warranting investigation of the underlying mechanisms of response and resistance.

Methods: Two INI1-deleted in-house generated proximal-type EpS (P-EpS) patient-derived xenograft (PDX) models, EpS-1 and EpS-2, and their matched cell lines were established and characterized. Both models were used to evaluate TZM and DOX, alone and in combination, and to investigate response and resistance mechanisms.

Results: TZM + DOX greatly inhibited tumor growth in EpS-1 in vivo, though regrowth occurred approximately three weeks after treatment cessation. EpS-2 displayed intrinsic resistance to all treatments. RNA sequencing of post-treatment PDXs revealed divergent transcriptional responses: in EpS-1 but not in EpS-2 TZM + DOX downregulated gene sets linked to chromatin organization and histone deacetylases (HDACs). Consistently, H3K27 acetylation (H3K27ac) accumulated exclusively in EpS-1, suggesting HDAC activity limits EZH2i-induced chromatin remodeling in resistant EpS. In EpS-2, co-treatment with TZM, DOX, and the pan-HDAC inhibitor vorinostat (SAHA) restored H3K27ac, induced apoptosis, and improved antiproliferative activity.

Conclusions: This study identifies distinct resistance profiles to EZH2i-based therapy in P-EpS PDXs. HDAC activity limits chromatin remodeling induced by EZH2i (±DOX), and its inhibition with SAHA restores sensitivity, supporting HDAC inhibition as a rational strategy to overcome EZH2i resistance.

No conflict of interest

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Poster Session: Functional Genomics

124 - PB-124 **Poster**

Targeted protein degradation models for the exploration of spliceosome-associated RNA helicases as therapeutic targets

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Background: Alternative splicing (AS) expands transcriptomic and proteomic diversity through regulated intron retention and exon skipping, generating multiple protein isoforms. Aberrant AS is a hallmark of cancer, driving abnormal isoforms that promote oncogenic signalling, tumour progression and therapeutic resistance. This dysregulation often arises from alterations to spliceosome components, including RNA-binding proteins and NTP-dependent RNA helicases. Beyond generating oncogenic isoforms, many tumours become dependent on core splicing machinery, demonstrating a non-oncogene addiction in which high transcriptional burden and proteotoxic stress heighten spliceosome demand and sensitise cells to its perturbation, positioning spliceosome components as therapeutic vulnerabilities. However, the extent to which individual helicases are required to maintain splicing throughput, fidelity and cell survival in solid tumours remains unclear. Here, we systematically investigate canonical DEAD- and DEAH-box spliceosome-associated helicases in tumour models.

Material and methods: Helicases were targeted across a panel of non-small cell lung cancer (NSCLC) lines, colon cancer cells and normal lung epithelial cells using siRNA knockdown and CRISPR-Cas9 knockout. To assess acute splicing consequences of helicase loss, we developed dTAG-V1-mediated targeted protein degradation (TPD) models in H1299 NSCLC cells, enabling high-depth RNA sequencing and downstream functional assays.

Results: siRNA and CRISPR-Cas9 targeting revealed heterogeneity across tumour models and relative to non-transformed cells. TPD models of the canonical spliceosome-associated helicases DHX8, DHX15, DHX16, DDX23, DHX38 and DDX46 in H1299 cells achieved complete protein degradation within two hours, confirmed by HiBiT and immunoblot. Surprisingly, complete loss of DHX16, DHX38 and DDX46 caused minimal global splicing disruption and no impairment of proliferation. In contrast, DHX15 loss induced alternative 3′ and 5′ splice site usage and increased exon skipping, suggesting roles beyond spliceosome disassembly and consistent with recent evidence implicating DHX15 in complex A formation and splicing fidelity via U2 snRNA interactions. Collectively, these findings challenge the assumption that canonical spliceosome-associated helicases are uniformly required for spliceosome function, instead supporting differential helicase dependencies shaped by tumour-specific genetic and epigenetic landscapes, transcriptional burden and tolerance of splicing infidelity.

Conclusions: These data underscore the value of integrative approaches for evaluating RNA helicases as therapeutic targets. Ongoing work aims to define patient-specific vulnerabilities, explore context-dependent differences in helicase essentiality, and prioritise helicases for future drug discovery.

No conflict of interest

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125 - PB-125 **Poster**

Genome-wide Cas9 and subsequent focussed Cas13d screening identifies potential gene dependencies in diffuse midline glioma

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Background: Diffuse midline glioma (DMG) is a fatal paediatric brain tumour with limited therapeutic options, yet genome-wide screening data to identify genetic vulnerabilities remains limited. To address this, we performed genome-wide Cas9 screening in patient DMG cell line models, with further implementation of a pooled Cas13d secondary screening strategy against top hits, providing preliminary validation in a gene KD context.

Methods: A guide library targeting 19,077 coding genes was used for Cas9 dropout screening in 8 cell lines; 6 high-grade gliomas (HGG), including 4 DMGs, and 2 non-HGG models. The data were analysed using CHRONOS in isolation, or combined with publicly available DepMap data, correcting for potential lineage-specific toxicities by using CNS-origin subsets. Empricial Bayes analysis in limma identified selective candidate genes, which informed design of a focussed Cas13d guide library targeting 66 genes. Preliminary screening was performed in a DMG and HGG cell line model, with statistical modelling identifying candidate genes showing strong dependency in this orthogonal KD context.

Results: An average of 447 (2.62 %) and 436 (2.55%) genes were identified in HGG and non-HGG lines with CHRONOS gene effect scores < -1, respectively, from the Cas9 screen. Although not statistically significant, empirical Bayes analysis identified 5 genes with strong selective dependency, including FGFR1. Increased power was achieved when including all Depmap models, identifying >2000 genes, showing selective dependency (FDR<0.01), which were prioritised by L2FC and concordance between analyses. Cas13d pooled screening preliminarily validated 10 and 5 targets (L2FC < -0.5, FDR < 0.05) in a DMG and HGG cell line model, respectively. Of these, 7 were unique to the DMG line, including FGFR1.

Conclusion: Through *in vitro* genome-wide Cas9 and focussed Cas13d screening in DMG, we identify potential novel gene dependencies that may help inform therapeutic discovery.

No conflict of interest

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Poster Session: Molecular profiling

126 - PB-126 **Poster**

Molecular profiling of invasive breast cancer and its association with clinicopathological characteristics in Kenitra, Morocco (2017–2023)

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Background: Breast cancer is a heterogeneous disease characterized by distinct molecular subtypes with variable prognostic significance. Immunohistochemistry (IHC)-based molecular classification remains a practical approach in resource-limited settings. This study aimed to describe the molecular profile of invasive breast cancer and its association with clinicopathological characteristics in a Moroccan population.

Material and methods: This retrospective study included 1083 cases of invasive breast cancer diagnosed between 2017 and 2023 in Kenitra, Morocco. Molecular profiling was available for 981 cases, which formed the analytical cohort. Tumor subtyping was based on ER, PR, HER2, and Ki-67 immunohistochemistry.Data analysis was performed using SPSS. Associations were tested using Chi-square or Fisher's exact test for categorical variables, and ANOVA or Kruskal–Wallis test for continuous variables. A p-value < 0.05 was considered statistically significant.

Results: The mean age at diagnosis was 51.68 ± 11.97 years (median 51; range 21–92). Most patients were aged >50 years (52.3%), and 61.3% lived in urban areas.Hormonal receptor analysis showed ER positivity in 69.6% (n=683) and PR positivity in 54.0% (n=530). HER2 IHC status (n=789) was positive in 26.0% (n=255), negative in 70.2%, and equivocal in 3.8%.Luminal A was the most frequent subtype (38.9%), followed by Luminal B (27.6%), TNBC (16.7%), HER2-enriched (13.3%), and unclassified (3.5%).Significant associations were observed between molecular subtypes and tumor aggressiveness. Grade III tumors were most frequent in TNBC (50.3%, p<0.001). TNBC showed the largest tumor size (4.34 ± 2.32 cm) and highest lymph node involvement (76.3%, p<0.001). Lymphovascular invasion was highest in TNBC (64.6%) and HER2-enriched (53.8%) compared to Luminal A (20.8%, p<0.001).Ki-67 varied significantly across subtypes (p<0.001), with the highest values in TNBC (47.63%) and Luminal B (31.17%), and lowest in Luminal A (8.08%). High Ki-67 (≥20%) was most frequent in Luminal B (75%) and TNBC (68%).No significant associations were found with age, menopausal status, or reproductive factors (p>0.05).

Conclusions: This study provides a comprehensive molecular profiling of invasive breast cancer in Morocco, demonstrating marked heterogeneity across molecular subtypes. TNBC and HER2-enriched tumors were associated with more aggressive clinicopathological features, while Luminal A remained the most frequent subtype. These findings highlight the clinical value of IHC-based molecular classification for prognostic stratification in resource-limited settings.

No conflict of interest

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127 - PB-127 **Poster**

BRAF/TERT Co-Mutations in Radioiodine-Refractory Differentiated Thyroid Cancer: Association with Aggressive Clinicopathological Features

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Background: Although differentiated thyroid cancer (DTC) is generally associated with a favorable prognosis, the development of radioiodine-refractory disease (RAIR-DTC) remains a major clinical challenge, leading to disease progression, limited therapeutic options, and poorer outcomes. The integration of molecular-genetic alterations with clinicopathological tumor characteristics may

improve risk stratification and facilitate the early identification of patients with an aggressive radioiodine-refractory phenotype.

Aim: This study aimed to evaluate the association between molecular-genetic alterations and clinicopathological patterns in patients with radioiodine-refractory differentiated thyroid cancer.

Materials and Methods: A retrospective single-center study was conducted among 167 patients with differentiated thyroid cancer treated between 2021 and 2023. Patients were stratified into two groups according to radioiodine response: radioiodine-sensitive DTC (RAI-sensitive DTC, n = 130) and radioiodine-refractory DTC (RAIR-DTC, n = 37). Clinical data, histopathological characteristics, archived postoperative hematoxylin and eosin slides, formalin-fixed paraffin-embedded tissue blocks, and molecular-genetic alterations were analyzed. Particular attention was given to the relationship between BRAF and TERT promoter alterations and aggressive tumor features.

Results: The findings demonstrated that the coexistence of **BRAF and TERT promoter mutations** was associated with a more aggressive and radioiodine-refractory phenotype of DTC. Tumors harboring BRAF + TERT co-mutations more frequently exhibited vascular invasion, incomplete or absent tumor encapsulation, less differentiated histological architecture, and more pronounced local tumor extension. These alterations were also linked to clinicopathological patterns reflecting higher biological aggressiveness and reduced responsiveness to radioiodine therapy.

Conclusions: The integration of molecular profiling into routine clinicopathological risk assessment may enhance the early identification of patients at high risk for radioiodine-refractory disease. In particular, combined assessment of **BRAF and TERT promoter mutations** may serve as a clinically relevant tool for refining risk stratification and personalizing therapeutic strategies in patients with differentiated thyroid cancer.

No conflict of interest

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128 - PB-128 **Poster**

Male breast cancer in Arab populations: A systematic review of molecular, genetic, and clinicopathologic characteristics

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Background: Male breast cancer (MBC) accounts for less than 1% of all breast cancer cases, yet its incidence is increasing worldwide. Research on MBC remains limited, particularly in Arab populations, where molecular and genetic characteristics are poorly characterized. Improved understanding of MBC biology is essential to support region-specific, biology-driven management strategies.

Methods: This systematic review was registered in PROSPERO (CRD42024607019) and conducted according to PRISMA guidelines. PubMed, Embase, and Scopus were searched from inception through December 2025. Eligible studies reported MBC cases from Arab countries and included data on molecular subtypes, receptor status, genetic alterations, and/or clinicopathologic characteristics. Data were extracted independently by four reviewers. Risk of bias was assessed using the Joanna Briggs Institute (JBI) critical appraisal tool, and findings were synthesized narratively with harmonization of tumor grade and stage where applicable.

Results: From 9,286 records, 54 studies comprising 1,549 MBC patients met inclusion criteria. Invasive ductal carcinoma was the predominant histological subtype (86.6%). Among patients with reported intrinsic subtypes (n = 335), luminal A (45.7%) and luminal B (40.9%) accounted for over 86% of cases, whereas HER2-positive (4.8%) and triple-negative (8.3%) tumors were uncommon, and triple-positive disease was rare (0.3%). Receptor status was reported for 902 patients, with high ER (91.8%) and PR (80.8%) positivity and low HER2 positivity (5.5%), alongside substantial heterogeneity in testing and reporting. Genetic data were available for 55 patients, most frequently identifying pathogenic truncating BRCA2 variants, although BRCA-negative cases were also reported. Surgery was the most reported treatment modality (n = 856), predominantly mastectomy-based, while endocrine therapy was frequently used and HER2-targeted therapy was infrequently reported.

Conclusion: Male breast cancer in Arab populations is predominantly hormone receptor–driven, characterized by luminal subtypes, high ER/PR positivity, and low HER2 expression. Genetic evidence, though limited, implicates BRCA2 as the most frequently reported susceptibility gene. These findings highlight the need for standardized molecular reporting and broader access to receptor profiling and genetic testing to support personalized, region-specific MBC management.

No conflict of interest

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129 - PB-129 **Poster**

RNA-seq analysis enhances detection of clinically relevant oncogene splice isoforms in solid tumors

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Background: While oncogene splice isoforms can drive tumorigenesis, affect targeted therapy response, and mediate resistance, they are often missed by routine DNA assays. To address this gap, we assessed the utility of tumor RNA-seq for detecting clinically relevant oncogene splice isoforms in a pancancer cohort to inform biomarker-guided treatment selection and drug development strategies.

Material and methods: RNA-seq and whole-exome sequencing data from 7,028 tumors were analyzed. Exon skipping was detected from split reads using SplAdder (v3.1.0). Events with exon-skipping fraction >1% were selected and manually reviewed in IGV. Somatic DNA events were used for orthogonal confirmation when possible.

Results: We identified oncogenic *EGFR*, *ERBB2*, and *MET* isoforms and resistance-associated *BRAF* and *AR* isoforms in 48 tumors, expanding the spectrum of tumor types known to be associated with these isoforms (**Table 1**). *EGFR* splice isoforms predominated and were enriched in CNS tumors (27/91, 29.7%). While *EGFRvII*, *EGFRvIII*, and *EGFRvIVb* were confined to CNS tumors, *EGFRvIVa* was also detected in non-CNS tumors. *BRAF3–9* and *BRAF1–11* were detected in therapy-naive *BRAF* fusion-positive anaplastic thyroid cancer and *BRAF V600E*-mutant melanoma, respectively. *ARv567es* was detected in prostate cancer after progression post-treatment with abiraterone. All six *METex14del* cases were supported by causative DNA mutations: c.3028G>A, c.3028G>C, c.2888-29_2892del, c.3028+1G>C, and c.3006_3028+4delinsTTC. In contrast, DNA evidence for *ERBB2ex16del* was present for only 3/12

cases (c.1899-1G > T, c.1899-20T > G, and c.1926_1946 + 125del) and was absent for all *EGFR*, *BRAF*, and *AR* cases.

Conclusions: Tumor RNA-seq can improve biomarker detection by identifying clinically relevant splice isoforms, especially when DNA assays cannot detect obvious causative DNA alterations underlying these splice isoforms or in treatment resistance settings. Our approach enhances patient selection and stratification, improves trial design, and supports target discovery across diverse tumor types.

Table 1. Summary of detected splice isoforms

Gene	Splice isoforms (n)	Tumor types	Cases with DNA evidence
EGFR	*EGFRvII* (1)	Glioblastoma (GBM)	0/1
	EGFRvIII (10)	GBM	0/10
	EGFRvIVa (14)	GBM, metastatic castration-resistant prostate cancer (mCRPC), gastrointestinal stromal tumor, lung squamous cell carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, colorectal cancer (CRC)	0/14
	EGFRvIVb (2)	GBM	0/2
ERBB2	*Ex16del* (12)	Ovarian, breast, bladder, adenoid cystic carcinoma, CRC, pancreatic ductal adenocarcinoma, head and neck squamous cell carcinoma, cancer of unknown primary (CUP)	3/12
MET	*Ex14del* (6)	GBM, non-small cell lung cancer, CUP	6/6
BRAF	*BRAF3-9* (1)	Anaplastic thyroid carcinoma	0/1
	BRAF1-11 (1)	Melanoma	0/1
AR	*ARv567es* (1)	mCRPC	0/1

Conflict of interest: Ownership: A. Butusova, A. Yudina, A. Bagaev: BostonGene Corporation (Stock or stock options)

Other Substantive Relationships: N. Makani: BostonGene Corporation (prior paid consultant), M. Castro: Cellworks Group, Inc (employment), A. Bagaev: BostonGene Corporation (employment, executive leadership, and IP), D. Chernyavskiy, I. Anosov, P. Oschepkova, K. Turin, A. Yudina, V. Senichkin, A. Butusova: BostonGene Corporation (Employment)

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131 - PB-131 **Poster**

RANBP1 promotes oral cancer progression through activating YAP1 and NDUFB3 derived from the database of single-cell sequencing

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Background: Oral cavity squamous cell carcinoma (OSCC) is the most common head and neck cancer, thriving in microenvironments composed of cancer cells, stromal tissue, and extracellular matrix. Extensive local invasion and cervical nodal metastasis can lead to poor treatment outcomes for OSCC.

Material and Methods: We created a single-cell transcriptomic database of OSCC using biopsies from 10 individuals to explore cellular heterogeneity. Ran-specific binding protein 1 (RANBP1) was identified as a gene with differential expression between malignant and normal epithelial cells.

Results: Functional tests showed that knocking down RANBP1 reduced cell proliferation and invasion by decreasing proteins involved in focal adhesion, invadopodia formation, and epithelial-mesenchymal transition. Inhibiting RANBP1 also decreased vascular spread in zebrafish tumor xenografts, while overexpressing RANBP1 had the opposite effect. The overexpression of RANBP1 significantly increased tumor growth in NOD/SCID xenografts. RANBP1 was positively correlated with the oxidative phosphorylation pathway. Cells with reduced RANBP1 showed lower levels of NADH ubiquinone oxidoreductase subunit B3 (NDUFB3) and had impaired mitochondrial function. Additionally, RANBP1 depletion decreased activation of Yes1 associated transcriptional regulator (YAP1). Treatment with YAP1 inhibitor verteporfin reversed these effects, emphasizing RANBP1's role in OSCC progression via the YAP1/NDUFB3 pathway.

Conclusion: RANBP1 enhances oxidative phosphorylation and NDUFB3 expression through YAP1 signaling activation, creating a more invasive microenvironment.

No conflict of interest

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132 - PB-132 **Poster**

A neural gene signature predicts recurrence of resected colorectal cancer liver metastases

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Background: Approximately 30% of patients with colorectal cancer liver metastasis (CRLM) are eligible for curative intent hepatic resection with recurrence experienced by 50-75% of patients. The degree of survival benefit of adjuvant chemotherapy after resection of CRLM remains controversial. Prognostic scores such as the Fong Clinical Risk Score (CRS) may guide patient selection, although its predictive value has changed with modern therapeutics. Therefore, examining alternative molecular signatures that account for tumor biology is critical to accurately identify high risk patients who may benefit most from perioperative therapy. Here, we examine transcriptomic signatures that may independently identify such high-risk patients.

Materials & Methods: We performed bulk sequencing of RNA extracted from snap frozen CRCLM samples of 54 patients undergoing hepatectomy. Gene ontology biological process analysis (GOBP) was applied to identify transcriptional programs associated with disease recurrence.

Results: 30 patients recurred after resection. Median follow up was 9 years. GOBP enrichment identified significant upregulation of neuronal programs in recurrent CRLM, including synaptic signaling, neurogenesis, synaptic vesicle cycle and chemical synaptic transmission. Enrichment was also observed for genes associated with TME remodeling (Table). The leading-edge genes from the GOBP were used to generate a neural signature (NS) for recurrence: RYR3,

CABP5, GFAP, PTPRZ1, KCNH3, GABRA2, IRX3, CDKL1, GRIN3A, EN1, SYT14, SLC17A7, GABRA1, GABRG2, GABRR1, SYT2, SYT5, MMP13, P4HA2, PI16, TMPRSS11D/E, CPA4. This was used to create a neural signature score (NSS) for the recurrent and non-recurrent groups. ROC analysis identified 0.40 as the optimal NSS cutoff by Youden's Index (52.9% sensitivity, 95.0% specificity, PPV 94.7%). Patients with NSS ≥ 0.40 demonstrated significantly shorter recurrence-free survival (HR 3.63; log-rank $p < 0.0003$). Cutoff scores of 0.26 and 0.47 also generated KM curves with $p < 0.0002$. Both NSS and multiple individual NS genes were significantly associated with recurrence after adjustment for CRS, indicating prognostic value beyond conventional clinical risk factors.

Conclusions*:* This pilot study identified an unexpected recurrence-associated neural transcriptional program in CRLM that was independently associated with postoperative recurrence. This nominates targets for potential therapeutic intervention in CRLM e.g., GABA signaling or the immunosuppressive phenotype (GRIN3A), and suggests that a neural signature can improve postoperative risk stratification in CRLM.

GOBP	*Normalized Enrichment Score*	*FDR Adjusted P-value*
Synaptic signaling	*2.28*	*0.00425*
Neurogenesis	*2.16*	*0.00340*
Regulation of membrane potential	*1.79*	*0.0272*
Chemical synaptic transmission	*1.76*	*0.0272*
Response to cytokines	*1.66*	*0.0348*
Transmembrane transport	*1.61*	*0.0473*
Synaptic vesicle cycle	*1.59*	*0.0473*

No conflict of interest

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133 - PB-133 **Poster**

Molecular Profiling in Gastrointestinal Cancers: Stratified Stepwise Use of Limited and Comprehensive Profiling in Molecular Tumor Board (MTB) Decision-Making

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Background: Genomic profiling in oncology is increasingly performed using comprehensive approaches, including large next-generation sequencing (NGS) panels, as well as whole-exome (WES) and whole-genome sequencing (WGS), all of which are associated with increasing costs and analytical complexity. So far, it remains unclear at what point in the course of gastrointestinal neoplasms the resource- and cost-intensive Molecular Tumor Board (MTB) analysis should be performed. Furthermore, it remains unclear whether smaller, more cost-effective targeted analysis may already provide clinically relevant information for treatment decision-making in a substantial proportion of patients, potentially prior to or in combination with more extensive analyzes.

Material and methods: Prospectively collected data were evaluated from 719 MTB patients with gastrointestinal neoplasms at the University Medical Center Goettingen. Variants identified using a small-targeted gene panel and a comprehensive panel such as TSO500 were annotated for pathogenicity and clinical actionable status using OncoKB. Actionable variants were defined as OncoKB Levels 1–3A. A sequential testing strategy was modeled in which comprehensive sequencing was performed only in patients without actionable findings in the small panel. Resource utilization was assessed based on relative costs and interpretation time.

Results: In the four most common cancer types (CRC, PDAC, BTC, gastric/esophagus), approximately 90% of patients had at least one (likely) pathogenic variant; over 65% had clinically actionable variants. In about 20% of cases, additional actionable variants were identified exclusively by the comprehensive panel, including new cases without prior targets as well as additional treatment options. Overall, for the majority of patients, limited analyses have already been sufficient to support individualized recommendations. Given constant resources, a sequential strategy could allow for the analysis of approximately 40% more patients. Molecular characterization was performed during last guideline-recommended treatment line leading to 20% to 45% of patients who could not benefit because of death during analysis or within 90 days of the MTB.

Conclusions: In gastrointestinal malignancies, small-targeted analysis capture a large proportion of clinically relevant and actionable genomic alterations. A sequential testing strategy represents an efficient approach that allows for broad patient coverage while reserving comprehensive analyzes for selected cases. This approach balances diagnostic performance with resource utilization and supports its integration into precision oncology workflows.

No conflict of interest

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134 - PB-134 **Poster**

Molecular and functional characterization of canonical and RAS-Related wild-type GTPases

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Background: The RAS superfamily is a group of small GTPases involved in important cellular processes such as cell proliferation, migration, apoptosis, and survival. Within this superfamily, the canonical RAS isoforms are KRAS (4A and 4B), NRAS, and HRAS, together with RAS-related proteins including MRAS and RRAS.

Canonical RAS proteins differ from RAS-related proteins in their biological functions, cellular localization and sequence homology. These differences are important because they provide both opportunities for functional redundancy and challenges for developing selective therapeutic strategies. This study focuses on the molecular and functional characterization of all RAS isoforms, including canonical RAS proteins and RAS-related GTPases.

Material and methods: We firstly generated the models from RASless (Kraslox/lox,Hras-/-, Nras-/-, RERTert/ert) mouse embryonic fibroblasts (MEFs), rescued with pBABE retroviral vectors expressing wild-type RAS isoforms. KRas endogenous depletion was achieved through 4-hydroxytamoxifen (4-OHT) treatment,

generating rescue models with only the RAS isoforms of interest. Expression levels and the ability of each isoform to support RAS-dependent cellular functions were evaluated and compared across the various reconstituted models using molecular and cellular techniques.

Results: Expression analysis revealed the selection of distinct levels of exogenous isoform expression among the different RAS-reconstituted models. Following 4-OHT treatment for 3, 5, 7, 10, 15 and 20 days, after the depletion of endogenous KRas, the exogenous RAS isoforms showed different levels of protein expression. Interestingly, RAS-related isoforms showed a distinct behavior compared with canonical RAS proteins. In particular, exogenous RRAS and MRAS were unable to rescue proliferation in RASless cells, suggesting that these proteins alone are not sufficient to confer complete functional compensation. Endogenous MRas exhibited a unique dynamic response upon KRas depletion in the RAS canonical isoforms cell lines, showing in the beginning a transient increase in expression following 4-OHT treatment. This behavior suggests a potential adaptive mechanism involving MRas as a player for signaling compensation.

Conclusions: Our study provides a comprehensive molecular and functional characterization of both canonical RAS proteins and RAS-related GTPases. These findings highlight the functional complexity within the RAS superfamily. These findings could contribute to a better understanding of the biological cross-talk of RAS-related isoforms, which has not yet been fully defined. Understanding the specific roles and interactions of wild-type RAS isoforms could be important to identify functional similarities and differences among family members and to facilitate the development of more effective and selective therapeutic strategies.

No conflict of interest

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135 - PB-135 **Poster**

SMARCA4 mutations as a biomarker for Non-Small Cell Lung Cancer: Prognostic significance and clinical perspectives

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Background: Non-Small Cell Lung Cancer (NSCLC) is the leading cause of cancer-related death worldwide. Patients without actionable mutations usually benefit from immunotherapy-based treatments, but biomarkers to stratify patients are urgently needed. In this setting, SMARCA4 mutations are emerging as promising biomarkers to identify patients that will more likely benefit from immunotherapy treatment.

Materials and Methods: We retrospectively enrolled 101 patients with advanced NSCLC (n. 50 SMARCA4 wild-type, and 51 SMARCA4 mutated) diagnosed between 2021 and 2025 at our Hospital. All patients underwent molecular diagnostics evaluation with Oncomine Comprehensive Assay (OCA v.3), Thermofisher, investigating 161 genes, including single nuecleotide variants (SNVs), insertions and deletions (indels), copy number variation (CNVs) and fusions, as well as genomic signatures, such as homologous recombination deficiency (HRD), tumour mutational burden TMB. All patients have been treated with chemotherapy (CT), chemo-immunotherapy (CT + IO) or immunotherapy alone (IO) based on the expression status of PD-L1. We retrieved clinical information from medical charts on demographics (e.g. age at diagnosis, sex, tumor histology) and response to therapy,and correlated them, together with SMARCA4 mutational status to clinical endpoints (e.g. overall survival and progression-free surival).

Results: In the overall case series, median age at diagnosis was 69,3 years old (IQR 61,7-75,2). 63 (63%) patients were male (38 females, 38%), 86 patients (86%) had an adenocarcinoma. Smoking habits were as follows: 13 never (13%), 43 former (43%) and 45 (45%) current smokers. 20 patients underwent CT + IO, 10 were treated with CT and 7 patients with IO. SMARCA4 mutations affected the ATPase domain (exons 17-28) in 29 patients (56,8%), 12 patients (23,5%) had a mutation in the bromodomain of the protein (exons 29-34), while the 19,7% of patients had a mutation in other protein domains. Interestingly, in 13 patients (25,5%) SMARCA4 was mutated in the glutamic acid codon, while 22 mutations (43,1%) lead to a stop codon. In wt SMARCA4 patients, 27 patients (54%) had a mutation in *TP53,* 20 patients (40%) had a mutation in KRAS, and 8 patients (16%) in STK11. In SMARCA4-mutated patients, 27 patients (52%) had a co-mutation in TP53, 22 patients (43%) had a mutation also in KRAS, and 13 patients (25,5%) of patients ha a mutation in STK11. Correlation of the molecular profile and patients clinical features with clinical endpoints is ongoing.

Conclusions: SMARCA4 is emerging as a new promising biomarker in NSCLC patients treated with immunotherapy, especially for its rate of mutation in advanced-stage patients. Our results could help to identify it as a prognostic biomarker for a better patient stratification.

No conflict of interest

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136 - PB-136 **Poster**

Comprehensive molecular profiling identifies frequent actionable drivers and distinct clinicopathological phenotypes in resected lung adenocarcinoma

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Background: Molecular profiling is increasingly relevant in early-stage lung cancer, particularly with the development of perioperative targeted therapies. However, the relationship between oncogenic alterations, pathological risk features such as spread through air spaces (STAS), and recurrence-free survival (RFS) remains incompletely defined. We aimed to characterize the molecular landscape of a real-world cohort of patients with surgically resected lung adenocarcinoma and to explore the association between actionable alterations and clinicopathological outcomes.

Methods: We retrospectively analyzed 381 patients with surgically resected lung adenocarcinoma. Clinical and pathological data, including smoking history, clinical stage, type of surgery, STAS and survival outcomes, were collected. Molecular testing was performed

using PCR, FISH, IHC, or NGS with the Oncomine Precision Assay. Actionable alterations were defined as EGFR mutations, ALK or ROS1 rearrangements, MET alterations, NTRK fusions, or KRAS G12C.

Results: Median age was 68.0 years (IQR 62.3–73.8), 52.9% were male, and 74.4% had clinical stage I disease. Lobectomy was performed in 52.8% and segmentectomy in 42.0%. STAS was present in 53.8%, lymphovascular invasion in 12.1%, and perineural invasion in 20.6%. Actionable alterations were identified in 107/381 patients (28.1%). EGFR mutations were detected in 59/353 tested patients (16.7%), while KRAS mutations were found in 47/117 (40.2%); among KRAS-mutant tumors, KRAS G12C was the most frequent subtype, accounting for 24/47 cases (51.1%). Actionable alterations were enriched among never-smoking women, in whom they were identified in 28/49 patients (57.1%). EGFR-mutant tumors were significantly associated with STAS negativity compared with EGFR wild-type tumors (64.3% vs 43.0%; OR 2.39; $p = 0.005$). EGFR-mutant status was also associated with improved RFS, with 5-year RFS of 83.7% versus 67.9% for EGFR wild-type tumors (HR 0.39, 95% CI 0.18–0.84; log-rank $p = 0.013$). KRAS mutations were more frequent among ever-smokers, although without statistical significance (87.2% vs 72.5%; $p = 0.068$), and were not associated with STAS positivity or inferior RFS. KRAS G12C was not associated with a more aggressive phenotype compared with other KRAS mutations.

Conclusions: In this real-world cohort of resected lung adenocarcinoma, actionable alterations were identified in nearly one-third of patients and were particularly enriched among never-smoking women. EGFR-mutant tumors showed a favorable clinicopathological profile, with lower STAS positivity and improved RFS. In contrast, KRAS mutations, including KRAS G12C, were not associated with poorer outcomes.These findings highlight the relevance of comprehensive molecular profiling even in early-stage disease, given the high prevalence of potentially targetable oncogenic drivers.

No conflict of interest

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137 - PB-137 **Poster**

An FFPE-compatible phosphoproteomic assay for profiling signalling pathway activity in breast cancer

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Background: Protein phosphorylation provides a functional readout of pathway activity not afforded by genomics, transcriptomics, or proteomics. CDK4/6 and PI3K/Akt/mTOR inhibitors are important targeted therapies in high-risk adjuvant and advanced hormone receptor (HR)+/HER2− breast cancer (BC); however, there is a lack of predictive biomarkers to guide selection of these therapies and more data are needed about how signalling may change at recurrence. We therefore aimed to identify phosphoproteomic compound-target activity markers (CTAMs) of key pathways, including CDK4/6, PI3K, Akt and mTOR signalling, and demonstrate the feasibility of their measurement in formalin-fixed paraffin-embedded (FFPE) breast cancer tissue.

Materials and Methods: We first identified CTAMs of CDK4/6, PI3K, Akt, mTOR, and HR inhibitors in MCF7 cells through the use of untargeted phosphoproteomics by means of high-dimensional mass spectrometry (MS). Phosphopeptides that were consistently downregulated following treatment, and detectable in our previous analyses of patient FFPE material, were considered CTAMs. These markers, in addition to canonical sites representing mitogen-activated protein kinase (MAPK) and receptor-mediated signalling, were then incorporated into a targeted, clinically-deployable MS assay. Treatments with palbociclib, capivasertib, and epidermal growth factor (EGF) in additional cell lines were then performed to confirm that the assay's readouts were consistent with the expected signalling changes in independent BC models. Our previously developed FFPE phosphoproteomic processing workflows were then used to process 5 μm FFPE scrolls from 72 patient blocks in order to confirm the applicability of the workflow to patient breast tumour material.

Results: Our assay provided quantitative measurements of >10 key signalling pathway activities. Candidate CTAMs were reproducibly downregulated in independently-treated cell lines, with palbociclib and capivasertib suppressing, and EGF stimulating, the activity of their expected target pathways. Most importantly, however, high quality data were obtainable from 1-3, 5 μm FFPE scrolls in 97% of cases (with 92% of blocks providing the requisite material from 2 scrolls), thus demonstrating the practicality of the method in patient material.

Conclusions: Phosphoproteomic CTAMs discovered in cell lines were transferred to a clinically-scalable MS assay and validated in BC cell line models and FFPE patient tissue. This workflow supports pharmacodynamic and candidate predictive biomarkers for targeted therapy response and pathway-activity profiling in breast cancer. Clinical validation of the assay's readouts to predict response to CDK4/6 and PI3K/Akt/mTOR inhibition in patient samples is ongoing. Moreover, work to expand the assay with CTAMs of RAS (ON) inhibitor response and other cancers is underway.

Conflict of interest: Ownership: All Kinomica employees hold shares in the company.

Board of Directors: Prof. Cutillas is a co-founder of Kinomica Limited

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Poster Session: Translational Studies

138 - PB-138 **Poster**

Bridging Precision Oncology and Rural Cancer Care: Real-World Barriers to Molecular Profiling and Targeted Therapy Access in Eastern India

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Background: Advances in molecular profiling and targeted therapies have significantly improved outcomes for patients with several malignancies. However, implementation of precision oncology remains challenging in resource-constrained settings. Limited evidence is available regarding access to molecular diagnostics and targeted treatments among patients with cancer residing in rural India. This study evaluated real-world utilization of molecular

testing and identified barriers affecting access to biomarker-driven cancer care.

Materials and Methods: A retrospective observational study was conducted among 500 patients with advanced solid malignancies treated at a rural oncology center in Eastern India between January 2023 and December 2025. Clinical records were reviewed for demographic characteristics, cancer diagnosis, recommendations for molecular profiling, completion of testing, identification of actionable biomarkers, and receipt of targeted therapies. Barriers to testing and treatment access were categorized as financial, geographic, logistic, and health-system related.

Results: Among 500 patients evaluated, molecular profiling was recommended for 320 (64.0%) patients. Only 125 (25.0%) patients completed molecular testing. The most frequently requested biomarkers included EGFR, ALK, ROS1, HER2, BRCA1/2, KRAS, and PD-L1. Actionable molecular alterations were identified in 48 of 125 tested patients (38.4%). Despite the presence of actionable findings, only 22 patients (45.8% of biomarker-positive patients) received matched targeted therapy. The leading barriers to testing were financial constraints (62%), long travel distances to accredited laboratories (54%), delayed turnaround times (37%), and limited awareness regarding molecular testing (29%). Among patients eligible for targeted treatment, major barriers to therapy initiation included high out-of-pocket treatment costs (68%), lack of reimbursement support (51%), and limited drug availability (24%). Patients who completed molecular testing were substantially more likely to receive personalized treatment recommendations compared with untested patients.

Conclusions: Significant disparities in access to molecular profiling and targeted therapies persist among patients with advanced cancer in rural India. Although actionable genomic alterations were identified in more than one-third of tested patients, most eligible individuals did not ultimately receive biomarker-matched treatment. Expanding affordable molecular diagnostics, strengthening referral networks, and improving access to targeted therapies are critical steps toward equitable implementation of precision oncology in underserved populations.

No conflict of interest

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139 - PB-139 **Poster**

Oenothein B from Epilobium angustifolium Suppresses CD47 and PD-L1 Expression in B16-F10 Melanoma Cells through PI3K/AKT/NF-κB/HIF-1α Signalling Pathway

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Background: Melanoma is an immunotherapy-sensitive malignant tumour. Oenothein B (OB), a bioactive natural compound, has potential anti-cancer effects. Nevertheless, its immunopharmacological mechanisms against melanoma remain unclear. This study investigated the anti-tumour activity of OB in melanoma and explored its underlying immune regulatory mechanisms.

Materials and Methods: B16-F10 melanoma cell-based in vitro and in vivo models were used to evaluate the anti-melanoma and immunomodulatory effects of OB. Western blotting, flow cytometry and RT-qPCR were performed to detect CD47 and PD-L1 expression after OB treatment. RNA sequencing (RNA-Seq) was conducted to screen key signalling pathways, with the predicted mechanisms validated via immunofluorescence and immunohistochemistry. Molecular docking and DARTS assays confirmed the direct binding between OB and target proteins. Neutral red staining and multiple molecular assays assessed OB-mediated regulation of macrophage phagocytosis and polarisation. A B16-F10 cell and T cell co-culture system was used to detect changes in T cell tumour-killing ability induced by OB.

Results: OB dose-dependently inhibited the proliferation, migration, invasion and cell cycle progression of B16-F10 cells and promoted their apoptosis in vitro. In a mouse subcutaneous melanoma model, OB suppressed tumour growth and remodelled the tumour immune microenvironment by increasing macrophage and T cell infiltration. OB significantly downregulated the expression of immune checkpoints CD47 and PD-L1. RNA-Seq results revealed that OB inhibited the PI3K/AKT/NF-κB signalling pathway, thereby suppressing HIF-1α transcription and inactivating the HIF-1 signalling pathway, which mediated the downregulation of CD47 and PD-L1. Molecular docking and DARTS assays confirmed the direct binding of OB to PI3K and HIF-1α. Functionally, OB blocked the PI3K/AKT pathway to shift macrophage polarisation from pro-tumour M2 to anti-tumour M1 phenotype, enhancing macrophage phagocytosis of melanoma cells. Moreover, OB pretreatment markedly strengthened the cytotoxic tumour-killing capacity of CTLs.

Conclusion: OB effectively inhibits melanoma growth and progression in vitro and in vivo. Mechanistically, OB suppresses CD47 and PD-L1 expression via the PI3K/AKT/NF-κB/HIF-1α axis, remodels tumour immune microenvironment, promotes M1 macrophage polarisation, and enhances CTL anti-tumour cytotoxicity. This study elucidates the novel immunological anti-melanoma mechanism of OB and provides a new theoretical basis for its application in melanoma immunotherapy.

No conflict of interest

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140 - PB-140 **Poster**

Targeting the PI4K2A lysosomal pathway is a promising approach for lung cancer therapy

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We have shown that Pac 1 selectively inhibits the proliferation of various cancer cells and is a cancer-specific inhibitor of the PI4K2A-associated lysosome complex, which serves as a crucial clearance mechanism for cancer cell survival by eliminating misfolded/abnormal proteins and their toxic effects. In the current study, we evaluated sensitivity to Pac 1 in 127 lung cancer cell lines and found that Pac 1 inhibited the growth of most of the cancer cells at nanomolar concentrations. In addition, lung cancer cells with high *PI4K2A* gene expression or *VCAN* mutation had increased sensitivity to Pac 1. We also demonstrated that in vivo administration of Pac 1 inhibited tumor growth in lung cancer PDX models with high *PI4K2A* expression and *VCAN* mutation but not in models with low *PI4K2A* expression and wild-type *VCAN*. We further demonstrated that Pac 1 impairs lysosomal function and causes protein aggregation and lung cancer cell death in Pac 1-sensitive cells but not in Pac 1-resistant cells. High levels of *PI4K2A* or *VCAN* gene expression were associated with low overall survival rates in lung cancer patients. We conclude that the PI4K2A complex is a clinically significant potential therapeutic target that is required for cancer cell survival, and effectively targeting this pathway can provide significant cancer-specific therapeutic activity in lung cancers.

No conflict of interest

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141 - PB-141 **Poster**

Dosimetric Outcomes and Survival Analysis in Nasopharyngeal Carcinoma Treated with Simultaneous Integrated Boost Intensity-Modulated Radiotherapy (SIB-IMRT): A Single-Institution Retrospective Study

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Background Nasopharyngeal carcinoma (NPC) is a radiosensitive malignancy with a predilection for locally advanced presentation. Simultaneous integrated boost intensity-modulated radiotherapy (SIB-IMRT) enables the delivery of differential dose levels to tumour volumes in a single treatment session, potentially improving target coverage while sparing adjacent organs at risk (OARs). Despite growing adoption of this technique, dosimetric and survival data from sub-Saharan African institutions remain limited. This study reports the dosimetric profile, OAR sparing, and early survival outcomes of NPC patients treated with SIB-IMRT at our institution.

Methods: A retrospective analysis was conducted on 25 consecutive patients with histologically confirmed NPC treated with SIB-IMRT at Medserve-LUTH Cancer Centre. The prescribed dose fractionation scheme delivered 70 Gy, 59.4 Gy, and 54 Gy in 33 fractions to three simultaneously treated planning target volumes (PTV_{70}, $PTV_{59.4}$, and PTV_{54}, respectively). Dosimetric parameters — including $D_{2\%}$, $D_{50\%}$, $D_{95\%}$, $D_{98\%}$, Dmin, Dmax, Dmean, conformity index (CI), and homogeneity index (HI) — were extracted from dose-volume histograms. Mean doses to OARs, including bilateral parotid glands, spinal cord, brainstem, optic chiasm, optic nerves, lenses, oral cavity, esophagus, and submandibular glands, were recorded. Concurrent chemotherapy was administered where indicated. Overall survival (OS) was estimated using the Kaplan–Meier method.

Results: The mean age was 45.16 ± 16.52 years, with a male predominance (64%). Most patients presented with locally advanced disease: Stage III (44%) and Stage IV (40%). Excellent target coverage was achieved across all PTVs; mean $D_{95\%}$ values closely approximated prescribed doses for $PTV_{54\ Gy}$, $PTV_{59.4\ Gy}$, and $PTV_{70\ Gy}$, with favorable homogeneity and conformity indices. Organs-at-risk (OAR) doses were within acceptable tolerance levels, particularly for the spinal cord and brainstem. Kaplan–Meier survival analysis yielded a mean OS of 34.4 months (95% CI: 29.3–39.5 months) over a follow-up period of 6 to 36 months. The median survival was not reached, indicating that more than 50% of patients remained alive at the time of analysis. The 6-month and 12-month OS rates were 96% and 87%, respectively.

Conclusion SIB-IMRT achieves highly conformal and homogeneous dose delivery to multiple target volumes in NPC while maintaining OAR doses within established tolerance thresholds. The favourable early survival outcomes with a 6-month OS of 96% and a 12-month OS of 87% support the efficacy of this technique in a predominantly locally advanced cohort. These findings contribute important institutional evidence to the growing literature on SIB-IMRT for NPC, particularly from low- and middle-income.

Keywords: Nasopharyngeal Cancer, Simultaneous Integrated Boost, IMRT, Sub-Saharan Africa.

No conflict of interest

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142 - PB-142 **Poster**

Evaluation of antitumor activity of oral elraglusib in B16F10 melanoma model

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Background: Elraglusib (9-ING-41), a glycogen synthase kinase-3 inhibitor, exhibits a multimodal mechanism of action in human cancer. We previously reported that intravenous elraglusib combined with gemcitabine/nab-paclitaxel (GnP) met its primary endpoint of improved survival when compared to GnP alone in a randomized Phase 2 trial (the 1801 Part 3B trial, NCT03678883) in patients with metastatic pancreatic cancer. Here, we report, for the first time, the antitumor efficacy and immunomodulatory effects of oral elraglusib used as a single agent in a syngeneic mouse model of melanoma.

Materials and Methods: Oral elraglusib was evaluated in the B16F10 syngeneic melanoma mouse model. Immunophenotyping of blood and tumor samples was performed using a 42-parameter spectral flow cytometry assay.

Results: In the B16F10 melanoma model, daily administration of oral elraglusib induced potent antitumor response. The activity of elraglusib was attributed to direct antitumor effect on cancer cells and to an increase and accumulation of CD8+ and NK cells together with decreased Ly6G+ neutrophil/PMN-MDSC-like cells in B16F10 tumors as determined by tumor immunophenotyping. These findings suggest that oral elraglusib shifts the tumor microenvironment toward a more immune-permissive and less myeloid-suppressive state, thereby enhancing antitumor immune responses.

Conclusions: This is the first *in vivo* study to demonstrate that daily treatment with oral elraglusib is well tolerated, significantly inhibits tumor growth, and enhances antitumor immunity in the poorly immunogenic, highly aggressive B16F10 melanoma model. These results provide preclinical proof of concept for the immunomodulatory and antitumor activity of oral elraglusib and support the clinical evaluation of elraglusib tablets in cancer patients.

Conflict of interest: Ownership: Dr. Andrew Mazar is an equity holder in Actuate Therapeutics. Dr. Andrey Ugolkov is an equity holder in Actuate Therapeutics.

Advisory Board: NA

Board of Directors: NA

Corporate-sponsored Research: Dr. Casey Ager declares research funding from Actuate Therapeutics. Dr. Wenan Qiang declares research funding from Actuate Therapeutics.

Other Substantive Relationships: Dr. Andrew Mazar is an employee of Actuate Therapeutics. Dr. Andrey Ugolkov is a an employee of Actuate Therapeutics.

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143 - PB-143 **Poster**

Functional characterization of KRAS/PIK3CA co-altered colorectal cancers identifies combination therapeutic vulnerabilities

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Background: Colorectal cancer (CRC) is molecularly heterogeneous, but how genomic co-alterations shape tumor behavior and therapeutic responses remain elusive. RAS or PI3Kα inhibitors have shown limited efficacy in CRC despite activity in other cancers. We hypothesized that RAS/PI3K pathway co-alteration promotes tumor progression and limits the efficacy of single-pathway inhibition through parallel MAPK and PI3K pathway activation.

Material and methods: We performed retrospective pan-cancer analysis of 9,871 NewYork-Presbyterian (NYP) cancer patients (2003-2023), TCGA analysis, and sequencing of our CRC patient-derived organoid (PDO) biobank. *In vivo* effects of *PIK3CA* and *KRAS* co-mutation was assessed using spontaneous and inducible $Villin^{Cre/CreERT}$ models and orthotopic transplantation of PDOs into the distal colon. Ribonucleoprotein-based CRISPR base and prime editing were used on *KRAS/PIK3CA*-wild-type PDOs to generate isogenic lines carrying $PIK3CA^{E545K}$ alone or with $KRAS^{G12V}$. Parental and engineered PDOs were treated with low-dose PI3K pathway agents (alpelisib, zovegalisib, tersolisib, MS-21, a PI3Kα:RAS breaker) alone or with daraxonrasib.

Results: TCGA and NYP pan-cancer analyses revealed *KRAS/PIK3CA* co-mutation specifically in CRC. Our CRC PDO biobank includes 90 sequenced samples, of which 38.9% are *KRAS*-mutant and 15.6% are *PIK3CA*-mutant. Among *PIK3CA*-mutant tumors, 85.7% harbor MAPK pathway alterations, including *KRAS* mutations in 75%. In inducible $Villin^{CreERT/+}$ models, wild-type controls and $Kras^{G12D/+}$ mice did not develop tumors, *PIK3CA*-mutant mice developed colonic tumors, and dual-mutant mice showed increased colonic tumor propensity. Interestingly, in the spontaneous $Villin^{Cre/+}$ model, dual-mutant mice died prematurely, with mean survival of 3.2 weeks in $R26^{Pik3ca/+};Kras^{G12D/+}$ mice and 2.5 weeks in $R26^{Pik3ca/Pik3ca};Kras^{G12D/+}$ mice. Base and prime edited PDOs showed genotype-dependent growth, with $PIK3CA^{E545K/E545K};KRAS^{G12V/+}$ clones growing faster than wild-type or *PIK3CA*-only clones and increased primary tumor incidence two weeks after orthotopic injection into immunocompromised mice. Low-dose monotherapies were largely ineffective in *KRAS/PIK3CA*-mutant PDOs, whereas daraxonrasib combined with PI3K pathway inhibition suppressed growth across all co-mutant PDO lines. Organoids from dual-mutant mouse colonic tumors confirmed these findings, with dual therapies significantly more effective than their respective monotherapies, except for zovegalisib-based combinations.

Conclusions: *KRAS* and *PIK3CA* co-mutations are enriched in CRC and cooperate to enhance tumorigenic and invasive phenotypes. Integrated clinical, base/prime-edited organoid, and mouse models support dual RAS and PI3K pathway inhibition as a rational targeted combination strategy to overcome the limited efficacy of targeting either pathway alone in CRC.

Conflict of interest: Other Substantive Relationships: Jian Jin is an inventor on a patent issued to the Icahn School of Medicine at Mount Sinai covering AKT degraders, including MS-21.

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144 - PB-144 **Poster**

Atebimetinib, a deep cyclic inhibitor of MEK, combined with chemotherapy: preclinical rationale for treatment of anaplastic thyroid cancer (ATC)

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Background: Anaplastic Thyroid Cancer (ATC) is among the most lethal solid cancers, with a median overall survival of 3-7 months and few options after relapse on targeted agents. MAPK pathway activation is a hallmark of ATC, driven by BRAF and RAS mutations in many patients. Unlike earlier chronic MEK inhibitors, which cause dose-limiting toxicities and resistance, atebimetinib is an oral once-daily drug achieving deep cyclic inhibition (DCI) of MAPK signaling in tumors. This pulsatile inhibition is designed to deprive tumors of sustained oncogenic signaling while sparing normal cells via near-zero daily trough levels. In combination with chemotherapy, atebimetinib showed encouraging survival in first-line pancreatic cancer (Phase 2, ASCO 2026) and is now in Phase 3 trial (NCT07562152, MAPKeeper 301).

Standard-of-care chemotherapy, including pemetrexed, carboplatin, and paclitaxel, remains primary treatment option in ATC. Emerging evidence suggests these cytotoxic regimens can induce adaptive MAPK reactivation, potentially limiting response durability and providing rationale for combination with pulsatile MEK inhibition. We used translational strategies to identify MAPK pathway addiction in ATC cell lines and explored sensitivity to atebimetinib alone and combined with these chemotherapy regimens.

Material and Methods: Tumor models were selected for patient alignment using databases such as AACR GENIE and tested in humanized 3D tumor growth assays (3D-TGA). Pharmacogenomic data were integrated to generate a model predictive of atebimetinib response and identify biomarker-enriched subpopulations. MAPK reactivation by chemotherapy was assessed via pERK quantification in selected models. Atebimetinib was then evaluated in combination with pemetrexed, carboplatin, and paclitaxel, individually and in doublet, across multiple ATC lines.

Results: Atebimetinib showed activity across 8 patient-aligned ATC models spanning diverse MAPK-driven genomic contexts, including BRAF V600E, NRAS Q61R, and KRAS G12R. Chemotherapy agents induced measurable MAPK reactivation, establishing a mechanistic basis for combination. In 3D-TGA, combining atebimetinib with these agents demonstrated synergistic/additive responses across multiple models versus either agent alone.

Conclusions: Using an integrated platform of patient-aligned 3D tumor models and genomic profiling, we observed atebimetinib's potential activity across diverse ATC genomic backgrounds, suggesting that chemotherapy-induced MAPK activation provides a rational basis for combining pemetrexed, carboplatin, and/or paclitaxel with atebimetinib. In vivo validation in BRAF V600E-mutant ATC xenograft models (8505C, 8305C) is planned to further investigate clinical translation. These data support possible clinical evaluation of atebimetinib combinations in ATC patients relapsing on BRAF + MEK inhibitor therapy.

Conflict of interest: Ownership: Shareholders of Immuneering Corporation

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145 - PB-145 **Poster**

Transcriptomic profiling defines responders to brain-penetrant SHP2 inhibition in glioblastoma

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Background: Glioblastoma (GBM) is a highly heterogeneous disease, and predictive biomarkers for targeted therapies remain largely unavailable. We investigated whether transcriptomic profiling of patient-derived glioblastoma stem cells (GSCs) could identify molecular determinants of response to our proprietary brain-penetrant SHP2 inhibitor I-1000233.

Materials and Methods: Drug sensitivity was evaluated in molecularly characterized, patient-derived GSC models. Bulk RNA sequencing was conducted on both sensitive and resistant models under basal conditions and at multiple time points following I-1000233 treatment. Downstream analyses included differential gene expression profiling (DEG), pathway enrichment, protein network modeling, and the projection of transcriptional signatures onto the Cancer Genome Atlas (TCGA) GBM cohort.

Result: Comparison of DEG profiles revealed a significant transcriptional convergence between drug sensitivity and GSC lineage. Specifically, 2,192 out of 3,166 genes (69.2%) identified when comparing poor-responder versus hyper-responder GSCs overlapped with those associated with the Mesenchymal versus Proneural subtypes. The baseline transcriptional state, rather than treatment-induced changes, was the major determinant of the response to SHP2 inhibition. Treatment effectively inhibited the MAPK pathway across all models, regardless of sensitivity. However, response profiles diverged: hyper-responders progressively lost programs related to the extracellular matrix, cellular structure, and microenvironment interactions, whereas poor-responders activated compensatory metabolic pathways, including ribosomal biosynthesis, nutrient transport, energy metabolism, and mTORC1 regulation. Finally, projection of the responder signature onto the TCGA GBM cohort identified a molecularly defined subgroup enriched in Proneural and Classical tumors, representing approximately 38% of patients.

Conclusions: These findings identify intrinsic transcriptional programs associated with response to SHP2 inhibition and define a candidate responder population for brain-penetrant SHP2-targeted therapy. This study supports a biomarker-driven strategy for the clinical development of SHP2 inhibitors in glioblastoma.

No conflict of interest

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146 - PB-146 **Poster**

METTL3 inhibition by STC-15 depletes cancer stem-like cells, drives adipocytic differentiation, and regresses dedifferentiated liposarcoma in vivo

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Background: Sarcomas arise from transformed mesenchymal stem/progenitor cells. Dedifferentiated liposarcoma (DDLPS) and leiomyosarcoma (LMS) retain a stem-like, dedifferentiated state that maintains tumor growth and confers therapeutic resistance. The N6-methyladenosine (m6A) mRNA methyltransferase METTL3 sustains stemness and restrains differentiation in acute myeloid leukaemia (AML). STC-15, an oral small-molecule METTL3 inhibitor, has achieved partial responses and durable benefit in sarcoma patients in a recently completed phase 1 study (ASCO 2026 Abstract #546786). We tested the hypothesis that, like in AML, METTL3 inhibition ablates stem-like populations through differentiation, impedes cell cycle progression, induces DNA damage and apoptosis, with the prevailing mechanism differing by sarcoma subtype (stemness in DDLPS, DNA damage in LMS).

Material and methods: STC-15 was profiled across several DDLPS, LMS and reference cell lines using viability (CTG), cellular m6A (MSD), caspase-3/7 (apoptosis), clonogenic/spheroid (stemness), and differentiation (CD133/ALDH, Bodipy) assays. In vivo efficacy, pharmacokinetics and tumour m6A target engagement was assessed in the SW872 DDLPS xenograft (female BALB/c nude, n = 12/group, oral STC-15) treated with a twice-daily (BID) dosing regimen. Transcriptome-wide m6A and expression in treated tumours were mapped to define operative stem cell and differentiation programmes; an assessment of patient-derived models of DDLPS are in progress.

Results: STC-15 inhibited cellular m6A (24.3 nM IC50 in SW872) and reduced viability across sarcoma lines; cellular viability (CTG) underestimated activity relative to phenotypic readouts, consistent with a differentiation/apoptosis mechanism that matures beyond 72 h. In SW872, efficacy was achieved by continuous dosing at 100 mg/kg BID and regressed tumours (TGI 101%; 9/12 responders, 7 mPR and 2 mCR) accompanied by a ~87% reduction of tumour m6A mRNA. All doses were well tolerated with no net body-weight loss.

Table. Efficacy in the SW872 CDX model of DDPLS

Arm (dose, schedule)	Tumour m6A (% vehicle)	TGI (%)	Best response (n/12)
Vehicle	100	0	mPD 12/12
STC-15 60 mg/kg BID	20	73	mPD 12/12
STC-15 100 mg/kg BID	13	101	7 mPR, 2 mCR (9/12)

Tumour m6A nadir (% of vehicle) and Day-18 tumour growth inhibition (TGI). SW872 DDLPS xenograft; source IVP-2026-01. Best response mRECIST – (mPR -30 to -80%, mCR < = -80%, mPD > + 20%) adapted from DOI: 10.1158/2159-8290.CD-24-0027.

Conclusions: METTL3 inhibition by STC-15 significantly reduces tumour m6A mRNA levels, depletes stem-like cancer cells, drives adipocytic differentiation and achieves dose-dependent regressions in an in vivo model of DDLPS. These data support multiple anti-tumor mechanisms of action including the induction of differentiation of mesenchymal-derived cancer stem cells.

Conflict of interest: Other Substantive Relationships: E. Martin, S. Uryu, M. Hutchinson, B. Thomas, K. McCaleb, J. McMahon are employed by Storm Therapeutics

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147 - PB-147 **Poster**

A comparative translational framework identifies conserved biomarkers and molecular pathways in metastatic osteosarcoma

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Background: Osteosarcoma (OSA) is an aggressive pediatric bone cancer with poor long-term survival, due to early lung metastasis and heterogeneity. Outcomes have not improved in over 40 years because the disease is rare, limiting available samples. Spontaneous canine OSA mimics human OSA, clinically, and by exhibiting conserved cellular subpopulations and gene expression patterns. Therefore, cross-species validation of gene transcription at the level of single nuclei will create a robust translational platform to study tumor progression and therapeutic resistance.

Materials and Methods: Publicly available single cell or nuclei (scRNA/snRNA) sequencing datasets of primary and metastatic lesions of humans and dogs were used. Datasets were integrated using Seurat v5 and cell populations were categorized using published annotations. Differential expression analysis comparing metastatic and primary tumor data was performed independently for both species using the Wilcoxon rank-sum test ($P_{adj} < 0.05$ and $|\log_2 \text{fold change}| > 1$ as threshold). Conserved differentially expressed genes (DEGs) between the species were identified in Seurat by intersecting orthologous gene sets. Functional enrichment analyses were performed using g:Profiler to identify significantly enriched Gene Ontology (GO), KEGG, Reactome and WikiPathways (g:SCS - $P_{adj} < 0.05$).

Results: Comparative analysis identified 46 conserved upregulated and 48 conserved downregulated DEGs in metastatic OSA across species. They included genes involved in extracellular matrix remodeling (*TGM2, COL6A3, COL11A1*), developmental plasticity (*SOX5, ZBTB16, AFF3*), and cell signaling (*PRKG1, CAV2, CALCRL*). Conversely, genes associated with osteogenic differentiation and immune regulation (*ACP5, FCER1G, C1QA, S100A9, IBSP*) were consistently reduced in metastatic tumors. Pathway enrichment demonstrated significant conservation of biological processes related to extracellular matrix organization, cell-cell adhesion and integrin-mediated signaling. There were shared similarities between the species involving genes that function in immune response regulation and vascular development which suggest a well-coordinated remodeling of the metastatic microenvironment. Additional enrichment analysis further highlighted conserved signaling networks associated with metastatic progression.

Conclusions: Multispecies comparative transcriptomic analysis of scRNA/snRNA data revealed shared molecular networks underlying osteosarcoma metastasis and demonstrated transcriptional concordance between spontaneous canine and human disease. These findings identify evolutionally conserved pathways involved in extracellular matrix remodeling, tumor plasticity and tumor microenvironmental adaptation. This also reinforces the value of comparative oncology for biomarker discovery and prioritization of future therapeutic strategies for metastatic OSA.

No conflict of interest

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148 - PB-148 **Poster**

Association of ctDNA Dynamics and Tumor Mutational Profiles With Clinical Outcomes in Recurrent Metastatic Epithelial Ovarian Cancer Patients Treated With CDK2 inhibitor in INCB123667-101

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Background: Inhibition of cyclin-dependent kinase 2 (CDK2) is a potential therapeutic approach for cancers with high Cyclin E1 levels. INCB123667, a potent and selective CDK2 inhibitor, was evaluated in the ongoing INCB123667-101 phase 1 study (NCT05238922) in patients with recurrent metastatic epithelial ovarian cancer (rmEOC). We report preliminary circulating tumor DNA (ctDNA) biomarker assessment of pharmacodynamic changes and baseline mutational profile to investigate associations with clinical outcomes in the monotherapy expansion cohort of INCB123667-101.

Materials and Methods: To be eligible for dose expansion, patients with rmEOC must have had *CCNE1* amplification based on local testing or centrally confirmed Cyclin E1 overexpression. Overall, 45 patients were enrolled in the dose-expansion part of the study and received INCB123667 (50 mg twice daily, 100 mg once daily, or 125 mg once daily). Plasma samples were collected for ctDNA analyses at predefined time points (cycle 1 day 1 [C1D1], C2D1, C4D1). ctDNA levels were assessed using next-generation sequencing (NGS) by PredicineCARE and low-pass whole genome sequencing

(LP-WGS) by Predicine Score assays. ctDNA levels were quantified as relative tumor fraction and copy number burden score.

Results: A consistent reduction in ctDNA levels was observed at C2D1 compared with baseline across patients. Durable ctDNA suppression, defined by maintenance of reduced ctDNA levels from C2D1 to C4D1, was associated with improved progression-free survival (PFS). Common alterations in baseline ctDNA by LP-WGS and NGS included *TP53* (80%), *CCNE1* (38%), *KRAS* (29%), *NF1* (27%), *P1K3CA* (27%), and *RB1* (16%). No significant difference in response rate or PFS was observed between patients with Cyclin E1 overexpression with or without *CCNE1* amplification. Responses were also seen regardless of tumor mutations in *BRCA*, *KRAS*, *RB1*, or *TP53*.

Conclusions: In this phase 1 study of rmEOC, ctDNA dynamics was a relevant pharmacodynamic marker of CDK2 inhibition. Responses were similar among patients with Cyclin E1 overexpression with or without *CCNE1* amplification. These findings further support the continued clinical development of INCB123667 in patients with advanced EOC.

Conflict of interest: Advisory Board: Domenica Lorusso: Served as advisory board member and invited speaker for AstraZeneca, Clovis Oncology, Corcept, Genmab, GSK, Immunogen, MSD, Seagen, Sutro.

Vanda Salutari: Advisory Board – AbbVie, AstraZeneca, EISAI, Menarini-Stemline, MSD.

Board of Directors: Silvia Damian: Leadership (Immediate Family Member) – Biofarma Group.

Corporate-sponsored Research: Domenica Lorusso: Received a grant for a founding academic trial for Clovis Oncology, GSK, MSD.

Silvia Damian: Reseach Funding – Amgen, Eli Lilly, Incyte Corporation, MSD Oncology, Nerviano Medical Sciences, Novartis, Pfizer, Phost'In Therapeutics, Revolution Medicines, Roche/Genentech, Servier.

Other Substantive Relationships: Ajay Obla, Hui Wang, Maikel van der Velden, Jason Howe, Louis Viviers, Michelle Kinder: Employment and stock options – Incyte Corporation, Domenica Lorusso: Served as consultant for Novartis, PharmaMar, and served as coordinator for ENGOT trial with institutional support for Clovis Oncology, Corcept, Genmab, MSD, Immunogen.

Vanda Salutari: Invited Speaker – AbbVie, AstraZeneca, EISAI, GSK, MSD, Pharma

Local PI – AbbVie, AstraZeneca, EISAI, GSK, Incyte Corporation, MSD

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149 - PB-149 **Poster**

A HIF-2α activity signature highlights the therapeutic potential of casdatifan as an HCC treatment

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Background: Clinical approval and ongoing investigation of HIF-2α inhibitors, both as monotherapy and in combination with other drugs, is changing the treatment paradigm for ccRCC. Despite a primary focus on ccRCC, similar biology has been highlighted across a variety of other cancer types. Notably, HCC has surfaced as a candidate for HIF-2α inhibitor therapy due to substantial overlap with treatments approved for ccRCC, including the combination of anti-angiogenic and IO based therapies. Benefit from HIF-2α inhibition has also been previously demonstrated in multiple mouse HCC models. The purpose of this study is to expand this assessment using both *in vivo* and *in vitro* data to better understand commonalities in HIF-2α driven biology between ccRCC and HCC, which may pave the way for future investigations of HIF-2α inhibitor therapy in HCC.

Material and methods: RNA-seq analysis was performed on *in vitro* data from ccRCC and HCC cell lines treated with HIF-2α inhibitors, and using tumor biopsies from the ARC-20 clinical trial assessing casdatifan (cas), a potent and selective HIF-2α inhibitor, in late stage ccRCC (NCT05536141). Gene sets associated with HIF-2α biology and those that changed in response to HIF-2α inhibition were further assessed in multiple publicly available datasets, including data from the Phase-3 trials IMmotion151(ccRCC) and IMbrave150 (HCC).

Results: We demonstrated elevated baseline expression of a literature-derived HIF-2α gene activity signature in both ccRCC and HCC. Additionally, gene signature expression was elevated with disease progression and HCC microvascular invasion. Furthermore, signature expression was directly downregulated in both ccRCC and HCC cell lines treated with HIF-2α inhibitors. Higher-than-median baseline expression of the signature is associated with longer PFS in ARC-20 ccRCC patients receiving cas monotherapy. Conversely, higher baseline expression was associated with shorter PFS for ccRCC patients treated with atezolizumab + bevacizumab (aPD-L1 + aVEGF-A), which was recapitulated by a trend towards shorter PFS in higher baseline HCC patients on the same regimen. Similar PFS trends were also noted in patients receiving anti-angiogenic TKI regimens (sunitinib or sorafenib) in both disease settings.

Conclusions: HIF-2α biology may play a distinct role in cancers beyond ccRCC. High expression of HIF-2α activity gene signature, which was previously associated with improved clinical responses to cas monotherapy in ccRCC, was conversely associated with worse clinical outcomes following therapies that represented standard of care in ccRCC and HCC. This highlights the potential utility of HIF-2α inhibition in improving outcomes in cancers with overlapping biological characteristics, such as in the case of HCC.

Conflict of interest: Ownership: All authors own stock or options in Arcus Biosciences

Other Substantive Relationships:

All authors are employees of Arcus Biosciences

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150 - PB-150 **Poster**

Single-nucleus Transcriptomics Reveals Prognostic Multicellular Programs in Colorectal Cancer Liver Metastasis

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Background: Progression of colorectal cancer (CRC) is shaped by interactions between tumor, immune, and stromal cells, particularly within the liver metastases (LM) microenvironment. Single-nucleus RNA sequencing (snRNA-seq) enables dissection of these interactions at cellular resolution.

Methods: Patients (pts) undergoing resection of matched primary CRC and LM were retrospectively selected and profiled with the spatial transcriptomic (ST) platform CosMx Spatial Molecular Imager with a 1k plex panel (Bruker Spatial) and snRNA-seq with the Flex kit (10x Genomics) within a partner-of-choice framework. Tissue sections were histopathologically annotated to define reference mucosa, premalignant lesions, and tumor regions. Rigorous QC removed low-quality cells, segmentation artifacts, and border effects, retaining high-confidence spatially resolved cells. Spatial domains and neighbourhood interactions were defined using graph-based approaches and analyzed by cell-type enrichment, molecular status, and clinical prognosis (px) (classified as good or bad based on OS (>or<3 years), and PFS from primary or LM surgery to progression (>6 months).

Results: Eighteen pts were included; 14 pts had stage IV disease (77.8%); 11 pts (61.1%) were classified as good px (Table). Cohort-level snRNA-seq analysis identified site-specific transcriptional programs, with LM enriched for IFN-low states and EMT, squamous, and fetal progenitor programs. Bad px pts clustered exclusively within IFN-low groups, whereas IFN-high profiles were restricted to good px pts. Multicellular factor analysis (MOFA) revealed a tumour-intrinsic proliferative program at the primary site (Factor 6) linked to favourable prognosis, with active proliferation pathways but suppressed EMT and invasion. Conversely, a healthy-hepatocyte program at the metastatic site (Factor 9), reflecting preserved liver detoxification and stress-response functions, scored higher in poor-prognosis patients.

Conclusions: Integrated snRNA-seq analyses show that primary and CRC LM are characterized by site-specific, prognosis-linked multicellular programs — an IFN-low metastatic microenvironment, a favourable tumour-intrinsic proliferative program at the primary site (Factor 6), and an adverse host-hepatocyte response at the metastatic site (Factor 9) — providing biological insight into the microenvironmental determinants of outcome and immune evasion in CRC pts.

	Good Prognostic 11 (61)	Bad Prognostic 7 (39)
Sex		
Fem	4(36)	4(57)
Male	7(64)	3(43)
Stage		
I	1(9)	0
II	1 (9)	1 (14)
III	1 (9)	0
IV	8 (73)	6(86)
Age		
Median (range)	61(30-74)	60(52-75)
Molecular Status		
***RAS*mut**	2(18)	3 (43)
***BRAF*mut**	1(9)	1 (14)
wt	8(73)	3 (43)
MMR		
MSS	11	6(86)
MSI	0	1(14)
Site		
Right	2(18)	4(57)
Left	9(82)	3(43)
Treatment before surgery LM		
CT	2(18)	1(14)
CT + EGFRi	7(64)	0
CT+ Bevacizumab	2(18)	5(72)
No treatment	0	1(14)

CT chemotherapy

Conflict of interest: Ownership: Arthur Lambert, Manisha Rao, Liat Amir-Zilberstein Nadia Martinez-Martin Asaf Rotem are employed by AstraZeneca and own AstraZeneca stock and/or options.

Jorge Zeron-Medina is employed by Daiichi Sankyo and own Daiichi Sankyo stock and/or options.

Other Substantive Relationships: Nadia Saoudi: Travel and Accommodation Expenses From Merck and Amgen. Speakers' Bureau: From AMGEN and Medistream OncoBites

Dr Elez reports the following personal financial interests: Honoraria, Consulting or Advisory Role, and Speakers's Bureau: Agenus, Amgen, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Cure Teq AG, GlaxoSmithKline, Hoffman-La Roche, Janssen, Johnson & Johnson, Lilly, Medscape, Merck Serono, MSD, Nordic Group BV, Novartis, Organon, Pfizer, Pierre Fabre, Repare Therapeutics Inc., RIN Institute Inc., Rottapharm Biotech, Sanofi, Seagen International GmbH, Servier, Takeda.

J.T. reports personal financial interest in the form of scientific consultancy roles for Accent Therapeutics,

Alentis Therapeutics, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Carina Biotech, Cartography Biosciences, Chugai, Daiichi Sankyo, F. Hoffmann-La Roche, Genentech, Johnson & Johnson/

Janssen, Kayak Therapeutics, Larkspur Biosciences, Lilly, Marengo Therapeutics, Menarini, Merus,

MSD, Novartis, One-carbon Therapeutics, Ono Pharma USA, Peptomyc, Pfizer, Pierre Fabre, Quantro

Therapeutics, Scandion Oncology, Scorpion Therapeutics, Servier, Sotio Biotech, Syntelios AG, Taiho,

Takeda Oncology, Theriva Biologics, and Tolremo Therapeutics. J.T. also reports stocks in Alentis Therapeutics, Oniria Therapeutics, 1TRIALSP, and Pangaea Oncology

Holger Heyn is co-founder and Chief Scientific Officer of Omniscope, scientific advisory board member of Nanostring, Bruker and MiRXES, consultant to Moderna and Singularity and received an honorarium from Genentech.

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151 - PB-151 **Poster**

Species prevalence in the human population predicts engraftment of live bacterial cell therapies

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Background: Bacterial cell therapies such as fecal microbiota transplant (FMT) have improved objective response rates (ORR) in six clinical studies of immune checkpoint inhibitor (ICI) combination therapy, including a randomized placebo-controlled study in which FMT nearly doubled the proportion of patients achieving progression-free survival at 12 months. As with other cell therapies, engraftment (whether the administered organisms establish in the patient) appears important for efficacy, but how to optimize it is unclear. Some providers use pre-treatment regimens involving invasive bowel preparation or medications such as antibiotics, which are discouraged in ICI patients. We built a multivariable model of

engraftment to determine how the composition and dose of bacterial therapy affect whether its species engraft.

Material and Methods: We analyzed 4,461 instances in which a bacterial species absent from a patient at baseline was administered by FMT and later detected using metagenomic sequencing. Model performance was measured with Leave-One-Patient-Out cross-validation (LOPO-CV, 35 folds), and each predictor's contribution was ranked using three importance metrics (Gini, permutation, and SHAP).

Results: Thirty-five melanoma patients receiving ICI plus FMT (median age 66, range 33-89;, 24 men, 11 women) had paired pre- and post-treatment stool samples sequenced. Candidate predictors included each species' administered dose and its prevalence in the healthy human gut, estimated using 428 reference samples across independent healthy cohorts (median reported age 60 years (IQR 48–66); 39% female). The model predicted engraftment with an AUC of 0.80. A species' prevalence in the healthy human gut was the dominant predictor, carrying roughly 3-fold the importance of administered dose (Gini importance = 0.37 vs 0.13). This ranking held across all three importance metrics.

Conclusions: How common a species is in the healthy human gut, rather than the dose given, is the strongest predictor of whether it will engraft. MBX-116, our investigational live bacterial therapy designed to improve ORR alongside ICI, was optimized around prevalent species. To our knowledge this association is novel and has been overlooked in prior modeling work. These results further support a rationale for prevalence-guided design of live bacterial therapies and a quantitative framework for optimizing engraftment across additional predictors and potentially without pre-treatment.

Conflict of interest: Ownership: Glen Weiss, Christopher Weidenmaier, Johannes Woehrstein

Corporate-sponsored Research: Glen Weiss, Sonia Timberlake, Kinga Zielinska, Christopher Weidenmaier, Johannes Woehrstein

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152 - PB-152 **Poster**

Patient-derived PDX and organoid models reveal distinct molecular mechanisms of acquired resistance to olaparib and enfortumab vedotin in genitourinary cancers

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Background: Acquired resistance limits the long-term efficacy of targeted therapies in genitourinary cancers, yet clinically relevant preclinical models remain scarce. We established patient-derived resistant models to define the molecular mechanisms driving resistance to the PARP inhibitor olaparib in prostate cancer and to the antibody-drug conjugate enfortumab vedotin (EV) in bladder cancer.

Materials and Methods: Therapy-resistant patient-derived models were generated by prolonged *in vivo* drug exposure from initially sensitive PDXs. Olaparib-resistant prostate cancer PDXs were established from PDXs harboring DNA damage repair alterations, including a neuroendocrine prostate cancer subtype. EV-resistant bladder cancer PDXs were generated from a PDX model expressing high levels of Nectin-4, followed by derivation of matched resistant organoids. Resistant models and their parental counterparts were characterized by histopathology, immunohistochemistry, flow cytometry, whole-exome sequencing, and RNA sequencing. Functional validation was performed using pharmacological inhibition assays.

Results: Despite both therapies targeting molecularly selected tumors, resistance evolved through fundamentally different biological processes depending on therapeutic modality. Olaparib-resistant prostate cancer PDXs exhibited transcriptional reprogramming of DNA damage response pathways, consistent with partial restoration of homologous recombination and activation of alternative DNA repair pathways. Conversely, EV-resistant bladder cancer PDXs and organoids exhibited reduced Nectin-4 expression associated with marked changes in drug efflux transporter ABCB1, FGFR3 and PPARg pathways. Notably, pharmacological inhibition of P-glycoprotein partially restored EV sensitivity, demonstrating a functional contribution of drug efflux to acquired resistance.

Conclusions: These clinically relevant resistant models provide a robust translational platform for investigating therapy-induced molecular adaptation in genitourinary cancers. Our findings reveal fundamentally distinct adaptive processes involving restoration of genome maintenance pathways following PARP inhibition and drug efflux reprogramming after ADC therapy. These models represent valuable preclinical resources for identifying predictive biomarkers and developing rational combination strategies to prevent or overcome therapeutic resistance.

No conflict of interest

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153 - PB-153 **Poster**

Lineage- and allele-specific coupling of KRAS alterations with NF-kB inflammatory pathway activity in solid tumours

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Background: KRAS-altered solid tumours are commonly approached as an actionable molecular subgroup, but KRAS biology is highly lineage- and allele-dependent. Nuclear factor kappa B (NF-kB) activation may represent a functional inflammatory state linked to survival signalling, immune remodelling and adaptive resistance. We evaluated whether KRAS alterations are associated with NF-kB pathway activity across selected solid tumours.

Material and methods: We integrated TCGA/cBioPortal KRAS mutation data with UCSC Xena/Toil RNA-seq expression. A sample-level NF-kB pathway score was computed across 9,186 TCGA primary tumours using a curated 33-gene NF-kB/TNF-inflammatory panel. KRAS mutation status and allele annotations were extracted for pancreatic adenocarcinoma (PAAD), colorectal adenocarcinoma (COADREAD) and lung adenocarcinoma (LUAD). NF-kB scores were compared between KRAS-mutant and KRAS-wildtype tumours and by KRAS allele using Welch testing with false discovery rate (FDR) correction. ClinicalTrials.gov was queried to contextualise KRAS-directed and NF-kB-adjacent therapeutic strategies.

Results: KRAS sample-level annotation was available for 1,051 tumours: PAAD (n = 177), COADREAD (n = 366) and LUAD (n = 508). KRAS-mutant PAAD showed higher NF-kB scores than KRAS-wildtype tumours (mean 0.415 vs 0.222; delta = +0.193; FDR = 0.032). This signal was allele-dependent, with enrichment in G12R (delta vs WT = +0.304; FDR = 0.014) and G12V (delta = +0.267; FDR = 0.038), whereas G12D showed a weaker association. In COADREAD, KRAS-mutant tumours had lower NF-kB scores than KRAS-wildtype tumours (mean 0.105 vs 0.251; delta = -0.145; FDR = 0.003), including an inverse signal in G12V (delta = -0.205;

FDR = 0.038). In LUAD, KRAS mutation status was not associated with NF-kB score (mean 0.405 vs 0.412; FDR = 0.837), including KRAS G12C. The therapeutic landscape included 242 trial records and 234 unique NCT identifiers, dominated by KRAS-direct and KRAS-immunotherapy strategies.

Conclusions: KRAS alterations do not define a uniform NF-kB-high state across solid tumours. KRAS/NF-kB coupling appears lineage- and allele-specific, with a positive signal in PAAD, particularly G12R/G12V, no evident association in LUAD and an inverse pattern in COADREAD. These findings support tumour-specific interpretation of KRAS-directed therapeutic development and nominate KRAS/NF-kB-high pancreatic cancer subsets for further validation using immune deconvolution, tumour purity adjustment and functional dependency datasets.

No conflict of interest

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Poster Session: Vaccines

154 - PB-154 **Poster**

Manganese metal-organic framework-coated whole-tumor-cell vaccine for cancer immunotherapy

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The continued development and improvement of cancer vaccines to retain the tumor antigens is an essential building block of tumor microenvironment-associated cancer vaccine therapies. Current tumor-vaccine preparation may lead to potential loss of tumor antigens and insufficient antitumor immune responses. We developed a manganese-based metal-organic framework (Mn-MOF)-coated whole-tumor-cell (WTC) vaccine combined with ultrasound (US) to preserve the cellular antigens and induce sonodynamic immunogenic cell death (ICD). Living WTC were coated with Mn-MOF, followed by US treatment and freezing before treatment. Material properties, coating stability, reactive oxygen species (ROS) generation, glutathione (GSH) depletion, calreticulin (CRT) exposure, high-mobility group box 1 (HMGB1) release, dendritic-cell (DC) uptake and maturation, biosafety, and antitumor efficacy were evaluated in vitro and in therapeutic and prophylactic tumor mouse models. Scanning electron microscopy-energy-dispersive X-ray spectroscopy (SEM-EDX) confirmed successful Mn-MOF coating of WTC, and the coating preserved cellular integrity under hypotonic conditions. Mn-MOF@WTC combined with US caused marked GSH depletion and increased ROS production. Mn-MOF@WTC also enhanced CRT expression and HMGB1 release, indicating the induction of ICD. The proportion of CD80/CD86-positive DC maturation also increased. In the therapeutic model, Mn-MOF@WTC combined with US produced the greatest tumor-growth suppression and increased mature splenic DCs and T-cell infiltration. Intratumoral CD4-positive and CD8-positive T-cell populations were significantly increased. Effector-memory T-cell populations were also increased. Major-organ H&E staining showed no evident treatment-related toxicity. Tumor H&E stain revealed reduced viable tumor cells, while caspase-3 indicated increased tumor-cell apoptosis. In the prophylactic model, vaccination before tumor challenge delayed subsequent tumor growth. Mn-MOF@WTC combined with US enhanced ROS production, ICD, DC maturation, and T-cell responses. The platform demonstrated therapeutic and prophylactic antitumor activity with favourable biosafety, supporting its potential as a WTC cancer vaccine.

No conflict of interest

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Poster Session: Angiogenesis and vascular disrupting agents

155 - PB-050 **Poster**

The effect of β-catenin on the selection of coactivators in HIF-α transcription

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Background: β-catenin is a membrane-associated protein that functions as a major oncogenic driver in colorectal cancer. β-catenin forms a complex with TCF/LEF transcription factors and enhances the transcription of target genes. The hypoxia-inducible factor HIF-α is a key transcription factor that supports cancer cell proliferation even under hypoxic and nutrient-deprived conditions. We previously demonstrated that β-catenin enhances HIF-α transcriptional activity in HepG2 cells but suppresses it in HeLa cells. This study aimed to elucidate how β-catenin regulates HIF signaling and to identify the mechanism underlying its cell type-specific effects.

Material and Methods: We focused on HIF-α isoforms and the transcriptional coactivators CBP and p300, which are shared by both HIF-α and β-catenin. Using HIF-α and CBP/p300-deficient cells, we evaluated the effect of β-catenin on HIF-α transcriptional activity using reporter gene assays and RT-qPCR. We also assessed the expression of HIF-α and CBP/p300 in HepG2 and HeLa cells using Western blotting. Furthermore, we evaluated the effect of β-catenin activation on the interactions between HIF-α and CBP/p300 using co-immunoprecipitation.

Results: Western blot analysis showed that HIF-1α expression did not differ significantly between HepG2 and HeLa cells, whereas HIF-2α was highly expressed in HeLa cells. While CBP was highly expressed in HeLa cells, no significant difference in p300 expression was observed between HepG2 and HeLa cells. Reporter gene assays showed that β-catenin suppressed HIF-α transcriptional activity in both the HeLa parental cells and p300-deficient cells. In contrast, in CBP-deficient cells, β-catenin enhanced HIF-α transcriptional activity. Furthermore, β-catenin suppressed HIF-α transcriptional activity in both HIF-1α- and HIF-2α-deficient cells, as observed in the HeLa parental cells, suggesting that differences in HIF isoforms are not the primary determinant of cell type-specific transcriptional regulation. RT-qPCR showed that in the HeLa parental cells and p300-deficient cells, mRNA expression of VEGF, a HIF-α target gene, was suppressed by β-catenin activation. In contrast, in CBP-deficient cells, β-catenin activation had no effect on VEGF mRNA expression. Co-immunoprecipitation analysis revealed that, in HeLa cells, β-catenin activation did not affect the binding of HIF-1α to CBP but inhibited the binding of HIF-1α to p300.

Conclusion: These results suggest that the transcription coactivators CBP and p300 contribute to the cell type-specific regulation of HIF-α transcriptional activity by β-catenin. Furthermore, CBP may

suppress HIF-α transcriptional activity, whereas p300 may enhance it. β-catenin may enhance or suppress HIF-α transcriptional activity by modulating the balance between the HIF-α-CBP complex and the HIF-α-p300 complex.

No conflict of interest

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Poster Session: Apoptosis inducers

156 - PB-051 **Poster**

Real-time imaging reveals radiation-induced intratumoral apoptosis mediated by vascular damage and microenvironmental alterations

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Background: Radiotherapy induces tumor cell death through both direct cytotoxic effects and indirect mechanisms involving the tumor microenvironment. However, the in vivo dynamics and mechanisms of radiation-induced apoptosis remain incompletely understood. This study aimed to visualize and elucidate radiation-induced tumor apoptosis in vivo using real-time bioluminescence imaging.

Methods: Tumor cell lines expressing a caspase-3-activated apoptosis reporter based on cyclic luciferase reconstitution were established. Both constitutive (CMV) and hypoxia-responsive (HRE) reporter systems were used. Bioluminescence imaging was performed in vitro and in vivo after X-ray irradiation. Tumor-bearing mice were used to monitor the temporal dynamics of apoptosis. Tumor vascular morphology, blood flow, and the effects of nutrient deprivation and hypoxia were also evaluated.

Results: Radiation-induced apoptosis was limited in several tumor cell lines in vitro. In contrast, in vivo bioluminescence imaging demonstrated a marked increase in apoptotic signals, peaking approximately 9 hours after irradiation. Irradiation caused tumor vascular damage, including vessel fragmentation and reduced blood flow, leading to nutrient and oxygen deprivation within the tumor microenvironment. Additional experiments demonstrated that both nutrient deprivation and hypoxia induced apoptosis. Similar results were observed in immunodeficient mice, suggesting that early immune responses contribute minimally to this process.

Conclusions: Radiation-induced tumor apoptosis in vivo is mediated predominantly by indirect mechanisms involving vascular damage and subsequent microenvironmental changes rather than direct cytotoxic effects alone. This real-time imaging approach provides a valuable platform for evaluating tumor responses and may improve our understanding of the in vivo mechanisms underlying radiotherapy.

No conflict of interest

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157 - PB-052 **Poster**

PTEN Functional Suppression via Anti miR Strategy Reduces Proliferation and Triggers Apoptosis in Ovarian Cancer Cells

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Background: PTEN is a well-established tumor suppressor involved in regulation of cell growth and survival. Targeted modulation of PTEN signaling may produce unexpected context-dependent effects in cancer cells.

To evaluate whether transient functional suppression of PTEN using a synthetic anti-miR mimic (anti-PTEN) affects proliferation and apoptosis in ovarian cancer cell lines.

Material and methods: Caov-3 and OVCAR-3 cells were treated with anti-PTEN mimic or a non-targeting control. Cell viability was measured by CCK-8 absorbance at 450 nm. Apoptosis was quantified by Annexin V/PI staining followed by flow cytometry. Time course and dose-response experiments were performed to confirm reproducibility.

Results: Anti-PTEN treatment produced a significant decrease in CCK-8 absorbance at 450 nm compared with control, indicating reduced cell proliferation. Apoptotic fraction measured by Annexin V/PI was significantly higher in anti-PTEN treated Caov-3 and OVCAR-3 cells than in controls. These effects were consistent across varied treatment durations and assay conditions.

Conclusions: Transient functional suppression of PTEN with an anti-miR approach inhibited proliferation and induced apoptosis in two ovarian cancer cell lines. Further mechanistic studies and in vivo validation are warranted to assess therapeutic potential.

No conflict of interest

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Poster Session: Chemoprevention

158 - PB-053 **Poster**

Phase II Clinical Chemoprevention Trial of Green Tea Catechins in Men on Active Surveillance for Prostate Cancer (NIH-NCI 1 R01 CA235032-01A1)

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Background: The purpose of this randomized double-blinded clinical trial is to evaluate the bioavailability, safety, effectiveness and validate the mechanism utilizing a standardized formulation of whole Green Tea Catechin (Sunphenon® 90D (Taiyo International, Inc., Minneapolis, MN, USA, IND:143615), containing 405 mg EGCG (BID) vs. Placebo, administered for 24 months in a cohort of men on active surveillance for low grade PCa.

Material and methods: We will assess the rate of treatment-related clinical progression from baseline to end of study in men on active surveillance, with rate of clinical progression defined as a composite outcome on repeat prostate biopsy >33% of biopsy cores

positive for cancer or >50% of any biopsy tissue core positive for cancer or adverse reclassification of Gleason score >6 (3+3) or > 7 (3+4) respectively, or prostatectomy at end of study (EOI) biopsy; evaluate treatment-related modulation of biomarkers and validate the potential molecular mechanism of GTC, we will measure changes in: (i) Ki-67; (ii) apoptosis by Caspase 3; (iii) Ki-67: apoptosis index; and (iv) NF-kB signaling, from baseline to EOI biopsy; evaluate change in: (a) PSA and PSA kinetics (PSA doubling time,); (b) serum for proteomics from baseline to EOI; evaluate (i) bioavailability and bio-distribution as indicated by change in EGCG in plasma; (ii) safety, as indicated by incidence of adverse events and toxicities (Toxicity, CBC, CMP, LFTs);(iii) number of high grade PCa in the post-intervention biopsy; (iv) adherence and acceptability (diet logs and pill counts); and (e) changes in lower urinary tract symptoms (LUTS) and quality of life (SF36), from baseline to EOI.

Results: We have completed recruitment of subjects in this trial and have randomized a total of 118 subjects in the trial. We currently have 13 in follow up at Moffitt; 7 at George Washington Cancer Center and 7 at U of Kansas Cancer Center. The minimum number of subjects needed for a one-sided log rank test with α = 0.10 and 90% power was 107 and a maximum of 135.

Conclusions: Initial observations of this clinical trial will be presented at this meeting.

No conflict of interest

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Poster Session: DNA Repair Modulation (e.g. PARP, CHK, ATR, ATM)

159 - PB-054 **Poster**

An integrated approach to the discovery of drivers and biomarkers of the response of ovarian cancer to PARP inhibition

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Background: High-grade serous ovarian cancer (HGSOC) remains a difficult-to-treat and lethal disease, mainly due to the lack of strategies for early detection and for preventing tumor relapse. PARP inhibitors (PARPi) substantially improved the prognosis of HGSOC patients with mutations in BRCA1/2 or in other homologous DNA recombination-related genes. However, not all homologous recombination deficient (HRD) patients benefit from PARPi, and resistance often occurs during treatment. Thus, a thorough investigation of the molecular mechanisms accounting for response or resistance to PARPi in clinically relevant systems is urgently needed.

Materials and Methods: We built a platform of *in vitro* patient-derived organotypic models, which reproduces the architecture of human omentum through 3D co-cultures of primary human omental fibroblasts and mesothelial cells. HGSOC cell lines were then integrated in these co-cultures, thus recapitulating the microenvironment of HGSOC peritoneal lesions. These organotypic models were treated with the PARPi Olaparib, and the response of tumor cells to the drug was analyzed both in terms of viability and at the transcriptomic and proteomic levels.

Results: This approach allowed us to identify genes, proteins or pathways that can discriminate between responders and nonresponders to the treatment. Olaparib treatment significantly regulated 393 genes (adjusted p-value < 0.05 and $|\log FC| > 0.3$) and 410 proteins adjusted p-value < 0.05 and $|\log FC| > 0.5$) in organotypic models. Preliminary results are providing novel insights on Olaparib-induced stress response in models sensitive to the drug and point to the maintenance of genome stability as a prominent factor in regulating sensitivity to PARPi. Selected candidates emerging from our molecular profiles are being tested as drivers/modulators of PARPi response, aimed at elucidating the underlying molecular mechanisms and designing strategies to enhance the efficacy of the treatment. In parallel with the functional validation of these targets, candidate biomarkers that could potentially predict patients' response to PARPi are also being validated in fully annotated retrospective cohorts of HGSOC patients.

Conclusion: By integrating clinically relevant experimental approaches and advanced multi-omic profiling, this study will advance personalization strategies for the use of PARPi in HGSOC, thus helping to prevent its recurrence.

No conflict of interest

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160 - PB-055 **Poster**

Targeting PARP Inhibitor Resistance in BRCA-Mutated Ovarian Cancer Using RNA-Based Therapeutics

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Objective: Investigation into the miRNAs downregulated in highly aggressive BRCA1-mutated high-grade serous ovarian cancer (HGSOC) patient data and to analyse their ability to restore olaparib sensitivity

Background: Poly (ADP-ribose) polymerase inhibitors (PARPi) have transformed the management of ovarian cancer both as maintenance therapy and targeted treatment for tumors with homologous recombination deficiency, particularly those harboring BRCA1/2 mutations. Their mechanism involves catalytic inhibition of PARP enzymes and the trapping of PARP–DNA complexes at sites of single-strand DNA damage, leading to the accumulation of lethal double stranded DNA lesions. However, treatment acquired PARP resistance remains a major obstacle. The dysregulation of regulatory microRNAs (miRNAs) is one of the consequences of drug resistant. Consequently, therapeutic restoration of tumor-suppressive miRNAs represents a promising strategy to overcome PARPi resistance HGSOC, with the potential to enhance treatment response and improve patient outcome.

Materials and Methods: We analyzed three Gene Expression Omnibus (GEO) datasets to identify miRNAs that are consistently downregulated in patients with HGSOC. The expression of miRNAs was subsequently validated by qPCR in BRCA1 deficient ovarian cancer cell lines exhibiting either sensitivity or acquired resistance to olaparib. Putative target genes and associated signaling pathways were identified using TargetScan and DIANA bioinformatics tools, while immunoblotting was performed to validate changes in the expression of key target proteins. The genetic alteration frequencies of the identified target genes were further investigated using The Cancer Genome Atlas (TCGA) dataset through cBioPortal. Finally,

BRCA1-deficient ovarian cancer cell lines were transfected with miRNA agomirs to restore the expression of the selected miRNAs.

Results: The four miRNAs: miR200a, 200c, 34a and 7, were consistently downregulated in both patient data as well as in the olaparib resistant ovarian cancer cells. Target prediction analysis identified genes including RAD51, BRCA1/2, PARP1, TP53BP1 (53BP1), EGFR, ABCC1, ZEB1/2, VEGFA, and CD44. Pathway enrichment analysis further demonstrated that these targets are enriched in signaling pathways associated with homologous recombination, DNA damage response, epithelial–mesenchymal transition, and drug resistance. Immunoblot validation confirmed the dysregulated expression of selected target proteins in olaparib-resistant cells. Importantly, restoration of the downregulated miRNAs through agomiR transfection significantly resensitized resistant cells to olaparib.

Conclusion: Our findings underscore the therapeutic potential of tumor-suppressive miRNA replacement to overcome PARP inhibitor resistance and improve clinical outcomes in patients with BRCA1-mutated ovarian cancer.

No conflict of interest

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161 - PB-056 **Poster**

AVA6207 is a novel pre|CISION® technology compound delivering complementary TOPO1i and ATRi payloads to the tumor microenvironment following FAP cleavage

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The proprietary pre|CISION® technology incorporates a dipeptide substrate (D-Ala-L-Pro) that is specifically cleaved by Fibroblast Activation Protein α (FAP). FAP is a post-proline protease that is overexpressed on the surface of cancer associated fibroblasts (CAFs) in many solid tumors, and facilitates delivery of pre|CISION® medicines specifically to the tumor microenvironment (TME). Two pre|CISION® medicines are currently in clinical development, including AVA6103, in which the Topoisomerase I (TOP1) inhibitor exatecan is covalently linked to the pre|CISION® peptide.

We have developed the pre|CISION® technology to deliver two complementary payloads from a single molecule. AVA6207 has been designed to have an optimal kinetic profile for sustained release of both a TOP1 inhibitor and an Ataxia telangiectasia and Rad3-related protein (ATR) inhibitor in a FAP-dependent manner. This dual payload approach provides complementary mechanisms of action and may enable synthetic lethality in tumors with defects in DNA damage repair. For example, ATM-deficiency (observed in subsets of numerous indications including gastric, colorectal, prostate, lung and pancreatic cancer) are more reliant on ATR-mediated DNA damage repair.

AVA6207 demonstrates FAP-selective payload release, potent cytotoxicity and bystander activity in multiple *in vitro* assays, including tumor cell-fibroblast 3D co-culture models. Synergistic activity of two potentiating payloads and downstream pharmacodynamic markers for each payload has been evaluated in cancer cell lines with specific gene expression profiles, providing translational evidence for potential biomarkers and clinical indications.

In vivo, released payloads demonstrate a high tumor selectivity index, concentrating in mouse tumors at >100-fold concentration compared to plasma. In the same tumors, AVA6207 administration also elicits the expected on-target changes and pharmacodynamic biomarker effects. AVA6207 shows significant tumor growth inhibition in mouse PDX and cell-line derived tumor models and has shown improved tumor growth inhibition compared with Enhertu in a HER2-expressing gastric PDX model.

Gene expression data indicate that AVA6207 induces a FAP-dependent transcriptional response in tumor cells that diverges from the response to TOP1 inhibition alone. These changes are consistent with an altered response to DNA damage and downstream cellular processes.

AVA6207 delivers a therapeutically relevant combination of payloads specifically to the TME to elicit on-target activity, offering complementary activities with potential to exhibit synthetic lethality in appropriate settings. This pre-clinical data package supports the rationale to progress AVA6207 towards clinical development and supports wider utility of the pre|CISION® platform to target warheads to the tumor, while reducing systemic dose-limiting toxicities.

No conflict of interest

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162 - PB-057 **Poster**

Acrivon Predictive Precision Proteomics (AP3)-phosphoproteomics uncovers differential mechanisms driving superior activity of ACR-2316, a novel, clinical-stage WEE1/PKMYT1 inhibitor over clinical-stage WRN helicase inhibitors

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Background: Mechanism-driven precision oncology requires characterization of functional proteome activity states that govern drug response. While nucleic acid sequencing-based approaches infer cellular state indirectly, phosphoproteomics enables direct characterization of signaling network activity and pathway engagement. We applied Acrivon Predictive Precision Proteomics (AP3) to characterize and differentiate intracellular responses induced by our clinical-stage, novel dual WEE1/PKMYT1 inhibitor versus clinical stage WRN helicase inhibitors

Materials and methods: Integrated dose- and time-resolved LC-MS-based phosphoproteomics and proteomics studies were performed in human colorectal tumor cells treated with either of the clinical-stage WRN inhibitors, VVD-214 or HRO761, or with ACR-2316, a novel, clinical-stage dual WEE1/PKMYT1 inhibitor. Collectively, more than 90,000 phosphorylation sites and 10,000 proteins were quantified. AP3-derived kinase activity inference and pathway engagement analyses were used to construct proteome activity state maps across drug exposures and biological contexts. Drug sensitivity was further evaluated across a broader panel of microsatellite instability-high (MSI-H) cancer cell lines.

Results: AP3 uncovered distinct proteome activity states induced by WRN helicase and WEE1/PKMYT1 inhibition, resolving responses at both kinase and pathway levels. WRN inhibition selectively

engaged ATR-, ATM-, and Fanconi anemia-associated signaling in WRNi-sensitive HCT116 (MSI-H) cells, including phosphorylation of FANCA, FANCI, RAD50, and NBN-associated DNA damage response nodes, whereas WRNi-insensitive COLO205 (microsatellite-stable, or MSS) cells demonstrated minimal pathway engagement. Across a broader MSI-H panel, fewer than 30% of cell line models demonstrated substantial WRNi sensitivity, demonstrating MSI-H status alone is insufficient to predict response. In contrast, ACR-2316 induced broad and consistent anti-tumor activity and proteome activity state across both MSI-H and MSS models characterized by activation of CDK1/2 and PLK1 signaling, and engagement of mitotic and cell-cycle progression programs.

Conclusions: These findings demonstrate that AP3 can resolve drug-induced proteome activity states, differentiate intracellular mechanisms of action in intact cells, and identify protein modification-based determinants of drug response not evident from nucleic acid sequencing-based analyses. AP3 uncovered the differential mechanistic pathway effects driving the broad, potent anti-tumor efficacy of ACR-2316 observed in both MSI-H and MSS tumor cells, while WRN inhibitors were active in only MSI-H tumor cells, yet, MSI-H status alone was insufficient to predict response. Our study highlights the value of drug-regulated proteome activity state analyses for response stratification.

Conflict of interest: Ownership: All authors were employees of Acrivon Therapeutics, Inc. or Acrivon AB at the time the work was performed and hold equity interests in Acrivon Therapeutics, Inc.

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163 - PB-058 **Poster**

Alnodesertib (ART0380) potentiates the preclinical efficacy of TOP1 inhibitor-based ADCs across multiple tumour histologies

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Background: Alnodesertib (ART0380) is a novel small molecule inhibitor of ATR protein kinase that has been developed for therapeutic targeting of cancers with high replication stress.

Materials and Methods: To identify clinical settings where alnodesertib could be utilised, we explored the preclinical activity of alnodesertib treatment in combination with TOP1 inhibitor-based ADCs, an emerging therapeutic class of anti-cancer agent showing great promise in various clinical settings.

Results: Here, we provide preclinical evidence *in vitro* and *in vivo* to show that alnodesertib treatment in combination with a range of TOP1 inhibitor-based ADCs is effective and tolerable across multiple tumour models.

Conclusions: Our data highlight that alnodesertib is an effective potentiator of TOP1 inhibitor-based ADCs and provides new opportunities for potential clinical development for this molecule.

Conflict of interest: Corporate-sponsored Research: The work described was performed by employees and shareholders of Artios Pharma Limited

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164 - PB-059 **Poster**

Dual ATR-mTOR inhibitors for PTEN-deficient prostate cancer

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Background: Regulation of the DNA damage response (DDR) is key for genomic integrity and Ataxia telangiectasia and Rad3-related protein serine/threonine kinase (ATR) is a key regulator of this process, allowing cancer cells to survive under conditions of high replication stress. By inhibiting ATR, cancer cells are overwhelmed by DNA damage, leading to apoptosis. PTEN is a tumor suppressor gene controlling cell cycle progression and PTEN deficiency impairs DNA repair pathways and further increases replication stress. ATR inhibitors demonstrate synthetic lethality in PTEN-deficient disease. PTEN aberrations are among the most common genomic alterations in prostate cancer, with PTEN deficiency reported in up to 62% of prostate cancer patients and increasing prevalence of PTEN deficiency correlates with disease progression. PTEN deficiency also leads to activation of mTOR through PDK1 and AKT, contributing to cell survival under chronic replication stress. Accordingly, there is a rationale for concurrent ATR and mTOR inhibition to treat PTEN deficient disease. Combination therapies are often limited by overlapping toxicities and pharmacokinetic incompatibilities, highlighting the benefits of developing a single molecule that simultaneously targets both ATR and mTOR.

Methods: Enki™, a generative artificial intelligence platform, was used to design *de novo* molecules optimized for dual ATR/mTOR inhibition. Molecules were synthesized and evaluated for potency and selectivity in *in vitro* enzymatic activity and prostate cancer cell viability assays. Metabolic stability was evaluated *in vitro* and additional ADME properties were determined using *in vivo* pharmacokinetic studies.

Results: A series of novel compounds were prepared with varying levels of potency against ATR and mTOR, and varying degrees of selectivity against each of the targets. In broad terms, in vitro potency was consistent with predictions generated using Enki™. Compounds with promising activity against the targets were evaluated for metabolic stability, and pharmacokinetic profiling. Data generated from these assessments were used to further train Enki™ and support iterative optimization of candidate molecules for potency, selectivity and pharmacokinetic properties. Data will be presented on *in vitro* enzymatic activity against ATR and mTOR, selectivity against PIKK family enzymes including ATM, PI3Kα and DNA-PK, cell viability of isogenic PTEN deficient/proficient prostate cancer cell lines, *in vitro* metabolic stability and mouse pharmacokinetic profiling.

Conclusion: Dual action inhibitors of ATR and mTOR are a novel therapeutic opportunity for the treatment of PTEN deficient prostate cancer, among other PTEN deficient malignancies. Further characterization and development of these molecules may provide prostate cancer patients additional therapeutic modalities.

Conflict of interest: Ownership: Mads Daugaard, Jeffrey Bacha, Dennis Brown and John Langlands own stock for Rakovina Therapeutics. Sarah Truong, Louise Ramos, Fariba Ghaidi, Mona

Marzban, Samyuktha Suresh and Kally Singh have stock options for Rakovina Therapeutics.

Advisory Board: Dennis Brown is a member of the Rakovina Therapeutics scientific advisory board.

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Poster Session: Drug Delivery

165 - PB-060 **Poster**

CD19-Targeted Nanoparticles for B-Cell Lymphoma Therapeutics

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Background B-cell lymphoma (BCL) is one of the most prevalent hematological malignancies. Although novel treatments achieve meaningful initial responses, most patients eventually develop resistance and have poor outcomes. Non-specific targeting remains a major limitation for achieving effective BCL treatment; therefore, there is a need to develop a precision-targeting drug delivery platform to eradicate BCL. Poly(lactic-co-glycolic acid) (PLGA) is a well-established biocompatible copolymer widely used as nanoparticles (NPs) to safely deliver therapeutic agents. Driven by the prominent expression of CD19 on BCL membranes, anti-CD19 mAb was employed as a targeting moiety. Anti-CD19 mAb-functionalized PLGA nanoparticles (anti-CD19@PLGA) were constructed as an advanced drug carrier. This study demonstrates their capability as a highly effective tool for optimizing targeted therapeutic delivery to $CD19^+$ BCL.

Material and methods Anti-CD19 mAb was conjugated to PLGA-polyethylene glycol-maleimide (PLGA-PEG-MAL) NPs via succinimidyl acetylthioacetate-based thiolation and confirmed by bicinchoninic acid (BCA) assays. For *in vitro* and *in vivo* flow cytometry analysis, a fluorescent dye was encapsulated into the PLGA-PEG-MAL NPs. To evaluate *in vitro* targeting efficiency, BALB/c splenocytes and bone marrow cells were incubated with anti-CD19@PLGA or unconjugated PLGA NPs (i.e., bare PLGA) for 2 hours. For *in vivo* targeting efficiency, anti-CD19@PLGA was injected into the tail veins of naïve BALB/c mice, and spleens were harvested after 24 hours. Finally, to establish its therapeutic potential for BCL, anti-CD19@PLGA was incubated with $CD19^+$ A20 BCL cells and L929 cells as a negative control.

Results BCA assay confirmed the conjugation of anti-CD19 mAb to PLGA-PEG-MAL NPs, with approximately 5.53μg of mAb conjugated per 1 mg of PLGA-PEG-MAL NPs. Flow cytometry revealed that anti-CD19@PLGA exhibited highly specific binding to $CD19^+$ B cells within both splenocyte and bone marrow populations. Consistently, the *in vivo* evaluation in naïve mice showed significantly higher targeting of anti-CD19@PLGA toward splenic $CD19^+$ cells. To further investigate its capability to target BCL, we evaluated anti-CD19@PLGA against A20 cells *in vitro*. Anti-CD19@PLGA displayed highly selective binding toward A20 cells (approximately 79.71%), whereas the targeting efficiency to L929 cells was only 1.63%. Notably, a minimal dose (2 μg) of anti-CD19@PLGA achieved superior targeting, whereas bare PLGA remained ineffective at a 5-fold higher dose (10 μg).

Conclusion Anti-CD19@PLGA demonstrated highly selective targeting of primary B cells and BCL cells both *in vitro* and *in vivo* compared to bare PLGA. These findings support its potential as a targeted drug delivery platform for BCL. Future studies will evaluate the therapeutic efficacy of drug-loaded anti-CD19@PLGA in relevant lymphoma models.

No conflict of interest

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166 - PB-061 **Poster**

Microfluidic-Assisted Preparation of PLGA Nanoparticles for Neuroblastoma Applications

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Background: In Neuroblastoma (NB), a pediatric cancer of sympathetic nervous system arising from neural-crest cells, the tumor microenvironment is highly immunosuppressive and disables the function of tumor-infiltrating cytotoxic T lymphocytes. Identifying novel anticancer agents with immune-modulating proprieties could be essential to enhance patient responsiveness to immunotherapies. Lately, a screening of 182 FDA-approved immune-modulating agents in NB cell lines identified "Compound 1 (C1)" as a promising candidate.

Materials and Methods: Here, we developed C1-encapsulated poly(lactic-co-glycolic acid) (PLGA, MW 30-60 kDa, 50:50) and poly (lactide-*co*-glycolide)-*block*-poly(ethylene glycol) (PLGA-PEG, MW 25-5 kDa, 50:50) nanoparticles (PLGA-NP[C1]). NPs were synthesized by using a microfluidic-based device, with the following compositions: (i) PLGA:C1 (9:1, w/w), (ii) PLGA:PLGA-PEG:C1 (8.9:0.1:1, w/w), (iii) PLGA:PLGA-PEG:C1 (8.1:0.9:1, w/w). In some cases, PLGA-PEG with maleimide terminal group was added to functionalize NPs with the anti-GD2 mAb, specific for the recognition of the disialoganglioside GD2 expressed in NB cells. An organic phase containing PLGA, PLGA-PEG and C1 and an aqueous phase constituted by TrisHCl 10 mM and poly(vinyl alcohol) 0.5% were mixed with a flow rate ratio (FRR) 1:3, and a total flow rate (TFR) of 12 mL/min. The suspensions were dialyzed against water to remove the organic solvent and then characterized for their size, polydispersity index (PDI) and Zeta potential by Zetasizer. The encapsulation efficacy was assessed after freeze-drying: the obtained lyophilizates were disrupted with Dichloromethane, then the supernatants were evaporated and finally C1 was extracted with 70% Ethanol for UV-Vis spectrophotometric detection. C1 release from NPs was evaluated using a dialysis bag (14 kDa MWCO) in PBS at 37 °C.

Results: The formulations showed a mean diameter from 100 to 150 nm, PDI < 0.2 and negative charge (-20 mV). NPs size distribution remained constant at 4 and 37°C for up to 72 h, thus demonstrating good colloidal stability. Gravimetric analysis of lyophilizates indicated a high yield along with efficient C1

encapsulation (90-70%). C1 release studies demonstrated an initial burst release of about 30%, followed by a plateau phase up to 72 h. The PLGA:PLGA-PEG:C1 (8.1:0.9:1) formulation was selected for its PEG content, deemed more suitable for targeting applications. C1 *in vitro* cytotoxicity is currently under evaluation in a panel of NB cell lines.

Conclusions: PLGA-NPs represent a suitable drug delivery system for C1. By using a microfluidic device, a monodisperse and stable suspension was obtained. The incorporation of PLGA-PEG further enables the NPs functionalization with the anti-GD2 mAb, thereby supporting selective delivery to NB cells.

No conflict of interest

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167 - PB-062 **Poster**

A Bayesian pharmacokinetics-integrated Phase I–II design to optimize dose-schedule regimes

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The administration schedule of a drug has a profound impact on its toxicity and efficacy profiles by altering its pharmacokinetics (PK). Therefore, PK is an innate and indispensable component of dose-schedule optimization. Motivated by this, we propose a Bayesian PK-integrated dose-schedule finding (PKIDS) design to identify the optimal dose-schedule regime by integrating PK, toxicity, and efficacy data.

Based on the causal pathway wherein dose and schedule affect PK, which in turn affects efficacy and toxicity, we jointly model the three endpoints. We first specify a Bayesian hierarchical model for the marginal distribution of the longitudinal dose-concentration process. Conditional on the drug concentration in plasma, we jointly model toxicity and efficacy as a function of that concentration. We quantify the risk-benefit profiles of the regimes using a utility function—continuously updating the estimates of PK, toxicity, and efficacy based on interim data—and make adaptive decisions to assign new patients to appropriate dose-schedule regimes via adaptive randomization. Simulation studies demonstrate that the PKIDS design possesses desirable operating characteristics.

No conflict of interest

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168 - PB-063 **Poster**

Colloidal Behaviour and Therapeutic Promise of Zirconium Based Metal Organic Framework (UiO-66) for Meningioma Treatment

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Metal-Organic Frameworks (MOFs), recently recognized with the 2025 Nobel Prize in Chemistry, are highly porous, tunable nanomaterials for biomedical applications. Among MOFs, the zirconium-based UiO-66 offers a robust and versatile platform for drug delivery. However, its biomedical translation has been hindered by a limited understanding of its physiological stability, biodegradation under physiological conditions and cellular mechanism of UiO-66 transport. We have performed a comprehensive evaluation of UiO-66 as a nanocarrier for meningioma therapy. Uniform octahedral UiO-66 was synthesized and achieved a high DOX encapsulation efficiency (EE) of 84.4% within the porous framework. *In-vitro* stability studies demonstrated excellent stability in water, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), and cell culture media, whereas exposure to phosphate-buffered saline (PBS) induced framework disruption via linker displacement, highlighting the biodegradable nature of the nanocarrier under phosphate-rich physiological conditions. Functionally, DOX-loaded MOFs (DOX-UiO-66) exhibited both concentration and time-dependent cytotoxicity in IOMM Lee cells. Mechanistic investigations demonstrated that, unlike free DOX, which enters cells predominantly through passive diffusion, in contrast DOX-UiO-66 undergoes energy-dependent endocytic uptake. Importantly, this altered trafficking did not compromise therapeutic efficacy, as evidenced by downregulation of TOP2A, CDK1, and BCL2 expression, along with pronounced S-phase cell cycle arrest at 48 hrs post-treatment. At 48 hr timepoint, DOX-UiO-66 exhibited a comparable reduction in % of cell viability to that of free DOX. Furthermore, in 3D meningioma tumeroids, DOX-UiO-66 demonstrated efficient DOX penetration with broader fluorescence distribution across multiple spheroid depths, compared to free DOX. Collectively, these findings establish UiO-66 as a stable yet biodegradable nanocarrier capable of sustained intracellular drug delivery, effective molecular target inhibition, and enhanced tumor penetration, highlighting its potential for the treatment of meningioma.

No conflict of interest

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169 - PB-064 **Poster**

Overcoming diffusion barriers in solid tumours: Rapid tissue penetration achieved with bicyclic peptides targeting EphA2

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Background: Solid tumour treatment is often limited by the drug molecular size. Monoclonal antibodies (mAbs) diffuse poorly due to their large size (~150 kDa) and the "binding site barrier", resulting in heterogeneous distribution and poor efficacy in large, poorly vascularized and/or highly fibrotic tumours. Bicycle® molecules are small (~2.5 kDa), structurally constrained peptides that combine the high affinity and selectivity of mAbs with the rapid tissue penetration properties of small molecules. Ephrin type-A receptor 2 (EphA2) is highly expressed on the surface of poor-prognosis solid tumours like pancreatic cancers but targeting it via traditional Antibody-Drug Conjugates (ADCs) has previously failed due to severe toxicities and limited efficacy.

Material and Methods: EphA2-specific binders were identified using phage display and optimised for affinity, physicochemical properties, and stability. This targeting moiety was used to develop two EphA2-specific agents: 1) a therapeutic Bicycle® Drug Conjugate

(BDC®), nuzefatide pevedotin (nuzefa; formerly BT5528), carrying an MMAE payload via a cleavable valine-citrulline linker; and 2) a Bicycle® Radionuclide Conjugate (BRC®) radiolabelled with ^{68}Ga for PET/CT imaging. Preclinical pharmacokinetics, biodistribution, and anti-tumour activity were evaluated in various *in vitro* and *in vivo* models. For clinical translation, first-in-human imaging of the BRC® in pancreatic cancer patients has been achieved.

Results: In preclinical models, nuzefa was rapidly distributed systemically and cleared from plasma while achieving fast intra-tumour uptake and sustained MMAE levels for at least 48 hours. This rapid penetration translates directly into nuzefa efficacy over a comparator ADC in large-size patient-derived xenograft (PDX) models where antibodies struggle to penetrate and diffuse homogenously. Accordingly, no difference in anti-tumor activity was observed in small-size tumour models, where large molecules diffusion is less impaired. Importantly, nuzefa showed anti-tumour activity in pancreatic PDX models of immature, intermediate and mature desmoplastic grades. This physical advantage was further validated by BRC® imaging in preclinical models and in humans, showing rapid, deep tumour uptake within 15 minutes and permitting the detection of metastasis in the clinic within 1 hour, accompanied by fast renal clearance.

Conclusions: The small-format Bicycle® platform overcomes the critical diffusion and extravasation barriers faced by antibody-based therapies. The unique properties of Bicycle® molecules, which combine rapid tumour penetration with fast systemic clearance, allow the targeting of previously intractable cancer cell-surface proteins, providing the opportunity to develop both best- and first-in-class solid tumour therapies.

Conflict of interest: Ownership: Laura Diaz-Gil, Anusha R. Regupathy, Jitka Rield, Luca Mascheroni, Alex Rigby, Lukas Stanczuk, Gemma E. Mudd, Gavin S. Bennett, Inma Rioja, Michael Skynner own stocks/shares in Bicycle Therapeutics, Inc.

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Other Substantive Relationships: Laura Diaz-Gil, Anusha R. Regupathy, Jitka Rield, Luca Mascheroni, Alex Rigby, Lukas Stanczuk, Gemma E. Mudd, Gavin S. Bennett, Inma Rioja, Michael Skynner are employees of Bicycle Tx.

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170 - PB-065 **Poster**

Nanopaticle-Mediated Docetaxel Delivery: A promising Approach for Glioblastoma Treatment

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Background: Glioblastoma (GBM) is the most aggressive and lethal primary brain malignancy, characterized by rapid proliferation, extensive invasion, and poor patient survival despite multimodal therapy. It is the most aggressive type of brain tumor accounting for 60% of all brain tumors, with a median survival of 15 months. Docetaxel is an anti-cancer agent that showed an effectiveness in metastatic breast cancer with a reasonably high response rate. In addition, It has also showed a higher effectiveness and safety against non-small-cell lung cancer compared with vinca alkaloid as first line therapy as well as in metastatic prostate cancer, Docetaxel has showed a longer overall survival. It has an anti-microtubule effect, which impede microtubule by binding to the β-subunit of tubulin, thereby causing depolymerization of the microtubule, thus preventing shortening and lengthening of microtubule and inhibiting normal cell function. Therefore, our study is aimed to explore the the antitumor efficacy of novel nanoparticle formulations of docetaxel compared with the marketed formulation in glioblastoma cells.

Materials and Methods: Glioblastoma cells were treated with two novel nanoparticle formulations of Docetaxel, the marketed Docetaxel formulation, and corresponding vehicle controls. Cell viability was evaluated using the MTT assay to determine cytotoxicity and calculate the half-maximal inhibitory concentration (IC_{50}). Morphological alterations were assessed by microscopy, apoptosis was analyzed by flow cytometry, and the wound-healing (scratch) assay was performed to evaluate the inhibitory effects on cell migration.

Results: Treatment with nanoparticle-based Docetaxel formulations produced pronounced morphological changes indicative of enhanced cytotoxicity compared with the marketed formulation and untreated controls. Furthermore, nanoparticle formulations significantly suppressed glioblastoma cell migration, suggesting a greater ability to inhibit tumor invasiveness. Notably, while the marketed docetaxel achieved an IC_{50} of 25 nM after 48 hours, one nanoparticle formulation reached a comparable IC_{50} (25.39 nM) within 24 hours, demonstrating a substantially faster therapeutic response. These findings indicate that nanoparticle-mediated delivery enhances the anticancer activity of docetaxel by accelerating its cytotoxic effects and improving its anti-migratory potential.

Conclusion: Novel nanoparticle-based formulations markedly enhanced the therapeutic performance of Docetaxel against glioblastoma cells by promoting earlier cytotoxicity and more effectively inhibiting cell migration than the marketed formulation. These findings underscore the potential of nanoparticle-enabled Docetaxel as a promising strategy for improving glioblastoma treatment and provide a strong rationale for further preclinical development and translational evaluation.

No conflict of interest

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171 - PB-066 **Poster**

Modulation of AhR/Nrf2 signaling suppresses Wnt/β-catenin activity through competition for transcriptional co-activators in colorectal cancer

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Colorectal cancer (CRC) remains one of the leading causes of cancer incidence and mortality in Japan, highlighting the urgent need for novel therapeutic strategies. Although anti-EGFR therapies have improved clinical outcomes in selected patients, they are ineffective in many CRCs harboring KRAS mutations. Therefore, the development of alternative molecular-targeted approaches is required. In this study, we investigated whether modulation of the aryl hydrocarbon receptor (AhR) pathway, which regulates xenobiotic metabolism, and the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, a master regulator of antioxidant responses, could suppress oncogenic Wnt/β-catenin signaling in CRC.

Previous studies have demonstrated functional crosstalk between AhR and β-catenin signaling, including the ability of β-catenin to enhance AhR-dependent transcription. Because multiple

transcriptional programs share co-activators such as CREB-binding protein (CBP) and p300, we hypothesized that activation of AhR/Nrf2 signaling suppresses Wnt/β-catenin signaling through competition for these transcriptional co-activators.

Consistent with this hypothesis, activation of either AhR or Nrf2 signaling by selected agonists reduced Wnt/β-catenin transcriptional activity in colorectal cancer cells. To further investigate the underlying mechanism, we examined the interactions between the Wnt transcription factor TCF4 and its transcriptional partners β-catenin and CBP by co-immunoprecipitation using HCT116 cells. Sulforaphane, a dual activator of the AhR and Nrf2 pathways, markedly reduced the formation of both TCF4/β-catenin and TCF4/CBP complexes, suggesting that activation of AhR/Nrf2 signaling interferes with the assembly of the Wnt transcriptional complex.

To further assess the involvement of CBP-mediated transcriptional regulation, cells were treated with E7386, a selective inhibitor of the β-catenin/CBP interaction. E7386 significantly attenuated sulforaphane-induced activation of AhR/Nrf2 signaling, supporting the involvement of CBP-dependent transcriptional regulation in both pathways. These findings collectively suggest that modulation of AhR/Nrf2 signaling suppresses Wnt/β-catenin signaling through competition for shared transcriptional co-activators, including CBP.

Rather than directly inhibiting β-catenin, this study proposes an alternative therapeutic strategy based on rebalancing intracellular signaling networks through transcriptional co-activator redistribution. These findings provide a mechanistic rationale for targeting co-activator dynamics as a novel molecular therapeutic approach for colorectal cancer.

No conflict of interest

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Poster Session: Drug Design

172 - PB-067 **Poster**

Development of next-generation MRTF-A inhibitors for hepatocellular carcinoma therapy and design of fluorescent tool compounds

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Background: Hepatocellular carcinoma (HCC) is the third common cause of cancer-related mortality worldwide and effective targeted treatment options are urgently needed. Myocardin-related transcription factor A (MRTF-A) and its cofactor serum response factor (SRF), regulate the expression of genes involved in proliferation, migration and organization of the actin cytoskeleton and triggers HCC progression. We previously identified NS8593, a negative gating modulator of TRPM7, as an inhibitor of MRTF-A/SRF transcriptional activity and HCC xenograft growth. The aim of the present study was to further optimize this lead compound NS8593 in order to generate more potent MRTF-A inhibitors and to develop fluorescent dye conjugates to visualize MRTF-A nuclear export.

Material and methods: Four consecutive generations of NS-derived compounds were evaluated in HCC cell models, including HuH7 cells. Biological activity was assessed using SRF reporter gene activity assays and proliferation assays. One selected second-generation compound was subsequently tested in a tumor xenograft model and MRTF/SRF target gene expression was analyzed in tumor samples. To visualize MRTF-A subcellular distribution, a separate approach was pursued by conjugating a fourth-generation compound to a fluorescent dye and analyzing it using confocal microscopy.

Results: Starting from the NS8593 lead structure, four generations of derivatives were developed by stepwise structural modification. Out of the first and second generation the most promising compound was further evaluated in xenograft tumor models, where reduced expression of MRTF/SRF target genes such as myoferlin (MYOF) was detected. Based on these findings, the third and fourth generations were designed around biphenyl-containing motifs with altered substitution patterns, while the fourth generation predominantly introduced triazole-containing residues. Through this stepwise structural optimization, we observed increased inhibitory activity compared with the lead compound, including up to 120-fold higher activity in SRF reporter assays and up to 30-fold stronger effects in proliferation assays in HCC cell models. A fluorescently labelled fourth-generation derivative impaired HCC proliferation and reduced SRF transcriptional activity.

Conclusions: We identified improved MRTF-A inhibitors with enhanced biological activity in HCC models. The *in vivo* data further support the relevance of this compound class by showing reduced expression of MYOF in tumor samples. Furthermore, the fluorescent fourth-generation analogue inhibited HCC cell proliferation and SRF transcriptional activity.

No conflict of interest

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173 - PB-068 **Poster**

De novo design of peptide-MHC binders targeting histone H3 mutations in pediatric high-grade gliomas

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Background: Pediatric high-grade gliomas (pHGGs) are deadly brain tumors with limited treatment options. Histone H3 mutations are recurrent clonal drivers in pHGGs, involving hotspot residues K27M and G34R/V, with H3.3K27M being the most frequent subtype. Although H3 mutations are compelling therapeutic targets, their intracellular nature has limited targeting by conventional therapies. Mutant H3-derived peptides, however, can be presented by major histocompatibility complex (MHC) molecules, generating tumor-specific peptide-MHC (pMHC) targets on the cell surface. Therefore, de novo design of binders that selectively recognize these mutant pMHCs could enable novel targeted therapies and immunotherapies for pHGGs.

Methods: Neoepitope prediction was performed using pVACbind to select a target pMHC. De novo nanobody binders against the target pMHC were generated using RFantibody. Initial designs were filtered based on RoseTTAFold2 confidence scores, followed by AlphaFold3 modeling. Filtered designs were screened by the predicted binder complementarity-determining region 3 (CDR3) proximity to the K27M residue. To predict specificity, comparative AlphaFold3 modeling was performed against the corresponding wild-type pMHC. Candidates were further ranked using additional scoring metrics that reflect binder-target contacts, aggregation propensity, and post-translational modifications predicted in silico.

Results: H3.3K27M p26-36 (RMSAPSTGGVK) - HLA-A*03:01 complex was selected as the target pMHC. We generated 39,282

designs against the target pMHC, of which 322 designs passed initial filtering based on confidence scores by RoseTTAFold2 and AlphaFold3. Among these, 96 designs showed CDR3 proximity to the K27M residue in AlphaFold3-predicted structures, with 16 demonstrating predicted hydrogen bonds. Comparative AlphaFold3 modeling against the corresponding wild-type pMHC (RKSAPSTGGVK - HLA-A*03:01) suggested loss of predicted binding against wild-type pMHC for 44 candidates. 22 of these candidates were also predicted to recognize the H3.1K27M pMHC (RMSAPATGGVK - HLA-A*03:01) while maintaining loss of predicted binding to both wild-type counterparts.

Conclusions: Our de novo binder design and computational screening pipeline have identified a set of mutant-specific H3K27M pMHC binder candidates for experimental validation. This approach will be further applied to other H3 mutation subtypes and a broader range of intracellular clonal drivers.

No conflict of interest

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174 - PB-069 **Poster**

Discovery of JZY3032, a First-in-Class DALTAC Rewiring AR-p300 Demonstrate Lineage-Selective Anti-tumor Efficacy in Advance Prostate Cancer Models

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Resistance to androgen receptor (AR)-targeted therapies persists as a major challenge in castration-resistant prostate cancer (CRPC). A key mechanism involves AR cooperating with histone acetyltransferase p300 to form cancer-specific "neo-enhanceosomes" that drive aberrant oncogenic transcription. Although multiple p300/CBP inhibitors and degraders have been developed, their global suppression raises concerns about potential on-target toxicity in normal tissues, highlighting the urgent need for tissue-specific targeting strategies. Here, we introduce a mechanistically distinct modality, Domain-ALTeration Chimeras (DALTACs), a novel class of chemical-induced proximity compounds selectively miswire endogenous protein complexes by enforcing non-productive domain–domain interactions between physiological partners. Our first-in-class DALTAC, JZY3032, promotes proximity between the AR ligand-binding domain and the p300 bromodomain, locking the complex into inert conformations that disable complex activity. JZY3032 demonstrated superior antiproliferative activity in AR positive prostate cancer cells compared to combination treatments of AR antagonist and p300 inhibitor, while sparing AR-negative but p300 dependent cancer cells, underscoring the striking lineage selective tumor inhibitory effects of DALTAC compound. Furthermore, it induces robust anti-tumor efficacy in multiple prostate cancer models with favorable tolerability, supporting its potential as a promising therapeutic candidate for advanced prostate cancer. Taken together, our findings establish DALTACs as a novel therapeutic paradigm that achieves lineage-selective transcriptional disruption through targeted rewiring of protein complex topology. The compelling efficacy and favorable safety profile of JZY3032 support its further investigation as a promising therapeutic strategy in CRPC.

No conflict of interest

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175 - PB-070 **Poster**

Novel HBS1L degraders identified from APROX™ and Directed Neosubstrate Degrader (DNsD) platforms for the treatment of FOCAD-deleted cancers

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Genomic deletion of tumor suppressors can often lead to the co-deletion of adjacent genes, creating synthetic lethal dependencies. One such dependency arises in cancers with loss of FOCAD, a key component of the mRNA surveillance SKI complex. Loss of FOCAD results in ribosome stalling on aberrant mRNA transcripts, burdening ribosome rescue, and recycling system, which primarily involves HBS1L/PELO complex. This establishes HBS1L/PELO as a highly specific synthetic lethal therapeutic target pair in FOCAD-deleted cancers, where their degradation leads to catastrophic translational stress and selective cell death.

We utilized our proprietary APROX™ and Directed Neosubstrate (DNsD) platforms to rapidly discover and optimize a novel chemical series of "glue-like" HBS1L degraders. Our best-in-class, highly potent HBS1L degraders show significant dose-dependent degradation of HBS1L, leading to destabilization of its binding partner, PELO. Lead degraders exhibit a selective neosubstrate profile and sub-nanomolar anti-proliferative potency with exceptional selectivity (>1000-fold) in FOCAD-deleted cell lines over their wild-type counterparts. Identified novel HBS1L degraders exhibit good oral bioavailability. Profiling of lead compounds in rodent tolerability and efficacy studies in relevant CDX models is in progress.

This work validates the potential our APROX™ and Directed Neosubstrate (DNsD) Degrader platforms as highly efficient engines for identification and optimization of molecular glues for novel targets. Efforts are in progress to nominate a development candidate for HBS1L by Q4 2026.

No conflict of interest

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176 - PB-071 **Poster**

Optimisation of targeted BCL3 inhibitors and degraders (PROTACs) directed towards treatment of advanced colorectal and breast cancers

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Background: B cell lymphoma 3 (BCL3) is a transcriptional facilitator protein and anti-cancer drug target driving intracellular cancer signalling pathways including NF-kB (advanced breast) and Wnt-β-catenin (colorectal), governing pro-oncogenic processes such as tumour initiation, metastasis and therapy resistance. The purpose of this study was twofold:

- to extend our previously published work on a BCl3-p50 interface protein-protein inhibitor (JS6; 2-fluoro-*N*-(2-((2-morpholinoethyl)carbamoyl)phenyl)benzamide), and a structurally related orally bioavailable preclinical candidate, to synthesise new JS6-chemical analogues for structure-activity based optimisation, alongside novel conformationally restricted analogues.
- to design and synthesise the first BCL3 PROTACs, to compare and contrast therapeutic activity between BCL3 inhibitors and PROTAC-based targeted degraders.

Materials and Methods: Our previously published computational model of the BCL3/p50 interface was updated for the new inhibitor target molecules, through the use of AlphaFold, Schrödinger's Maestro and Molecular Operating Environment (MOE). A range of published chemical synthetic methods were applied to synthesise anthranilic acid-based and conformationally restricted analogues, and pomalidomide-based PROTACs of previous BCL3 inhibitory lead compounds. New compounds were purified (automated column chromatography) and characterised (e.g. NMR spectroscopy, mass spectrometry). In vitro evaluation of new BCL3 inhibitors within established cellular models of advanced breast and colorectal cancer is underway.

Results: To date, several synthetic pathways to the synthesis of novel Bcl3 inhibitors, JS6 analogues and PROTACs have been explored. For example, new analogues of JS6 were synthesised using anthranilic acid in a nucleophilic acyl substitution reaction, followed by the incorporation of varied alkyl chain length morpholines. Early in vitro evaluation indicates that the new compounds are devoid of general cytotoxicity in normal and triple-negative breast cancer cell models and induce BCL3 degradation (PROTACs).

Conclusions: The successful design and synthesis of a series BCL3 inhibitors and PROTAC degraders have been completed, and work is ongoing to profile their BCL3 binding affinity and therapeutic profile as potential oral BCL3-targeted anticancer drug candidates.

No conflict of interest

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177 - PB-072 **Poster**

A fast and robust development process providing new highly internalized anti-hHER2 antibody–drug conjugates

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Background: The aim of this study was to establish an accelerated and de-risked workflow for the generation of potent anti-hHER2 antibody–drug conjugates (ADCs), addressing key bottlenecks that currently limit the efficiency, predictability, and overall success rate of ADC discovery.

Material and Methods: We implemented a fully integrated workflow. (1) Mice were immunized with recombinant HER-2 extracellular domain using an optimized protocol to induce robust anti-hHER2 responses. (2) Plasma cells of interest were selected on the Bruker Beacon single-cell platform based on the simultaneous measurement of antibody production and HER-2 binding, combined to compute a relative affinity score for 200 anti-HER-2 antibodies prior to sequencing and recombinant expression. (3) Eighteen antibodies spanning this affinity range were selected, expressed, and purified. (4) These antibodies, a reference antibody, and an isotype control were conjugated to MMAF at a controlled drug-to-antibody ratio (DAR) using a two-step transglutaminase/click chemistry strategy. (5) Binding affinity was measured by bio-layer interferometry; internalization kinetics, before and after conjugation, were measured using a pH-sensitive probe; and EC50 values were determined on a HER2-expressing cell line. (6) Finally, cytotoxicity of the ADCs was assessed on the same HER2+ cell line.

Results: The integrated workflow produced highly internalized anti-hHER2 antibodies, some surpassing the reference antibody. The enzymatic conjugation protocol consistently produced DAR4 ADCs, as confirmed by SEC-UPLC and LC-MS. Each parameter generated for the antibody panel was tested, individually or in combination, as a predictor of ADC cytotoxicity. A receiver operating characteristic (ROC) approach showed that affinity measured directly on Beacon, combined with naked-antibody internalization, was the strongest predictor of ADC cytotoxicity (AUC = 0.852, leave-one-out cross-validation), providing 100% sensitive early triage of hits. Notably, this predictor relies solely on measurements acquired before conjugation to the toxin, enabling efficient prioritization of clones early in the development process.

Conclusions: This integrated and optimized workflow accelerates ADC generation from immunization to functional readout while reducing technical risk at each stage. It enabled the rapid identification of novel anti-hHER2 antibodies with enhanced internalization and highly potent ADC derivatives. This approach is broadly applicable to future ADC discovery programs targeting diverse antigens.

Conflict of interest: Corporate-sponsored Research: All co-authors are full-time employees of MImAbs SAS

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178 - PB-073 **Poster**

Gene age and pleiotropy improve discrimination of drug targets from CRISPR dependency mapping in endometrial cancer

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Background: Genome-wide CRISPR-Cas9 screens identify cancer genetic dependencies, but translating these into clinically actionable drug targets remains challenging. We asked whether adding evolutionary gene age (phylostratigraphy) and disease-association breadth (pleiotropy) to CRISPR dependency profiles improves identification of druggable targets in molecularly stratified endometrial cancer (EC).

Materials and Methods: CRISPR-Cas9 gene effect scores from Cancer Dependency Map (DepMap) Public 2302 were obtained for 28 EC cell lines stratified as mismatch repair-deficient (MMRd, n = 16) and ARID1B-deficient (n = 3). Gene age was assigned by phylostratigraphy using the integrative phylogenomic toolkit of Strizzi & Natterson-Horowitz (2026), mapping genes to 27 phylostrata (PS1–PS27) spanning cellular organisms (~4,200 MYA) to Homo sapiens-specific genes (~0.3 MYA). Pleiotropy was quantified as log-transformed disease association counts (Open Targets Platform). Four logistic regression models were trained by 5-fold cross-validation to classify 107 FDA-approved or clinical-stage oncology drug targets against 12,748 background genes. Subtype-specific dependencies were identified by Mann-Whitney U test with Benjamini-Hochberg (BH) FDR correction. Model performance was compared by DeLong's test and bootstrap 95% CI (10,000 resamples).

Results: Differential dependency analysis (BH FDR < 0.05) identified 632 MMRd-selective genes, with WRN ($p = 0.008$), YRDC ($p = 0.0004$), and PELO ($p = 0.004$) as top hits, and 479 ARID1B-selective genes led by YARS2 ($p = 0.0006$) and MYC; the ARID1B analysis (n = 3) should be considered exploratory. CRISPR

dependency alone achieved AUC-ROC 0.680 (MMRd; 95% CI 0.628–0.719) and 0.677 (ARID1B; 95% CI 0.653–0.710). Adding pleiotropy yielded AUC-ROC 0.898 (MMRd) and 0.880 (ARID1B), ΔAUC +0.218 and +0.203 respectively (DeLong $p < 0.0001$). The full model (CRISPR + age + pleiotropy) reached AUC-ROC 0.904 for both MMRd and ARID1B comparisons, with gene age contributing modest incremental gain over pleiotropy alone (+0.034).

Conclusions: Integrating disease association breadth and evolutionary gene age with CRISPR dependency profiles substantially improves druggable target discrimination (ΔAUC ~0.20–0.22; DeLong $p < 0.0001$), with pleiotropy driving the majority of improvement. The framework accurately prioritizes subtype-specific dependencies including WRN in MMRd EC — a synthetic lethal target already under clinical investigation in MSI-high cancers — supporting its utility for precision oncology target discovery across molecular subtypes.

No conflict of interest

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179 - PB-074 **Poster**

ER-BRD4 RIPTAC: Bridging Target Engagement to a Target-Dependent Therapeutic Window

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RIPTAC (Regulated Induced Proximity Targeting Chimeras) introduces a novel strategy that leverages induced proximity to achieve selective cancer cell killing. Using an ER–BRD4 RIPTAC as a tool compound, we integrated biochemical screening, computational docking, and multi-level cellular assays to establish a direct link between target engagement and therapeutic efficacy. Biochemical evaluation confirmed binary and ternary affinity, with computational simulations predicting novel ER–BRD4 ternary protein–protein interactions (neoPPIs) consistent with cooperativity observed experimentally. Cellular assays demonstrated that the ER–BRD4 RIPTAC induces ternary complexes in Flp-In 293 T-Rex ER-inducible cell and the ER positive breast cancer cell line MCF-7, showing that ternary assembly is preserved across biochemical and cellular contexts. Two pairs of RIPTAC molecules were evaluated for ternary complex formation (PPI), which successfully differentiating potency across the series. ER–BRD4 RIPTAC was highly potent in ER-high expression models, with efficacy correlating with ER expression levels, correlating with strong inhibition of BRD4 (TE assay). Moreover, clinically relevant ER mutants retained robust ternary complex formation, highlighting a mechanistic correlation between ER expression and therapeutic effect. This positions RIPTAC to address resistance mechanisms, including ER amplification and point mutations. Beyond ER–BRD4, RIPTAC expands the induced proximity landscape, aligning with TCIP paradigms and demonstrating broader applicability across oncogenic drivers. Together, computational and experimental evidence converge to highlight ternary complex stability and ER expression dependence as the mechanistic drivers of RIPTAC's therapeutic window. Importantly, our induced proximity platform, built on extensive expertise in targeted protein degradation (TPD), can be rapidly migrated to other target pairs, enabling first-in-class drug discovery programs and supporting both domestic and international partners.

No conflict of interest

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180 - PB-075 **Poster**

Rational Design and Molecular Dynamics Optimization of Heterobifunctional Degraders Targeting Integrin α4 Identified Through IFI27-Associated Network Analysis in Gastric Adenocarcinoma

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Background: Gastric adenocarcinoma lacks effective therapies for many dysregulated signaling proteins, motivating the computational desigBn of proteolysis-targeting chimeras (PROTACs) against integrin α4 (ITGA4), identified through IFI27-associated transcriptomic network analysis.

Material and methods: RNA-seq datasets were analyzed using DESeq2, weighted gene co-expression network analysis (WGCNA), and protein-protein interaction (PPI) network analysis to identify IFI27-associated therapeutic targets. The integrin α4 ligands bio5192 and firategrast were conjugated to the cereblon ligands thalidomide and lenalidomide through systematically enumerated alkyl and polyethylene glycol linkers using RDKit. Candidate PROTACs underwent physicochemical profiling and ADME filtering before ternary complex modeling. Protein-protein docking, intermolecular affinity prediction with PRODIGY, geometric vector analysis in PyMOL, and molecular dynamics simulations were performed to evaluate ternary complex stability and degrader geometry with GROMACS.

Results: Network analysis prioritized integrin α4 (ITGA4) as a therapeutically actionable protein within an IFI27-associated molecular network. Five lead PROTAC candidates were generated, including firategrast_PEG1_len3 and firategrast_PEG2_len2. The initial protein-protein docking identified a baseline separation of 35.6 Å between the CRBN tri-tryptophan binding pocket (Trp380, Trp386, Trp400) and the target interface. Ternary complex modeling identified linker conformations that reduced this distance while maintaining favorable intermolecular geometry. Molecular dynamics simulations demonstrated stable root mean square deviation (RMSD) plateaus throughout 100 ns, with MM-PBSA binding free energies ≤ -30 kcal/mol. Distance vector analysis indicated a final CRBN-to-target lysine separation of < 30 Å, consistent with a ternary complex geometry compatible with targeted protein degradation.

Conclusions: This computational workflow identified structurally and thermodynamically favorable PROTAC candidates targeting integrin α4 through IFI27-associated network analysis in gastric adenocarcinoma. The predicted ternary complex stability and degrader geometry support prioritization of these candidates for chemical synthesis and experimental validation, providing a rational framework for the development of targeted protein degradation strategies in gastric adenocarcinoma.

No conflict of interest

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181 - PB-076 **Poster**

AR–BRD4 RIPTAC Induces Expression-Dependent Ternary Complex Formation to Achieve Tumor-Selective Target Engagement in Prostate Cancer

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RIPTAC (Regulated Induced Proximity Targeting Chimeras) introduces a novel strategy that leverages induced proximity to achieve selective cancer cell killing. Using AR–BRD4 RIPTAC II-5 as a tool compound, we integrated biochemical screening, computational docking, and multi-level cellular and *in vivo* assays to establish a direct link between target engagement and therapeutic efficacy. Biochemical evaluation confirmed binary and ternary affinity, supported by computational simulations that predicted novel AR–BRD4 ternary protein–protein interactions (neoPPIs) consistent with cooperativity observed experimentally. II-5's distinct slow on/off binding kinetics stabilize ternary complexes, translating into superior activity in ternary formation and downstream signaling modulation. Cellular assays demonstrated that II-5 induces ternary complexes in HEK293T AR OE, VCaP, and LNCaP cells, correlating with strong inhibition of BRD4-driven signaling (c-Myc) while only moderately inhibit AR signaling (reporter and PSA). Transcriptomic profiling (RNA-seq) further identified novel pharmacodynamic biomarkers within these signaling cascades, providing deeper mechanistic insights into RIPTAC-mediated pathway rewiring. BRD4 target engagement assays independently confirmed ternary complex formation, demonstrating that BRD4 functional loss is selectively dependent on high AR expression, thereby defining AR expression as a critical determinant of the therapeutic window and tumor selectivity. *In vivo* CDX models further validated ternary complex formation, PSA reduction, and pharmacodynamic biomarker responses, showing that ternary assembly is preserved across biochemical, cellular, and tumor tissue contexts. II-5 was highly potent in AR-high prostate cancer models, with efficacy scaling across AR mutants and expression levels, highlighting a mechanistic correlation between AR expression and therapeutic effect. This enables RIPTAC to address resistance mechanisms such as AR amplification, point mutations, *etc*. Safety panel profiling indicates an overall favorable profile with limited off-target activity. Beyond AR–BRD4, RIPTAC expands the induced proximity landscape, aligning with TCIP paradigms and demonstrating broader applicability across oncogenic drivers. Together, computational and experimental evidence converge to highlight ternary complex stability and AR expression dependence as the mechanistic drivers of RIPTAC's therapeutic window. Importantly, our induced proximity platform, built on extensive expertise in targeted protein degradation (TPD), can be rapidly migrated to other target pairs, enabling first-in-class drug discovery programs and supporting both domestic and international partners.

No conflict of interest

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182 - PB-077 **Poster**

MJ34, a novel GSK3β inhibitor, restores autophagic flux and suppresses breast cancer growth

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Background: Glycogen synthase kinase-3β (GSK3β) is an attractive therapeutic target in breast cancer; however, clinically relevant inhibitors with validated target engagement remain limited. We evaluated the preclinical efficacy and mechanism of action of MJ34, a novel GSK3β inhibitor, in breast cancer.

Materials and Methods: Target engagement was assessed by GSK3β kinase assay and molecular docking. Antitumor activity was evaluated in MCF-7 cells using cell viability, clonogenic survival, cell-cycle, apoptosis, oxidative stress, mitochondrial membrane potential, and immunoblotting. Autophagic flux was assessed by LC3-II, p62, lysosomal acidification, and cathepsin D maturation. Antitumor efficacy was validated in an MCF-7 xenograft model.

Results: MJ34 potently inhibited GSK3β kinase activity (IC_{50} = **15.4 nM**). Molecular docking predicted stable binding within the ATP-binding pocket of GSK3β (binding affinity **−9.0 kcal/mol**). MJ34 significantly inhibited MCF-7 cell proliferation ($IC_{50} \approx$ **4 μM**), suppressed clonogenic survival, induced G1-phase arrest, increased reactive oxygen species, disrupted mitochondrial membrane potential, and promoted apoptotic cell death. Mechanistically, MJ34 increased inhibitory phosphorylation of GSK3β (Ser9) while reducing activating Tyr216 phosphorylation. Importantly, MJ34 restored productive autophagic flux, evidenced by reduced p62 accumulation, enhanced lysosomal acidification, and increased cathepsin D maturation despite minimal changes in LC3-II levels. These effects translated into significant suppression of tumor growth in the MCF-7 xenograft model.

Conclusions: MJ34 is a potent, target-validated GSK3β inhibitor with significant preclinical antitumor activity. Restoration of productive autophagic flux together with induction of apoptosis represents a key mechanism underlying its anticancer activity, supporting the further development of MJ34 as a targeted therapeutic for breast cancer.

No conflict of interest

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Poster Session: Drug Screening

183 - PB-078 **Poster**

Predictive MYC synthetic lethal screening reveals uncharacterized polo-like kinase 1 vulnerability in MYC high triple-negative breast cancer cells

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Background: MYC is a major cancer driver and an attractive therapeutic target, but effective and specific MYC-targeted therapies remain elusive. We therefore sought to identify and exploit vulnerabilities associated with MYC overactivity. Our work focused on triple-negative breast cancer (TNBC), a biologically aggressive subtype with limited targeted therapies, poor prognosis, and frequent MYC aberrations.

Material and methods: We applied the previously developed MYC V1V2 gene signature to classify 15 TNBC cell lines into MYC-high and MYC-low groups and analyzed drug sensitivity data from

five different screens to identify compounds selectively reducing viability in MYC-high cells. To validate MYC-specific drug responses, we generated inducible isogenic TNBC models and evaluated compounds in high-throughput viability assays. Finally, top hits were validated in additional isogenic MYC models by high-content imaging of fluorescent cell death markers and immunoblot analysis of cleaved caspase-3 and PARP to confirm differential viability and apoptotic responses between MYC-high and MYC-low states.

Results: Integrated *in silico* cell fitness data identified ~50 candidate drugs targeting established and novel MYC vulnerabilities, including topoisomerases, mechanistic target of rapamycin (mTOR), cyclin-dependent kinases (CDKs), and polo-like kinases (PLKs). *In vitro* screening in isogenic TNBC models validated roughly 50% of the *in silico* predicted MYC-selective drugs, with top hits targeting PLK1, kinesin spindle protein (KSP), histone deacetylase (HDAC), as well as paclitaxel. Validation of the targeted drugs in additional isogenic MYC cell line models yielded consistent MYC-high selectivity for KSP and PLK1, while HDAC inhibitor showed a heterogenous response. PLK1 is known to suppress MYC degradation by inhibiting E3 ubiquitin ligase FBXW7. However, this might play a lesser role in models where MYC is acutely induced. This prompted us to exam MYC protein levels along with cell death markers by immunoblotting upon concurrent MYC induction and PLK1 inhibition. MYC protein levels were unaffected by PLK1 inhibition across multiple MYC-inducible models, PLK1 inhibitors, and PLK1-targeting siRNAs, while cell death markers were consistently upregulated. The phenotype was further confirmed in a cell line with long-term MYC overexpression, suggesting that direct MYC protein regulation is not the primary driver of the synthetic lethality associated with PLK1 inhibition in MYC-high cells.

Conclusions: We combined i*n silico* and i*n vitro* drugs screening using unmodified and engineered cell line models combined with downstream functional validation to identify actionable cancer therapeutic targets that MYC high cells depend on. Particularly, PLK1 Inhibition uncovered a novel MYC protein level-independent vulnerability in MYC-high-signature TNBC cells.

No conflict of interest

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184 - PB-079 **Poster**

Discovery of novel anticancer seeds streptospherins A-F targeting cancer stem cells

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Background: Cancer stem cells (CSC) are one of the major causes of tumor recurrence because of their high malignancy and resistance to conventional anticancer agents and radiotherapy. We previously established a new CSC spheres culture system using human colorectal adenocarcinoma HT29 cells in a three-dimensional (3D) culture; which exhibited elevated CSC markers (Sox2, Nanog, and Oct4) and resistance to anticancer agents such as camptothecin and paclitaxel. Using this CSC culture system, we have re-discovered the polyether ionophore lenoremycin as a potent CSC inhibitor via induction of reactive oxygen species.

During our continuous screening of novel CSC inhibitors from in-house microbial culture broths, we found that *Streptomyces* sp. KUSC-240 produced novel CSC inhibitors named streptospherins A-F.

Materials and methods: *Streptomyces* sp. KUSC-240 was cultured in each production medium for 4-7 days, and streptospherins A-F were purified through a combination of silica gel column chromatography and reverse-phase HPLC. Their chemical structures were determined by extensive analyses of HR-ESI-MS, 1D/2D NMR, and ECD spectra and a synthetic approach.

HT29 cells cultured on poly(2-hydroxyethyl methacrylate) in 3D Tumorsphere Medium XF generate spheres with enhanced CSC-like properties. The inhibitory activities against CSC spheres were observed under microscopy and evaluated by a WST assay using Cell Counting Kit-8.

Results: The molecular formulae of streptospherins A-F were confirmed as $C_{23}H_{36}O_7$, $C_{24}H_{38}O_7$, $C_{23}H_{36}O_5$, $C_{24}H_{38}O_5$, $C_{25}H_{40}O_5$, and $C_{19}H_{30}O_5$, respectively. Their chemical structures were determined by 1D NMR, 2D NMR including COSY, HMQC, HMBC, and NOESY, and ECD. To determine the absolute configuration of streptospherin A with the five-substituted benzene and tetrahydropyran moieties, its asymmetric total synthesis was completed via a titanium-mediated cross-aldol reaction as a key reaction. Streptospherins B-F were revealed to consist of the same five-substituted benzene in the left fragment of streptospherin A and diverse linear polyketide side chains in the right fragment.

Streptospherins A-F inhibited CSC sphere formation and suppressed CSC growth. Among them, streptospherins C-E showed more potent inhibitory activity than streptospherin A, suggesting that these linear polyketide side chains are important for exhibiting their inhibitory activity. Detailed mode-of-action studies including target identification for streptospherins are currently underway in our laboratory.

Conclusion: Streptospherins have quite different pharmacophores compared with those of reported CSC inhibitors such as lenoremycin and napabucasin, indicating that streptospherins are promising anticancer seeds targeting CSC for cancer chemotherapy.

No conflict of interest

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185 - PB-080 **Poster**

High-throughput synergy screening of blood-brain-barrier penetrant compounds identifies druggable targets that potentiate BTK inhibition in CNS lymphomas

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Background: Primary CNS lymphoma is an aggressive form of DLBCL, genetically defined by the MCD/C5 cluster and driven by activating mutations in the BCR/MYD88 axis. BTK inhibitors, first ibrutinib, then the more selective tirabrutinib, now approved for this indication, have shown real clinical activity in PCNSL. Yet responses tend to be partial and rarely durable, and any combination strategy is constrained from the outset by the need for adequate CNS penetration. To identify synergistic, clinically translatable partners for BTK inhibitors, we screened a library of over 800 BBB-permeant compounds.

Methods: We screened a medicinal chemistry library of 824 BBB-penetrant compounds in TMD8, an MCD/C5-DLBCL cell line used as a PCNSL model since it bears *MYD88* and *CD79* mutations. Each compound was tested at 1000, 100, and 10 nM, alone and combined with a fixed dose of ibrutinib (0.5 nM), in two biological replicates. Viability was measured and the drug interaction quantified by the coefficient of drug interaction (CDI = viability_combo / [viability_A

× viability_B]); CDI < 1 indicates synergy. Hits were defined as minimum CDI < 0.85 reproduced in at least 3 of 6 valid readouts, and in both replicates.

Results: 98 compounds (approximately 12% of the whole library) met the synergy criteria, spanning over 50 annotated target classes, with synergy detected across the full 10-1000 nM range. Mechanistically coherent enrichment converged on the BCR-proximal PI3K/AKT/mTOR axis: three brain-penetrant PI3K inhibitors (GNE-317, bimiralisib, buparlisib) and mTOR modulators (PQR620, everolimus, rapamycin) potentiated ibrutinib, consistent with co-targeting signaling parallel to BTK. Other recurrent druggable classes included CDK inhibitors (abemaciclib, palbociclib, ribociclib, flavopiridol), HDAC inhibitors (vorinostat showed one of the deepest synergies, CDI 0.09), LRRK2 (GNE-7915, PFE-360), and pan-BCL2 inhibition (obatoclax). Notably, the screen independently recovered the clinical PCNSL backbone, methotrexate, and glucocorticoids (dexamethasone, methylprednisolone, prednisolone).

Conclusions: A BBB-penetrant synergy screen identified the PI3K-mTOR axis, CDK4/6, HDAC, and LRRK2 as the most promising partners, including several clinical-stage agents, to improve BTK-inhibitory activity in PCNSL. Identification of the PCSNL established methotrexate/steroid therapeutic backbone validated the platform. These leads should be prioritized to potentially improve outcomes for PCNSL patients.

No conflict of interest

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186 - PB-081 **Poster**

3D patient-derived cancer models for target validation and drug discovery

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Background: 3D Patient-derived cancer models (PDCMs) bridge the gap between conventional two-dimensional (2D) cancer cell cultures and *in vivo* patient-derived xenograft (PDX) models, offering several key advantages for translational cancer research. PDCMs more accurately preserve the intrinsic heterogeneity of human tumours, capturing both inter-patient variability and intra-tumour complexity. In contrast to 2D cell cultures, they self-organise into three-dimensional architectures that better recapitulate the structural and functional features of native tumour tissue. Furthermore, co-culture systems incorporating stromal components enable investigation of tumour–microenvironment interactions while maintaining a scalable and experimentally tractable platform.

Materials and Methods: A comprehensive panel of colorectal, lung, and breast cancer PDCMs has been established and molecularly characterised, with associated cancer-relevant gene mutation data, transcriptomic profiles, and proteomic datasets. Strategic partnerships with hospitals and commercial partners provide access to fresh and cryopreserved patient specimens for model generation. Robust and standardised workflows have been implemented to support the efficient expansion of the PDCM collection.

Results: Colorectal PDCMs were successfully characterised using histomorphological assessment (H&E staining) and proteomic profiling, confirming their ability to recapitulate key features of the original patient tumours and supporting their clinical relevance. Under-represented patient profiles have been identified and new models representing major KRAS mutations in CRC are being developed as well as expanding to pancreatic cancer (PDAC).

Drug response studies demonstrated target-specific sensitivities, with molecularly matched responses to BRAFV600E-specific and RAS(ON)-directed therapies, while heterogeneous responses were observed across conventional chemotherapy regimens. Internalisation and cell killing assays demonstrated ability to characterise therapeutic antibodies. To enable target validation studies, transfectability has been shown for many models, while a case study confirmed BRAF- and KRAS-dependency by RNAi. We are currently establishing an in vitro-to-in vivo PDCM platform enabling predictive in vivo efficacy validation.

Conclusions: These findings highlight the potential of PDCMs as clinically relevant preclinical models for investigating tumour biology, biomarker-driven therapeutic responses, and precision oncology approaches. We aim at increasing the number of available models to adequately represent patient diversity and clinical needs.

Conflict of interest: Other Substantive Relationships: All authors are full employees of Evotec

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Poster Session: Immune checkpoints

187 - PB-082 **Poster**

Age and tumor microenvironment informs anti-PD-1 checkpoint therapy efficacy in mice with TNBC

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Triple-negative breast cancer (TNBC) is characterized by highly aggressive tumorigenesis and poor survival rates. The two primary populations of women that are impacted by TNBC are young (20-40 years old) and older women (>70 years old). TNBC also demonstrates relatively high immune infiltration due to its high tumor mutational burden making it susceptible to immune checkpoint therapy (ICT), such as anti-PD-1. However, ICT success has been limited in TNBC (ORR ~18-20%) possibly due to immune-suppressive factors present in the tumor microenvironment (TME). Thus, to elucidate the contribution of the TME and age to anti-PD-1 therapy efficacy, E0771$^{GFP/Luc}$ TNBC cells were orthotopically implanted into old (>15-month-old) and young (2–5-month-old) female C57BL/6 mice. Tumor growth and *in vivo* imaging to track metastasis was assessed 2x/week. When tumors reached ~300 mm^3, anti-PD-1 therapy (5 mg/kg) was initiated 2x/week up to humane end points. Primary and metastatic tumors were imaged *ex vivo* and collected for immunofluorescence, flow cytometry, and single cell RNA sequencing (ScRNA-seq) to compare immune and stromal populations between anti-PD-1 responders, non-responders, and isotype control mice.

Anti-PD-1 therapy significantly decreased tumor volume in both young and old mice. Old mice treated with anti-PD-1 displayed responses ranging from complete tumor regression without recurrence, tumor regression with recurrence, and unresponsive tumors. In contrast, young mice did not experience complete regression or tumor recurrence, displaying a more aggressive tumor development phenotype. Immunofluorescence revealed that anti-PD-1 responders had a greater percentage of CD8$^+$ T-cells within the core of the

tumor, a greater percentage of tumor associated macrophages (TAMs), less cancer-associated fibroblasts (CAFs), less CAF-derived immunosuppressive ECM molecules, less T-regulatory cells, as well as less T-cell exhaustion. Flow cytometry illustrated that anti-PD-1 responders have less $FOXP3^+$ T-regs whereas non-responders showed less $CD4^+$ T-helper cells, less cytotoxic $CD8^+$ T-cells, and $CD86^+$ macrophages, and more $Ly6G^+$ polymorphonuclear myeloid derived suppressor cells. ScRNA-seq revealed an upregulation in genes related to immune cell function, apoptosis and tumor suppression, and immunological memory and a downregulation of genes related to the cell cycle, immune checkpoints, and tumor progression in anti-PD-1 responders. Moreover, ScRNA-seq demonstrated differences in immune cell populations between anti-PD-1 responders and non-responders, with durable responders exhibiting less TAMs, more $CD8^+$ T-cells, activated B cells, and plasma B cells. These findings indicate that the TME can affect ICT efficacy in the two primary TNBC populations and that anti-PD-1 therapy may increase efficacy in an older population due to TME immune and CAF differences.

No conflict of interest

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188 - PB-083 **Poster**

Signal Peptide–Derived Synthetic Peptides of CTLA4, TIM3, and LAG3 Inhibit CTLA4–B7 Binding

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Background: Immune checkpoint molecules that negatively regulate T-cell activation are key targets in cancer immunotherapy. CTLA4 binds B7-1 (CD80) and B7-2 (CD86) on antigen-presenting cells and suppresses T-cell responses. While anti-CTLA4 antibodies are used clinically, there is growing interest in alternative modalities such as peptides because of their lower cost and ease of manufacturing.

Materials and Methods: Synthetic peptides derived from the signal peptide (SP) sequences of CTLA4, TIM3, and LAG3 were designed. Representative peptides consisted of CTLA4-SP, TIM3-SP, or LAG3-SP fused to a LIMK2-derived NoLS auxiliary sequence, were C-terminally amidated, and were synthesized by Fmoc solid-phase peptide synthesis. CTLA4–B7 binding inhibition was assessed using commercial CTLA4–B7-1 (biotinylated) and CTLA4–B7-2 (biotinylated) assay kits. Peptides (5 or 10 μM) were incubated with plate-immobilized CTLA4 and biotinylated B7-1 or B7-2; binding was quantified using streptavidin-HRP chemiluminescence. Controls included a PD-1-derived SP peptide, the auxiliary sequence alone, and a no-peptide control.

Results: Peptides containing sequences derived from CTLA4-SP, TIM3-SP, or LAG3-SP inhibited CTLA4–B7-1 binding at 5 and 10 μM and also reduced CTLA4–B7-2 binding. In contrast, strong CTLA4 binding to B7-1/B7-2 was detected in the absence of peptide, and the PD-1-derived SP peptide and the auxiliary sequence alone showed no detectable inhibition, supporting that inhibitory activity derives from the SP sequences of CTLA4, TIM3, and LAG3 rather than from the auxiliary sequence.

Conclusions: SP-derived peptides from CTLA4, TIM3, and LAG3 inhibit CTLA4 interactions with B7-1 and B7-2, suggesting the potential of a peptide-based immune checkpoint inhibition approach as an alternative to anti-CTLA4 antibodies.

Conflict of interest: Corporate-sponsored Research: TOAGOSEI Co.,Ltd Research Award

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189 - PB-084 **Poster**

CEACAM6 and immune checkpoints in Pancreatic Ductal Adenocarcinoma modulate an immunosuppressive tumor microenvironment: insights from single cell, spatial and cell line studies

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Background: Carcinoembryonic cell adhesion molecule 6 (CEACAM6), a cell adhesion immune checkpoint receptor of the Ig-family is a poor prognostic marker overexpressed in both KRAS mutant and wild type and all subtypes of Pancreatic Ductal Adenocarcinoma (PDAC) (Pandey et al. Sci Rep 2019). Here, we profile PDAC cell types across multiple single-cell and spatial datasets to characterize checkpoint ligand and receptor expression and show that CEACAM6 knockout remodels the immune tumor microenvironment (TME) in PDAC cell lines. Given that PD-L1/PD-1 blockade fails in PDAC, our objective is to identify which checkpoint pathways are functionally relevant in this uniquely immunosuppressive TME. The findings will inform combination therapy pairing for our anti-CEACAM6 monoclonal antibody and derivatives.

Methods: scRNA-Seq and spatial datasets were obtained (GSE212966, PRJCA001063, GSE199102, E-MTAB16856, GSE277116, GSE327056). Pipelines with Seurat and Squidpy were used to analyze gene-cell data matrices and spatial coordinates. Expression was log-normalized per section, and markers were visualized per spot as violin, box and spatial feature plots. Dimensionality reduction methods (UMAPS, PCA) were used to identify distinct clusters. SingleR, celldex R packages and celltypist were used for cell type marking. CellChat and Liana were used to identify known ligand receptor pairs. CEACAM6 Knockout BxPC3 cells lines were used to study T cells infiltration in a co-culture system (Tumor cells with $CD8^+$ T cells).

Results: CEACAM6 was found to be enriched in epithelial cell types, had higher expression in both treated and untreated specimens and expressed in immune, cancer associated fibroblasts (CAFs) and stroma. CEACAM1 and CD276 (B7-H3) were highly expressed in epithelial cells across data sets but were expressed in other cell types too. CTLA4, LAG3 and TIGIT were found in abundance in multiple PDA cells across couple of datasets. CEACAM1 and CEACAM6 were found to be highly expressed in treated samples compared to other immune markers. Cell-cell communication analysis showed crosstalk within epithelial types and between epithelial and immune and fibroblasts respectively. CEACAMs had strong interaction signals within epithelial cells. BxPC3 and HPAFII cell line studies revealed that $CD8^+$ T cells efficiently infiltrated the tumor in CEACAM6 KO spheroids compared to CEACAM6 WT demonstrating a critical role for CEACAM6 in the recruitment of $CD8^+$ T cells. The KO also had reduced TIM3 and LAG3 compared to WT cells. CEACAM6 expression levels influence the differentiation states of T cells and promote an exhaustion state.

Conclusion: CEACAM6 functions as an immunosuppressive receptor and is a promising complementary immune checkpoint target. Deciphering the complex immunosuppressive landscape of the TME in PDAC informs novel therapeutic interventions in the clinic.

No conflict of interest

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190 - PB-085 **Poster**

Quantitative Vascular Tortuosity (QVT) Radiomics Identifies Therapeutic Response Beyond RECIST 1.1 in Heavily Pretreated NSCLC Patients Receiving Ateganosine/THIO-Based Immunotherapy

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Background: RECIST 1.1 remains the standard method for radiologic response assessment in solid tumors but relies primarily on changes in lesion size and may underestimate biologic responses induced by immunotherapy. This limitation may be particularly relevant in heavily pretreated non-small cell lung cancer (NSCLC), where objective response rates are often in the single-digit range and identification of even a small number of additional responders can meaningfully affect clinical interpretation. THIO-101 acts to induce tumor cell death resulting in decreased interstitial pressure and vascular normalization, improving ICI delivery. Quantitative radiomics approaches evaluating tumor-associated vascular architecture may provide earlier and more sensitive indicators of treatment activity. We explored the ability of the Quantitative Vessel Tortuosity (QVT) Score to characterize treatment response in patients enrolled in the THIO-101 study.

Methods: Serial CT scans from heavily pretreated advanced NSCLC patients treated with THIO-based therapy were analyzed using the Picture Health Px Platform generating a composite QVT score derived from vascular metrics including vessel branching, curvature, torsion, radius, and volume. Longitudinal QVT changes were compared with conventional RECIST 1.1 target lesion assessments.

Results: Twenty-four evaluable imaging time points from nine patients were analyzed. RECIST 1.1 classified all assessments as stable disease (SD). However, QVT analysis demonstrated significant changes in tumor vasculature that are not captured by lesion size alone, with one patient being assessed as having a partial response (PR), including marked reductions in QVT scores in several patients who remained categorized as SD by RECIST 1.1. Notably, radiomics-derived response patterns in certain SD patients closely resembled those observed in the RECIST-defined SD patient, suggesting underlying biologic activity not fully captured by size-based criteria. In a population where response rates are typically low, early recognition of an additional PR response could have a meaningful impact on reported efficacy outcomes.

Conclusions: QVT radiomics detected dynamic treatment-associated vascular remodeling that was not captured by conventional CT-based RECIST 1.1 assessments, with one patient being assessed as having a partial response (PR). These findings suggest that radiomics-based vascular evaluation may complement standard imaging by identifying biologically responsive patients who would otherwise be classified as having stable disease. In heavily pretreated NSCLC populations, where objective response rates are typically low, the identification of even a small number of additional responders may have a meaningful impact on the assessment of therapeutic benefit. Future work will include prospective validation to confirm these observations.

Conflict of interest: Ownership: MAIA Biotechnology Inc

Other Substantive Relationships: Employment at MAIA Biotechnology Inc

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Poster Session: Molecular Targeted Agents

191 - PB-086 **Poster**

Phase Ib study of OMO-103 in combination with gemcitabine and nab-paclitaxel in first-line metastatic pancreatic ductal adenocarcinoma

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Background: MYC is a central oncogenic driver dysregulated in most cancers and associated with therapeutic resistance. OMO-103 is a first-in-class MYC inhibitor with demonstrated target engagement and clinical activity. This Phase Ib study (NCT06059001) evaluates the safety, pharmacodynamics, and preliminary efficacy of OMO-103 in combination with gemcitabine and nab-paclitaxel in first-line metastatic pancreatic ductal adenocarcinoma (mPDAC).

Materials and methods: Patients with untreated mPDAC received intravenous OMO-103 plus gemcitabine/nab-paclitaxel. The study included a safety run-in followed by expansion. Tolerability was optimized following a protocol amendment separating OMO-103 infusion from chemotherapy administration. Primary endpoint was safety; secondary endpoints included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), pharmacokinetics/pharmacodynamics, and exploratory biomarkers. Tumor biopsies, circulating tumor DNA (ctDNA), and transcriptomic analyses were performed.

Results: At data cutoff (end of March 2026), 26 patients were enrolled. OMO-103 was well tolerated, with no treatment-related serious adverse events; 13% of adverse events (mostly grade 1 and 2) were considered possibly related or related. Protocol optimization eliminated infusion-related reactions and enabled sustained treatment. In the optimized cohort (n = 12), ORR was 33% by RECIST (44% by volumetric analysis) and DCR was 83%, with a 33% PFS rate at 8 months. ctDNA analysis showed 75% molecular responders (> 50% reduction). OMO-103 was detected in tumor tissue in 10/10 patients, confirming tumor delivery. Paired biopsies from 8 patients demonstrated suppression of MYC target gene sets and downregulation of KRAS-associated programs. Clinical benefit was associated with MYC transcriptional shutdown, whereas progressive disease lacked this effect. Higher baseline MYC activity correlated with response. Exploratory analyses suggest that ATM-altered tumors may derive enhanced clinical benefit, consistent with MYC-dependent modulation of DNA damage response pathways. In parallel, circulating soluble factors are under evaluation as predictive biomarkers, potentially reflecting treatment-associated immune modulation.

Conclusions: OMO-103 combined with gemcitabine and nab-paclitaxel shows a favorable safety profile, clear evidence of tumor delivery and MYC pathway inhibition, and encouraging preliminary efficacy in first-line mPDAC. Biomarker analyses support a mechanistically driven, patient-selection strategy and warrant further clinical development.

Conflict of interest: Ownership: MEB, LS are founders and shareholders of Peptomyc SL. SCS LF and MN are shareholders of Peptomyc SL

Advisory Board: AJMM is in the following advosry boards: GSK, Pfizer, BMS-Celgene, Sanofi, AstraZeneca, MSD, Lilly, Servier, Roche, Taiho, Leo Pharma, Regeneron, Jazz Pharmaceuticals

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Other Substantive Relationships:

SCS, LF, MEB, MN and LS are or were employees employees of Peptomyc at the time of this work. AJMM: Speakers' bureau: Rovi, Menarini, Stada, Medscape, Incyte

Patents/intellectual property: genomic risk score model for venous thromboembolism in cancer patients

liquid biopsy technology. TM: Honoraria/speaking/educational activities: BioNTech, Daïchi, Esteve, Janssen, Jazz Pharmaceuticals, Lilly, Novartis

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192 - PB-087 **Poster**

REC-7735: A potent, mutant-selective PI3Kα H1047R inhibitor with preclinical efficacy across multiple solid tumors and no hyperglycemia or other metabolic liabilities

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Background: The *PIK3CA* H1047R mutation is a primary oncogenic driver in multiple solid tumors, including breast, colorectal, endometrial, and ovarian cancers. While current PI3Kα inhibitors (e.g., alpelisib, inavolisib) have demonstrated clinical benefit, their lack of selectivity over wild-type (WT) PI3Kα results in significant systemic toxicities including severe hyperglycemia and

hyperinsulinemia in >60% of patients. These adverse events often require dose reductions or discontinuation, leaving many patients unable to tolerate and therefore unable to benefit from existing PI3Kα-targeting therapies. Furthermore, underlying diabetes or pre-diabetes renders a large subset of patients entirely ineligible for treatment with approved PI3Kα inhibitors. Moderately selective pan-mutant PI3Kα inhibitors in clinical development have shown reduced rates of severe hyperglycemia; however, more than 30% of patients still experienced mild to moderate hyperglycemia. REC-7735 is an AI-precision-designed, orally bioavailable inhibitor that selectively targets the H1047R mutant protein while sparing WT PI3Kα, with the potential to overcome the limitations of current PI3Kα inhibitors.

Material and methods: REC-7735 potency and selectivity were evaluated in biochemical and cellular assays. *In vivo*, antitumor activity was characterized in multiple human cancer xenografts (breast, H&N, lung, ovarian, and colorectal). Metabolic safety concerning hyperglycemia and hyperinsulinemia was assessed in naïve Balb/c mice and Zucker diabetic fatty (ZDF) rats.

Results: *In vitro*, REC-7735 demonstrates potent inhibition of PI3Kα H1047R with >100-fold selectivity over the WT. In contrast, approved PI3Kα inhibitors show no mutant selectivity, and pan-mutant PI3Kα inhibitors in late clinical development demonstrate only ~5–10-fold selectivity. *In vivo*, REC-7735 shows dose-dependent tumor growth inhibition across multiple models, outperforming or synergizing with standard-of-care selective estrogen receptor degraders (SERDs) and CDK4/6 inhibitors. In contrast to non-selective and moderately selective inhibitors, REC-7735 did not impact blood glucose, insulin levels, or other metabolic markers in naïve or diabetic animals even at supra-efficacious doses.

Conclusions: By selectively targeting the H1047R mutation and sparing WT-mediated glucose metabolism, REC-7735 offers a potentially improved therapeutic window. This profile may allow for higher dose intensity and prolonged treatment duration, potentially leading to superior clinical outcomes in patients with *PIK3CA* H1047R-mutated solid tumors, including pre-diabetic and diabetic cancer patients who are ineligible for existing PI3Kα-targeting treatments. REC-7735 is being developed for the treatment of *PIK3CA* H1047R-mutated solid tumors, including breast, colorectal, endometrial, and ovarian cancers.

Conflict of interest: Ownership: All authors are current or previous employees of Recursion Pharmaceuticals Inc, with real or optional ownership interest in Recursion.

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193 - PB-088 **Poster**

ASP2453, a novel KRAS G12C inhibitor, shows potent anti-tumor activity in various KRAS G12C-mutated preclinical models including genetically engineered mouse model

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Background: KRAS is one of the most frequently mutated oncogenes across various cancers and remains an important therapeutic target. Several inhibitors targeting KRAS G12C mutant protein have been approved for clinical use, and additional agents are in clinical trials with promising therapeutic benefit. In this presentation, we describe the anti-tumor activity of ASP2453, a KRAS G12C selective inhibitor, in preclinical models, including subcutaneous and orthotopic xenograft mouse models as well as syngeneic mouse models. Furthermore, to better reflect the biology of KRAS G12C-driven lung cancer, we evaluate the anti-tumor activity of ASP2453 in genetically engineered mouse model (GEMM) with lung-specific expression of Kras G12C.

Material and methods: We evaluated the *in vitro* inhibitory activity of ASP2453 on KRAS-GTP and cell proliferation using a RAF-RBD pulldown assay and a CellTiter-Glo assay in KRAS G12C-mutated human cancer cell lines. We assessed the anti-tumor activity of ASP2453 *in vivo* in subcutaneously, orthotopically xenografted models and in syngeneic models using cancer cells harboring KRAS G12C mutation. For GEMM studies, we generated Cre-ER$^{(+/+)}$/Kras$^{G12C(+/-)}$/p53$^{flox/flox}$ mice by breeding Scgb1a1-CreER^{TM} mice, p53$^{flox/flox}$ mice and Kras G12C knock-in mice. Lung tumorigenesis was induced by tamoxifen, and the anti-tumor effect of ASP2453 was evaluated.

Results: ASP2453 selectively suppressed the KRAS-GTP and inhibited the growth of KRAS G12C-mutated cancer cells *in vitro*. *In vivo* studies, once-daily oral administration of ASP2453 induced tumor regression and/or prolonged survival in subcutaneous and orthotopic xenograft models and in syngeneic models. In the GEMM, lung tumor formation was confirmed following tamoxifen-induced Cre recombination, and treatment with ASP2453 prolonged survival and reduced the number of lung tumor foci.

Conclusions: ASP2453 demonstrated robust anti-tumor activity across multiple *in vitro* and *in vivo* preclinical models, including a lung-specific KRAS G12C GEMM that may better recapitulate the biology of human KRAS G12C-mutated lung adenocarcinoma. Collectively, these results may support the clinical translational potential of KRAS G12C inhibition and provide a foundation for advancing broader KRAS-directed drug development.

Conflict of interest: Other Substantive Relationships: All authors are employees of Astellas Pharma Inc.

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194 - PB-089 **Poster**

MLK4 mutations define a targetable AKT–mTOR dependency in colorectal cancer

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Mixed lineage kinase 4 (MLK4) is recurrently mutated in colorectal cancer (CRC), yet its therapeutic significance remains poorly defined. We investigated whether MLK4 alterations create a targetable signalling dependency in CRC.

Isogenic HCT116 MLK4 wild-type and knockout models, endogenous MLK4-mutant CRC cell lines, and patient tumour datasets were analysed using transcriptomic, proteomic, and metabolic profiling. Functional studies included MLK4 reconstitution, acute protein degradation, kinase inhibitor screening, immunoblotting, and Seahorse extracellular flux analysis.

MLK4-mutant tumours were associated with inferior clinical outcome and enrichment of AKT–mTOR signalling programmes. Loss or mutation of MLK4 enhanced AKT pathway activation and increased mitochondrial respiratory capacity. MLK4-deficient cells displayed increased dependence on glutamine metabolism and altered glutathione homeostasis, indicating rewiring of mitochondrial carbon utilisation and redox adaptation. Importantly, MLK4-mutant and MLK4-null models exhibited selective sensitivity to AKT–mTOR pathway inhibition, including everolimus and dual PI3K/

mTOR blockade. Multi-omic analyses further revealed coordinated mitochondrial and biosynthetic adaptations associated with MLK4 loss.

MLK4 mutations define a therapeutically vulnerable CRC subtype characterised by AKT–mTOR pathway dependency and associated mitochondrial metabolic rewiring. These findings support MLK4 status as a predictive biomarker for AKT–mTOR-directed therapies and provide a rationale for clinical evaluation of pathway inhibitors in MLK4-altered CRC.

No conflict of interest

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195 - PB-090 **Poster**

Mapping Hidden Vulnerabilities in Genetically Stratified Colorectal Cancer with ONCO Prime

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Colorectal cancer (CRC) remains a major clinical challenge, highlighting the need for therapeutic strategies that move beyond single-gene alterations and capture functional dependencies driven by oncogenic pathway activation. To address this need, we developed ONCO Prime, an integrated discovery and validation platform designed to identify actionable vulnerabilities in genetically defined cancer contexts.

ONCO Prime combines clinically relevant model systems, including healthy human intestinal stem cells, engineered isogenic CRC models carrying key oncogenic drivers such as APC and KRAS alterations, and patient-derived primary cultures. These models are amenable to genetic perturbation and high-throughput pharmacological testing, enabling functional interrogation of tumor-specific dependencies. Molecular profiling, transcriptomic analyses, and computational approaches further support patient stratification and help link functional phenotypes with pathway states.

Using genome-wide CRISPR/Cas9 loss-of-function screening followed by orthogonal validation in patient-derived CRC models, we identified multiple synthetic lethal interactions associated with WNT and RAS/MAPK pathway dysregulation. The platform enabled prioritization of novel targets with first-in-class therapeutic potential and also revealed opportunities for drug repurposing using clinically advanced or approved agents. In genetically stratified CRC models, selected pharmacological interventions demonstrated robust in vitro activity, including context-dependent responses and combination potential.

Together, these findings demonstrate that ONCO Prime can systematically connect cancer genotype, pathway activity, and functional vulnerability to nominate therapeutically relevant targets. The platform provides a scalable foundation for precision oncology drug discovery and supports the development of both first-in-class therapeutic programs and repositioning strategies for defined CRC patient populations.

No conflict of interest

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197 - PB-092 **Poster**

ANS05, a Novel Irreversible Brain-penetrant HER2 TKI, Targets Clinically Relevant HER2 Alterations and Demonstrates Potent Broad-Spectrum Preclinical Activity

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Background: HER2 alterations (amplification/overexpression/mutations) drive tumorigenesis primarily via MAPK and PI3K/AKT pathways, occurring in breast (15–20%), gastric (10–20%), NSCLC (1–4%), and other solid tumors. Despite available therapies, key unmet needs persist: (1) no standard targeted therapy after ADC progression; (2) limited selective oral TKIs for HER2-overexpressing cancers beyond breast; (3) inadequate CNS penetration; (4) narrow therapeutic indices due to EGFR-related toxicities. These gaps support the development of ANS05, a novel irreversible, brain-penetrant, HER2 TKI with broad-spectrum activity and an EGFR-sparing safety profile.

Material and methods: Comprehensive non-clinical studies were conducted to evaluate the mechanism of action, pharmacological function, kinetics of system exposure, and the safety profile of ANS05.

Results: ANS05 is a novel, highly selective covalent HER2 inhibitor with potent broad-spectrum activity across HER2 alterations. Kinase profiling at 1 μM confirmed high specificity, with >99% inhibition restricted to HER2/HER4. In cellular assays, ANS05 showed potent broad-spectrum activity against HER2 tyrosine kinase domain (TKD) mutations (L755S, V777L, L869R, Ex20ins; IC_{50} = 0.1–12.7 nM), HER2-amplified/overexpressing cancer cells (breast, gastric, esophageal, ovarian, NSCLC; IC_{50} = 0.8–25.6 nM), and HER2-NRG1 fusion (IC_{50} = 3.3 nM), outperforming Zongertinib. Notably, ANS05 exhibited markedly weaker activity against wild-type EGFR in A431 cells (IC_{50} = 7495 nM) compared to Zongertinib (926.4 nM), yielding a substantially higher selectivity index for HER2 alterations over wild-type EGFR (293–74950-fold for ANS05 vs. 1.3–4632-fold for Zongertinib). This enhanced selectivity supports a broader therapeutic window and a lower risk of EGFR-mediated toxicities.

In vivo, ANS05 was well tolerated and showed potent, dose-dependent antitumor activity across multiple HER2-altered models. In subcutaneous HER2-amplified/overexpressing xenografts, BID dosing (1–20 mg/kg) achieved tumor growth inhibition (TGI) of 39–107% in OE19 esophageal cancer and 103–126% in BT-474 breast cancer. In a Ba/F3 HER2 Ex20ins (A775-G776insYVMA)

model, 10–40 mg/kg BID achieved 85–101% TGI. In an intracranial NCI-N87 gastric cancer model, ANS05 (10/30 mg/kg BID; 60 mg/kg QD) demonstrated robust brain penetration and durable tumor suppression (TGI ≥103%) with significant survival benefit, outperforming Zongertinib and inducing regression in Zongertinib-refractory tumors. PK/PD analyses confirmed a clear exposure-response relationship and effective target engagement.

Conclusion: ANS05 is a selective, brain-penetrant, covalent HER2-TKI exhibiting broad-spectrum preclinical activity against HER2 alterations and favorable *in vivo* PK/PD/tolerability, and is now poised for Phase 1 clinical study.

No conflict of interest

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198 - PB-093 **Poster**

ANS02, a Novel, Non-covalent, Brain-penetrant EGFR TKI, Overcomes Clinically Relevant Resistance Mutations and Demonstrates Broad Preclinical Activity in EGFR-Mutant NSCLC Models

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Background: EGFR-mutant non-small cell lung cancer (NSCLC) harbors diverse EGFR variants: classical (ex19del, L858R), exon 20 insertions (ex20ins), and atypical mutations. While EGFR tyrosine kinase inhibitors (TKIs) have markedly improved clinical outcomes, their utility is limited by acquired resistance and incomplete subtype coverage. The acquired T790M mutation confers resistance to first-/second-generation TKIs, whereas C797S renders the third-generation osimertinib ineffective. Given that no approved TKI covers the full EGFR variant spectrum, highly selective pan-mutant inhibitors are urgently needed.

Material and methods: Comprehensive non-clinical studies were conducted to evaluate the mechanism, pharmacology, pharmacokinetics, and safety of ANS02.

Results: ANS02, a novel non-covalent EGFR inhibitor, demonstrated potent and broad-spectrum activity against diverse EGFR mutations. It inhibited classical mutations (ex19del, L858R) and T790M with IC_{50} values (0.4-7.6 nM) comparable to osimertinib. Notably, its non-covalent binding mode conferred superior efficacy against osimertinib-resistant C797S mutations, with IC_{50} of 0.7 nM against dual mutants (ex19del/C797S, L858R/C797S) and 3.7–7.5 nM against triple mutants (ex19del/T790M/C797S), respectively. ANS02 also effectively inhibited atypical mutations (G719X, S768I, etc.; IC_{50} = 5.4–12.4 nM) and exon 20 insertions. Importantly, it exhibited markedly weaker inhibition of wild-type EGFR (IC_{50} = 1288 nM vs. osimertinib's 426 nM), achieving a higher mutant selectivity index (ANS02: 12–3220 fold vs. osimertinib: 7–426 fold), suggesting a broader therapeutic window. Kinase profiling at 1 μM confirmed high specificity, with >99% inhibition limited to EGFR/HER2/HER4.

In vivo, ANS02 demonstrated favorable tolerability and potent, dose-dependent antitumor efficacy across diverse EGFR-mutant models. It achieved robust tumor growth inhibition (TGI 110–126%) in the sensitive PC-9 model (ex19del) at 1–9 mg/kg/day, and significant activity (TGI 33–105%) in the acquired resistance Ba/F3 model (L858R/C797S) at 0.6–6 mg/kg/day. Complete tumor regression was observed in a triple-mutant PDX model (ex19del/T790M/C797S) at doses ≥3 mg/kg/day. A key finding was its excellent intracranial efficacy in a brain metastasis model (NCI-H1975-luc, L858R/T790M), where all tested doses (3–12 mg/kg QD; 24 mg/kg QOD) induced potent tumor suppression (TGI ≥ 95.4%) and significantly extended survival, doubling the median survival at the highest dose compared to vehicle (37.0 vs. 18.0 days). Supportive PK/PD analyses confirmed favorable brain penetration and sustained target inhibition.

Conclusions: ANS02, a highly selective, brain-penetrant, non-covalent EGFR-TKI, demonstrates potent broad-spectrum preclinical activity along with favorable pharmacokinetics and safety, and is now advancing in Phase 1 studies in both the US and China.

No conflict of interest

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199 - PB-094 **Poster**

CRBN-Based Pan-KRAS PROTAC Degraders with Sub-Nanomolar Potency and Broad In Vivo Efficacy Across Clinically Relevant KRAS Mutant Tumors

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Background: KRAS mutations, including G12D, G12V, G12C, and G12A, represent major oncogenic drivers across multiple cancers. Cereblon (CRBN)-recruiting PROTACs offer a compelling strategy capable of eliminating these mutant proteins. Here we report the preclinical development of potent pan-KRAS PROTAC degraders designed to address this broad mutational landscape.

Materials and Methods: Leveraging novel high-affinity cyclic CRBN E3 ligase ligands to expand ternary-complex design space, we developed a focused series of bifunctional pan-KRAS degraders. Degradation potency and kinetics were quantified by HiBiT reporter assay; anti-proliferative activity was measured in cancer cell lines harboring KRAS G12D, G12V, G12C, or G12A mutations. Pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor efficacy were characterized in corresponding mouse xenograft models; cross-species PK was evaluated in rats, dogs, and monkeys.

Results: The lead degrader, CW-11055, achieved sub-nanomolar cellular potency (DC50 ≤1 nM; IC50 ≤1 nM) across all four mutant KRAS contexts. Once-weekly IV dosing produced dose-dependent tumor regression or growth inhibition of 60%–>95% TGI across G12D (SW1990, Gp2d), G12V (SW620), G12C (MIA PaCa-2, SW1116), and G12A (RERF-LC-Ad1) xenograft models. Robust tumor penetration was confirmed (965 ng/g at 168 h), correlating with sustained target depletion and downstream signaling suppression. Cross-species PK was favorable, and once-weekly doses up to 60 mg/kg were well tolerated in mice with no overt systemic toxicity.

Conclusions: CW-11055 demonstrates potent, broad-spectrum anti-tumor activity across clinically relevant KRAS mutant models with a favorable preclinical PK and safety profile, supporting its

advancement as a clinical candidate for diverse KRAS-driven malignancies.

No conflict of interest

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200 - PB-095 **Poster**

Structure-based optimization of orally bioavailable EP300-selective degraders

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Background: EP300 and CBP are lysine acetyltransferases (KATs) that regulate gene expression, cell proliferation, and differentiation, functionally compensating for each other in normal tissues. In malignant contexts, their frequent dysregulation makes them compelling therapeutic targets; however, their high sequence homology has historically impeded the development of selective small-molecule inhibitors. Given their redundant biological roles, dual inhibition elicits severe hematopoietic toxicities, notably thrombocytopenia, thereby highlighting the urgent need for paralog-selective interventions. To address this challenge, targeted protein degradation (TPD) represents a powerful modality that enables the precise modulation of such highly homologous proteins.

Methods: Heterobifunctional degraders targeting EP300 were optimized through structure-based drug design (SBDD). Molecular dynamics (MD) simulations and high-precision free-energy perturbation (FEP) were utilized to optimize the stability of the formed EP300–CRBN ternary complex. Additionally, solid tumor models potentially responsive to EP300 degradation were prioritized using a machine-learning model trained on DepMap datasets.

Results: This rational optimization yielded highly potent and selective EP300 degraders. Mechanistic studies confirmed that the lead compound operates *via* a ubiquitin–proteasome system (UPS)-dependent pathway and demonstrates stable ternary complex formation as assessed by TR-FRET analysis. Through cell-based assays, we experimentally validated the indications predicted by our machine-learning model, where the lead compounds demonstrated robust antiproliferative activity. These findings indicate that the cellular response is driven by a distinct dependency on EP300, independent of its paralog protein, CBP. Proteome-wide profiling further supported this on-target selectivity, showing minimal off-target degradation. Driven by its excellent oral bioavailability, the optimized leads successfully translated these findings into observable antitumor efficacy in mouse xenograft models.

Conclusions: These results validate our FEP-driven SBDD framework for the rational design of selective degraders and establish these differentiated EP300-selective leads, backed by robust PK profiles, as promising candidates for advanced preclinical evaluation.

Conflict of interest: Other Substantive Relationships: All authors are current employees of Hanmi Pharmaceutical Co., Ltd.

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201 - PB-096 **Poster**

NVL-249 is an allosteric covalent inhibitor of AKT1 E17K with selectivity over wild-type AKT in preclinical studies

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Background: AKT1 E17K is an oncogenic hotspot mutation detected in ~6% of metastatic HR+/HER2- breast cancer and in ~1% of all cancers. Capivasertib, an FDA-approved ATP-competitive pan-AKT inhibitor, has shown clinical efficacy in solid tumors with PI3K/AKT pathway alterations; however, on-target inhibition of wild-type AKT (AKT1/2/3) has been associated with dose-limiting toxicities of capivasertib, including hyperglycemia, diarrhea, and rash. NVL-249 is a novel allosteric inhibitor designed to covalently target the mutant lysine in AKT1 E17K and inhibit oncogenic signaling with selectivity over wild-type AKT.

Material and methods: Compounds were profiled using AKT phosphorylation and/or cell viability assays in LAPC4 (AKT1 E17K) and ZR-75-1 (wild-type AKT) human cancer cell lines. Covalent engagement with AKT1 E17K was assessed using X-ray crystallography. Antitumor activity was studied in mice bearing patient-derived xenograft (PDX) models of HR+/HER2- (ST3632) and triple-negative (HBCx-2) breast cancer. Hyperglycemia was assessed using insulin tolerance test in non-tumor-bearing mice following 5 days of AKT inhibitor treatment.

Results: NVL-249 inhibited LAPC4 (AKT1 E17K) with $IC_{90} < 20$ nM in the AKT phosphorylation assay and $IC_{50} < 10$ nM in the cell viability assay. NVL-249 exhibited >50-fold selectivity for AKT1 E17K over wild-type AKT in the cell viability assay, compared to capivasertib (<10-fold). Crystallography indicated a covalent adduct between NVL-249 and the mutant lysine in AKT1 E17K. NVL-249 treatment induced tumor regression at well-tolerated doses in HR+/HER2- and triple-negative breast cancer PDX models expressing AKT1 E17K. Hyperglycemia was not observed in mice treated with efficacious doses of NVL-249 but was observed in mice treated with capivasertib.

Conclusions: The preclinical characteristics of NVL-249, including potent inhibition of AKT1 E17K and selectivity over wild-type AKT, warrant further research into its potential for targeting AKT1 E17K-mutant solid tumors while limiting toxicities associated with PI3K/AKT-pathway inhibition.

Keywords: AKT, AKT1 E17K, Breast Cancer, Covalent Inhibitor, Allosteric Inhibitor

Conflict of interest: Ownership: SK, FG, KLA, TN, AT, JCH and HEP are employees and stockholders of Nuvalent, Inc.

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202 - PB-097 **Poster**

ALTA3263, a KRAS-selective, pan-mutant (ON/OFF) KRAS inhibitor, demonstrates potent monotherapy activity and synergistic combination with EGFR blockade in KRAS-mutant colorectal and pancreatic cancer models

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Background: KRAS mutations are present in approximately 50% of colorectal cancers (CRC) and over 90% of pancreatic ductal adenocarcinomas (PDAC) and represent a major driver of resistance to EGFR-targeted therapy. ALTA3263 is an oral, non-covalent pan-KRAS inhibitor engaging KRAS in both GTP-bound (ON) and GDP-bound (OFF) states with sub-nanomolar cellular potency and >500-fold selectivity for KRAS over NRAS and HRAS, potentially enabling a more favorable therapeutic index relative to pan-RAS approaches.

Materials and Methods: Antiproliferative activity (72h CTG) was assessed across a broad KRAS-mutant cell line panel with comparative profiling against a RAF/MEK inhibitor, an OFF-state inhibitor, and a tricomplex pan-RAS inhibitor. In vivo efficacy was evaluated in a KRAS-mutant CRC xenograft model (LS180 G12D) as monotherapy and in combination with cetuximab, and in KRAS-mutant PDAC xenograft models in combination with other anticancer agents. DUSP6 expression by qPCR served as the pharmacodynamic readout.

Results: ALTA3263 demonstrated potent antiproliferative activity across KRAS-mutant CRC and PDAC cell lines, with sub-nanomolar to low-nanomolar IC50 values and sustained pathway suppression reflecting continuous target engagement. In vivo, ALTA3263 demonstrated superior tumor growth inhibition (TGI) activity in several tumor models. In a KRAS-mutant CRC xenograft model, the combination of ALTA3263 with cetuximab demonstrated additive antitumor activity, supporting co-inhibition of KRAS and EGFR as a rational therapeutic strategy in CRC, where EGFR reactivation is a recognized resistance mechanism. In KRAS-mutant PDAC xenograft models harboring MTAP deletion, the combination of ALTA3263 with other anticancer agents demonstrated synergistic antitumor activity, providing preclinical rationale for combining KRAS inhibition with synthetic lethality in PDAC.

Conclusions: ALTA3263 is a potential best-in-class pan-KRAS inhibitor with compelling monotherapy activity in multiple KRAS-mut and WT CRC and PDAC models and isoform-selective tolerability in KRAS-mutant CRC and PDAC, and demonstrates combination benefit with cetuximab in CRC and with other anticancer agents in PDAC. These data support clinical investigation of ALTA3263 in KRAS-mutant CRC and PDAC, including in combination with EGFR-directed therapy. ALTA3263 is under clinical investigation in KRAS-mutant solid tumors (NCT06835569).

No conflict of interest

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203 - PB-098 **Poster**

Engineered p53 mRNA Analogs Restore Tumor Suppressor Function in TP53-Mutant Cancers

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TP53, the gene encoding the tumor suppressor protein p53, plays a pivotal role in regulating cell cycle progression and apoptosis. Alterations in TP53 represent one of the most prevalent oncogenic events across diverse cancer types, significantly contributing to tumorigenesis and unfavorable clinical outcomes. Various therapeutic approaches have been explored to restore wild-type p53 activity, including small molecules that reactivate mutant p53, inhibitors targeting negative regulators of p53 to prevent its degradation, and adenoviral vector-based gene delivery systems. However, these strategies are often limited by the heterogeneity of TP53 mutations and suboptimal clinical efficacy.

In this study, we introduce an advanced synthetic mRNA-based therapeutic platform designed to restore p53 function in cancers with high frequencies of TP53 mutations. Instead of utilizing the native wild-type p53 sequence, we engineered an enhanced p53 analog with superior transcriptional potency to address the functional diversity of TP53 mutations. The Hanmi p53 mRNA construct was extensively optimized, incorporating tailored 5′ and 3′ untranslated regions (UTRs), an improved open reading frame (ORF), and proprietary 5′ capping technology to enhance expression and stability. The therapeutic potential of this engineered mRNA was assessed in both in vitro and in vivo models of TP53-mutant cancers, including lung, ovarian, and hepatocellular carcinoma models.

Our findings demonstrate that the Hanmi synthetic p53 mRNA analog effectively suppresses tumor cell proliferation by promoting apoptosis and inducing cell cycle arrest in TP53-mutant cancer models. Notably, the engineered p53 analog exhibited enhanced tetramerization capacity relative to the wild-type protein, leading to increased transcriptional activity. In an ovarian cancer xenograft model, treatment with the p53 mRNA analog resulted in significant tumor growth inhibition without detectable toxicity as measured by body weight changes. In vitro, robust anti-proliferative activity was also observed in hepatocellular carcinoma cell lines, comparable to that seen in ovarian cancer cells, and a synergistic effect was further demonstrated when combined with lenvatinib. Furthermore, in taxane-resistant cancer cell lines, the p53 mRNA analog showed greater efficacy compared with wild-type p53 mRNA.

Taken together, these results highlight the therapeutic potential of the Hanmi p53 mRNA analog as a novel strategy for targeting TP53-mutant cancers and overcoming drug resistance, thereby offering a promising avenue for precision oncology.

No conflict of interest

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204 - PB-099 **Poster**

Engineered STING mRNA Analog Enables Dual Antitumor Activity Through Immune Activation and Tumor-Intrinsic Signaling

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The emergence of immunotherapy has fundamentally transformed the treatment landscape in oncology; however, durable clinical responses remain confined to a limited subset of patients. There is a growing need for strategies that effectively activate innate immune signaling to induce robust and sustained antitumor immunity. The Stimulator of Interferon Genes (STING) pathway plays a central role in regulating type I interferon responses and orchestrating antitumor immunity. Despite promising preclinical data in syngeneic tumor models, first-generation STING agonists have demonstrated limited clinical efficacy, primarily due to challenges in systemic delivery, toxicity concerns, and tumor-intrinsic resistance mechanisms such as low STING expression.

To address these limitations, we developed a systemically deliverable mRNA-based therapeutic platform encoding a ligand-independent STING analog, designed to bypass dependence on endogenous STING activation. Optimization of STING mRNA candidates was conducted using both mouse and human reporter systems to achieve high functional activity. In human peripheral blood mononuclear cells (hPBMCs), treatment with the optimized STING mRNA induced robust secretion of IFN-β and IL-6, as quantified by

ELISA. Activation of downstream STING signaling pathways was further confirmed in both cancer and immune cells using qRT-PCR and western blot analyses. Comprehensive immune profiling was performed through RNA sequencing of treated hPBMCs to identify transcriptional signatures associated with immune activation.

Systemic administration of the optimized STING mRNA resulted in significant tumor growth inhibition in MC38 and LL/2 syngeneic mouse models. Notably, in the immune-cold LL/2 model, treatment led to reprogramming of the tumor microenvironment, characterized by a reduction in pro-tumorigenic immune cell populations and enhancement of antitumor immune responses. STING mRNA treatment increased the proportion of activated dendritic cells and M1-like macrophages, supporting its potent immunostimulatory capacity. Furthermore, platform optimization effectively reduced hepatic accumulation of STING, thereby improving tolerability by minimizing excessive liver-associated STING activation.

Collectively, these findings demonstrate that a ligand-independent, mRNA-encoded STING analog can overcome key limitations of conventional STING agonists, including delivery inefficiency and reduced target expression. Transient systemic activation achieved through this platform facilitates durable antitumor immunity, highlighting the potential of STING mRNA therapeutics as a next-generation modality in cancer immunotherapy.

No conflict of interest

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205 - PB-100 **Poster**

SC3613, a Mutant-Selective EGFR Degrader, Demonstrates Improved Safety and Durable Antitumor Activity in Combination with Amivantamab in TKI-Resistant NSCLC

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Background: Acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), particularly driven by secondary mutations such as C797S, remains a major therapeutic challenge in non-small cell lung cancer (NSCLC). In addition, limited selectivity over wild-type (WT) EGFR contributes to dose-limiting toxicities, including skin adverse events. Mutant-selective EGFR degradation represents a promising strategy to achieve potent and sustained pathway suppression while minimizing WT-associated toxicity. Furthermore, combination approaches with EGFR-targeting antibodies may enable more comprehensive inhibition of EGFR signaling and improve response durability.

Materials and Methods: SC3613, a heterobifunctional mutant-selective allosteric EGFR degrader, was evaluated for mutant selectivity and safety profile, including WT EGFR sparing and skin toxicity in BALB/c nude mice. Antitumor efficacy was assessed as monotherapy and in combination with amivantamab in BaF3 allograft models harboring EGFR L858R/C797S mutations. Comparative analyses included lazertinib alone and in combination with amivantamab. Tumor growth inhibition, regression kinetics, post-treatment durability, and tolerability were evaluated.

Results: SC3613 selectively degraded mutant EGFR while exhibiting minimal activity against wild-type (WT) EGFR and no significant reduction in total EGFR levels, confirming its strong mutant selectivity. Notably, SC3613 demonstrated a superior safety profile, particularly with respect to skin toxicity. In BALB/c nude mice, both SC3613 and osimertinib showed high distribution to tumor and skin tissues (Kp > 1), indicating comparable tissue exposure. However, SC3613 was associated with markedly reduced skin toxicity, whereas osimertinib induced dose-dependent inflammatory skin lesions. These findings suggest that the improved safety profile of SC3613 is attributable to WT EGFR sparing rather than reduced tissue exposure.

As a monotherapy, SC3613 induced rapid and profound tumor regression in EGFR TKI–resistant models. Amivantamab and lazertinib monotherapies exhibited limited and variable efficacy, and their combination achieved only partial and less durable tumor control. In contrast, SC3613 combined with amivantamab produced consistent and sustained tumor suppression across all subjects, resulting in deeper tumor regression than the lazertinib-based combination and no detectable tumor regrowth after treatment cessation. The combination was well tolerated, with no significant body weight loss observed.

Conclusions: SC3613 demonstrates strong mutant selectivity and WT sparing–driven safety, including reduced skin toxicity. Its combination with amivantamab enables deeper, consistent, and durable tumor control beyond current therapies, supporting further development in EGFR TKI–resistant NSCLC.

Conflict of interest: Ownership: The authors are employees of Dong-A ST, which sponsored this study.

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206 - PB-101 **Poster**

Transcriptional and epigenetic inducers of proximity as antitumor agents in marginal zone lymphomas

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Background: Marginal zone lymphomas (MZLs) have an indolent course, but they can transform into aggressive lymphomas (Arribas et al, 2015; Florindez et al, 2024). BCL6 is not usually expressed in MZL cells (Laurent & Bertoni, 2026), but it can be expressed during progression or histologic transformation (Bult et al, 2025).

Transcriptional/epigenetic inducers of proximity (TCIPs) are a promising class of compounds. TCIP1 is a molecule in which the BCL6 binder BI3812 is covalently linked to the BET protein family binder JQ1 (Gourisankar et al, 2023). TCIP1 rewires cellular transcriptional circuits by recruiting the transcriptional activator BRD4 to BCL6-repressed genes, thereby re-expressing them.

Here, we assessed the benefit of targeting BCL6 with TCIP1 as a single agent and in combination with the BTK inhibitor ibrutinib in MZL cell lines, providing a rationale for future exploration of this novel therapeutic approach for MZL patients.

Material and Methods: Antiproliferative activity was assessed using the MTT assay. The effect of the combinations was estimated using the Chou-Talalay combination index and the MuSyC algorithm.

Results: We observed a dose-dependent antiproliferative effect of TCIP1 in parental MZL cell lines, with IC50 values in the nM range at 72h (SSK41, 11 nM; VL51, 29 nM; Karpas1718, 56 nM). The effect

was largely maintained in the derivatives VL51-Ibru and Karpas1718-Ide, both of which are resistant to BTK inhibitors (Arribas et al, 2024; Arribas et al, 2026). Reduced activity was observed in the SSK41-Vene cell line, resistant to BCL2 inhibitors, compared with its parental cell line.

The activity observed with TCIP1 was specific, as it was always higher than that achieved with the negative controls Neg1 (BRD4 non-binding) and Neg2 (BCL6 non-binding).

The IC50 values were approximately 10-fold higher than those reported in diffuse large B-cell lymphoma models (Gourisankar et al., 2023), consistent with the distinct roles of BCL6 in DLBCL and MZL. Importantly, the most sensitive model, SSK41, showed the highest BCL6 expression paired with multiple lesions in the gene's 5′ noncoding/first-intron regulatory region, and its IC50 was comparable to that of DLBCL.

The addition of TCIP1 to the BTK inhibitor ibrutinib was strongly synergistic in both the SSK41 and its BCL2 inhibitor-resistant derivative. A small benefit was also observed in the Karpas1718 parental cells, whereas none was observed in VL51.

Conclusions: The BCL6-targeting TCIP1 shows single-agent, dose-dependent activity in MZL models, with greater activity at higher BCL6 expression. Notably, its activity might not be affected by the development of resistance to BTK inhibition, and it could even enhance the activity of BTK inhibition. BCL6-targeting TCIPs might be of interest in selected MZL patients with BCL6 expression at the time of progression or transformation.

No conflict of interest

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207 - PB-102 **Poster**

First characterization of the synthetic peptide CIGB-552 in B-cell lymphomas demonstrates antitumor activity in drug-resistant models and enhancement of BTK-targeted therapies

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Background: Despite major advances in targeted therapies, relapse and acquired resistance remain major challenges in B-cell lymphomas. CIGB-552 is a synthetic antitumor peptide that stabilizes COMMD1, promoting RelA (NF-κB) degradation and modulating HIF1A and oxidative stress pathways (Fernandez et al, 2013). A Phase 1 study has shown early signs of clinical activity with no significant adverse events in patients with advanced solid tumors (Vallespi et al, 2021). Here, we investigated its antitumor preclinical activity, mechanism of action, and therapeutic potential across B-cell lymphomas.

Material and methods: CIGB-552 activity was evaluated in cell lines derived from marginal zone lymphoma (MZL; n = 6), mantle cell lymphoma (MCL; n = 5), activated B-cell-like diffuse large B-cell lymphoma (ABC-DLBCL; n = 3), germinal center B-cell-like DLBCL (GCB-DLBCL; n = 4), and canine DLBCL (n = 1), as well as in MZL models with acquired resistance to BTK, PI3K, or BCL2 inhibitors (i) (n = 8). Antitumor activity was assessed using MTT and live-cell imaging assays. Mechanism of action was investigated through analyses of cell death, cellular internalization, transcriptomic and proteomic profiling, and immunoblotting. Combinations with BTK-targeting agents were evaluated using the Chou–Talalay combination index and the MuSyC algorithm.

Results: CIGB-552 displayed dose-dependent antitumor activity across all lymphoma subtypes, with the greatest sensitivity observed in MZL (median IC50, 18 μM) and MCL (21 μM) models, while maintaining activity in ABC-DLBCL (44 μM), GCB-DLBCL (37.5 μM), and canine B-cell lymphoma (22 μM). Activity was retained in MZL models with acquired resistance to BTKi, PI3Ki and BCL2i. Importantly, no significant growth inhibition was observed in non-malignant B-cell lymphoblastoid cells at concentrations that were active in lymphoma cells. Peptide uptake occurred predominantly through endocytosis. CIGB-552 induced context-dependent cell death, including apoptosis, necrosis, or mixed phenotypes depending on the lymphoma model. Integrated multi-omics and immunoblot analyses showed suppression of BCR/NF-κB, PI3K/AKT/mTOR, MAPK and JAK/STAT signaling together with reduced RelA, AKT, ERK, cyclin D1, BCL2, and MCL1 levels.

CIGB-552 enhanced the activity of BTK-targeting therapies, including inhibitors (ibrutinib, zanubrutinib, pirtobrutinib) and degraders (NX-5948), in parental and resistant MZL cells.

Conclusions: This study provides the first characterization of CIGB-552 in B-cell lymphomas and identifies it as a promising peptide-based therapeutic candidate with activity across MZL, MCL and DLBCL, including models with acquired resistance to BTKi, PI3Ki and BCL2i. Its multimodal activity and enhancement of BTK-targeted therapies support its further preclinical development as both a single agent and combination partner.

No conflict of interest

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208 - PB-103 **Poster**

NMS-812, a clinical stage dual PERK and GCN2 modulator, is effective in AML as monotherapy and in combination with venetoclax/azacitidine in venetoclax resistant setting

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Background: Recent findings have shown that Integrated stress response (ISR) plays a key role in AML insurgence and chemoresistance through promotion of leukemogenesis and maintenance of leukemic stem cells. ISR has also been involved in chemoresistance. PERK and GCN2 kinases are fundamental components of ISR modulating endoplasmic reticulum (ER) stress and amino acid deficiency, respectively. Both kinases converge indeed on the regulation of the transcription factor ATF4, a master transcriptional regulator of stress response. ATF4 plays a role both in survival and in cell death, depending on the context and extent of stress. Alteration of ATF4 levels in cancer cells exposed to stress is expected to convert ATF4 from a survival factor to a pro-apoptotic factor.

Materials and methods: The effect of NMS-812 was tested in vitro and in vivo in AML models and characterized by analyzing in vitro proliferation, mechanism of action by western blot and transcriptomic analysis, in vivo efficacy, and combination studies with standards of care (SoC).

Results: NMS-812 single agent treatment caused tumor regression in the p53-mutant and venetoclax-resistant AML MOLM16 model at well tolerated doses. The antitumor effect was correlated with clear biomarker modulation in vitro and ex-vivo. NMS-812 rapidly induced ATF4 and downregulated anti-apoptotic proteins such as MCL1, while inducing pro-apoptotic proteins such as Noxa and Puma, and ATF3, which is a negative regulator of Bcl-XL, with rapid apoptosis induction even at low doses. Synergism with venetoclax was observed in vitro in both venetoclax-resistant and venetoclax-sensitive cell lines. In vivo combination of NMS-812 with venetoclax or venetoclax-azacitidine resulted in synergistic effect at well tolerated doses even in the venetoclax-resistant model MOLM16.

Conclusion: NMS-812, a first-in-class dual PERK/GCN2 inhibitor, is endowed with regression activity as a single agent and in combination with SOC in venetoclax resistant TP53 mutated AML model, suggesting PERK/GCN2/ATF4 axis modulation as a new targeted therapy for AML even in chemo-resistant settings. Based on these data, a Phase 1 clinical trial has been initiated in AML patients, with the possibility of opening a combination arm with venetoclax/azacitidine in the R/R setting.

No conflict of interest

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209 - PB-104 **Poster**

A potential best-in-class anti-GDF15 sweeping antibody for the treatment of cancer cachexia

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Background: Conventional antibodies, by complexing with the antigen (Ag), can cause Ag accumulation, thereby requiring higher and more frequent dosages. In contrast, a "sweeping" antibody endowed with pH-dependent binding, releases the Ag in the acidic endosome, leading to rapid Ag clearance, while itself can be reused for repeated Ag binding via FcRn. GDF15, an abundant catabolic cytokine in most cancers, is the main culprit of cancer-associated cachexia. A GDF15 neutralizing antibody was efficacious in a phase 2 trial, but treatment caused massive and sustained increase in total GDF15 levels, suggesting that GDF15 may be a prime target for sweeping antibody development. Here we report a next-generation GDF15-clearing antibody with potentially improved cachexia control.

Methods: After analyzing the AI-predicted structure of human GDF15 in complex with a blocking antibody, we introduced histidine substitutions in its CDRs to effectuate dissociation at acidic pH. We also engineered the Fc to enhance FcγRIIb (for immune complex (IC) internalization) and FcRn binding (for antibody recycling). We measured pH-dependent binding by SPR, determined specificity across the TGFβ family by ELISA, and assessed internalization using pH sensor dyes. Finally, we monitored the body weight and serum free GDF15 in hGDF15-producing MC38 tumor-bearing h*FcγRIIb*/h*FcRn* double knock-in mice.

Results: Cryo-EM of the GDF15/Fab complex (overall resolution: 3.0 Å) confirmed AI-predicted structural modeling and showed H chain residues Q50 and E95 making close contact with GDF15 at S232 and R233. Histidine substitutions maintained hGDF15 binding at pH 7.4 with K_D = 0.27 nM but led to 68-fold weaker binding at pH 6.0, contrasting with the pH-insensitive parental antibody. The resulting antibody V149 recognized human and cynomolgus GDF15 but not other TGF-b family proteins. Fc engineering increased FcγRIIb binding by 3-fold at pH 7.4 and FcRn binding by 11-fold at pH 6.0, leading to rapid internalization. Notably, a single injection of V149 at 10 mg/kg produced a 3.3% weight gain in tumor-bearing mice by day 14 in contrast to 10.7% and 10.0% weight loss by vehicle control and the parental antibody, respectively ($p < 0.05$). A lower dose (3 mg/kg) of V149 was also more effective in delaying weight loss. Serum free GDF15 was suppressed by 99% within 1 day of V149 injection and remained at a low level for more than 14 days, as opposed to the massive rebound observed by day 7 with the parental antibody, mirroring the weight recovery. The profound sweeping effect extended to the source of GDF15 as demonstrated by markedly lower intra-tumor GDF15 levels than the parental blocking antibody group.

Conclusion: A GDF15 sweeping antibody discovered through AI-assisted structure design mediates rapid and sustained GDF15 clearance *in vivo*, resulting in superior body weight preservation in cancer cachexia.

Conflict of interest: Ownership: Xiaodan Cao and Taylor Guo hold stock options in the Jeyou.

Other Substantive Relationships: All authors are employees of Shanghai Jeyou Pharmaceutical Co.,Ltd.

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210 - PB-105 **Poster**

The role of mutant p53R175H in de novo activation of von Willebrand factor expression in tumor cells

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Background: Von Willebrand factor (VWF) is an adhesive glycoprotein central to hemostasis and thrombosis. Normally, it is exclusively expressed in endothelial cells and megakaryocytes. However, recently, its expression has been detected in some non-endothelial/megakaryocytic cancer cells. We previously showed de novo VWF expression in osteosarcoma cells, and its association with increased GATA6 (activator) and reduced NF-IB (repressor) binding to the VWF promoter. NF-IB is a downstream target of the transcription factor p53, which is frequently mutated in cancer. Thus, we explored the role of p53 in this process.

Materials and methods: We surveyed the Human Protein Atlas and p53 database to assess NF-IB and TP53 status across various cancer cell lines. We used the H1299 non-small cell lung carcinoma cell line, which is null for p53 and plakoglobin (a p53-interacting/modifying factor), to examine the effect of exogenously expressed p53 [wild type (WT) and mutants] on VWF expression. The findings were validated in ovarian cancer lines with endogenous p53 variants. We assessed the molecular mechanisms and functional consequences of de novo VWF expression.

Results: The analyses of 100 VWF-positive cancer cell lines revealed NF-IB downregulation and/or p53 mutation. Expression of hotspot mutant p53R175H (conformational), but not p53R273H (contact) or wild-type, activated VWF expression in H1299 cells. Mechanistically, p53R175H interacted with NF-IB and GATA6, preventing NF-IB repressive and promoting GATA6 activating functions, leading to VWF transcriptional activation. Functionally, p53R175H-induced VWF expression was associated with markedly

enhanced cancer cell-platelet heteroaggregates formation, a process that could contribute to cancer-associated thrombus formation and increased metastasis. Co-expression of plakoglobin reversed VWF upregulation and reduced platelet adhesion. siRNA-mediated VWF knockdown significantly reduced both endothelial adhesion and heteroaggregates formation, directly supporting a functional contribution of cancer cell-derived VWF in these processes. Furthermore, we compared two ovarian cancer cell lines, p53R175H-expressing TYK-nu cells and p53-WT A2780 cells. Only TYK-nu cells expressed VWF and showed mechanism of expression and functional consequences similar to those observed in VWF-expressing H1299 and osteosarcoma cells.

Conclusions: These findings identify a novel mechanism of mutant p53-induced VWF expression and reveal plakoglobin as a potent antagonist of this pathway.

No conflict of interest

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211 - PB-106 **Poster**

Hypoxia-inducible factor-2α inhibition with casdatifan combines with checkpoint receptor modulation to enhance tumor control

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Background: Hypoxia-inducible Factor (HIF)-2α is regulated in an oxygen-dependent manner: hypoxic or pseudohypoxic conditions stabilize HIF-2α protein, resulting in pro-tumorigenic gene transcription. Inhibition of HIF-2α has been demonstrated to control tumor growth, particularly in cancers like clear cell renal cell carcinoma (ccRCC) where HIF-2α is a tumorigenic driver. ccRCC is also clinically responsive to immune checkpoint inhibition, making these tumors an attractive opportunity to combine a cancer cell-targeted approach with immune-modulating agents. Combining therapeutic modalities involves weighing the potential additive or synergistic therapeutic benefit with the respective combination toxicity profile.

Methods: We leveraged multiple approaches to determine if the pharmacology associated with HIF-2α inhibition combines favorably with checkpoint receptor blockade. Primary human $CD14^+$ monocyte-derived M2-polarized macrophages (used to model pro-tumorigenic tumor-associated macrophages) and T cell subsets were subjected to small molecule HIF-2α inhibition in normoxia and hypoxia. Following this treatment, HIF protein stabilization was quantified by Western blot, transcriptional changes were probed by RNAseq, and cell functionality was monitored through proliferation and cytokine secretion. *In vivo,* efficacy of combining HIF-2α inhibition with checkpoint receptor blockade was determined using a humanized ccRCC model, whereas toxicity was assessed in an immune checkpoint inhibitor-induced hepatotoxicity (ICIH) mouse model and through standard assessments in rats and dogs.

Results: Hypoxia alone did not result in HIF-2α protein accumulation in resting primary human T cells; however, T cell receptor stimulation triggered HIF-2α accumulation in hypoxia. Inhibition of HIF-2α with the clinical small molecule casdatifan (cas) did not affect the functionality of primary human $CD4^+$ (regulatory or conventional) or $CD8^+$ T cells. Unlike T cells, hypoxia alone stabilized HIF-2α in M2 macrophages, and over a third of hypoxia-driven transcriptional changes were HIF-2α-dependent. Additionally, M2-polarization specific genes upregulated in response to hypoxia were reversed with HIF-2α inhibition. Combination of cas with immune checkpoint blockade afforded the practical benefits of both therapies in tumor control: rapid reduction in ccRCC tumor size and durable responses. In the ICIH model, cas did not exacerbate hepatotoxicity as assessed by multiple markers, and when cas was evaluated as a single agent in rats and dogs, no evidence of peripheral or pathological immunotoxicity nor hepatotoxicity occurred at exposures equivalent to supratherapeutic doses in humans.

Conclusions: The risk-benefit profile for combining HIF-2α inhibition with checkpoint inhibition appears favorable with preclinical evidence of increased efficacy and low risk of added toxicity.

Conflict of interest: Ownership: Abstract authors are current or former employees of Arcus Biosciences, Inc. with stock ownership.

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212 - PB-107 **Poster**

A Potent, Highly Selective and Non-Racemic CDK2 Molecular Glue Degrader A01-2

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Background Cyclin dependent kinase 2 (CDK2) plays a key role in cell cycle progression and has become an important cancer target. However, CDK2 kinase inhibitors often off-target other CDK family members, causing toxicity and limitation of clinical development. A molecular glue degrader (MGD) has the potential to significantly improve selectivity and avoid CDK-associated off-targets.

Materials and Methods A01-2 was incubated in human plasma to assess racemic conversion. Degradation activity, Rb phosphorylation and Cyquant assays were run on various cell lines following regular protocols. Four cell types (tumor cells and PBMCs) were treated at 1 μM for DIA proteomics. Human CD34 + hematopoietic stem cells (HSCs) and a normal human colon epithelial cell line NCM460 were used to assess the safety window of A01-2. Pharmacokinetic (PK) parameters were obtained in CD-1 mice, SD rats and cynomolgus monkeys. Multiple mouse cancer models were utilized to test A01-2 alone or in combination with a CDK4/6 inhibitor ribociclib. The *in vivo* safety were evaluated on rats and monkeys following 14-day repeated dose.

Results A01-2 potently and nearly completely degrades CDK2 in HEK293 and T47D cells (DC50 2∼4 nM, 24 h). Proteomics from all tested cells showed robust CDK2 degradation (∼15% remaining) without other CDK affected (all > 90% remaining) and no other off-targets at 24 h (1 μM, 8000–10000 proteins/assay). CDK1 degradation was tested and DC50 of A01-2 was > 30 μM. Unlike other MGDs prone to racemic conversion (up to 50%), A01-2 was stable in human plasma. A01-2 potently inhibited Rb phosphorylation and cell cycle progression in tumor cell lines. On human HSCs and NCM460 cells, the CDK2 kinase inhibitor PF4091 strongly inhibited viability (IC50 1.6 and 2.4 μM, respectively), whereas A01-2 showed no obvious inhibition even at 30 μM, suggesting excellent safety of A01-2. PK studies showed > 40% bioavailability in mice, rats and monkeys. For efficacy, A01-2 dose-dependently inhibited the growth of CCNE1-amplified tumors (Kuramochi, MKN1). In MKN1, A01-2 at 10/30/100 mg/kg BID gave TGIs of 85.9%, 104.5% and 111.1%, much more potent than PF4091 at 100 mg/kg BID (TGI 80.9%). As

expected, A01-2 alone was inactive or weak in non-CCNE1 tumors (4 triple negative breast cancer models and 2 ER+/HER2− breast cancer models), but combined with ribociclib showed potent inhibition in all tested models. For example, in Hs578T, monotherapy TGIs were 55.7% (A01-2 alone) and 58.8% (Ribociclib alone), but combination TGI reached 102.3%. In 14-day repeated dose toxicity studies, no drug-related adverse effects were seen in rats or monkeys even at highest tested dose (exposure >200,000 h·ng/mL).

Conclusions A01-2 is a potent, highly selective, non-racemic CDK2 and safe molecular glue degrader, an ideal candidate for monotherapy or combination with CDK4/6 inhibitors.

No conflict of interest

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213 - PB-108 **Poster**

Phase 1 Multicenter Study of ACE1831, an Allogeneic Anti-CD20 Antibody-Conjugated Gamma Delta T-Cell Therapy, in Adult Subjects with Relapsed/Refractory CD20-Expressing B-Cell Malignancies

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Background: Autologous CAR-T therapy has been used to treat B-cell lymphoma; however, CAR-T manufacturing requires genetic modification, resulting in high costs and potential safety concerns. ACE1831 is an off-the-shelf allogeneic gamma delta T cell (gdT) therapy chemically conjugated with an anti-CD20 antibody, designed to overcome autologous limitations while reducing risks of Graft-versus-Host Disease (GvHD) and cytokine release syndrome. This first-in-human study evaluated safety, PK, pharmacodynamics, and preliminary efficacy of ACE1831 as monotherapy or in combination with obinutuzumab.

Material and Methods: In this Phase 1 multicenter trial (NCT07061938), a 3+3 dose-escalation design enrolled adults who failed ≥2 prior therapies. Group A received up to 4 cycles of ACE1831 monotherapy (300, 600, 1000×10^6 cells), and Group B received up to 4 cycles of ACE1831 (600, 1000×10^6) with obinutuzumab. Risk-adapted lymphodepleting chemotherapy (cyclophosphamide/fludarabine) preceded each infusion. Responses were assessed by Lugano criteria. Cellular PK was analyzed by ddPCR and flow cytometry.

Results: A total of 16 patients were treated (monotherapy, n=12; combination, n=4). Most had aggressive B-cell lymphomas (predominantly DLBCL) and advanced disease (stage III/IV: 83.3% and 100%) and were heavily pretreated (median prior lines: 5.5 [2–13] and 4.5 [3–5]).

No dose-limiting toxicities or treatment discontinuations due to TEAEs occurred, and no Grade 5 events were attributed to ACE1831. No cases of GvHD, ICANS, or clinically significant cytokine release syndrome were observed. Toxicities were primarily transient cytopenias related to lymphodepletion.

ORR was 25.0% in both monotherapy (3/12) and combination (1/4), with no clear dose or combination effect; CR rates were 8.3% vs 25.0% and PR 16.7% vs 0%. One monotherapy CR was durable (16.4 months) and one combination CR remains ongoing (2.6+). Median DoR was 1.3 and 2.6+ months; median PFS was 1.8 (95% CI: 0.7–3.8) and 1.9 months (95% CI: 0.6–NE), with 37.5% (6/16; 5/12 vs 1/4) achieving PFS ≥3 months.

PK analysis showed median T_{max} values of 3-9 days with no accumulation following repeat dosing. Cytokine profile remained within a safety range across cycles, supporting a favorable safety profile.

	Monotherapy (N=12)	Combination Therapy (N=4)	Total (N=16)
ORR, n (%)	3 (25.0)	1 (25.0)	4 (25.0)
CR	1 (8.3)	1 (25.0)	2 (12.5)
PR	2 (16.7)	0	2 (12.5)
SD	3 (25.0)	0	3 (18.8)
PD	5 (41.7)	2 (50.0)	7 (43.8)
Not evaluable	1 (8.3)	1 (25.0)	2 (12.5)
Median DoR (mo) + Censored value	1.3 (1.0–16.4)	2.6+	1.3

Conclusions: ACE1831 demonstrated a favorable safety profile with no GvHD, ICANS, or treatment-related mortality. Antitumor activity was observed in heavily pretreated patients. Repeat dosing was feasible without accumulation, supporting further development of this allogeneic gdT platform.

Conflict of interest: Ownership: Sonny Hsiao

Board of Directors: Sonny Hsiao

Corporate-sponsored Research: Don Stevens, Amelia Langston, Jason Romancik, Rushang Patel, Ranjit Nair, Shang-Ju Wu, Tung-Liang Lin, Kuan-Der Lee, Tsai-Yun Chen, Eric Tse

Other Substantive Relationships: Erick Huang, Albert Lin, Cathy Kao, Lin Jia, Sai-Wen Tang, Arthur Foo, Steph Chien, Janet Pan

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215 - PB-110 **Poster**

GPNMB as a switch for tumor-associated macrophages reprogramming: development and application of a cross-species nanobody toolbox

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Background: M2-like tumor-associated macrophages (TAMs) orchestrate an immunosuppressive tumor microenvironment (TME) that drives cancer progression. Glycoprotein non-metastatic B

(GPNMB) is a critical molecular switch that enforces this M2 phenotype while synergistically driving cancer metastasis. Therefore, elucidating GPNMB's oncogenic mechanisms is essential. Here, we introduce a set of novel nanobodies (Nbs) as a toolbox to manipulate GPNMB functions. Leveraging these Nbs' precision to target distinct epitopes, we evaluate their ability to reprogram TAMs and suppress tumor invasion, while dissecting domain-specific GPNMB signaling.

Material and methods: A library of mouse/human cross-reactive anti-GPNMB Nbs was generated and screened. Functional efficacy was evaluated in macrophage-cancer cell co-cultures (Thp-1, SK-MEL-28). Nb-mediated TAM transcriptional reprogramming was quantified via qRT-PCR. To assess disruption of aggressiveness, melanoma cells (SK-MEL-28, B16-F10) were evaluated via wound-healing and 3D spheroid assays. To link structural engagement with biological response, in silico models of GPNMB-Nb complexes were generated. Supported by epitope binning via Octet, functional interfaces triggering TAM repolarization were mapped.

Results: We isolated high-affinity Nbs demonstrating potent immunomodulatory and anti-invasive properties. In co-cultures, Nb treatment drove robust TAM repolarization, down-regulating M2 markers (GPNMB, CD206, Arginase 1) and up-regulating pro-inflammatory M1 signatures (TNF-α, CXCL10). Concurrently, specific Nbs disrupted tumor cell motility, significantly inhibiting SK-MEL-28 migration in wound-healing assays, with 3D spheroid validations. Mechanistically, in silico analysis revealed that Nbs engage distinct GPNMB extracellular domains. Epitope binning validated these predicted spatial clusters, mapping how domain-specific interference uncouples the synergistic GPNMB signaling axis.

Conclusions: This study establishes our novel Nb toolbox as a powerful platform to both probe and modulate GPNMB biology within TME. Having demonstrated that targeted Nb intervention reprograms TAMs and limits tumor motility, structural mapping defined how spatial epitope engagement dismantles this pro-tumoral crosstalk. Ultimately, we offer a clinically translatable framework to rationally design next-generation, GPNMB-targeted immunotherapies.

Data table

Candidate	Binding Affinity (KD)	Epitope Cluster	GPNMB Expression	CD206 Expression (M2 marker)	TNF-α Expression (M1 marker)
Control	/	/	1.0 (Baseline)		
Nb-H4	<1.0E-3 nM	Domain 1, 2	0.36 ±0.021*	0.87 ± 0.145	12.48 ± 1.036*
Nb-H6	<1.0E-3 nM	Domain 3	0.75 ±0.032*	0.68 ± 0.088	5.78 ± 0.564*
Nb-H81	1.51 nM	Domain 3	0.49 ±0.010*	0.37 ± 0.044*	6.83 ± 0.482*
Nb-M62	0.079 nM	Domain 2	0.44 ±0.015*	0.56 ± 0.159*	13.43 ± 0.471*

*p < 0.01

No conflict of interest

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216 - PB-111 **Poster**

Anti-tumor efficacy of the selective oral KRAS G12D dual ON/OFF inhibitor VS-7375 as a single agent and in combination with pan-RAS inhibition

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Background: VS-7375 is a selective oral reversible switch-II pocket KRAS G12D ON/OFF inhibitor (G12Di) with high affinity (K_D ~15 pM) and long residence time (18–24 h). VS-7375 is currently in clinical trials as monotherapy and in combinations for patients with KRAS G12D pancreatic, colorectal, non-small cell lung and other cancers (TARGET-D 101; TARGET-D 201). We evaluated potential advantages of VS-7375 (ON/OFF) monotherapy vs the ON-only tricomplex inhibitors zoldonrasib (KRAS G12D) and daraxonrasib (pan-RAS) and also compared the combination of VS-7375 + daraxonrasib vs zoldonrasib + daraxonrasib combination.

Materials and methods: Antitumor activity of VS-7375, zoldonrasib and daraxonrasib alone or in combinations were compared in KRAS G12D xenograft models. Gene expression analyses were performed to assess target inhibition and resistance mechanisms.

Results: Across KRAS G12D xenograft models, VS-7375 demonstrated greater antitumor activity than either zoldonrasib or daraxonrasib. In the KP4 pancreatic cancer model, all three agents initially induced tumor regression; however, after ~20 days of continuous dosing, tumors treated with zoldonrasib or daraxonrasib resumed growth, whereas VS-7375 maintained tumor regressions. Pharmacodynamic analyses showed that loss of efficacy at day 20 with zoldonrasib or daraxonrasib correlated with reduced cyclophilin A expression, increased expression of receptor tyrosine kinase (RTK) ligands, activation of phospho-RTKs, and poor inhibition of MAPK, MYC, and PI3K signaling. In contrast, none of these resistance mechanisms were observed with VS-7375. These results show that several mechanisms of resistance shared by zoldonrasib and daraxonrasib do not limit the durability of VS-7375 efficacy. Therefore, we next evaluated whether the combination of the G12Di VS-7375 with daraxonrasib (pan-RASi) would be superior to the combination of the G12Di zoldonrasib with daraxonrasib which is currently under clinical evaluation. VS-7375 + daraxonrasib showed deep regression for the entire 80-day dosing period in contrast to the zoldonrasib + daraxonrasib combination which only maintained tumor regression for approximately 20 days. Pharmacodynamic analyses at day 20 showed numerous Molecular Signatures Database Hallmark signatures that were uniquely affected by the VS-7375 + daraxonrasib combination but not by the combination of zoldonrasib + daraxonrasib. For example, VS-7375 + daraxonrasib strongly inhibited MYC signaling whereas zoldonrasib + daraxonrasib did not.

Conclusions: VS-7375 demonstrated deeper and more sustained antitumor activity than the ON-only tricomplex inhibitors zoldonrasib or daraxonrasib. Durable tumor regressions observed with VS-7375 + daraxonrasib support the clinical evaluation of the combination of the switch-II pocket ON/OFF KRAS G12D inhibitor VS-7375 with an ON-only tricomplex pan-RAS inhibitor.

Conflict of interest: Other Substantive Relationships: SC and JAP are employees at Verastem Oncology

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217 - PB-112 **Poster**

Integrated Organoid Screening Approaches Enable Preclinical Assessment of Targeted Protein Degrader Efficacy and Target Engagement

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Background: Targeted Protein Degraders (TPD), e.g. PROTACs and Molecular Glues, are emerging therapeutics that enable selective protein degradation and offer new strategies for targeted cancer treatment. To determine whether TPDs function as designed, functional screening in clinically and physiologically relevant preclinical models is essential. This study establishes a preclinical functional screening platform for TPDs using patient-derived (xenograft) tumor organoids (PD(X)O) and matched in vivo patient-derived xenograft (PDX) counterparts. The platform integrates in vitro efficacy, mode-of-action, engineered resistance and off-target toxicity modeling, and in vivo translatability.

Materials and Method: The cereblon (CRBN)-mediated protein degrader of GSPT1, CC-885, was tested across 98 next-generation sequencing-characterized organoids spanning six cancer types (colorectal, cervical, gastric, head and neck, lung, and pancreatic), including non-diseased controls, using the OrganoidXplore™ CellTiter-Glo (CTG) assay. Sensitivity was confirmed in selected models by high-content imaging (HCI), with GSPT1 degradation assessed simultaneously by immunofluorescence. To model CC-885 resistance and off-target toxicity, CRBN-knockout and GSPT1-mutant organoids were engineered. In vivo translatability of in vitro responses was evaluated in 5 matched PDX models. Based on these findings, we expanded the preclinical screening capabilities to VHL, MDM2 and DCAF15 dependent TPDs using engineered isogenic knockout organoid pairs.

Results: Organoid screening revealed heterogeneous responses to CC-885 (IC50 ~0.1–50 nM) that did not correlate with GSPT1 or CRBN mRNA levels. HCI validated OrganoidXplore™ responses and immunofluorescent monitoring of GSPT1 demonstrated target engagement and time-dependent GSPT1 degradation, linking efficacy to the designed mechanism-of-action of CC-885. CRBN knockout and GSPT1 mutation each abolished drug sensitivity, confirming target specificity without off-target on-tumor toxicity. In vitro model sensitivity was reflected in vivo in patient-matched PDXs (n = 5).

Conclusions: PD(X)O/PDX models provide physiologically and clinically relevant patient-derived systems that capture patient diversity and response heterogeneity. The platform presented here facilitates, for the first time, functional preclinical screening of efficacy, mode-of-action, resistance, and toxicity of TPDs in matched PD(X)O/PDX models. These results establish organoid-based screening platforms such as OrganoidXplore™, combined with CTG and HCI methods, as robust tools for preclinical protein degrader evaluation. By identifying responsive tumor subtypes and capturing both efficacy and mechanistic effects, this approach can strengthen biomarker discovery; alignment with PDX models further highlights its value for early oncology drug development and target selection.

No conflict of interest

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218 - PB-113 **Poster**

Selective VRK1 inhibition reduces glioblastoma growth via synthetic lethality in vitro and in vivo

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Vaccinia-related kinase 1 (VRK1) is a nuclear kinase involved in mitosis and the DNA damage response. Genetic screens have identified VRK1 as a selective dependency in several cancers, including glioblastoma (GBM), where low VRK2 expression creates synthetic lethal vulnerability.

With the goal of developing new therapeutic breakthroughs in oncology, we used Sprint Bioscience fragment- and structure-based drug discovery platform to generate novel and exclusive VRK1 inhibitors (VRK1i) with sub-nanomolar potencies in biochemical and biophysical assays. Moreover, our VRK1i achieves excellent selectivity against the rest of the human kinome, including a 400-fold selectivity against VRK2.

Testing our lead VRK1i across a panel of GBM cell lines, we observed inhibition of BANF1 phosphorylation, mitotic cell arrest, and cell death with functional dependency on VRK2 status.

Moreover, in a U-118 MG glioblastoma xenograft model, treatment with our lead VRK1i was well tolerated and achieved significant tumor growth inhibition of up to 44%. Pharmacokinetic (PK) and pharmacodynamic (PD) analyses confirmed tumor exposure and target engagement *in vivo*.

These findings validate selective VRK1 inhibition as a promising therapeutic approach for GBM and support low VRK2 expression as a predictive biomarker for patient selection.

Conflict of interest: Ownership: All authors own shares in Sprint Bioscience.

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219 - PB-114 **Poster**

Discovery of novel Surface Protein Conformer (SPC) targets in RAS colorectal cancer

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Background: Colorectal cancer (CRC) is the second-leading cause of cancer-related deaths globally and the leading cause of cancer deaths in people under 50 years old. Structural Protein Conformers (SPCs), which adopt a disease-specific conformational state, represent an innovative class of molecules that could serve as

ideal anchors for highly specific therapeutic modalities. Novel surfaceome targets may help overcome resistance to current standards of care, such as anti-EGFR therapies. These targets may also expand treatment options for patients with microsatellite-stable (MSS) tumors, who often respond poorly to immunotherapy, and strengthen biomarker-driven precision oncology approaches. In this study, the surfaceomes of KRAS-mutant CRC patient-derived cancer organoid (PDCO) cultures and corresponding normal colon tissue-patient derived organoid (PDO) cultures lacking KRAS or other pathogenic mutations were analyzed for structural protein conformation changes (SPCs) to identify actionable new CRC drug targets.

Materials and Methods: Protein-tagging reagents were used to quantify changes in amino acid solvent-accessible surface accessibility (SASA) via quantitative LC-MS/MS. Using this innovative approach, changes in the global structural surfaceome of seven KRAS-mt PDCO lines and six KRAS-wt PDO lines were compared. Peptides with significant SASA changes (FDR: $q < 0.05$; log2 fold-change $> +/-1$) were filtered using a surfaceome localization score, and conformational ensembles generated for triaged proteins were scored with a custom, GNN-based, structure encoder fine-tuned on surface proteomics data.

Results: The global surfaceome analysis identified 18,208 modified peptides from 3,575 proteins, of which 1076 peptides from 602 proteins showed significant changes in SASA. These proteins were categorized by function and family and used to map changes in the global KRAS-associated surfaceome response. Intensity-Based Absolute Quantification (iBAQ) was performed on select benchmarking therapeutic proteins identified in the dataset, including CEACAM5, EGFR, and TROP-2 to compare novel targets to established targets for ADC development. A total of 69 unique SPCs specific to the PDCO cohort were identified. These CRC SPCs have been ranked as development candidates for targeted therapeutics, including antibody-drug conjugates (ADCs).

Conclusion: Due to their lack of mutations, the unique CRC SPC targets identified in this study are undetectable by conventional genomics- and transcriptomics-based target ID approaches. The surface proteomics target-discovery algorithm identified KRAS-mt-associated, PDCO-specific SPCs. The SPC epitope data are being used to generate mAbs for the highest-value curated SPC targets. These will be validated by screening tumor tissue arrays to determine the therapeutic target profiles of each SPC candidate.

Conflict of interest: Ownership: Immuto Scientific: D. Benjamin, F. Choudhury, N. Goodwin, H. Marble, A. Ritter, and R. Sadecki

Board of Directors: Immuto Scientific: D. Benjamin and F. Choudhury

Corporate-sponsored Research: Immuto Scientific, Inc.

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220 - PB-115 **Poster**

First-in-human study of SA53-OS, an oral MDM2 inhibitor, in advanced p53 wild-type solid tumors

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Background Mouse double minute 2 (MDM2) suppresses p53 signaling and is frequently amplified in solid tumors, including dedifferentiated liposarcoma. Clinical development of MDM2 inhibitors has been limited by class-typical cytopenias, particularly thrombocytopenia, neutropenia and anemia. SA53-OS is an oral, selective MDM2 inhibitor designed to restore p53 activity. This first-in-human study evaluated the safety, tolerability, pharmacokinetics (PK) and preliminary antitumor activity of SA53-OS.

Material and methods LB-SA53-101 (NCT06578624) is an ongoing, open-label phase 1/2a study sponsored by Lamassu Bio Inc. Adults with p53 wild-type locally advanced or metastatic refractory solid tumors receive SA53-OS monotherapy orally once daily on days 1–3 of each 21-day cycle. Phase 1 uses single-patient dose escalation followed by 3 + 3 cohorts. Endpoints include safety, dose-limiting toxicities (DLTs), maximum tolerated dose/recommended phase 2 dose, PK and preliminary antitumor activity. Safety and PK were analyzed descriptively.

Results Four patients received SA53-OS at 0.054, 0.11, 0.22 or 0.44 mg/kg/day. No DLTs, serious adverse events, grade ≥2 treatment-emergent adverse events, clinically significant platelet or hemoglobin decline, or hepatic safety signal have been observed to date. Dose escalation is ongoing and the maximum tolerated dose has not been reached. Absorption was rapid, with median time to maximum concentration (Tmax) of 1 h. On day 1, maximum plasma concentration (Cmax) increased from 94 to 609 ng/mL and area under the concentration-time curve over the dosing interval (AUC-tau, 0–24 h) increased from 755 to 5890 h·ng/mL.

Conclusions SA53-OS demonstrated rapid oral absorption, increasing systemic exposure and encouraging early tolerability in the initial dose-escalation cohorts. The absence to date of class-typical thrombocytopenia, hemoglobin decline or hepatic toxicity supports continued dose escalation and further evaluation in p53 wild-type or MDM2-amplified solid tumors, including dedifferentiated liposarcoma.

Conflict of interest: Ownership: Lamassu Biotech
Advisory Board: Lamassu Biotech
Board of Directors: Lamassu Biotech

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221 - PB-116 **Poster**

Preclinical characterization of PLX-66140, a potent and selective CDK2 degrader, for the treatment of CCNE1 amplified solid tumors and CDK4/6i resistant HR + /HER2- breast cancers

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Background: The dysregulation of Cyclin-Dependent Kinases (CDKs) and their regulatory cyclin partners drive uncontrolled tumor proliferation and altered transcription. Many aggressive malignancies become uniquely addicted to overactive CDK2 signaling due to CCNE1 amplification or overexpression. CCNE1 dependent CDK2 activation also mediates resistance to CDK4/6i in $HR^+/HER2^-$ breast cancer. CDK2 targeted therapies have shown single agent activity and are being considered as a part of CDK4/6i-based regimens. CDK2i dose limiting heme toxicity reflects diminished selectivity due to high similarity of the ATP-binding site across the CDK family, reducing their combinability with CDK4/6i. Molecular glue degraders of CDK2 offer an attractive alternative strategy to achieve selective downregulation of CDK2 providing potential for improved clinical benefit.

Results: Plexium's integrated monovalent degrader platform supported the discovery of our development candidate, PLX-66140, a novel, potent and selective cereblon (CRBN) based CDK2 molecular glue degrader. Treatment with PLX-66140 induces CRBN:PLX66140:CDK2 ternary complex formation and CRBN-mediated, proteasome dependent degradation of CDK2 in cell-based assays. Global proteomics confirms that PLX-66140 selectively degrades CDK2 without modulating known cereblon neosubstrates or other CDKs and exhibits dose dependent modulation of E2F target genes. Degradation results in robust inhibition of RB phosphorylation, cell cycle arrest and antiproliferative activity in a panel of CCNE1 amplified cancer cell lines. PLX-66140 exhibits preferential growth inhibition in CCNE1 amplified vs. non-amplified cancer cell lines superior to ATP-competitive inhibitors, consistent with PLX-66140's greater selectivity profile. In addition, PLX-66140 does not inhibit the proliferation of $CD34^+$ HSPC cells suggesting a low risk of myelosuppression and preferential combinability with CDK4/6i. Oral administration of PLX-66140 in tumor bearing mice demonstrates robust CDK2 degradation and anti-tumor activity in multiple CCNE1 amplified xenograft models at well tolerated doses. PLX-66140 also shows robust combination benefit with endocrine therapy and CDK4/6i in ER^+ breast cancer models both *in vitro* and *in vivo*.

Conclusion: Our development candidate, PLX-66140 provides compelling preclinical evidence and scientific rationale that targeting the CDK2-CCNE1 axis with a selective molecular glue degrader addresses an oncogenic vulnerability in CCNE1 amplified or CDK4/6i resistant cancers. The potential for non-overlapping toxicity profiles with CDK4/6i can further maximize therapeutic benefit for HR^+ breast cancer patients. These results support clinical development in CDK4/6 inhibitor-naive and -resistant $HR^+/HER2^-$ breast cancer and CCNE1 amplified solid tumors.

No conflict of interest

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222 - PB-117 **Poster**

Determinants of response and rational combination strategies for plixorafenib (PLX8394/FORE8394) in models of BRAF-altered colorectal cancer

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BRAF V600 mutation occurs in ~8% of colorectal cancer (CRC) and is an aggressive tumor with poor prognosis. Responses to BRAFi monotherapy in BRAF-altered CRC have been dismal and remain a high unmet need. Plixorafenib, as a novel paradox and dimer breaker BRAFi, has a unique mechanism of action and reduced rate of acquired resistance compared to other RAFi. We evaluated the efficacy of plixorafenib in 11 BRAF-altered CRC models including 8 patient-derived xenograft (PDX) (7 V600E, 1 AGAP3-BRAF fusion) and 3 V600E cell line-derived xenograft (CDX). Molecular characterization was performed to identify resistance mechanisms, including genomic profiling and transcriptomic analyses, and combination studies were conducted to assess strategies to enhance therapeutic response and overcome resistance.

Plixorafenib exhibited single-agent activity across 8 PDX models, with 7 models exhibiting tumor growth inhibition (TGI) of 40–83% and one with 17% TGI. Two of the 7 V600Emut PDX were previously treated by chemotherapy and cetuximab and had the deepest responses ($\geq$80% TGI), suggesting plixorafenib retains activity after standard therapies. CDX models were similarly responsive to plixorafenib (HT29 34%, COLO205 73% TGI), with one being relatively resistant (RKO 5% TGI). Pharmacodynamic profiling by RNAseq confirmed on-target MAPK suppression (DUSP6 expression) in V600Emut PDX.

3 of the 4 PDX with TGI < 50% and the resistant RKO model had underlying PIK3CA mutations (3 of which were H1047R), implicating PI3K activity for intrinsic resistance. Baseline transcriptomic analyses showed that lower sensitivity correlated with innate immunity, apoptosis/DNA repair, PI3K-AKT, and elevated MET or EGFR expression, whereas higher sensitivity was associated with metabolic programs, B cell differentiation, and PD-1/PD-L1 and T-cell receptor signaling.

Based on these results and known adaptive resistance of MAPK/EGFR pathway to early generation BRAFi, such as encorafenib, plixorafenib was tested in combination with other targeted therapies in vitro, and exhibited synergy with pan-RASi, PI3Ki, and CDK4/6i, particularly in resistant cell lines. In CDX models, plixorafenib combined with cetuximab and FOLFOX (80% TGI) demonstrated significantly stronger tumor inhibition than monotherapy (61% TGI) and was more potent than encorafenib/cetuximab/FOLFOX (72% TGI). Plixorafenib with irinotecan or targeted therapies (pan-RASi and CDK4/6i) displayed enhanced activity (54.1% TGI and 52.1% TGI, respectively) versus monotherapy (34% TGI).

In multiple models, plixorafenib demonstrates preclinical efficacy in BRAF-altered CRC. PIK3CA mutation, baseline inflammatory/RTK-associated programs, and adaptive activity of the MAPK pathway may correlate with resistance, supporting rational combination strategies, including chemotherapy and pathway-directed agents, to overcome resistance in CRC.

Conflict of interest: Ownership:

Stock ownership: Fore Biotherapeutics, AbbVie, Abbott, BridgeBio

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224 - PB-119 **Poster**

Early ctDNA dynamics assessed by aggregate VAF (aggVAF) and maximum VAF (maxVAF) as potential biomarkers of response to targeted therapies (TT) in early-phase clinical trials (EPCTs)

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Background: Liquid biopsy (LB) can identify actionable alterations, support TT access and inform response. However, the optimal metric for longitudinal targeted panel ctDNA monitoring remains undefined. We assessed the association between early ctDNA changes (ΔctDNA), using aggVAF (sum of variant allele frequencies (VAFs) of baseline pathogenic mutations) or maxVAF (mutation with highest baseline VAF), and radiological response in patients (pts) treated with TT in EPCTs.

Methods: Patients enrolled in the 360Resistance prospective observational study with longitudinal ctDNA monitoring using

VHIO360, an institutional ISO-accredited 74-gene Guardant360-based LB panel. Main analysis required pretreatment baseline LB and first on-treatment LB pre-cycle 2 (pre-C2), before first CT scan. For ΔctDNA assessment, baseline pathogenic mutations were longitudinally tracked using aggVAF or maxVAF. Germline/clonal haematopoiesis variants were excluded. Primary endpoint: association of ΔctDNA with DCR (objective response or stable disease) at first CT by RECIST 1.1. Secondary endpoints: association of ΔctDNA with objective response rate (ORR) at first CT, progression-free survival (PFS) and lead time from molecular progression (>50% aggVAF or maxVAF increase from nadir or reappearance after clearance) to radiological progression.

Results: Between 01/2025 and 04/2026, 20 pts underwent LB monitoring; median age 64 (44–81), F:M 12:8, all ECOG 0–1, median prior lines 2 (1–8). Treated alterations: *HER2* (n = 17), *BRAF* (n = 2), *NRAS* (n = 1). 86 samples analysed; 17 pts (85%) had detectable ctDNA at baseline, 2 pts had pre-C2 LB after first CT and 1 pt had no baseline. 14 pts met main analysis criteria. Median time to on-treatment LB from TT initiation: 21 days (d) (4–27). Pts with DCR at first CT showed a greater early reduction in aggVAF than pts with progression (−71.0% vs +6.49%; p = 0.019), whereas no significant association was observed for maxVAF (−73.0% vs 0.0%; p = 0.387). Any early aggVAF reduction was associated with higher DCR (100% vs 25%; p = 0.011) and longer PFS (5.0 vs 1.2 months; HR 0.09, 95% CI 0.02–0.51; p = 0.007). Any maxVAF reduction showed a trend toward higher DCR (90.9% vs 33.3%; p = 0.093) and was associated with longer PFS (3.97 vs 1.21 months; HR 0.15, 95% CI 0.03–0.77; p = 0.010). Complete aggVAF clearance was associated with higher ORR (66.7% vs 0%; p = 0.033) and prolonged PFS (not reached vs 2.5 months; log-rank p = 0.027), whereas maxVAF showed non-significant trends for ORR (50.0% vs 0%; p = 0.066) and PFS (not reached vs 2.5 months; log-rank p = 0.103). In 7 evaluable pts for lead time analysis, lead time was 28d (15–209) using both aggVAF and maxVAF.

Conclusions: Early aggVAF reduction showed more consistent associations with DCR, ORR and PFS than maxVAF, suggesting that aggregate longitudinal tracking may better predict treatment response in pts receiving TT in EPCTs.

Conflict of interest: Ownership: Rodrigo Dienstmann: Trialing (stocks), Elena Garralda: 1TRIALSP, (stocks), Ana Vivancos: Reveal Genomics (stocks), Victoria Sanchez Perez: Gilead (stocks)

Advisory Board:

Rodrigo Dienstmann: Foundation Medicine, Illumina, Pfizer, Roche

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Maria Vieito: BMS

Irene Braña: Achilles Therapeutics, Bicara Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, eTheRNA Immunotherapies, Gilead Sciences, Guidepoint, Merck Sharp & Dohme/MSD, Merus, PCI Biotech, Pyxis, Rakuten Pharma.

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Rodrigo Dienstmann: AstraZeneca, Daiichi-Sankyo, GlaxoSmithKline, Merck, Novartis, Pfizer.

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Alberto Hernando Calvo: Gilead

Ana Vivancos: Bristol Meyers Squibb, Incyte, Roche

Maria Vieito: AstraZeneca, BeiGene, C4 Therapeutics, Novartis, Roche, Taiho Oncology, and Thermo Fisher Scientific

Other Substantive Relationships:

Francesco Bruzzone: Boehringer Ingelheim - Travel Grant

Giulia Pretelli: Pierre Fabre and Roche, Travel and accommodation expenses.

Rodrigo Dienstmann: Oncoclínicas (part time or full time employment), Invited Speaker: Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Gilead, GlaxoSmithKline, Guardant Health, Ipsen, Johnson and Johnson, Libbs, Lilly, Merck Sharp & Dohme, Pfizer, Roche, Sanofi, Servier, Takeda,

Elena Garralda: NEXT Oncology, Full or part-time Employment. Lilly, Expert Testimony. Invited Speaker: AEFI, Alcura, Aran, AstraZeneca, CDDF, COR2ED, Doctaforum, Elservier Ltd, ESMO, ESO (European School of Oncology), Fundación ECO, Fundación SEOM, Horizon CME, Karger, Medscape, MeetingPharma, MSD, MSKCC, Novartis, PPD, Roche, SeaGen, Springer Nature, Swiss cancer Research Foundation, Tactics, The Ricky Rubio Fundation

Maria Vieito: BMS, Debiopharm Group, HutchMed, Incyte, Mundipharma, Novartis, PharmaMar, Roche, Servier, and Taiho Oncology, Novocure (Speakers Bureau)

Victoria Sanchez Perez: Clinical Trials (Institutional): Adaptimmune LLC, Affimed Gmbh, Amgen SA, Anaveon AG, AstraZeneca AB, Bicycletx Ltd, BioInvent International AB, Biontech SE, Biontech Small Molecules Gmbh, Boehringer Ingelhem International Gmbh, Catalym Gmbh, Cyclacel Biopharmaceuticals, Cytovation AS, Cytomx, F.Hoffmann La Roche Ltd, F-Star Beta Limited, Genentech Inc, Genmab B.V., Hifibio Therapeutics, Hutchison Medipharma Limited, Icon, Imcheck Therapeutics, Immunocore Ltd, Incyte Corporation, Incyte Europe Sàrl, Janssen-Cilag International NV, Janssen-Cilag SA, Laboratorios Servier SL, Medimmune Llc, Merck & Co, Inc, Merck Kgga, Novartis Farmacéutica, S.A, Peptomyc, Pfizer Slu, Relay Therapeutics, Replimmune, Ribon Therapeutics, Ryvu Therapeutics SA, Seattle Genetics Inc, Sotio as, Sqz

Biotechnologies, Symphogen A/S, Taiho Pharma Usa Inc, T-Knife Gmbh, BioNTech.

Boehringer Ingelheim Principal Investigator, DUKE Street BIO Principal Investigator, Eikon Therapeutics Principal Investigator, GSK Principal Investigator, British Medical Association Member, Medical Defence Union Member SEOM Member

Irene Braña: Local PI: Adlay/Nortye, AOP Pharma, AstraZeneca, Aveo Pharmaceuticals, Bayer, Bicara Therapeutics, Bicycle Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Debiopharm, Dragonfly Therapeutics, Gilead, GlaxoSmithKline, Gliknik, Immutep, Incyte, ISA Pharmaceuticals, ISA Therapeutics, Janssen Oncology, Kura, MacroGenics, Merck Serono, Merck Sharp & Dohme/MSD, Merus, Nanobiotix, Northern Biologics, Novartis, Odonate Therapeutics, Pfizer, Pharmamar, Regeneron, Roche, Sanofi, Seattle Genetics, Servier, Shattuck Labs, Tango Therapeutics, VCN Biosciences. Invited speaker: Bristol Myers Squibb, Merck Serono, Merck Sharp & Dohme/MSD, Roche.

Expert testimony: Cancer Expert Now, Merck Serono. Others: Cancer Core Europe, Principal Investigator “Basket of Baskets”, ASCO member, EORTC Head and Neck Group member, SEOM member.

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225 - PB-120 **Poster**

Translational Activity of the Pan-KRAS Inhibitor SAR449336 Across KRAS-Driven Preclinical Tumor Models

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Background: KRAS mutations are prevalent oncogenic drivers in multiple tumor types including colorectal (CRC), pancreatic, and lung cancers, leading to tumor growth and maintenance due to sustained activation of KRAS dependent signaling pathways, including the mitogen-activated protein kinase cascade. Recent advancements have been limited to either mutation-specific KRAS inhibition that could lead to acquired resistance to different KRAS variants or multi-RAS inhibition that could lead to off-target toxicity and limit achievable drug exposure. Pan-KRAS inhibition suppresses KRAS-specific signaling across diverse mutant alleles and tumor contexts while sparing HRAS and NRAS, inhibition of which is associated with toxicity.

Material and methods: We evaluated SAR449336 (SAR'336), a potent, orally bioavailable small molecule pan-KRAS inhibitor across KRAS driven preclinical xenograft and syngeneic tumor models harboring G12D, G12V, G12C, and G13D mutations across different indications to evaluate anti-tumor activity and target engagement in monotherapy or in combination with standard of care (SoC). Anti-tumor activity was measured as tumor growth inhibition (TGI) *versus* vehicle-control animals, calculated as %TGI = $[1-(TV_{treated,\ final} - TV_{treated,\ initial})/ (TV_{vehicle,\ final} - TV_{vehicle,\ initial})]*100$. Target engagement was evaluated by measuring phosphorylated extracellular signal-related kinase (pERK) in tumor and non-tumor tissues (e.g. skin) via an AlphaLISA assay.

Results: In cell line (CDX) and patient derived xenograft (PDX) models across different indications, SAR'336 demonstrated strong anti-tumor activity across multiple KRAS mutation subtypes. Most CDX tumors regressed (TGI: 100–150%) at the highest dose tested except in CRC G12V and G13D mutations (TGI: ~90%). SAR'336 also generated strong anti-tumor responses (TGI: 35–135% across 19 models) in PDX studies. Pharmacodynamic analyses using pERK as a biomarker confirmed modulation of KRAS pathway signaling in tumors, consistent with on-target activity. Additionally, SAR'336 achieved greater and selective pERK suppression in KRAS-mutant tumors *versus* skin, with minimal skin inhibition despite comparable exposure. Lastly, SAR'336 also demonstrated strong synergistic efficacy in combination with SoC agents (chemotherapy and anti-EGFR monoclonal antibody) across KRAS-mutant xenograft models.

Conclusions: These findings highlight the translational potential of SAR'336 and support continued clinical investigation of pan-KRAS inhibition in KRAS-mutant cancers. Strong anti-tumor efficacy combined with sparing target modulation outside of tumor tissue in preclinical models suggests potential for less severe off-target toxicity, such as skin rash, in patients. SAR'336 is currently being evaluated in a phase 1/2 clinical trial (NCT07629960) in patients with advanced solid tumors harboring KRAS mutations.

Conflict of interest: Other Substantive Relationships: Employees of Blueprint Medicines Corporation, a wholly owned subsidiary of Sanofi.

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226 - PB-121 **Poster**

A Novel Molecular Glue Degrader Synergizes with Pan-RAS Inhibition to Enhance Antitumor Activity in Pancreatic Ductal Adenocarcinoma

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Background: Activating RAS mutations are a hallmark of pancreatic ductal adenocarcinoma (PDAC), occurring in more than 90% of cases. Daraxonrasib (RMC-6236) is a noncovalent pan-RAS(ON) inhibitor that selectively targets the active, GTP-bound state of RAS and has demonstrated promising anti-tumor activity in patients with RAS-mutant cancers. However, adaptive and acquired resistance may limit the durability of clinical responses, highlighting the need for rational combination therapeutic strategies.

Targeted protein degradation (TPD) has emerged as a promising therapeutic strategy for cancer treatment. GSPT1 has recently gained attention as an attractive degradation target, whereas ZFP91 is highly expressed in PDAC and has been implicated in tumor progression and poor clinical outcomes. Our previous studies demonstrated that a dual molecular glue degrader targeting GSPT1 and ZFP91 preferentially suppresses the growth of SMAD4-deficient tumors. SMAD4 loss occurs in approximately 50% of PDAC cases and becomes increasingly prevalent during disease progression, particularly in advanced and metastatic tumors. It is strongly associated with aggressive disease, poor prognosis, and therapeutic resistance, highlighting a substantial unmet clinical need for this molecular subtype.

Based on these findings, we hypothesized that CXB-6485, a novel dual molecular glue degrader targeting GSPT1 and ZFP91, with Daraxonrasib could enhance antitumor efficacy and overcome adaptive resistance through complementary mechanisms of action. To test this hypothesis, we evaluated the therapeutic efficacy of this combination in RAS-mutant PDAC models.

Material and Methods: Cell viability and GSPT1/ZFP91 degradation following CXB-6485 treatment were evaluated in PDAC cells using SRB assay, clonogenic assay, proteomics, Western blotting, and the HiBiT degradation assay. Daraxonrasib-resistant models were established by continuous drug exposure, and the antitumor activity of CXB-6485 alone or in combination with Daraxonrasib was evaluated in both parental and resistant models.

Results: CXB-6485 reduced cell viability across a panel of PDAC cell lines. Consistent with its potent anti-proliferative activity, CXB-6485 induced robust degradation of GSPT1 and ZFP91 in vitro. Combination treatment with CXB-6485 and daraxonrasib demonstrated synergistic anti-tumor activity, resulting in significantly greater inhibition of cell viability than monotherapy across multiple RAS-mutant PDAC cells. In subcutaneous PDAC xenograft models, combination treatment with CXB-6485 and Daraxonrasib demonstrated enhanced antitumor efficacy compared with monotherapy.

Conclusions: The combination of CXB-6485 and Daraxonrasib demonstrated enhanced anti-tumor activity and represents a promising therapeutic strategy for overcoming RAS inhibitor resistance in RAS-mutant PDAC.

No conflict of interest

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227 - PB-122 **Poster**

Characterization of KRAS-G12D ubiquitination and degradation by setidegrasib (ASP3082) and its combination potential in preclinical models

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Background: KRAS is one of the most frequently mutated oncogenes in all cancers including pancreatic, colorectal and lung cancers and is associated with a poor prognosis. Therapeutic targeting of KRAS is an active area of clinical development and the KRAS G12D protein degrader setidegrasib (ASP3082) has shown promising clinical activity in advanced solid tumours with KRAS G12D mutations. KRAS mutations are known to result in constitutive activation of GTP-bound state of KRAS, which activate downstream signaling. The ability of a drug to bind both GTP-bound and GDP-bound states may confer broader and more durable therapeutic benefits to patients. We investigated 1) the binding affinity to both the KRAS GTP-bound "on" and GDP-bound "off" states, 2) ubiquitination and 3) degradation of KRAS by setidegrasib. Furthermore, we tested the combination efficacy of setidegrasib with certain standard of care (SOC) chemotherapies in tumor xenograft models.

Material and methods: The binding affinity of setidegrasib to the KRAS G12D protein on/off states and VHL was evaluated by Surface plasmon resonance (SPR) biosensor analysis. KRAS ubiquitination was detected by Western blot after immunoprecipitation, and KRAS degradation was evaluated by In-Cell Western blot in pancreatic cancer cell lines. We evaluated the combination efficacy of setidegrasib with the chemotherapies, gemcitabine or nab-paclitaxel in pancreatic cancer xenograft models and 5-FU, irinotecan or oxaliplatin in colorectal cancer xenograft models.

Results: Setidegrasib binds to KRAS G12D protein and VHL protein individually to form binary complexes, and forms a higher affinity binding ternary complex compared to the binary complexes with KRAS, regardless of whether the KRAS is in the GTP-bound "on" or GDP-bound "off" form. Setidegrasib ubiquitinates KRAS protein and causes dose-dependent KRAS degradation in cancer cells without evidence of a hook effect. To evaluate the combination benefit of setidegrasib with SOC chemotherapies, we administered setidegrasib with or without gemcitabine or nab-paclitaxel in pancreatic cancer xenograft models, and a significant combination effect with nab-paclitaxel was observed. Furthermore, we tested the combination effect of setidegrasib with 5-FU, irinotecan and oxaliplatin in colorectal cancer xenograft models. Setidegrasib and irinotecan also showed significantly more potent antitumor efficacy than setidegrasib or irinotecan alone.

Conclusions: Setidegrasib binds to both GTP- and GDP-bound KRAS, enabling degradation across activation states and contributing to antitumor activity in KRAS G12D-mutant cancers, including conditions influenced by receptor tyrosine kinase signaling. Combination with chemotherapeutic agents further enhances antitumor efficacy in xenograft models, supporting its clinical evaluation in combination regimens.

No conflict of interest

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228 - PB-123 **Poster**

A Phase 1 Study to Evaluate Safety, Tolerability and Pharmacokinetics of LNP8701 (SOS1 inhibitor) in Subjects with Metastatic Solid Tumors

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Background: SOS1 is a key regulator of RAS pathway that promotes tumor cell proliferation and survival. LNP8701 is an investigational SOS1 inhibitor being evaluated in first-in-human phase 1 study. The safety and efficacy results were published earlier. Here we present the results of pharmacokinetic (PK) profile of LNP8701 following single and multiple-dosing, including assessment of the effect of food on its systemic exposure.

Material and Methods: This multicenter, open-label study of LNP8701 was conducted in patients with metastatic solid tumors. LNP8701 was administered orally once daily in 28-day cycles using a dose-escalation design. PK was assessed following single and multiple doses and the effect of food on PK was evaluated in a single dose crossover sub-study.

Results: A total of 20 patients (10 males and 10 females) with Stage IV cancer received LNP8701 at doses of 100 mg (n = 1), 200 mg (n = 7), 300 mg (n = 7), 400 mg (n = 5). Blood samples for PK analysis were collected pre-dose and up to 24 hours post-dose on C1D1 and C1D8. In the food-effect sub-study, PK sampling done from pre-dose to 24 hours post-dose under fed and fasted conditions with a 7 days washout period in between.

Following single dose of LNP8701, mean peak plasma concentrations (C_{max}) were 23.68, 267.20, 216.14 and 356.26 ng/mL in the 100 mg, 200 mg, 300 mg, and 400 mg cohorts, respectively. The median time to peak concentration (T_{max}) ranged from 0.5 to 2 hours across dose levels. Total systemic exposure, assessed by AUC_{last} over a 24-hour sampling period, was 204.03, 1177.76, 1996.64, and 2550.42 h*ng/mL in the 100 mg, 200 mg, 300 mg, and 400 mg cohorts, respectively. The median terminal half-life (t½) was 6.07 to 14.31 hours across the dose levels.

Following multiple-dose administration of LNP8701, mean C_{max} were 45.16, 323.20, 247.21 and 617.26 ng/mL in the 100 mg, 200 mg, 300 mg, and 400 mg cohorts, respectively. The median T_{max} ranged from 1 to 2 hours across dose levels. AUC_{last} was 428.53, 2497.36, 2143.55, and 3375.31 h*ng/mL following repeated oral administration of 100 mg, 200 mg, 300 mg, and 400 mg, respectively.

The exploratory pharmacodynamic assessment showed stable whole-blood DUSP6 expression post-treatment; together with PK exposure and disease stabilization in some patients, supporting LNP8701 biological activity.

In food-effect sub study, the geometric mean ratios (fed/fasted) for LNP8701 were 120.9% for C_{max}, 124.5% for AUC_{last}, and 108.8% for $AUC_{inf.}$

Conclusion: LNP8701 demonstrated rapid oral absorption and increasing exposure across the dose levels following single and repeated oral doses. The elimination half-life remained consistent throughout the dose range supporting once daily dosing. No significant food effect on systemic exposure was observed. The overall pharmacological profile supports continued development of LNP8701.

Conflict of interest: Ownership: Dr. Rajender Kamboj, Dr. Chirag Shah and Dr. Neelam Kardekar own stocks in Lupin Limited

Advisory Board: Dr. Rajender Kamboj holds advisory role in Lupin Limited

Other Substantive Relationships: Dr. Chiraj Shah, Dr. Shashank Deoghare, Dr. Sarita Dabba, Dr. Neelam Kardekar, Ms. Shraddha Ekhatpukar, Mr. Prashant Bajpai are the employees of Lupin Limited

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229 - PB-124 **Poster**

Molecular glue stabilization of the β-catenin/14-3-3 interaction as a novel strategy to modulate Wnt signaling

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The Wnt/β-catenin signaling pathway plays a crucial role in the regulation of cell growth and differentiation. Activation of the Wnt/β-catenin signaling pathway leads to stabilization and accumulation of β-catenin, and its transcriptional activation after nuclear translocation. Aberrant activation of β-catenin occurs in the majority of colorectal cancers. However, inhibition of Wnt signaling remains challenging due to the role of β-catenin in adherens junctions, causing on-target gastrointestinal tract toxicity for Wnt pathway inhibitors and β-catenin-targeting PROTACs.

To overcome this challenge, we developed molecular glues that stabilize the interaction between β-catenin and 14-3-3 scaffold proteins. These molecular glues aim to inhibit the transcriptional activity of β-catenin while preserving its cytoplasmic functions. The molecular glues bind within the pocket formed at the interface between phosphorylated β-catenin and 14-3-3, resulting in a cooperative ternary complex. Residues C-terminal to the phosphorylated Ser675 of β-catenin (VELTSSLF) contribute to molecular glue binding and stabilization of the complex.

The structure-based design of the molecular glues was guided by X-ray protein crystallography. Stabilization of the β-catenin/14-3-3 interaction was first quantified using fluorescence polarization with a phospho-Ser675 peptide, yielding low nanomolar potencies. This translated to a full-length protein format using homogenous time-resolved fluorescence (HTRF), where molecular glues displayed potencies of ~200 nM. In surface plasmon resonance (SPR) experiments with 14-3-3 and phospho-Ser675 β-catenin peptide, the affinity of the β-catenin/14-3-3 interaction was strongly increased upon addition of the molecular glues.

Cellular target engagement was demonstrated in DLD-1 cells by immunoprecipitation coupled to mass spectrometry (IP-MS), confirming stabilization of the β-catenin/14-3-3 complex in cells while providing insight into compound selectivity across the 14-3-3 interactome. Finally, the molecular glues were profiled in cell viability assays with both Wnt-dependent and -independent cell lines. Gene and protein expression levels were additionally evaluated using qPCR and Western blotting, respectively, to reveal the relationship between targeting of the Wnt/β-catenin signaling pathway and the cellular profile of the molecular glues.

Together, these findings highlight stabilization of the β-catenin/14-3-3 interaction as a promising molecular glue strategy to selectively modulate Wnt/β-catenin signaling and provide a potential therapeutic approach for Wnt-driven cancers with improved pathway selectivity.

Conflict of interest: Ownership: Loes M. Stevers, Rens M.J.M. de Vries, Laura C. Demmers and Christian Ottman hold stock options in Ambagon Therapeutics B.V.

Board of Directors: Christian Ottman is member of the Board of Directors of Ambagon Therapeutics B.V.

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230 - PB-125 **Poster**

Results from a phase 1 study of LY4066434, an orally bioavailable pan-KRAS inhibitor, in KRAS-mutant solid tumors

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Background: *KRAS* is altered in ~15% of all cancers and is an oncogenic driver in non-small cell lung cancer (NSCLC), pancreatic cancer (PDAC), colorectal cancer (CRC), and others. LY4066434 is a selective inhibitor of G12C, G12D, G12V, G12A, G12S, G13D-mutants and wild-type (WT) KRAS. LY4066434 binds KRAS in the GDP-off state, exhibits high selectivity for KRAS over WT HRAS and NRAS, and, based on this selectivity, is hypothesized to have an improved toxicity profile compared to pan-RAS inhibitors. Here, we present results from the phase 1 study of LY4066434 in patients (pts) with *KRAS*-mutant solid tumors (NCT06607185).

Methods: This multicenter, first-in-human phase 1 trial enrolled adults with *KRAS* G12C, G12D, G12V, G12A, G12S, or G13D mutated cancer (tissue or circulating tumor DNA), ECOG PS 0-1, and measurable disease (per RECIST v1.1). Dose escalation evaluated LY4066434 monotherapy and followed the mTPI-2 method;

dose expansion planned to evaluate LY4066434 as monotherapy and in combination with standard of care (SOC) agents. Key objectives were to determine the safety, PK, and antitumor activity of LY4066434 per RECIST v1.1.

Results: As of 6 Apr 2026, 99 pts with PDAC (56), NSCLC (24), CRC (9), and other solid tumors (10) received LY4066434 (40-400 mg BID). Median age was 63 years (range, 27-86). Median number of prior systemic therapies was 3 (range, 1-10), including prior immunotherapy in 29%. Doses ≥240 mg achieved and maintained predicted efficacious exposure at steady state; the estimated half-life of ~6-12 hours across dose levels supported BID dosing. The maximum tolerated dose was not identified, but dose escalation ceased at 400 mg BID due to the overall safety profile. Across all dose levels, the most frequent TEAEs (any grade [G]/G≥3) ≥20% in occurrence were diarrhea (82%/9%), edema (65%/5%), vomiting (51%/2%), nausea (50%/3%), anemia (47%/23%), hypoalbuminemia (44%/4%), fatigue (30%/4%), and rash (22%/1%). TEAEs led to dose reduction in 34%, dose hold in 68%, and discontinuation in 19%. Across the 93 efficacy evaluable pts, ORR was 7% (6/93) and DCR was 56% (52/93) with 6 PR (5 confirmed, 1 ongoing and pending confirmation) and 46 SD. Best responses in individual tumor types are shown in the table.

Conclusions: LY4066434 demonstrated limited efficacy across multiple tumor types. Updated data including in combination with SOC agents will be presented.

Table

	PDAC (N = 52)	NSCLC (N = 24)	CRC (N = 8)	Other solid tumors (N = 9)
ORR, % (n/N)	2% (1/52)	21% (5[b]/24)	-	-
DCR[a], % (n/N)	42% (22/52)	71% (17[b]/24)	75% (6/8)	78% (7/9)
BOR, n (%)				
PR	1 (2%)	5[b] (21%)	-	-
SD	21 (40%)	12 (50%)	6 (75%)	7 (78%)

Efficacy evaluable pts are those who had both baseline and at least 1 post baseline assessment or those who discontinued before the 1st post baseline assessment. [a]DCR = PR + SD. [b]Includes 1 uPR, ongoing and pending confirmation.

Conflict of interest:

Ownership:

Aparna Parikh: Equity- C2i Genomics, Khora, OneCell, Xgenomes, Cadex, Parithera, Roon.

David Hong: Founder- OncoResponse, Telperian.

Michael Axelson: Shareholder- Eli Lilly and Company.

Matt Hanley: Shareholder- Eli Lilly and Company.

Jian Li: Shareholder- Eli Lilly and Company.

Victor Lincha: Shareholder- Eli Lilly and Company.

Rohan Nanda: Shareholder- Eli Lilly and Company.

Advisory Board:

Uwe Martens: Advisor/Consultant- AstraZeneca, Bristol-Myers Squibb, Roche, Sanofi-Aventis, GSK, Novartis, Pfizer, Pierre Fabre, Takeda, Iomedico, Astellas, MSD, Guardant Health.

Aparna Parikh: Advisor/Consultant- Astra Zeneca, Takeda, Guardant, Zola, CVS, Phesi, Xilio, 3T Biosciences, Do More Diagnostics, Summit Therapeutics, Regeneron, GSK, Foundation Medicine, Careset, Value Analytics Lab, Adroya, Scare, Hookipa, Abbvie, Seagen, Mirati, PMV, Pfizer, CVS, Eli Lilly, Kahr, Sirtex, Takeda, Merck, Amgen, Delcath, Exact, Caris, BMS, Incyte, Phesi, Value Analytics Labs, Pheon, Natera, Neogenomics, J&J, Novartis, Boehringer Ingelheim, Exelixis, Illumina, Saga (2026), Third Rock Ventures, Genentech, MPM Capital, Science for America (non-profit).

Rona Yaeger: Advisor/Consultant- Mirati Therapeutics, Revolution Medicines, Loxo@Lilly, Erasca, Merck, Parabilis Medicines, Bayer, Pfizer, Alterome.

Jih-Hsiang Lee: Consultant- AstraZeneca, Boehringer-Ingelheim, Takeda Oncology, Eli Lilly and Company, Novartis, Daiichi Sankyo.

David Hong: Consultant/Speaker/Advisory role-Abbvie, Acuta, Alpha Insights, Amgen, Axiom, Blueprint, Beigene, Boxer Capital, BVF consulting, ClearView Oncology, COR2ed, Cogent Therapeutics, CureBio, Ecor1, Erasca, GLG, Guidepoint, HuyaBio, Immunogenesis, Kanaph Therapeutics, Kayak Therapeutics, Kestrel Therapeutics, Medscape, Morgan Stanley, Nextech Ventures, Pfizer, PharmaResearch, Revolution Medicine, T-Knife, WebMD

Advisor- BreakThrough Bio, CrossBridge Bio, Molecular Match, OncoResponse, Telperian, Interact Therapeutics.

Nehal Lakhani: Consulting/Advisory Role- Janssen Oncology.

Benjamin Herzberg: Consulting Fees- Amgen, Boxer Capital, Eli Lilly, Johnson and Johnson, Astellas.

Corporate-sponsored Research:

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Shigehisa Kitano: Grants- Eli Lilly (during the conduct of the study) and Astra Zeneca, Pfizer, Nippon Boehringer Ingelheim, MSD, Eisai, Astellas, Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb, Rakuten Medical, Takara Bio Inc., GSK, Daiichi-Sankyo, Chugai Pharma, Incyte, Merck KGaA, Takeda, Eli Lilly/LOXO Oncology, Abbvie, Kyowa Kirin, Syneos Healthe Clinical, Moderna, Medpace outside the submitted work.

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Benjamin Herzberg: Grants/Contracts to Institution: Amgen, Repare, Ideaya, Astellas, Revolution Medicines, Astra Zeneca, Seagen, Monte Rosa Therapeutics, Eli Lilly, Genentech

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Other Substantive Relationships:

Uwe Martens: Travel/Accommodation- Lilly, Pierre Fabre, Roche, Beigene, Pfizer, Ipsen.

Shigehisa Kitano: Personal fees- Astra Zeneca, Pfizer, Nippon Boehringer Ingelheim, Taiho, Novartis, MSD, Eisai, Astellas, Ono Pharmaceutical Co., Ltd., from Bristol-Myers Squibb, Rakuten Medical, GSK, Daiichi-Sankyo, Chugai Pharma, Merck KGaA, Takeda, Kyowa Kirin, United Immunity outside the submitted work.

Takafumi Koyama: Personal Fees- Chugai, AstraZeneca, and Sysmex, Takeda outside the submitted work.

Aparna Parikh: Fees- Reversing Early Recurrence (non-profit) Chief Scientist, Up To Date

Travel Fees- Karkinos Healthcare.

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Jih-Hsiang Lee: Honoraria- Novartis, AstraZeneca, Boehringer-Ingelheim, Pfizer

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David Hong: Travel expenses- AACR, Immunogenesis, Medscape, Telperian.

Brandon Huffman - Honoraria for Advising/Consulting- Eli Lilly, TD Cowen, Slingshot Insights

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231 - PB-126 **Poster**

SAR449336: A Potent, Orally Bioavailable, HRAS and NRAS Sparing, Small Molecule Pan-KRAS Inhibitor With Broad Biochemical and Cellular Activity

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Background: KRAS mutations are key oncogenic drivers across multiple tumor types, including colorectal (CRC), pancreatic ductal adenocarcinoma (PDAC), and non-small cell lung cancer (NSCLC). Oncogenic KRAS mutations drive tumor initiation and maintenance through persistent activation of downstream signaling pathways, including the mitogen-activated protein kinase (MAPK) cascade. While recent advances have demonstrated the feasibility of direct KRAS inhibition, most approaches remain mutation-specific, limiting broader applicability. Pan-KRAS inhibition represents a strategy to directly target KRAS signaling across multiple oncogenic variants. Here we describe the preclinical antitumor activity of SAR449336 (SAR'336), a novel, orally bioavailable, HRAS and NRAS-sparing pan-KRAS inhibitor.

Materials and methods: SAR'336 was evaluated in biochemical assays to assess potency across oncogenic KRAS variants and selectivity *versus* HRAS and NRAS. Inhibition of GDP-bound KRAS was measured using a nucleotide exchange assay, while inhibition of GTP-bound KRAS was assessed using a protein–protein interaction assay measuring KRAS–CRAF binding. Inhibition of proliferation was evaluated in a cell panel against multiple KRAS variants, including G12D, G12V, G12C, G13D, G12S, and G12A. Antitumor activity and target engagement were assessed in 3 cell-derived xenograft (CDX) models: SW620 (CRC; KRAS G12V), PANC 04.03 (PDAC; KRAS G12D), and NCI-H358 (NSCLC; KRAS G12C).

Results: SAR'336 demonstrated high biochemical potency (for both GDP- and GTP-bound forms) against multiple oncogenic KRAS variants, including G12D, G12V, G12C, G13D, G12S, and G12A, while maintaining high selectivity over HRAS (>400x) and NRAS (>2000x). *In vitro*, SAR'336 inhibited proliferation of CRC, PDAC, and NSCLC cell lines harboring various KRAS mutations (G12C, G12D, G12V, G12A, G12S, and G13D) with IC_{50} less than 12.3 nM for the majority of the cell lines tested and minimal antiproliferative activity for KRAS wild-type cell lines with IC_{50} over 350 nM. SAR'336 monotherapy demonstrated robust and dose-dependent anti-tumor activity in 3 CDX *in vivo* models, SW620, PANC 04.03, and NCI-H358. Preclinical pharmacokinetic-pharmacodynamic analyses showed potent pathway inhibition (reduction of tumor pERK protein levels and expression of DUSP6 and SPRY4, key downstream targets of the RAS/MAPK pathway). These findings confirm on-target inhibition of KRAS signaling by SAR'336.

Conclusions: Collectively, these data support SAR'336 as a pan-KRAS inhibitor with biochemical and cellular activity against a broad range of pathogenic/oncogenic KRAS mutations and provide a strong mechanistic basis for its ongoing clinical development across KRAS-driven tumors. SAR'336 is currently being evaluated in a phase 1/2 study in patients with advanced solid tumors harboring KRAS mutations (NCT07629960).

Conflict of interest: Other Substantive Relationships: Employees of Blueprint Medicines Corporation, a wholly owned subsidiary of Sanofi.

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232 - PB-127 **Poster**

SF3B1 splicing modulation to overcome platinum and PARP inhibitor resistance in ovarian cancer

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Background: SF3B1 splicing modulators (such as H3B-8800 or E-7107) cause mis-splicing of DNA damage repair genes, loss of viability, and increased sensitivity to poly (ADP-ribose) polymerase (PARP) inhibitors and chemotherapy in DNA damage repair-deficient blood cancers, such as cohesin-mutant acute myeloid leukemia. Ovarian cancers frequently have deficient homologous recombination (HR) DNA repair (e.g. driven by mutations in *BRCA1* or *BRCA2*) and we hypothesized that they may be susceptible to SF3B1 splicing modulation.

Material and methods: We evaluated the effects of H3B-8800 treatment, alone or in combination with platinum chemotherapy or PARP inhibitors, in ovarian cancer cell lines using microscopy-based cell counting and live cell imaging over 6-14 days. The cell line panel included high-grade serous and clear cell ovarian cancer cell lines, both *BRCA1/2* mutant and wild-type, including paired HR-deficient and HR-proficient cell lines UWB1.289 and UWB1.298 + BRCA1. We performed RAD51 foci formation assays using immunofluorescent staining following gamma irradiation to quantitate HR DNA repair function in these cell lines.

Results: Ovarian cancer cell lines exhibited a range of sensitivities to single-agent H3B-8800 and reduction in cell viability. Short-term pre-treatment with H3B-8800 resulted in significant sensitization of a subset of ovarian cancer cell lines to treatment with carboplatin or the PARP inhibitor olaparib. Of note, H3B-8800 pre-treatment had a greater effect on HR-deficient cell lines. RAD51 foci formation assays demonstrated decreased RAD51 foci in HR-deficient compared to HR-proficient cell lines, with further decrease in RAD51 foci formation induced by H3B-8800 in both HR-proficient and HR-deficient cell lines. Mechanistic investigations of the effects of H3B-8800 treatment on DNA repair proteins in ovarian cancer cell lines are ongoing.

Conclusions: Treatment with SF3B1 splicing modulator H3B-8800, or similar compounds, may enhance platinum and PARP inhibitor sensitivity in ovarian cancer. Splicing modulators may represent a potential new strategy to overcome platinum and PARP inhibitor resistance to improve outcomes in ovarian cancer.

No conflict of interest

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233 - PB-128 **Poster**

Evaluation of a novel LKB1 inhibitor OICR38964 using in vitro three-dimensional models of ovarian cancer metastasis

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Background: Epithelial ovarian cancer (EOC) is an aggressive malignancy often diagnosed after extensive spread in the peritoneal cavity. Approximately 80% of patients relapse following surgery/chemotherapy, underscoring the need for new therapeutics. EOC spreads by multicellular spheroids that survive in suspension before attaching to secondary sites. Spheroids represent a dormant, chemotherapy-resistant state that drives disease recurrence. Detachment-induced bioenergetic stress activates the Liver kinase B1 (LKB1)-AMP activated protein kinase (AMPK)/Nua kinase 1 (NUAK1) signalling to maintain spheroid integrity, cell viability, and metastatic potential. Herein, we present the development of OICR38964, a novel LKB1inhibitor to explore the therapeutic potential of targeting this signalling axis in metastatic EOC.

Material and Methods: Binding of OICR38964 to recombinant LKB1 trimeric complex was determined by Cryo-EM. Inhibition of LKB1 activity was assessed by in vitro kinase and cell-based NanoBRET assays. Adherent EOC cell lines and spheroids were treated with OICR38964 to assess spheroid morphology, reattachment, and cell dispersion. LKB1 inhibition was confirmed by pAMPK (T172) immunoblotting and potential CDK inhibition by ppRB (S807/811). Fibronectin expression was quantified by RT-qPCR and immunoblotting. Drug efficacy was examined in adherent cultures, spheroids, and patient-derived organoid models representing multiple EOC histotypes.

Results: We confirmed interaction of OICR38964 within the ATP-binding pocket of LKB1. In vitro kinase and NanoBRET assays revealed similar LKB1 IC_{50} values of 70 nM and 64 nM, respectively. OICR38964 inhibited spheroid-induced LKB1 signalling in pAMPK-positive cell lines (OVCAR8, KOC7C, VOA6406) but not in pAMPK-negative models (COV362, 105C). Interestingly, OICR38964 had broad inhibitory activity against multiple CDKs, which was confirmed with a reduction in ppRB. Transcriptomic and proteomic analyses of LKB1 and NUAK1 deletion cell lines demonstrated fibronectin as a key downstream target affected by pathway loss in spheroids. Indeed, inhibition of LKB1 (OICR38964) or NUAK1 (ON123300) reduced fibronectin transcript and protein levels, producing disaggregated spheroids with impaired reattachment and reduced dispersal. OICR38964 reduced viability across all adherent cell lines tested, while selectively impairing cell survival of pAMPK-positive spheroids only, with encouraging early results observed in patient-derived organoids.

Conclusions: OICR38964 combines inhibition of LKB1-dependent survival pathways with anti-proliferative CDK activity, which we propose as a dual mechanism capable of targeting both dormant spheroid cells and actively-growing tumour cells. These findings support development of OICR38964 or similar agents as a promising strategy to overcome progression and recurrence in advanced EOC.

No conflict of interest

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234 - PB-129 **Poster**

IAM-C1, a potent and selective dual CDK2/CDK4 inhibitor, demonstrates robust antitumor activity and a favorable preclinical tolerability profile

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Background: The clinical benefit of CDK4/6 inhibitors in HR +/HER2- metastatic breast cancer validates G1/S control as a therapeutic strategy, however, intrinsic and acquired resistance is common, highlighting the need to address broader mechanisms of dysregulated G1/S transition. Evidence suggests tumors may depend on both CDK4/cyclin D as well as CDK2/cyclin E signaling. Therefore, selective, dual CDK2/CDK4 inhibition may suppress heterogeneous G1/S dysregulation while sparing CDKs associated with dose-limiting toxicities.

Materials and Methods: Iambic's AI/ML models Enchant and NeuralPlexer, along with a high-throughput experimental platform were used to aid our drug discovery team to rapidly design and optimize CDK2/4-selective dual inhibitors with favorable drug-like properties. IAM-C1 selectivity was evaluated using the Eurofins Discovery KINOMEscan kinase profiling panel. Tumor xenograft models were used to assess potency, target engagement, and antitumor activity. A 14-day repeat-dose rat study evaluated hematologic toxicity. CDK4/6 inhibitors and selective CDK2 and CDK4 inhibitors, alone or in combination, were used as comparators.

Results: IAM-C1 was highly selective across the kinome and demonstrated cellular target engagement, as evidenced by inhibition of retinoblastoma protein phosphorylation and induction of G1/S arrest. IAM-C1 showed antiproliferative and antitumor activity in models representing a spectrum of CDK4 and/or CDK2 dependencies. IAM-C1 achieved antitumor activity comparable or superior to selective CDK2 and CDK4 inhibitors in CDK2- and CDK4-dependent models, respectively, and demonstrated greater antitumor activity than selective CDK2, CDK4, or CDK4/6 inhibitors in a CDK2/4 co-dependent xenograft model. Furthermore, IAM-C1 demonstrated greater antitumor activity when combined with fulvestrant or imlunestrant, an oral SERD, than the respective single agents.

In a 14-day rat study, at matched efficacious exposure multiples, IAM-C1 showed a marginal decrease in neutrophils, whereas combined selective CDK2 and CDK4 inhibitor treatment, showed a greater neutrophil reduction, demonstrating a favorable hematopoietic tolerability profile for IAM-C1 compared to key benchmark compounds.

Conclusion: Together, these findings show that IAM-C1 selectively inhibits CDK2 and CDK4, suppresses cell-cycle signaling, and demonstrates strong antitumor activity across models with CDK4 and/or CDK2 dependencies. The favorable preclinical tolerability profile and endocrine therapy combination data support continued development of IAM-C1 in HR+/HER2- breast cancer and in other cancer types characterized by cell-cycle dysregulation.

Conflict of interest: Other Substantive Relationships: All authors are employees of Iambic Therapeutics.

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235 - PB-130 **Poster**

The CBP/EP300 inhibitor TT125-802 shows antitumor activity in marginal zone lymphoma models and can improve the effects of BTK inhibitors

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Background: CREB-binding protein (CBP) and p300 acetyltransferases are crucial epigenetic regulators that are mutated in multiple cancer types, including marginal zone lymphomas (MZLs). Cancer cells appear to depend on CBP/p300 for their survival, as loss of function mutations in the genes coding for them are mutually exclusive. TT125-802 is a novel, highly selective CBP/p300 bromodomain inhibitor that has shown therapeutic potential as a single agent in patients with advanced solid tumors. Here, we studied the anti-tumor activity of TT125-802 in models derived from marginal zone lymphoma (MZL), including derivatives with acquired resistance to PI3K, BTK, and BCL2 inhibitors, as a single agent and in combination with ibrutinib.

Material and methods: MZL cell lines (VL51, Karpas1718, and SSK41) and their corresponding derivatives with acquired resistance to targeted agents generated through prolonged drug exposure (one derivative per parental cell line), were exposed to increasing concentrations of TT125-802 or DMSO (control) for 72 h followed by MTT assay. The effect of the combination with ibrutinib was assessed with the Chou-Talalay, ZIP, and HSA synergy models.

Results: The CBP/p300 inhibitor TT125-802 exhibited antiproliferative activity in the low nM range (median IC50 7.4 nM 0.88-31.4 95% CI) in the MZL models wild-type for CBP/p300: (VL51, 13 nM; SSK41, 1 nM; Karpas1718, 12 nM). The anti-tumor activity decreased but remained dose-dependent in models with acquired resistance to the BTK inhibitor ibrutinib (VL51-IBR, IC50 78 nM) and the BCL2 inhibitor venetoclax (SSK41-VEN, IC50 3 nM). Notably, the response in the model with resistance to the PI3K-delta inhibitor Idelalisib was higher than that of its parental line (Karpas1718-IDE, IC50 = 1nM). The combination of TT125-802 with BTK inhibitor ibrutinib was beneficial in Karpas1718, VL51 and SSK41 models. The benefit was maintained in derivatives with acquired resistance to PI3K, BCL2, and BTK inhibitors.

Conclusions: CBP/p300 inhibition with TT125-802 has *in vitro* antitumor activity and is beneficial when combined with the BTK inhibitor ibrutinib in MZL models, and this activity is maintained in models with acquired resistance to PI3K, BTK, or BCL2 inhibitors. These findings support clinical investigation of the compound in MZL, suggesting its potential use beyond solid tumors.

No conflict of interest

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236 - PB-131 **Poster**

EO3001 (elesclomol), a copper ionophore that exploits ferredoxin-1 (FDX1) to drive cuproptosis in ARID1A-mutant solid tumors: preclinical rationale and design of an all-comer Phase I/II dose-escalation study with prospective ARID1A biomarker stratification

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Background: ARID1A is a core subunit of the SWI/SNF (BAF) chromatin-remodeling complex, mutated in approximately 10% of solid tumors and most prevalent in ovarian clear cell carcinoma (OCCC, up to 56%). ARID1A-containing SWI/SNF complexes remodel chromatin at the SLC7A11 promoter, enabling NRF2-driven transcription of this cystine transporter. ARID1A loss represses SLC7A11, reducing cystine uptake and glutathione synthesis and shifting cells toward OXPHOS dependence. This creates a synthetic lethal vulnerability: Agents that selectively disrupt OXPHOS preferentially kill ARID1A-deficient cells while sparing ARID1A-wild-type cells with intact glutathione defenses. Elesclomol (EO3001), a copper ionophore, delivers copper into mitochondria, where ferredoxin-1 (FDX1) reduces Cu(II)-elesclomol to the more reactive Cu(I), diverting FDX1 from Fe-S cluster biogenesis and driving proteotoxic stress (cuproptosis) impairing mitochondrial electron transport. In isogenic OVCA429 cell lines (± ARID1A loss), live-cell imaging confirmed this synthetic lethal relationship, with selective growth suppression of ARID1A-mutant cells at low nanomolar elesclomol concentrations. Elesclomol has an established safety profile from prior third-party trials in over 1,000 patients, supporting expedited clinical development.

Material and Methods: EOHC-3001-01 is planned as an open-label, multicenter Phase I/II study to be conducted under the Australia/New Zealand CTN regulatory scheme at up to 10 sites. The study enrolls adults with locally advanced, unresectable, or metastatic solid tumors refractory to standard therapy, irrespective of ARID1A status. Dose escalation follows a modified 3 + 3 design (starting dose 400 mg/m^2 IV weekly, Days 0/7/14/21 of a 28-day cycle) with an MTD expansion cohort of up to 20 patients. The starting dose was established as well-tolerated in prior third-party clinical trials. ARID1A status is assessed prospectively by liquid biopsy in all patients and stratified to enable early insight into differential clinical signal between ARID1A-deficient and wild-type subgroups. Primary endpoints are safety/tolerability and DLT/MTD; secondary endpoints include RP2D, ORR, PFS, DOR, and OS (RECIST 1.1).

Results: NA. Trial in preparation; CTN submission planned; first-patient dosing anticipated following site activation.

Conclusions: An all-comer dose-escalation design enables efficient RP2D determination, while prospective ARID1A stratification allows early insight into whether ARID1A-mutant tumors show differential clinical benefit consistent with the hypothesis that these tumors are selectively sensitive to elesclomol-driven, FDX1-mediated cuproptosis and OXPHOS disruption. This approach leverages elesclomol's extensive prior human safety database to support efficient advancement toward a biomarker-directed, registration-directed trial in ARID1A-mutant solid tumors.

Conflict of interest: Ownership: Edison Oncology Holding Corp.
Board of Directors: Edison Oncology Holding Corp.
Corporate-sponsored Research: Edison Oncology Holding Corp.

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237 - PB-132 **Poster**

Phase 1–2a Dose Escalation and Expansion of EO1001, an Oral Brain-Penetrant Pan-ErbB Inhibitor, in Advanced ErbB-Driven Solid Tumors: Safety, Pharmacokinetics, and Preliminary Clinical Activity Following Completion of Enrollment

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Background: Extracellular domain (ECD) mutations in ErbB-family receptors (EGFR, HER2, HER4) are a distinct, under-targeted class of oncogenic driver, occurring across multiple solid tumor types. These mutations drive ligand-independent signaling and confer resistance to approved EGFR inhibitors, including osimertinib and anti-EGFR antibodies, while preserving receptor activity. EO1001 is an oral, brain-penetrant, irreversible pan-ErbB inhibitor targeting wild-type and structurally altered EGFR, HER2, and HER4. We report updated safety, pharmacokinetic (PK), and preliminary efficacy findings from the completed dose-escalation/expansion phase of an ongoing first-in-human Phase 1-2a trial (ACTRN12620000583943).

Materials and Methods: This open-label, multi-centre, first-in-human trial enrolled adults with advanced/metastatic ErbB-positive solid tumors who had failed ≥1 prior line of therapy. Dose escalation used accelerated titration transitioning to standard 3 + 3 upon a first ≥Grade 2 treatment-related AE, followed by an expansion cohort at the recommended Phase II dose (RP2D). Primary objectives were safety, tolerability, and RP2D confirmation. Secondary objectives included PK characterization and preliminary antitumor activity by RECIST 1.1/RANO. Exploratory biomarker assessment included EGFR/HER2 alteration status, with attention to EGFR ECD variants.

Results: 52 patients were screened and 34 enrolled across seven escalating dose cohorts (2.5-90 mg po once daily) and an expansion cohort, completing planned enrollment. The RP2D was established at 50 mg once daily based on integrated safety, tolerability, and PK data. EO1001 was generally well tolerated; the most frequent treatment-related adverse events were diarrhoea, rash, and fatigue, predominantly Grade 1-2 and consistent with known class effects of ErbB inhibitors. Dose-limiting toxicity (diarrhoea) was observed at higher dose levels. PK exposure increased in a dose-proportional manner. Preliminary antitumor activity, including disease control and objective responses, was observed across multiple ErbB-driven tumor types. Clinical benefit was also observed in patients harboring EGFR ECD alterations across diverse tumor types, supporting a biomarker-directed approach independent of tumor site of origin.

Conclusions: EO1001 demonstrates a manageable safety profile at the established RP2D of oral 50 mg once daily, with encouraging early antitumor activity across ErbB-driven solid tumors across multiple disease settings, including biomarker-defined EGFR ECD-mutant tumors. These findings support continued clinical

development of EO1001 as a biomarker-directed pan-ErbB therapy. Enrollment is now complete; updated efficacy, PK, and biomarker data will be presented at the meeting.

Conflict of interest: Ownership: Edison Oncology Holding Corp.

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238 - PB-133 **Poster**

Discovery of clinical candidate SD-1240, a potent and selective STAT3 PROTAC degrader

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STAT3 is a transcription factor and a promising therapeutic target for cancer and other human diseases. Here, we describe the structure-based design and development of SD-1240, a clinical candidate that is a highly potent, selective, and efficacious STAT3 PROTAC degrader. We first designed a series of novel, high-affinity, conformationally constrained VHL ligands. Employing these optimized VHL ligands with our high-affinity STAT3 inhibitors, we discovered a new class of STAT3 degraders, among which SD-1240 emerged as the lead compound. SD-1240 induces potent STAT3 degradation, with a DC_{50} of 3 nM and a Dmax exceeding 95%, while exhibiting exceptional selectivity over other STAT family proteins and more than 7,000 additional proteins analyzed. To elucidate the structural basis for its potent and selective activity, we determined the cryo-electron microscopy (cryo-EM) structure of the STAT3–SD-1240–VHL ternary complex. SD-1240 demonstrates an excellent pharmacokinetic profile across multiple preclinical species and shows no significant ADME or hERG liabilities. A single intravenous dose of SD-1240 (1–10 mg/kg) induces complete and durable STAT3 degradation in both xenograft tumors and normal mouse tissues. STAT3 degradation by SD-1240 results in robust suppression of the STAT3-regulated transcriptional network in leukemia and lymphoma cells. Consistent with this mechanism, SD-1240 potently inhibits the growth of a subset of acute myeloid leukemia (AML) and anaplastic large cell lymphoma (ALCL) cell lines. Weekly intravenous administration of SD-1240 at 1 mg/kg produces complete and durable tumor regression in leukemia and lymphoma xenograft models. Although SD-1240 has minimal effects on the proliferation of triple-negative breast cancer (TNBC) cell lines and murine cancer cell lines in vitro, it exhibits strong antitumor activity in corresponding mouse tumor models, suggesting that its in vivo efficacy extends beyond direct inhibition of tumor cell proliferation. SD-1240 was well tolerated in mice, rats, and dogs. Investigational New Drug (IND)-enabling efficacy and safety studies for SD-1240 have been completed, and IND application is currently being prepared. Following IND clearance, clinical trials will be initiated to evaluate SD-1240 for the treatment of human cancers and other STAT3-driven diseases.

No conflict of interest

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239 - PB-134 **Poster**

Profound changes of the p53 network induction on the translatome and proteome levels determine cellular response to MDM2 inhibition

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The p53 network possesses unparalleled tumor suppressive capacity among human cell signaling pathways. By transactivating hundreds of target genes, p53 orchestrates approximately ten anti-oncogenic cellular functions, most notably cell cycle arrest and apoptosis. This concentrated control necessitates tight regulation through multiple feedback loops to maintain dynamic stability at both cellular and organismal levels. Our recent work revealed that stress-induced inhibition of canonical translation profoundly impacts cellular responses to p53 activation, eliciting remarkably strong apoptosis even in otherwise resistant cells. Since over 80% of p53-induced genes are protein-coding, gene-specific regulation at the translational level may critically determine how cells execute p53-triggered transcriptional programs. We therefore investigated how the p53 network is modulated across the transcriptome, translatome, and proteome.

The Integrated Stress Response (ISR) characteristically inhibits canonical translation and can be initiated by stimuli that also activate p53. We used the eIF2α inhibitor nelfinavir to mimic ISR and the MDM2 inhibitor nutlin to activate p53. While each drug individually induces cell cycle arrest, their combination triggers rapid cell death in all TP53 wild-type systems tested. To elucidate the mechanistic basis of this phenotypic shift, we performed RNA-seq, Ribo-seq, and mass spectrometry in three colorectal carcinoma cell lines, followed by comprehensive signaling pathway analysis.

Our data reveal that ISR enhances p53 network induction at the transcriptomic level. However, phenotype-specific regulation emerges at the proteome level, where pro-apoptotic p53 target genes are further amplified while other p53-governed programs are selectively downregulated.

These findings demonstrate that the translatome and proteome represent underappreciated regulatory layers for modulating cellular responses to p53 activation.

Conflict of interest: Other Substantive Relationships: Z.A. is a co-inventor in a patent for employing dual activation of the p53 and ISR networks in cancer therapy (U.S. Provisional Patent Application 63/356,432).

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Poster Session: New agents for paediatric oncology

240 - PB-135 **Poster**

Combined polyamine depletion and irinotecan drive durable tumour clearance in MYC-amplified Group 3 medulloblastoma

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Background: Group 3 medulloblastoma (MB) is an aggressive paediatric brain tumour with frequent MYC amplification and poor survival. MYC drives polyamine biosynthesis, creating a metabolic dependency. Polyamine depletion is an approved therapy in MYCN-driven neuroblastoma. We previously showed dual blockade of polyamine synthesis (DFMO) and transport (AMXT 1501) is active and brain-penetrant in diffuse midline glioma. Group 3 MB shares this MYC-family dependency and epigenetic dysregulation in the brain. We therefore tested this strategy in Group 3 MB and its capacity to potentiate chemotherapy.

Materials and methods: Polyamine pathway expression and prognosis were assessed in paediatric MB datasets (CCMA, ZERO) and single-cell cohorts. In MYC-amplified Group 3 MB lines, DFMO, AMXT 1501, and SN-38 (active irinotecan metabolite) were tested for proliferation, clonogenicity, apoptosis, ATP, mitochondrial reactive oxygen species (ROS), and transcriptomes (RNA-sequencing). Efficacy, pharmacokinetics, and tolerability were tested in two orthotopic models (D425-Luc, MED-2112).

Results: Polyamine pathway activation was associated with inferior Group 3 patient survival and enriched within stem-like malignant MB populations. Dual DFMO + AMXT 1501 depleted intracellular polyamines, synergistically suppressed proliferation and clonogenicity, and induced apoptosis across MYC-amplified models. RNA-sequencing revealed suppression of proliferative, metabolic, and DNA-repair programs. A ten-agent chemotherapy screen identified SN-38 as the strongest partner: triple therapy produced complete tumour cell killing at low nanomolar concentrations, with a wide therapeutic window compared to normal brain cells, accompanied by reactive oxygen species accumulation, ATP depletion, DNA damage signalling (γH2AX), cleaved PARP, and apoptosis. In two independent orthotopic models, dual therapy significantly extended median survival (D425: 68.5 vs 18 days, $p = 0.0024$; MED-2112: 65 vs 29 days, $p = 0.034$); adding irinotecan produced profound, reproducible responses across both models: in D425, median survival was not reached with 7/8 animals tumour-free at endpoint, and in MED-2112, median survival more than tripled from 29 days to 100 days ($p < 0.0001$). Long-term survivors showed no detectable residual tumour, while intratumoral irinotecan exposures achieved in vivo overlapped active in vitro concentrations at clinically achievable doses.

Conclusions: Dual polyamine inhibition creates a therapeutically exploitable vulnerability to irinotecan, an agent already used in relapsed medulloblastoma, producing profound and reproducible anti-tumour across two orthotopic Group 3 MB models at clinically achievable exposures. Building on adult Phase I safety data for the DFMO/AMXT 1501 combination, these findings provide a strong rationale for clinical evaluation in children with high-risk MB.

No conflict of interest

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241 - PB-136 **Poster**

Safety and efficacy of autologous tumor infiltrating lymphocyte therapy in pediatric and adolescent patients with immune checkpoint inhibitor-refractory metastatic melanoma: Results from a phase I clinical trial

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Background: Lifileucel is an autologous tumor infiltrating lymphocyte (TIL) therapy approved for adults with unresectable/metastatic melanoma previously treated with a PD-1 inhibitor and/or targeted therapy. Pediatric data are lacking. We report safety, feasibility, and efficacy results from the melanoma cohort of a multicenter phase I study evaluating lifileucel in pediatric and adolescent patients (NCT06566092).

Methods: Patients underwent surgical resection of a metastatic lesion (≥ 1.5 cm) for ex vivo TIL generation. Manufacturing required approximately 4 weeks, during which bridging therapy was permitted. Treatment consisted of lymphodepletion (LD) with cyclophosphamide and fludarabine, a single infusion of lifileucel, and up to six doses of high-dose interleukin-2 (IL-2).

Results: 5 patients enrolled across 3 sites. Median enrollment age was 15 years (range, 14–17) and follow-up was 7.5 months (range, 2–9). All patients had metastatic melanoma and had received multiple prior therapies: surgery (n = 5), radiotherapy (n = 3), immune checkpoint inhibitors (ICI) (n = 5), and targeted therapy (n = 4). TIL manufacturing was successful in 4 patients. 3 patients completed treatment. 1 patient experienced rapid disease progression and died prior to receiving therapy. Grade 3–4 treatment-related adverse events related to LD included cytopenias (n = 2), atrial thrombosis (n = 1), depressed level of consciousness (n = 1), hypotension (n = 2), hypoxia (n = 1), fever (n = 2), urinary tract infection (n = 2). IL-2-related toxicities included capillary leak syndrome, hypervolemia, hypoxia and cytokine release syndrome which were manageable. No deaths related to LD or IL-2 were observed. 1 patient developed grade 2 uveitis related to TIL therapy. Among treated patients, two achieved confirmed partial responses (PR) per RECIST v1.1, while one experienced symptomatic improvement with resolution of malignant pleural effusions despite radiographic evidence of progressive disease (PD). One patient developed thrombotic microangiopathy with dialysis-dependent renal failure approximately 16 weeks after infusion and was treated with eculizumab, resulting in hematologic recovery but subsequently died (cause unknown) approximately 10 months after receiving TIL. At last follow-up after TIL therapy, two patients remained alive at 6 months (ongoing PR) and 9 months (PD).

Conclusions: In the first reported pediatric/adolescent experience, lifileucel manufacturing and administration were feasible in adolescents with heavily pretreated ICI refractory metastatic melanoma. Early evidence of clinically meaningful antitumor activity was observed, including confirmed PRs in 2 of 3 treated patients. The

safety profile was generally consistent with prior adult experience and supports long-term surveillance and multidisciplinary supportive care for delayed toxicities in this patient population.

Conflict of interest: Other Substantive Relationships:
Brian Gastman: Employment: Iovance Biotherapeutics
Stock or Stock Options: Iovance Biotherapeutics
Travel, Accommodations, Expenses: Iovance Biotherapeutics
Adam Greenbaum: Employment: Iovance Biotherapeutics
Stock or Stock Options: Iovance Biotherapeutics
Travel, Accommodations, Expenses: Iovance Biotherapeutics
Terri Seiders: Employment: Iovance Biotherapeutics
Stock or Stock Options: Iovance Biotherapeutics
Travel, Accommodations, Expenses: Iovance Biotherapeutics

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Poster Session: New therapies in immuno oncology

242 - PB-137 **Poster**

Targeting the CD24–Siglec-10 Axis with S10FC Promotes Phagocytosis and Enhances Immunotherapy Efficacy in Lung Cancer

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Immune checkpoint blockade has transformed lung cancer treatment; however, only 15–30% of patients derive durable clinical benefit due to an immunosuppressive tumor microenvironment and alternative immune evasion mechanisms. To overcome these limitations, we developed a Siglec-10-Fc fusion protein (S10FC) targeting the CD24–Siglec-10 axis, a critical antiphagocytic checkpoint that enables tumor cells to escape innate immune surveillance. S10FC was generated by fusing the extracellular domain of Siglec-10 to the Fc region of human IgG1. ELISA and competitive ELISA demonstrated high-affinity binding of S10FC to CD24 and effective blockade of CD24–Siglec-10 signaling in a dose-dependent manner. Functional analyses using time-lapse live-cell imaging, image-based phagocytosis assays, and flow cytometry showed that S10FC enhanced macrophage-mediated phagocytosis, increased phagolysosomal activity, promoted M1 macrophage polarization, and reduced cancer cell viability. In PBMC-humanized tumor xenograft models, S10FC significantly inhibited tumor growth and reduced tumor burden. Histological and spatial transcriptomic analyses further revealed increased infiltration of M1 macrophages and NK cells, enhanced immune cell recruitment, and expanded regions of tumor cell death following treatment. Moreover, combination therapy with atezolizumab exhibited synergistic antitumor activity (CDI = 0.65) and further increased intratumoral $CD8^+$ T-cell and $iNOS^+$ M1 macrophage infiltration. Collectively, these findings demonstrate that S10FC effectively enhances macrophage-driven antitumor immunity, remodels the tumor microenvironment, and potentiates the efficacy of PD-L1 blockade, supporting CD24–Siglec-10 targeting as a promising immunotherapeutic strategy for lung cancer.

No conflict of interest

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243 - PB-138 **Poster**

Single-Shot Discovery of Highly Specific pHLA Antibodies for T Cell Engagers against Solid Tumors

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Introduction: Solid tumors possess a limited repertoire of tumor-specific antigens (TSAs) on the cell surface, restricting the application of T Cell Engager (TCE) based immunotherapy. An opportunity to expand this repertoire lies in targeting intracellular-derived peptides presented in HLA class I complexes (pHLAs). However, developing specific high-affinity TCEs is challenging due to off-target toxicity, and affinity-driven discovery often yields cross-reactivity.

We introduce TACTICS, a pHLA-targeting TCRmimic Antibody discovery platform that prioritizes specificity to identify highly specific and high-affinity antibodies that can be converted into TCEs. With epitope mapping and structural off-target screening, we can identify promising pHLA targets and design TCEs against tumor-specific epitopes in a single-shot process.

Methods: Fab libraries were screened against recombinant pHLA complexes. Antibodies were screened by flow cytometry against pHLA complexes with sequence- and structural similarity to target antigens (TACTICS complexes). Antibody affinity was determined by flow cytometry and/or SPR. Leads were expressed as TCEs for cytotoxicity screening. Additionally, multiple TCE formats were evaluated with one lead to assess the impact of format design on functional activity and potency. Tumor cytotoxicity, T cell activation and proliferation were assessed by flow cytometry and IFN-γ ELISA. Target specificity was confirmed by X-scan mutagenesis.

Results: Phage display identified antibody panels against multiple pHLA targets. Several candidates exhibited single-digit nanomolar EC50 values, while maintaining exceptional specificity with no detectable binding to wild-type peptides or variants identified through peptidome- and mutagenesis analysis. Compared to previously-reported antibodies against similar epitopes, TACTICS-derived antibodies exhibited superior specificity while maintaining high affinity.

Lead TCEs maintained high specificity in functional assays and mediated potent T cell-dependent cytotoxicity against target-positive tumor cell lines, with no activity against control cells presenting wild-type epitopes. Robust tumor cell killing was observed even in cells expressing single-digit target copy numbers. To assess impact of TCE format on anti-tumor activity, multiple TCE formats were generated using the IM810 p53R175H pHLA-targeting antibody, revealing that TCE format significantly influences functionality, including target cell-killing potency and kinetics.

Conclusions: TACTICS enables fast discovery of highly specific, high-affinity TCEs targeting intracellular tumor-associated peptides, overcoming key limitations of conventional affinity-driven approaches. The resulting TCEs demonstrate potent, selective anti-tumor activity, highlighting TACTICS' potential to expand the targetable antigen repertoire for next-generation immunotherapies.

No conflict of interest

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245 - PB-140 **Poster**

Targeting MCAM and CD228 with CD3- and CD16a-directed bispecific engagers in cutaneous and uveal melanoma

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Background: Cutaneous melanoma (CM) is the most lethal skin cancer, while uveal melanoma (UM) is the leading noncutaneous intraocular melanoma; both show high metastatic risk and limited treatment options. Bispecific T-cell and killer-cell engagers (BiTEs/BiKEs) simultaneously bind immune effector cells (T cells via CD3, NK cells via CD16a) and tumor-associated antigens, driving targeted cytotoxicity. Although blinatumomab and tebentafusp are approved for hematological malignancies and UM, unmet needs remain. We developed and characterized BiTEs and BiKEs against MCAM × CD3/CD16a and CD228 × CD3/CD16a in CM and UM models.

Material and methods: MCAM- and CD228-specific scFv sequences were cloned into a CD3- or CD16a-containing pBiTE/pBiKE backbone plasmids via Golden Gate Assembly, followed by DH5α transformation and plasmid isolation. Constructs were transiently expressed in HEK293 cells. Binding to four CM and four UM cell lines (A375, A2058, UACC257, G361, 92.1, OMM2.5, MP41, MM28) was quantified by flow cytometry. Functional assays included luciferase-based T-cell activation (6-24 h), macrophage RAW264.7/CD16a phagocytosis of CFSE-targets ($CD11b^+CFSE^+$, 3 h), xCELLigence cytotoxicity with NK-92/CD16a and PBMCs (48 h), and Annexin V/PI apoptosis (48 h) with NK-92/CD16a and $CD8^+$ T cells.

Results: Cloning was confirmed by gel electrophoresis and Sanger sequencing. Transfection efficiency ranged from 36% to 77%. MCAM- and CD228-BiTEs/-BiKEs achieved ~100% binding across all CM lines. In UM, MCAM-scFv binding reached ~100%, while CD228-scFv binding varied (11-22%). Both BiTEs significantly increased luciferase activity in CM and UM; BiKEs showed comparable activation in CM. BiKEs enhanced macrophage phagocytosis, strongly in 92.1/MM28 and modestly in OMM2.5/MP41. xCELLigence RTCA confirmed BiKE cytotoxicity in two CM and three UM lines with NK-92/CD16a, and BiTE cytotoxicity in three UM lines with PBMCs. Annexin V/PI showed increased apoptosis for A375/A2058 with $CD8^+$ T cells and NK-92/CD16a.

Conclusions: MCAM- and CD228-directed CD3- and CD16a-bispecific constructs showed specific binding and functional activation of T cells, NK cells, and macrophages, supporting their potential as immunotherapeutics for CM and UM.

No conflict of interest

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246 - PB-141 **Poster**

BCG024: A Novel DLL3 × CD3 × 4-1BB Trispecific T Cell Engager Enhances T Cell Persistence and Functionality in Preclinical Models

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Background: CD3-based T cell engagers (TCEs) as powerful therapeutic agents have demonstrated clinical success in both hematologic malignancies and solid tumor indications. One major obstacle to TCE therapies in treating solid tumors is T-cell exhaustion due to conventional TCEs lacking co-stimulatory signaling, limiting their therapeutic durability. To address this challenge, integrating a co-stimulatory signal such as 4-1BB into TCEs could be an attractive approach to enhance T cell function and durability.

Methods: We developed a trispecific antibody (TriAb) targeting DLL3, CD3, and 4-1BB using a VHH 4-1BB agonist derived from RenNano® mice to achieve tumor antigen-dependent co-stimulation. *In vitro* assays included repeated stimulation assay and cytotoxicity against DLL3-positive small cell lung cancer (SCLC) cell line. *In vivo* efficacy and T cell proliferation were evaluated in xenograft mouse models bearing established SCLC tumors. The toxicity study was evaluated in CD3ε × 4-1BB humanized mice.

Results: The DLL3 TriAb demonstrated significantly enhanced T cell proliferation while maintaining high cell viability and cytotoxicity following repeated stimulation. However, the benchmark and bsAb counterparts showed marked reductions in cell viability and activity. *In vivo*, mice treated with benchmark caused dose-dependent reductions in serum T cell number, whereas those treated with DLL3 TriAb maintained stable T cell populations. That indicated TCE integrated 4-1BB nanobody co-stimulation indeed enhances T cell durability and functionality. In SCLC xenograft models, DLL3 TriAb exhibited robust antitumor efficacy in a monovalent antigen-binding format rather than a bivalent antigen-binding format. Notably, contrasting with non-specific TriAb controls, DLL3 TriAb displayed favorable safety profiles in CD3ε × 4-1BB humanized mice even at high doses, with no significant body weight loss or systemic cytokine elevation observed.

Conclusions: Our DLL3 × CD3 × 4-1BB TriAb demonstrates tumor-dependent co-stimulation, enhanced T cell persistence and functionality, further exhibiting superior anti-tumor efficacy in preclinical SCLC model and good safety profiles at high dose. These findings highlight the DLL3 TriAb as a next-generation immunotherapy, offering enhanced T cell functionality and clinical translatability.

No conflict of interest

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247 - PB-142 **Poster**

Population Pharmacokinetic Modeling and Exposure–Safety Analysis of Neutropenia Incidence Using Data from a BAL0891 Dose-Escalation Trial

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Background: BAL0891 is a small-molecule inhibitor with dual activity against TTK and PLK1 that is expected to induce aberrant mitosis and tumor cell death in tumors with chromosomal instability. In early-phase dose escalation, neutropenia is a clinically relevant hematologic toxicity for interpreting tolerability across dose levels. This analysis aimed to develop a population pharmacokinetic model for BAL0891 and characterize the exposure–neutropenia relationship using Cycle 1 data from a Phase I dose-escalation study.

Material and Methods: BAL0891 plasma concentration data from Substudy 1 and Substudy 3 were analyzed by nonlinear mixed-effects modeling in NONMEM version 7.5 with FOCE-I. The pharmacokinetic dataset included 1,748 plasma concentration records from 73 patients. Exposure–neutropenia modeling was performed separately using completed Cycle 1 data from Substudy 1 Regimen A, in which BAL0891 monotherapy was administered as a 1-hour intravenous infusion on Days 1 and 8 of each 3-week cycle. Other substudy/regimen data were excluded to minimize confounding from early therapeutic G-CSF use. Individual predicted clearance from the final model was used to derive individual predicted AUCinf, which was log-transformed for exposure–safety modeling. Grade ≥ 3 and Grade ≥ 4 neutropenia recorded as CTCAE v5.0 adverse event terms before G-CSF were analyzed as separate binary endpoints. Probit models related log-transformed individual predicted AUCinf to neutropenia incidence. Population-level dose–risk curves were generated by marginalizing over population variability in ln(CL).

Results: BAL0891 pharmacokinetics were described by a two-compartment model with linear elimination. Estimated clearance, central volume, peripheral volume, and intercompartmental clearance were 24.4 L/h, 211 L, 854 L, and 200 L/h, respectively. Interindividual variability was estimated for each structural parameter, and no covariate was retained. The exposure–neutropenia dataset included 42 patients in Substudy 1 Regimen A across BAL0891 dose levels of 5–240 mg. During Cycle 1 before G-CSF, Grade ≥ 3 and Grade ≥ 4 neutropenia occurred in 16 and 9 patients, respectively. Neutropenia probability increased with log-transformed model-derived AUCinf. For descriptive interpretation of the dose–risk curves, BAL0891 doses corresponding to a reference predicted probability of 25% were estimated as 84 mg for Grade ≥ 3 neutropenia and 121 mg for Grade ≥ 4 neutropenia.

Conclusions: A population pharmacokinetic model was developed for BAL0891 using Phase I plasma concentration data, and model-derived exposure was related to Cycle 1 neutropenia incidence in Substudy 1 Regimen A. This exploratory exposure–safety analysis quantified the exposure–neutropenia relationship and may support upper exposure and dose boundary considerations during RP2D evaluation.

Conflict of interest: Ownership: SillaJen Bio/SillaJen Biotherapeutics: disclosed by applicable SillaJen-affiliated author(s), as relevant.

Corporate-sponsored Research: SillaJen Bio/SillaJen Biotherapeutics: AIMS BioScience has a contractual agreement with SillaJen to provide clinical pharmacology and pharmacometrics consulting and analysis services related to BAL0891. Seunghoon Han and Sungpil Han are employees of AIMS BioScience.

Other Substantive Relationships: Sujin Lee, Hyun Jin Kim, and Seunghyun Ma are affiliated with SillaJen/SillaJen Biotherapeutics.

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248 - PB-143 **Poster**

A novel biparatopic DLL3 T Cell Engager utilizing a cis-binding CD58 demonstrated superior potency and remarkable safety profile

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Background: Small cell lung cancer (SCLC) is an aggressive malignancy with limited therapeutic options and a dismal prognosis. Delta-like ligand 3 (DLL3) is highly and selectively expressed in SCLC, making it an ideal therapeutic target. While T-cell engagers (TCEs) targeting DLL3 show clinical promise, issues like antigen escape, suboptimal T-cell costimulation, and systemic toxicities limit their efficacy. To address these challenges, we engineered a first-in-class tetraspecific antibody combining biparatopic DLL3 targeting with a novel CD2-binding CD58 fusion protein costimulatory arm to maximize potency while minimizing adverse events.

Methods: A tetraspecific molecule incorporates two distinct non-overlapping epitopes against DLL3, an anti-CD3 arm, and a CD58 fusion protein. In vitro cytotoxicity, T-cell activation, and cytokine secretion were evaluated across a panel of DLL3-low and DLL3-high SCLC cell lines. In vivo efficacy was evaluated in humanized mouse models bearing SCLC xenografts. A non-human primate (NHP) exploratory toxicity and pharmacokinetic (PK) study was conducted at a dose of to assess safety and tolerability.

Results: The tetraspecific design allowed the anti-CD3 arm and the CD58 fusion protein to bind T cells simultaneously in a *cis* configuration, effectively preventing T-cell fratricide. In vitro, the molecule demonstrated overwhelming, superior potency and triggered robust T-cell activation and sustained T cell proliferation against SCLC lines. In vivo, it induced complete and durable tumor regression in xenograft models without significant weight loss. In the NHP exploratory toxicology study, it demonstrated a remarkable safety profile at 5 mg/kg QW with no cytokine release syndrome (CRS), minimal systemic toxicity, and an excellent, prolonged PK half-life.

Conclusions: Our biparatopic DLL3 CD58 tetraspecific T-cell engager represents a next-generation platform for SCLC immunotherapy. By integrating dual-epitope targeting with *cis*-mediated CD58 costimulation, this molecule overcomes antigen escape and achieves extraordinary potency both in vitro and in vivo, supported by highly encouraging NHP safety data. These findings strongly support its clinical development.

No conflict of interest

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249 - PB-144 **Poster**

Targeted cDC1 Activation via Anti-CLEC9A ISAC Potentiates Anti-Tumor Immunity

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Background: Type 1 conventional dendritic cells (cDC1) play a critical role in cross-presenting tumor antigens and priming tumor-specific $CD8^+$ T cell responses, making them essential for successful cancer immunotherapy. However, systemic administration of cyclic dinucleotide STING (stimulator of interferon genes) agonists often triggers dose-limiting toxicities and off-target inflammation. To overcome these limitations, we developed a novel Immune Stimulating Antibody Conjugate (ISAC) by coupling a STING agonist to a monoclonal antibody targeting CLEC9A, a surface receptor highly restricted to cDC1. This study evaluates the targeted delivery, activation kinetics, and therapeutic efficacy of this anti-CLEC9A ISAC.

Methods: The binding affinity and specificity of the anti-CLEC9A ISAC were assessed in vitro across multiple immune cell subsets using flow cytometry. cDC1 activation was determined by CD86 expression. In vivo therapeutic efficacy, immune cell infiltration, and systemic toxicity profiles were evaluated in syngeneic murine tumor models both as a monotherapy and in combination with anti-PD-1 checkpoint inhibitor.

Results: The anti-CLEC9A ISAC demonstrated highly selective binding to target cDC1, with negligible cross-reactivity to other myeloid or lymphoid lineages. In vitro, the CLEC9A ISAC selectively activated CLEC9A-positive cDC1 cells. In vivo, systemic administration of the CLEC9A ISAC mediated significant tumor growth inhibition and led to complete regressions in a subset of mice. High-dimensional immune profiling revealed a marked increase in activated cDC1 within the tumor microenvironment. Notably, the anti-CLEC9A ISAC demonstrated synergistic efficacy when combined with anti-PD-1 therapy and induced long-term immunological memory against tumor rechallenge. Minimal systemic cytokine release or weight loss was observed, confirming a favorable safety profile.

Conclusions: Our novel anti-CLEC9A ISAC successfully bridges innate and adaptive immunity by selectively delivering a potent STING payload directly to cDC1. This targeted approach achieves robust anti-tumor efficacy and establishes durable immune memory while minimizing systemic toxicities. These data support the clinical development of anti-CLEC9A ISACs as a promising next-generation therapeutic strategy for immuno-oncology indications.

No conflict of interest

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250 - PB-145 **Poster**

Discovery of First-in-Class Zα-Domain-Selective ADAR1 p150 Inhibitors AVA-ADR-568/598 with Oral Bioavailability and Anti-PD-1 Combination Efficacy in Interferon-High Melanoma Models

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Background: ADAR1 p150, the interferon (IFN)-inducible isoform of adenosine deaminase acting on RNA 1, restrains innate sensing of endogenous double-stranded RNA in IFN-high tumours, and knockout experiments validate it as an immuno-oncology target. Deaminase-domain-directed approaches lack isoform selectivity and carry liabilities including ADAR2-linked neurotoxicity and ADAR1 p110-linked haematopoietic toxicity. We report preclinical data for AVA-ADR-568 and AVA-ADR-598, small molecules binding to the Zalpha domain of ADAR1 p150 for isoform-selective inhibition.

Material and Methods: Zα binders were identified by thermal shift and FRET assay; selectivity was confirmed with a PROTAC-based degrader. On-target activity was assessed via IFN-beta induction, interferon-stimulated gene (ISG) expression and protein kinase R (PKR) phosphorylation, and cytotoxicity in OE21 cells. Pharmacokinetics of the compounds were evaluated in mice. Efficacy (monotherapy and combination with anti-PD-1), was tested in checkpoint-refractory B16F10 melanoma under low- and high-IFN conditions.

Results: AVA-ADR-486, AVA-ADR-568 and AVA-ADR-598 bind to Zα of ADAR1 with nanomolar to sub-micromolar potency and competitively displaced Z-DNA (KD 6.9 nM). A PROTAC analogue of the AVA-ADR series degraded p150 selectively over p110. AVA-ADR compounds demonstrated ISG upregulation; PKR phosphorylation, and sub-nanomolar IFN-dependent cytotoxicity. Oral bioavailability of AVA-ADR-486 was around 50% and 100% for AVA-ADR-568 and AVA-ADR-598); healthy mice showed mild ISG elevation, replicating similar observations in Zα-mutant mice reported previously. Interestingly, in low-IFN tumours, oral monotherapy matched or exceeded anti-PD-1 (Table); whereas in high-IFN conditions combination with anti-PD-1 demonstrated >90% tumour growth inhibition (TGI).

Table. Tumour growth inhibition, B16F10 melanoma

Compound	Monotherapy (low IFN)	+ anti-PD-1 (high IFN)
AVA-ADR-486	45%	85%
AVA-ADR-568	49%	86%
AVA-ADR-598	59%	91%

Conclusions: AVA-ADR-568 and AVA-ADR-598 compounds are first-in-class, orally bioavailable molecules that selectively inhibit ADAR1 p150 via Zα-domain binding rather than deaminase-domain engagement. On-target pharmacology, drug-like pharmacokinetics, and single-agent/anti-PD-1 efficacy in IFN-high tumours validates first-in-class AVA-ADR as an oral agent.

Conflict of interest: Ownership: Aditya Kulkarni, Sandeep Goyal, Avijit Goswami and Princy Khurana own equity in Avammune.

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251 - PB-146 **Poster**

FF01, a novel heavy chain antibody targeting the human endogenous retrovirus envelope, displays anti-lymphoma activity

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Background: Human endogenous retroviruses (HERVs) are transposable elements (TEs) originating from ancestral retroviral infections that integrated into the germline millions of years ago. Although they constitute ~8% of the human genome, their biological role remains largely undefined. HERV-K, one of the most recently integrated families, retains open reading frames with potential for coding. Among its subgroups, HML-2 is the most active and has attracted particular interest in disease-related research. HERVs are expressed in embryonic stem cells but silenced in normal adult tissues. Aberrant HERV expression has been reported in human tumors, including lymphoma. This prompted us to investigate HERV-K as a therapeutic target in B-cell lymphomas.

Methods: TE expression was quantified from RNA-seq data using Telescope. Findings were validated by qPCR, Western blot, flow cytometry, and ELISA. The envelope (Env) structure was modeled with AlphaFold, and peptides were synthesized (GenScript). Antibody-dependent cellular cytotoxicity (ADCC) was measured with the ADCC Reporter Bioassay (Promega) and in NK-cell co-cultures. Internalization was assessed using Incucyte Fabfluor-pH labeling reagents.

Results: Comparing RNA-Seq datasets from diffuse large B-cell lymphoma (DLBCL) and healthy donor B cells, multidimensional scaling separated neoplastic from healthy samples, indicating distinct TE and HERV expression profiles. Within tumors, DLBCL segregated into four prognostic clusters, and comparable patterns across a panel of 47 B-cell lymphoma cell lines. Many HML-2 family members were upregulated in patient tumors. We confirmed RNA and protein expression of the HML-2 envelope (Env) in lymphoma cell lines, with surface Env shown in two of them. Env-specific siRNA reduced Env levels and decreased proliferation, supporting Env's contribution to lymphoma growth. *In silico* analysis of Env identified four linear antibody binding regions, and corresponding peptides were synthesized; serum from 150 lymphoma patients was positive for anti-peptide antibodies against all four. A phage-display screen yielded the nanobody FF01, binding one peptide. In the reporter assay, FF01 selectively induced ADCC in Env-high but not in Env-negative cell lines. Most importantly, co-cultures with NK cells confirmed robust target-dependent ADCC and effective killing of Env+ lymphoma cells beyond the reporter signal. FF01 was also internalized by Env-expressing cells, providing proof of principle for an antibody-drug conjugate.

Conclusions: HERVs are aberrantly expressed in DLBCL patients, and FF01 is a promising new candidate to target HERV Env+ lymphomas; its activity in NK-cell co-cultures confirms the capacity to drive effector-mediated killing of Env+ tumor cells. These data highlight HERVs as promising targets for lymphomas and other Env + cancers.

No conflict of interest

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252 - PB-147 **Poster**

A novel virus-like drug conjugate for the treatment of cutaneous melanoma

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Background: AU-011 (belzupacap sarotalocan) is a novel human papillomavirus (HPV) virus-like drug conjugate (VDC) in which the cytotoxic payload (sarotalocan, a phthalocyanine dye) is conjugated to the virus-like particle (VLP). AU-011 can bind to modified heparan sulfate proteoglycans found on the surface of many tumor cells. Upon binding tumor cells, the VDC is activated with near-infrared (NIR) light resulting in acute cytotoxicity, often leading to complete tumor eradication and long-term protection from tumor re-challenge in several murine models. AU-011 is currently in phase 3 clinical development for the treatment of patients with early choroidal melanoma. Here we present the pre-clinical data demonstrating anti-tumor efficacy of AU-011 in cutaneous melanoma models.

Materials and Methods: Three syngeneic melanoma models, M1, M2, and M3, developed at the NCI to recapitulate various immunologically "hot to cold" subclasses of human cutaneous melanoma were tested in murine flank models. AU-011 was delivered intravenously, and 12 hours later the tumor was exposed to NIR light. AU-011 was tested either alone or in combination with checkpoint inhibitors, anti-CTLA-4, anti-PD-1, anti-PD-L1 or anti-LAG3. Tumor free surviving mice were re-challenged with tumor after 100 days and followed for an additional 100 days.

Results: Previously the three melanoma models (M1, M2 and M3) proved to be resistant to complete responses with checkpoint inhibitors alone. We observed complete responses with a single administration of AU-011 alone in all three models, M1 (50%), M2 (25%), and M3 (12%). When AU-011 was combined with individual checkpoint inhibitors, we noted enhanced survival rates in the M1 and M3 models compared to AU-011 alone. Combination with anti-CTLA-4 was the most robust combination therapy, however long-lasting memory responses were observed when AU-011 was combined with all checkpoint inhibitors. All complete responders were rechallenged with the homologous tumor after 100 days, and protection from rechallenge was observed in all models, M1 (50%), M2 (100%), and M3 (100%). In animals receiving the combination treatments, equivalent or enhanced protection from rechallenge was observed.

Conclusions: Using AU-011 alone, we demonstrated that tumor eradication was possible in diverse murine melanoma models after a single AU-011 treatment. Consistent with the immunogenic nature of AU-011 mediated tumor killing, checkpoint inhibitors enhanced this response. Protection from tumor rechallenge indicated a potent tumor antigen agnostic adaptive immune response was generated even in a cold tumor model.

Conflict of interest:

Ownership: E. de los Pinos and J. Hopkins are employees of Aura Biosciences and own shares of the company stock.

Corporate-sponsored Research: This research was, in part, funded by a cooperative research agreement between Aura Biosciences and the NIH.

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253 - PB-148 **Poster**

A novel FcRL5-targeting T-cell engager with a cis-binding CD58 costimulatory arm enhances anti-tumor efficacy while mitigating CRS and T-cell fratricide

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Background: T-cell engagers (TCEs) have shown significant therapeutic promise in multiple myeloma (MM) and B-cell mediated autoimmune diseases. However, their clinical utility is frequently bottlenecked by systemic toxicity, including cytokine release syndrome (CRS), insufficient T-cell persistence due to a lack of costimulation or activation-induced T-cell fratricide. We engineered a next-generation FcRL5 TCE incorporating a highly selective FcRL5-binding arm, an affinity-attenuated anti-CD3 domain combined with a CD58 (LFA-3) costimulatory fusion protein arm to optimize the therapeutic index.

Methods: A multispecific molecule incorporates a highly selective FcRL5-binding arm, an affinity attenuated anti-CD3 arm, and a CD58 fusion protein. Binding specificity of the FcRL5-targeting arm was evaluated against FcRL5 and related Fc receptor-like family members. In vitro cytotoxicity, T-cell activation, T-cell proliferation, and cytokine secretion were evaluated across a panel of FcRL5-expressing multiple myeloma cell lines. In vivo efficacy was evaluated in humanized mouse models bearing multiple myeloma xenografts.

Results: The FcRL5-binding arm showed high selectivity for FcRL5 with minimal binding to related Fc receptor-like family members. The tetraspecific multispecific design allowed the anti-CD3 arm and the CD58 fusion protein to engage T cells in a cis configuration through CD3 and CD2, effectively preventing T-cell fratricide. In vitro, the molecule demonstrated superior potency and triggered robust T-cell activation and sustained T-cell proliferation against MM lines. In vivo, it induced complete and durable tumor regression in xenograft models without significant weight loss.

Conclusions: Our FcRL5 × CD3 × CD58 multispecific T-cell engager represents a next-generation platform for multiple myeloma and B cell-mediated autoimmune diseases. By integrating highly selective FcRL5 targeting with cis-mediated CD58 costimulation, this molecule enhances tumor-restricted T-cell activation, improves antitumor efficacy, and may mitigate key liabilities associated with conventional TCEs, including CRS and T-cell fratricide both in vitro and in vivo.

No conflict of interest

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254 - PB-149 **Poster**

Preclinical Evaluation of CDR609, an LGR5-Directed T Cell Engager, Supporting Clinical Development for Gastrointestinal Cancers

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Background: Gastrointestinal (GI) cancers remain a leading cause of cancer-related mortality, with patients diagnosed with or progressing to advanced disease responding poorly to current therapies. The majority of tumors are microsatellite stable and poorly infiltrated by T cells, limiting the efficacy of immune checkpoint inhibitors. LGR5 is broadly expressed in GI malignancies and is implicated in tumor maintenance, plasticity, and resistance, while showing limited expression in healthy tissues, making it an attractive immunotherapeutic target. CDR609 is a novel LGR5-targeted T cell engager (TCE) for solid tumors based on the M-gager® format, a platform with emerging clinical validation through CDR404 in Phase I (NCT06402201).

Methods & Results: To characterize the pharmacological activity of CDR609, in vitro potency was assessed in GI cancer models across a range of effector-to-target (E:T) ratios, including low E:T conditions intended to reflect limited T cell infiltration in GI tumors. Functional readouts included T cell activation, cytokine release, and T cell-mediated cytotoxicity. CDR609 demonstrated robust activity across tested conditions and a favorable cytokine profile, inducing IFNγ production consistent with T cell activation while eliciting only minimal IL-6 release. This uncoupling of pharmacological activity from pro-inflammatory cytokine release supports the differentiated pharmacological profile of CDR609 and its potential for an improved therapeutic window.

Consistent with these findings, CDR609 induced durable tumor regression in humanized CDX mouse models and demonstrated antitumor activity in PDX models of gastric and colorectal cancer. Tumor responses were associated with increased intratumoral CD8 + T cell infiltration and depletion of LGR5-positive tumor cells, consistent with the proposed mechanism of LGR5-directed T cell-mediated cytotoxicity.

In a dose-range finding study in cynomolgus monkeys, CDR609 exhibited dose-proportional pharmacokinetics with sustained systemic exposure and demonstrated good tolerability at doses up to 30 mg/kg, including gut integrity assessments with relevant biomarkers. Observed findings were consistent with the expected on-target pharmacology, while key TCE liabilities, including cytokine release, lymphopenia, and hepatotoxicity, were largely de-risked. Collectively, these data support GLP repeat-dose toxicity studies to further characterize the toxicological profile, safety margins, and reversibility of potential effects.

Conclusion: CDR609 demonstrated activity under conditions reflecting immune-excluded tumors and induced durable antitumor responses in vivo. Together with PK characterization and encouraging safety findings, these data are expected to support first-in-human dose selection and provide a strong rationale for the clinical evaluation of CDR609 in patients with advanced GI malignancies.

No conflict of interest

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255 - PB-150 **Poster**

Biomimetic Lipid Nanoparticles for Targeted Delivery of an Immunomodulatory Compound in Neuroblastoma

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Background: Neuroblastoma (NB) is a pediatric malignancy characterized by highly immunosuppressive tumor microenvironment that limits the efficacy of immunotherapy. In a previous screening of 182 FDA-approved immunomodulatory compounds, Compound1 (C1) emerged as promising therapeutic candidate. To enhance C1 tumor-selective delivery and therapeutic efficacy, we developed NB cell membrane-coated biomimetic lipid nanoparticle formulations (bio-LNP) to exploit homologous targeting, increase cellular uptake and drug delivery. C1-loaded bio-LNPs were evaluated in NB spheroids for antitumor activity and in NB spheroids-PBMC co-culture to investigate tumor-immune crosstalk by profiling extracellular vesicle (EVs) secretome.

Materials and Methods: Bio-LNPs encapsulating Compound 1 (C1) were fabricated using a two-step microfluidic approach. Cell membranes (CMs) were isolated from SK-N-BE(2)-C and Kelly NB cell lines and subsequently used to coat C1-loaded LNPs generated with a herringbone microfluidic mixer (TFR = 2 mL/min; FRR = 1:1, LNP:PBS + CMs). Bio-LNPs were characterized for particle size, polydispersity index (PDI) and encapsulation efficiency by dynamic light scattering (DLS) and HPLC. Biohybrid formation was confirmed by dual-fluorescence flow cytometry of CMs and lipid components, while intracellular uptake was assessed by confocal microscopy through fluorophore co-localization. Antitumor activity of free C1 and C1-loaded bio-LNPs was evaluated in NB spheroids using dose-response assay. To investigate tumor-immune crosstalk, EVs were isolated from conditioned media of SK-N-BE(2)-C and Kelly spheroids co-cultured with healthy donor PBMCs and treated with sub-toxic concentrations of bio-LNPs. EVs were purificated using a resin-based spin-column chromatography method and analyzed by flow cytometry.

Results: Bio-LNPs exhibited a mean particle size of approximately 130 nm, a narrow size distribution (PDI < 0.25) and an encapsulation efficiency of approximately 30% for C1. Flow cytometry analysis showed co-localization of CM and lipid fluorescence signals of about 80%, confirming successful biohybrid formation, while confocal microscopy revealed extensive cellular uptake of Bio-LNPs within NB spheroids. Preliminary data showed that C1-loaded Bio-LNPs exhibited greater antitumor activity than free C1, decreasing the IC_{50} by approximately 40% in both SK-N-BE(2)-C and Kelly spheroids. EVs secretome profiling is currently ongoing.

Conclusions: C1-loaded Bio-LNP formulations represent a promising strategy to improve targeted drug delivery in NB by enhancing tumor cell uptake and antitumor efficacy. Ongoing EVs secretome profiling will further elucidate the therapeutic potential and immunomodulatory effects of formulations.

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No conflict of interest

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256 - PB-151 **Poster**

INB-619, A Novel Pan-Gamma-Delta (γδ) T Cell Engager for CD19+ B Cell Depletion without CD3 mediated Toxicities

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Background: CD19 is a validated target for B cell malignancies, where CAR-T and CD3-directed T cell engagers (TCEs) have been shown to be clinically effective. However, CD3 based TCEs cause significant dose-limiting toxicities, including cytokine release syndrome (CRS) and immune exhaustion due to broad, non-selective T cell activation. The resulting B cell aplasia also leaves patients vulnerable to significant infections. γδ T cells bridge innate and adaptive immunity, offering direct intrinsic cytotoxicity and tissue-homing with a favorable safety profile relative to αβ T cells. Unlike CD3-directed TCEs, INB-619 a novel pan-γδ T cell engager, selectively expands and directs γδ T cells to target cells, harnessing potent effector function while potentially minimizing the toxicities such as CRS and infections. INB-619 induces potent cytotoxicity while driving in vivo activation and expansion of both Vδ1 and Vδ2 T cells, potentially combining therapeutic depth with an improved tolerability window and anti-infective immune competence during B cell depletion.

Material and Methods: INB-619 activation and expansion of γδ T cells and target cell depletion was assessed in vitro by NALM-6 cells (CD19+ B-ALL) co-cultured with healthy donor PBMCs and either INB-619, blinatumomab (BLI) or mosunetuzumab (MOS) assessed over 10 days for lymphocyte dynamics, CD19+ target cell depletion and cytokine section. Cytotoxicity, target specificity, and γδ T cell activation, maturation, and checkpoint marker expression (CD69, CD25, CD107a, PD-1, LAG-3, TIM-3, granzyme, perforin) were quantified by flow cytometry. The in vivo activity of INB-619 was subsequently evaluated in a humanized mouse model engrafted with PBMCs with concomitant assessment of CRS-associated cytokines.

Results: INB-619 induced specific dose-dependent activation and expansion of γδ T cells and elimination of NALM-6 cells, comparable to commercially available B cell TCEs with minimal release of CRS associated cytokines (IL-6, IL-10 and TNFα). Analysis of cell populations showed INB-619 induced expansion of γδ T cells concurrent with B cell depletion, with a correlation between the level of depletion and γδ T expansion (increases in CD107a, granzyme, and perforin) without expansion of CD4 and CD8 cells. In murine models, INB-619 showed effective B cell depletion in PBMC-engrafted mice with a favorable cytokine profile.

Conclusions: INB-619, a novel CD19-targeting pan-γδ TCE, expands and activates both major γδ T cell subtypes to eliminate CD19+ cells. The combined expansion and favorable cytokine pattern, suggests that INB-619 could provide cell depletion with an improvement in safety over current methods, while enhanced γδ T cell function could help maintain anti-infective defenses during B cell depletion supporting continued development for CD19+ hematologic malignancies.

Conflict of interest: Ownership: Stock and/or stock option IN8bio Inc.: K. Rochlin, L. Ding, Y. Li, M. ter Haak, L. Lamb
Advisory Board: Intrommune, K. Rochlin
Other Substantive Relationships: Employee IN8bio Inc.
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Poster Session: Radiation Interactive Agents

257 - PB-152 **Poster**

TRA-1-60- targeted radioligand enables selective tumor targeting in ovarian cancer

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Background: Recurrent ovarian cancer (OC) remains a major clinical challenge with limited treatment options and poor outcomes, underscoring the urgent need for more effective therapies. Targeted approaches offer precision but are constrained in OC by the lack of highly selective tumor antigens. To address this, we developed a TRA-1-60 (TRA) - targeted radioligand directed against a cancer-specific glyco-epitope on podocalyxin (PODXL). Unlike the PODXL protein, which is expressed in both tumor and normal tissues, the TRA glyco- epitope is minimally present in healthy tissues, consistent with aberrant glycosylation as a hallmark of cancer. Here, we evaluate TRA as a targeting agent for OC.

Methods: TRA expression was evaluated by immunohistochemistry on a commercially available OC tissue microarray, with H-scores quantified using HALO (v4.1). *In vivo* studies used a OC model generated by intraperitoneal (i.p.) injection of mCherry-labeled triple-knockout (TKO; (*p53*LSL-R172H/+*Dicer*flox/flox*Pten*flox/flox *Amhr2*cre/+) mouse OC cells into C57BL/6 mice. For biodistribution, mice received a single i.p. dose of Cy7-conjugated anti-TRA antibody (100 µg), followed by *ex vivo*fluorescence imaging 4 days later to quantify tumor-to-liver and tumor-to-kidney signal ratios. For PET imaging, an engineered anti-TRA single-chain variable fragment Fc fusion protein (scFv-Fc) was conjugated to desferrioxamine (DFO), radiolabeled with zirconium-89, and administered intravenously (200 µCi/mouse). Serial PET imaging was performed to evaluate tumor targeting and biodistribution.

Results: Strong membranal TRA staining was observed in cancer cells, with minimal to no staining in the surrounding stroma. All tumor samples were TRA-positive, and H-scores in cancer tissues were significantly higher than in adjacent normal tissues. TRA expression did not significantly differ across OC histotypes or between early- and advanced-stage disease. *Ex vivo* fluorescence imaging demonstrated strong accumulation of the Cy7 signal in mCherry-positive tumors, with markedly lower signal in non-tumor organs, including the liver and kidneys. Quantitative analysis confirmed significantly higher tumor-to-liver and tumor-to-kidney signal ratios, indicating selective tumor uptake. Serial PET imaging demonstrated early tumor uptake with progressive accumulation and sustained retention of the radiotracer through 96 hours. Quantitative volume-of-interest analysis showed increasing tumor-associated signal over time, accompanied by a progressive decline in liver uptake, resulting in improved tumor-to-liver contrast.

Conclusion: We show the cancer-specific TRA glyco-epitope as a highly promising target for OC. Its consistent expression across tumor subtypes, combined with selective tumor localization and favorable imaging characteristics, supports its development as a theranostic platform.

No conflict of interest

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Poster Session: Animal Models

258 - PB-050 **Poster**

Effects of standard-of-care therapies in preclinical bone metastasis models of triple-negative breast cancer, castration-resistant prostate cancer and multiple myeloma bone disease

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Background: Metastases are the leading cause of death in many cancers. Bone is the preferred site of metastasis in many cancers, affecting 70-90% of advanced breast cancer (BC), prostate cancer (PC) and multiple myeloma (MM) patients. Clinical problems include insufficient response to cancer treatments and decreased quality of life of patients due to cancer-induced bone loss that leads to increased risk of fractures and bone pain. In order to enhance development of novel therapies for bone metastasis, we have established preclinical bone metastasis models for BC, PC and MM, referred to as “Bone Metastasis Technology Platform” (BMTP©). In this study we report the effects of standard-of-care (SOC) therapies in triple-negative BC (TNBC) and castration-resistant PC (CRPC) bone metastasis models, and in a MM bone disease model.

Material and methods: BMTP utilized intratibial inoculation of cancer cells into the bone marrow of mice to study effects of therapies on tumors growing in bone microenvironment, mimicking bone metastases. In this study, the following cancer cell lines and mouse strains were used: 4T1 mouse TNBC cells in BALB/c mice, RM-1 mouse CRPC cells in C57BL/6 mice, and RPMI-8226 human MM cells in immunodeficient NPG mice. Tumor growth was monitored by bioluminescence imaging, cancer-induced bone changes by X-ray imaging, and bone pain by Von Frey filaments (mechanical allodynia). SOC therapies included the tumor growth inhibitors doxorubicin (4 mg/kg, ip, BIW) in the TNBC model, docetaxel (10 mg/kg, ip, BIW) in the CRPC model and bortezomib (0.5 mg/kg, ip, BIW) in the MM model, and the cancer-induced bone loss inhibitor zoledronic acid (0.1 mg/kg, QW) in all models.

Results: A moderate anti-tumor response was observed with doxorubicin in the TNBC model, docetaxel in the CRPC model, and bortezomib in the MM model. In all models, zoledronic acid decreased moderately cancer-induced bone loss. None of the therapies decreased bone pain.

Conclusions: BMTP demonstrated the same clinical features and responses to therapies that are observed in patients with TNBC, CRPC and MM. We conclude that BMTP is a clinically relevant translational tool for predicting efficacy of experimental therapies on bone metastasizing cancers.

No conflict of interest

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259 - PB-051 **Poster**

The B-hCRBN Mice Model Facilitates PROTACs Studies Based on CRBN Ligands

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In recent years, CRBN ligands have gradually become popular E3 ligase ligands. They can be used to design and synthesize PROTACs

and molecular glue degraders, playing an important role in these fields.

CRBN, together with DDB1 (damaged DNA binding protein 1), Cul4A (Cullin 4A), and ROC1, forms the E3 ubiquitin ligase complex (CRL4). As a substrate receptor, CRBN binds certain proteins, promoting their ubiquitination and proteasome-dependent degradation. Through its E3 ligase function, CRBN regulates the degradation of various proteins, which is crucial for cell growth, differentiation, and apoptosis. CRBN is expressed not only in tumor cells but also in normal cells. In the treatment of multiple myeloma (MM), immunomodulatory drugs targeting CRBN (such as thalidomide and lenalidomide) show significant efficacy. These drugs alter the substrate specificity of CRBN, inducing degradation of tumor-associated proteins and thereby inhibiting cancer cell growth. Additionally, CRBN-based PROTACs (Proteolysis Targeting Chimeras) are currently being developed as a novel cancer treatment strategy. CRBN-based PROTACs recruit the CRBN complex to the target protein, leading to its polyubiquitination and subsequent proteasome degradation.

Biocytogen has developed the B-hCRBN mouse model. The CDS of the human CRBN gene that encodes the full-length protein was inserted into the mouse *Crbn* exons 2-3. The B-hCRBN mice will express the human CRBN protein, while mouse *Crbn* will no longer be expressed. Heart, liver, spleen, lung, kidney, stomach, small intestine, colon, and cortex were collected from homozygous B-hCRBN mice. Human *CRBN* mRNA was only detectable in homozygous B-hCRBN mice. The cortex, liver, lung, kidney, and spleen were collected from homozygous B-hCRBN mice, and then analyzed by western blot with anti-CRBN antibody. CRBN was detectable in homozygous B-hCRBN mice. Naïve CD4+ T cells from B-hCRBN mice have increased production of IL-2 when treated with Lenalidomide. CC-885 exhibits marked toxicity exclusively in B-hCRBN mice, with no detectable toxicity observed in wild-type mice. The body weight, complete blood count, and blood biochemistry of male and female B-hCRBN mice were analyzed. The main organs were dissected, weighed, and analyzed by H&E staining. No obvious abnormalities were found in all the organs detected (brain, heart, lung, liver, spleen, stomach, small intestine, colon, kidney, uterus, ovary, and testis).

In summary, the development of the B-hCRBN mouse model has been successful, as it successfully expresses the human CRBN protein and can be used functionally. Tumor cell lines inoculated in B-hCRBN mice can be used to study the *in vivo* efficacy and safety evaluation of CRBN small molecule drugs, molecular glue drugs based on CRBN, or PROTAC drugs based on CRBN.

No conflict of interest

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260 - PB-052 **Poster**

Utilizing a Humanized CD8 Mouse Model for Non-clinical Studies of Cancer Immunotherapy

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Background: The CD8 is a cell surface glycoprotein found on most cytotoxic T lymphocytes that mediates efficient cell-cell interactions within the immune system. The CD8 acts as a coreceptor with the T-cell receptor on the T lymphocyte to recognize antigens displayed by an antigen-presenting cell in the context of class I MHC molecules. The coreceptor functions as either a homodimer composed of two alpha chains or as a heterodimer composed of one alpha and one beta chain. Both alpha and beta chains share significant homology to immunoglobulin variable light chains. Cytotoxic CD8+ T cells of the adaptive immune system are the most powerful effectors in the anticancer immune response and constitute the backbone of cancer immunotherapy.

Methods: To more accurately evaluate the efficacy of drugs targeting the human immune system, Biocytogen generated a CD8 humanized mouse model that expresses the human CD8 protein.

Results: Protein expression analysis of this novel humanized CD8 mouse strain indicates that the model exclusively expresses human CD8 protein without mouse CD8 protein detection. Immunoprofilling analysis demonstrates that the proportions of various immune cell subsets remain unaffected following CD8 humanization. This model possesses normal T cell immunogenic function, as confirmed by OVA-induced immune responses. *In vivo* efficacy studies show that CD8+ T cells in this model can effectively kill tumor cells. These findings indicate that the CD8 mouse model serves as a powerful research tool, which can not only be used to study and validate the *in vivo* efficacy of anti-human CD8 agonistic antibodies, but also to investigate CD8-targeting drugs or their synergistic effects with other therapies (such as checkpoint inhibitors).

Conclusion: We have established a promising preclinical research model using CD8 humanized mice. This model serves as a powerful preclinical tool for assessing the efficacy of CD8+ T cell-based immunotherapies, including immune checkpoint blockers, neoantigen vaccines, CAR-T, and TCR-T cell therapies.

No conflict of interest

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261 - PB-053 **Poster**

Characterization of a Panel of PDX Models Derived from c-MET Targeting ADCs Pretreated Colorectal Cancer Patients for Therapeutic Evaluation

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Background: c-MET antibody-drug conjugates (ADCs) provide clinical benefit in c-MET expressing cancers, but resistance limits long-term efficacy. To better recapitulate clinically relevant resistance and advance precision therapy development, we established a panel of patient-derived xenograft (PDX) models derived from tumors pretreated with c-MET-targeting ADCs, providing a translational platform to investigate resistance mechanisms and assess novel treatment strategies.

Materials and Method: Ten PDX models derived from colorectal cancer patients pretreated with c-MET-targeting ADCs, including 3 paired pre- and post-treatment models, were established subcutaneously in immunodeficient mice (NOD.SCID, BALB/c nude, and NSG-like) and characterized by histology, immunohistochemistry (IHC), and RNA sequencing.

For *in vivo* efficacy studies, all models were treated with ABBV-400 (1 or 3 mg/kg, i.v., Q3W) following the clinical schedule. Tumor growth inhibition (TGI) was calculated as [1 - (mean treated tumor volume / mean control tumor volume)] * 100%.

Results: Ten PDX models were successfully established and showed high c-MET expression at both the gene and protein levels (IHC score 1.5+ to 3+). To evaluate the *in vivo* efficacy, the PDX

models were treated with the c-MET-targeting ADC, ABBV-400. CR9836 showed limited, dose-dependent tumor inhibition with ABBV-400 at both low and high doses compared with its paired pretreatment model CR9694 (TGI: ~5%–15% vs. ~51%–79%), consistent with clinical disease progression. A similar pattern was observed in another post-treatment model, CR9854, with a limited TGI (~10%–39%) compared with its paired pretreatment model CR9807 (~85%–100%), also consistent with clinical disease progression. Across the other PDX models, ABBV-400 also showed limited tumor inhibition. To explore potential resistance mechanisms, paired pre- and post-treatment models were further analyzed. No reduction in c-MET expression was observed between pre- and post-treatment tumors (IHC 3+). However, the post-treatment models showed increased gene expression of the ATP-binding cassette transporters ABCB1 and ABCC2 (CR9854 vs. CR9807: 2.304/0.400 to 6.188/1.304; CR9836 vs. CR9694: 1.495/0.545 to 5.113/4.855), suggesting enhanced drug efflux as a potential mechanism of resistance. In addition, upregulation of PI3K/AKT-related genes in CR9854 and Wnt/β-catenin-related genes in CR9836 was observed, suggesting a role for pro-survival signaling in resistance.

Conclusions: By developing this panel of PDX models derived from colorectal cancer tumors pretreated with c-MET targeting ADCs, we established a translational platform that recapitulates clinical disease progression. These models enable investigation of resistance mechanisms and evaluation of next-generation therapies and combinations, supporting preclinical decision-making.

No conflict of interest

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262 - PB-054 **Poster**

Establishing Preclinical Mouse Models for Translational Cancer Cachexia Research

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Background: Cancer cachexia (CC), characterized by involuntary weight loss, affects up to 80% of patients with advanced cancer and contributes to 20-30% of cancer-related deaths. Despite its clinical impact, no FDA-approved therapies exist for CC, underscoring a critical unmet clinical need. Growth Differentiation Factor-15 (GDF-15) has been shown to be elevated in cancer patients relative to healthy individuals, positioning it as a promising therapeutic target. To support anti-cachexia drug development, we established preclinical mouse models and a multimodal assessment platform to monitor disease progression and treatment response.

Materials and Method: HT-1080 fibrosarcoma model was used to evaluate therapeutic response to anti-GDF15 treatment. Food intake was recorded throughout the treatment period. On day 20 after tumor inoculation, fat mass and lean mass were quantified by Dual-Energy X-ray Absorptiometry (DXA). On day 21, soleus and gastrocnemius muscles, inguinal white (iWAT) and gonadal white (gWAT) adipose tissues, hearts, spleens, livers were collected and weighed, plasma was collected for GDF-15 analysis. Statistical analyses were performed using one-way ANOVA. In addition, longitudinal body weight changes were monitored across a panel of putative cancer cachexia models, including patient-derived xenograft (PDX) including PA9453 (pancreatic cancer), GA0037 (gastric cancer), LU1480 (lung cancer) and CR1520 (colorectal cancer), cell-derived xenograft (CDX) including HT-1080 and JHH-7 (liver cancer), syngeneic models including Colon-26 (colorectal cancer) and Renca (kidney cancer).

Results: Subcutaneous HT-1080 tumor-bearing mice developed CC signs from Day 11 after tumor cell injection with >5% body weight loss and reductions in skeletal muscle, white adipose tissue, and organ weight (independent of food intake), compared to tumor free mice. Notably, anti-GDF15 treatment at 10 mg/kg alleviated body weight loss, with 15% body weight gain by Day 21. DXA analysis and endpoint tissue weighing consistently demonstrated partial attenuation of CC, with no significant differences versus tumor-free mice (all $p > 0.05$). Furthermore, plasma GDF-15 was markedly elevated at 19.58 ng/mL while decreasing to 4.66 ng/mL after the anti-GDF-15 treatment. Additionally, progressive body weight loss was also observed across all models relative to when the tumors reached 100-200 mm3, suggesting that they may represent putative models of cancer cachexia.

Conclusions: We successfully developed a panel of translationally preclinical mouse models and a multimodal assessment platform for investigating cancer cachexia progression and therapy development. Our findings further indicate that GDF-15 blockade represents a promising therapeutic strategy for alleviating cancer cachexia, consistent with emerging clinical evidence supporting GDF-15 inhibition in this setting.

No conflict of interest

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263 - PB-055 **Poster**

THX based Humanized Mice as a Translational Platform for Evaluating NK Cell–Mediated HER2-Targeted Immunotherapies

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Humanized mice are an important platform for the development of innovative immune-oncology drugs. They have proven their predictivity in T cell related treatment strategies such as checkpoint inhibitors or T cell engagers. Testing non-T cell related I-O compounds remains to be challenging in preclinical mouse models. We have tested a THX based mouse model for its feasibility in determining efficacy for NK cell engagers as well as antibodies acting via ADCC. 24 NRG cKit mice (Janvier, France) have been humanized with huCD34+ hematopoietic stem cells and provided with estradiol via drinking water from week 14 on. Breast cancer cell line JIMT-1 was implanted subcutaneously and animals stratified into different treatment arms: trastuzumab, margetuximab and a bispecific antibody against HER2 and NKG2D which we developed in-house have been tested. Tumor volume and body weight were determined over time. Peripheral blood (PB), bone marrow (BM) and tumor have been analyzed by flow cytometry. In comparison to humanized NSG the THX mice displayed higher percentages of huCD45+ cells in PB as well as BM. The engraftment rate of the tumor cells was not influenced by the humanization protocol (>95% in all experiments). As expected JIMT-1 was resistant against trastuzumab. The bispecific antibody displayed significantly lower tumor volume as the trastuzumab group and the control arm (t-test, $p < 0.01$). Similarly, margetuximab, with an enhanced immune effector function (ADCC), induced a marked reduction of tumor volume compared to trastuzumab (t-test, $p < 0.01$). NK, B and myeloid cells could be detected in BM, PB and tumor tissue by FC until the end of the experiment (week four post tumor implant, week 25 post CD34+ engraftment).

Over the course of the experiment, the body weight reduced markedly reaching humane endpoints two weeks after start of treatment. Animals displayed signs of myeloid cell activation syndrome.

The THX mouse model supports stable engraftment of functional human immune cells, including NK cells and myeloid cells, and enables the assessment of immune-oncology therapies that depend on innate immune effector mechanisms. The antitumor activity observed with both the HER2 × NKG2D bispecific antibody and the ADCC drive antibody margetuximab, highlights the model's ability to discriminate between therapies with different mechanisms of immune activation.

These findings suggest that the THX model is a valuable preclinical platform for evaluating non-T-cell-mediated immunotherapies. Its improved human immune reconstitution and reproducible tumor growth makes it particularly suitable for studying ADCC-based mechanisms and advancing the development of next-generation immune-oncology therapeutics. Future experiments will investigate how to improve the overall condition of the animals and investigate the feasibility of the model for tumor vaccination studies.

No conflict of interest

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264 - PB-056 **Poster**

Dose-dependent modulation of tucatinib systemic exposure by clopidogrel in Sprague Dawley rats

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Background: Tucatinib, principle anti cancer drug used in predominantly breast cancer is an oral highly selective small molecule tyrosine kinase inhibitor of Her2 receptor, which is primarily metabolized by CYP2C8.(1) Tucatinib dose dependent increase is established with drugs like gemfibrozil but may not be useful for pharmcobooster effect at clinics due to significant toxicity. (2) Clopidogrel undergoes biotransformation into an acyl-β-D-glucuronide metabolite, which irreversibly inhibits CYP2C8.(3)The effect of this metabolite on the systemic exposure of tucatinib has yet to be experimentally established.

Materials and methods: Three groups of Sprague Dawley rats, each consisting of five rats, were used in this study. The rats received oral administration of tucatinib at a dosage of 5 mg/kg, either alone or in combination with clopidogrel at dosages of 10 mg/kg or 30 mg/kg. Serial blood samples were collected over 24 hours, and plasma tucatinib concentrations were quantified using a validated high-performance liquid chromatography–mass spectrometry (HPLC–MS) method. Pharmacokinetic parameters were estimated using non-compartmental analysis. The primary endpoints were maximum plasma concentration (Cmax) and area under the plasma concentration–time curve (AUC). One-way ANOVA was employed for statistical comparisons, followed by Tukey's post hoc test. IAEC Approval Number: 34/2026

Results: Clopidogrel resulted in a dose-dependent increase in tucatinib systemic exposure. The mean Cmax rose from 81.43 ng/mL (+/- SE 22.48) with tucatinib alone to 122.00 ng/mL (+/- SE 12.89) and 220.00 ng/mL (+/- SE 16.12)following co-administration with clopidogrel at doses of 10 and 30 mg/kg, representing increases of 1.50-fold and 2.70-fold, respectively. The corresponding mean AUC increased from 498.6 ng·h/mL(SE114.89) to 1136.2 ng·h/mL(SE 210.08) and 1646.8 ng·h/mL(SE154.07), representing increases of 2.28-fold and 3.30-fold. Overall treatment effects were significant for both Cmax ($p < 0.001$) and AUC ($p = 0.001$). Post hoc analysis revealed significant AUC increases at both clopidogrel doses, whereas Cmax was significantly elevated only at 30 mg/kg, indicating differential dose-dependent effects

Conclusion: Clopidogrel markedly enhanced tucatinib systemic exposure in a dose-dependent fashion, Although direct measurement of CYP2C8 metabolite formation or enzyme activity was not performed in this study. These results provide a preclinical basis for the translational assessment of clopidogrel's modulation of tucatinib exposure and if confirmed in human pharmacokinetic studies and subsequent safety and efficacy in clinical trials could eventually contribute to dose optimisation strategies.

Conflict of interest: Corporate-sponsored Research: The research drugs both tucatinib and clopidogrel is supported by MSN group

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Poster Session: Cancer Genomics

265 - PB-057 **Poster**

Super enhancer-driven IRF2BP2 promotes proliferation in glioblastoma

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Background: The aggressive progression of glioblastoma (GBM) is largely driven by rapid tumor cell proliferation. Super-enhancers (SEs) govern the elevated expression of critical oncogenes in GBM, yet the key SE-regulated effectors specifically required for GBM proliferation remain largely unidentified. Interferon regulatory factor 2 binding protein 2 (IRF2BP2), a transcription factor primarily implicated in immune regulation, has not been previously characterized in GBM pathogenesis.

Materials and Methods: To identify SE-driven oncogenes in GBM, we performed H3K27ac chromatin immunoprecipitation

sequencing (ChIP-seq) on five GBM cell lines (U251, LN299, T98G, U87, and DBTRG-05MG). IRF2BP2 expression was assessed by immunohistochemistry in clinical glioma specimens. Functional consequences of IRF2BP2 knockdown were evaluated using CCK-8 assays, colony formation assays, and flow cytometry. Tumor growth was examined in both subcutaneous and orthotopic xenograft models. Mechanistically, we integrated H3K27ac ChIP-seq, ATAC-seq, RNA-seq, CUT&Tag, and immunoprecipitation-mass spectrometry (IP-MS) to dissect transcriptional and post-translational regulation.

Results: We identified IRF2BP2 as a previously unrecognized, SE-driven oncogene essential for GBM proliferation. Clinically, IRF2BP2 expression progressively increased with WHO grade, peaked in GBM, and correlated with poor patient prognosis. Loss-of-function studies revealed that IRF2BP2 knockdown significantly suppressed proliferation, induced G2/M phase arrest, and promoted apoptosis across multiple GBM cell lines, and markedly reduced tumor growth in xenograft models. Mechanistically, IRF2BP2 is transcriptionally activated by a GBM-specific super-enhancer in a BRD4-dependent manner. Post-translationally, IRF2BP2 protein stability is reinforced by USP19-mediated deubiquitination. IRF2BP2 maintains chromatin accessibility and cooperates with c-Myc, STAT3, and NF-κB to transactivate FBLN1, thereby sustaining hypoxia signaling to drive GBM proliferation. Notably, overexpression of IRF2BP2 enhanced proliferation, an effect abrogated by the hypoxia inhibitor PX478. Furthermore, the pro-proliferative function of IRF2BP2 was partially dependent on FBLN1.

Conclusions: Collectively, our findings uncover the SE-IRF2BP2-hypoxia axis as a critical regulatory circuit driving GBM proliferation. Targeting IRF2BP2 may thus represent a potential therapeutic strategy for this devastating disease.

No conflict of interest

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266 - PB-058 **Poster**

Spatiotemporal Tumor Cell States and Niche Crosstalk: Temporal Progression and Translational Targets for Pancreatic Cancer Liver Metastasis

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Background: Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy with frequent liver metastasis and poor prognosis. Metastasis is a temporally ordered process relying on tumor cell state transitions and tumor microenvironment (TME) remodeling, but spatiotemporal regulatory mechanisms remain unclear. This study aimed to define the temporal progression of PDAC liver metastasis, identify stage-specific cellular programs and niche regulation, and discover translatable biomarkers and therapeutic targets for precision intervention.

Material and methods: We integrated snRNA-seq and spatial transcriptomic sequencing to profile para-cancerous, primary tumor and matched liver metastatic tissues from 12 treatment-naive PDAC patients. We used inferCNV for clonal evolution tracing, non-negative matrix factorization (NMF) for TME program annotation, Monocle2 and Spatrack for pseudotemporal trajectory inference, CellChat and NicheNet for cell–cell communication analysis, and siRNA-mediated gene silencing with migration/invasion assays for functional validation. Translational value was evaluated in tissue microarrays and independent clinical cohorts (TCGA, ICGC).

Results: We identified a temporally progressive metastatic cascade governing PDAC liver metastasis. In primary tumors, a pro-invasive tumor cell subset with enhanced epithelial-mesenchymal transition (EMT) and angiogenesis acts as metastasis-initiating cells. These cells colocalize with a specialized myofibroblastic cancer-associated fibroblast (myCAF) subset that builds a pro-metastatic niche via paracrine signaling and matrix remodeling. After liver seeding, initiating cells undergo adaptive reprogramming featuring cholesterol metabolism activation, elevated proliferation and mesenchymal-epithelial transition (MET) to form colonization-competent populations. Pseudotime and clonal analyses verified a continuous lineage from primary initiating cells to liver colonizing cells, with the PI3K-STAT2 axis as a key temporal regulator. The TME evolves temporally: early immune-suppressive programs in primary tumors shift to T-cell-excluded niches in liver metastases, mediated by distinct myCAFs and M2 macrophages to support colonization. Clinically, stage-specific signatures predict metastatic risk, early liver relapse and survival, supporting clinical translation.

Conclusions: PDAC liver metastasis is a temporally ordered, niche-dependent process marked by sequential tumor cell state transitions and spatiotemporal TME remodeling. Metastatic initiation and colonization are controlled by distinct cellular programs and regulatory niches, which serve as actionable translational targets. A temporal-guided, stage-targeted strategy blocking early initiation and disrupting late colonization can effectively intercept metastatic progression, providing a promising approach to improve PDAC patient prognosis.

No conflict of interest

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267 - PB-059 **Poster**

PTHrP and cancer cachexia: A context-dependent phenomenon?

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Background: Cancer mortality is typically attributed to metastasis, but it's unclear if this is a causal relationship. Cachexia is very common in the weeks prior to cancer deaths and can be viewed as the manifestation of wasting of normal tissues, likely via autophagy. PTHrP, a hormone, was recently implicated in cancer cachexia and is encoded by the PTHLH gene. HIF2, a protein that is increased in RCC due to von Hippel-Lindau (vHL) genetic inactivation, is a direct transcription factor for PTHLH. Notably, disruption of PTHrP in mouse models of renal cell carcinoma (RCC) extended survival even in animals harboring progressive tumors suggesting essential role for cachexia induing cancer mortality. In clinical circles, serum PTHrP is assayed only in the presence of hypercalcemia but has been recognized as an adverse prognostic indicator in various malignancies. We **hypothesized** that genetic alterations expected to increase PTHrP in RCC and other tumors will induce cachexia and limit survival.

Methods: We surveyed the cancer genome atlas (TCGA) for tumors harboring PTHLH/HIF2 amplification or vHL deletion and examined the impact of that on survival in a stage agnostic manner. We also used the PTHrP mRNA transcriptional levels in RCC as a threshold to assess an interaction with survival in other cancers.

Results: vHL deletion had a detrimental survival impact in all cases with this abnormality; the highest impact was seen in Acute Myeloid Leukemia (AML) [HR 4]. Colon, head and neck (H&N), and bladder cancers along with low grade glioma had HR of 1.5-2 for worse survival impact. HIF2 amplification was only detected in H&N

cancer and had a paradoxically improved outcome. Genetic PTHLH alterations were not detected in TCGA cases; PTHLH transcriptional upregulation was noted in ~4% in 7 histologies but had an adverse impact on survival only in RCC. For transcriptional output exceeding the r50th or 75th percentile levels in RCC, there was correlation with poorer survival in stomach cancer (both cutoffs); and in liver, uveal melanoma and AML using the 75th percentile.

Conclusions: The biologic role of PTHrP in cancer cachexia seems highly context dependent. Simple extrapolation to non-RCC cancers is cautioned. Despite widespread vHL loss/thereby HIF2 increase, PTHLH transcriptional upregulation was observed in only ~4% of RCC but had major detrimental impact on survival [HR 6]. vHL loss was observed in ~4% of other malignancies but with variable prognostic impact. Measuring serum PTHrP in the absence of hypercalcemia, prospectively, may provide valuable assessment of its value as an indicator of cachexia. Genetic deletion of vHL gene is encountered in cancers other than RCC and seems to portend adverse prognosis. Lastly, assessment of autophagy factors will likely complement the evaluation of cachexia in cancer.

No conflict of interest

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268 - PB-060 **Poster**

RNA-seq-based expression signature enhances clinical detection of retinoblastoma transcriptional corepressor 1 (RB1) loss in whole-exome sequencing

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Background: Loss of tumor suppressor RB1 drives cell cycle dysregulation and is an important biomarker for therapy selection. However, detection of *RB1* loss by whole-exome sequencing (WES) is challenging in low-purity samples and does not always reflect functional inactivation. We aimed to enhance the detection of clinically relevant RB1 deficiencies by developing an RNA-seq-based gene signature capturing transcriptional consequences of bona fide *RB1* loss.

Material and methods: We analyzed 3,732 clinical samples with matched WES and RNA-seq data. Differential expression analysis was performed to identify genes upregulated upon *RB1* loss, yielding a 44-gene signature. Sample-wise scores were computed using ssGSEA. Associations with genomic *RB1* states (gene loss, heterozygous deletion, copy-neutral) were assessed with the Mann–Whitney *U* test.

Results: The signature effectively distinguished *RB1* states, achieving an AUC of 0.93 for samples with vs. without *RB1* loss (neutral) and higher signature scores in the gene loss group ($p < 0.05$). Interestingly, while signature scores typically increased from neutral to *RB1* loss states, we consistently found high-scoring *RB1* deletion and neutral samples that harbored *RB1* loss-of-function mutations or misclassified copy number alteration (CNA) events. We also observed a substantial overlap between the heterozygous deletion and gene loss groups, indicating that single-copy loss might present a transcriptional phenotype similar to that of complete inactivation. These findings suggest that our signature could capture functional RB1 inactivation driven by second-hit or CNA events that WES had missed.

Conclusion: Our RNA-based signature provides a functional readout of RB1 activity, enhancing the detection of clinically relevant *RB1* loss that DNA-based analysis may miss. We envision it as an orthogonal tool for validating WES calls by spotlighting patients with bona fide RB1 inactivation, including those with deletions or combined genomic events that WES cannot detect. Deployed in a clinical setting, the signature may enhance biomarker-driven patient stratification and treatment decision-making, ultimately improving patient outcomes.

Conflict of interest: Ownership:

A. Butusova, A. Yudina, A. Bagaev: BostonGene Corporation (Stock or stock options)

S. Chawla: AADI, Cellestia Biotech, CounterPoint, Immix Biopharma (Stock or stock options)

Advisory Board: J. Mouabbi: GE HealthCare, AstraZeneca, PreludeDX, Agendia, Stemline, Natera, Celcuity, Novartis, PUMA, Gilead, Pfizer

Corporate-sponsored Research: E. Nassif Haddad: Springworks, Aadi, Lilly, Recursion

S. Chawla: Amgen, Roche, GSK, Threshold Pharmaceuticals, CytRx Corporation, Ignyta, Immune Design, TRACON Pharma, Karyopharm Therapeutics, Janssen, Advanchen Laboratories, Bayer, InhibRx, NKMax, Thyme

Other Substantive Relationships:

A. Bagaev: BostonGene Corporation (Employment, executive leadership, IP)

A. Makeeva. G Khegai, D. Stupichev, A. Korbut, A. Butusova, A. Yudina: BostonGene Corporation (Employment)

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269 - PB-061 **Poster**

Pathway Activity Inference Reveals Mechanistic Insights and Potential Therapeutic Vulnerabilities in MSS-CRC Molecular Subtypes

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Background: Mechanistic understanding of complex diseases benefits from integrating diverse molecular evidence, as crucial signals, such as pathway activation cascades, may not be captured by transcriptomics alone. Moreover, functional interactions between genes are often overlooked when focusing on individual gene-level changes. To address this and guide target identification efforts, we developed an integrative pathway activity inference (PAI) approach combining multi-omic data with a curated knowledge graph of molecular and functional interactions. We demonstrate its utility in microsatellite-stable colorectal cancer (MSS-CRC), which represents ~85% of all CRC cases and faces significant unmet need due to resistance to immune checkpoint inhibitors. Within MSS-CRC, two intrinsic epithelial subtypes, iCMS2 and iCMS3, have been defined by transcriptomic profiling (Joanito et al., Nat Gen 2022), with iCMS3 associated with worse prognosis and higher metastatic tendency.

Material and Methods: Gene expression and copy number profiles from ~300 MSS-CRC patients (TCGA), classified into iCMS subtypes by transcriptomic profiling, were integrated within a factor graph model grounded in a curated knowledge graph of molecular and functional interactions. Activity scores were derived for genes, complexes, and pathways via belief propagation, providing an integrative view of pathway activity across patients. Differential activity between iCMS subtypes was assessed, and a network search algorithm identified the highest-scoring differential subnetwork, representing the most differentially active biological processes between subtypes.

Results: PAI revealed significant differences in pathway activity between iCMS subtypes, uncovering signals not apparent from gene expression alone. Notably, MAPK pathway activation was recovered in iCMS3, consistent with MAPK activation being driven by gain-of-function mutations affecting phosphorylation cascades, validating the added value of our integrative approach. Furthermore, pathways related to cytoskeleton organization, cell migration, and response to hypoxia were differentially active in iCMS3. These findings highlight biologically coherent and potentially actionable pathway vulnerabilities in iCMS3 tumors.

Conclusions: The integrative PAI framework recovers biologically meaningful signals missed by transcriptomics alone. Beyond MSS-CRC, this generalizable computational strategy holds promise for patient stratification and mechanism-driven target discovery across oncology and other complex disease areas.

Conflict of interest: Ownership: All authors are full-time employees of Bristol Myers Squibb and may hold company stock/stock options.

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270 - PB-062 **Poster**

Virtual screening of subtype-matched NSCLC cell lines uncovers known and novel therapeutic dependencies

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Background: Lung cancer remains one of the leading causes of cancer-related death, with roughly 2.5 million cases worldwide. Non-small cell lung cancer (NSCLC) accounts for about 85% of cases and spans biologically diverse disease states, some of which are poorly captured by existing preclinical models, hindering the discovery of effective therapies.

Materials and Methods: In collaboration with Merck & Co., we characterized the genetic and transcriptomic programs shaping the evolution of proprietary patient-derived NSCLC subtypes, including a TP63/SOX2-driven proliferative squamous subtype and a KRAS/STK11-mutant subtype with NRF2-mediated oxidative stress adaptation. Both subtypes represent significant unmet clinical needs, owing to the lack of effective targeted therapies and the frequent emergence of resistance. To enable subtype-specific therapeutic discovery, we developed a computational framework that maps cell lines and other preclinical models to patient-derived subtypes using importance-weighted causal and phenotypic features.

Using these mapped cell lines, we applied Turbine's Simulated Cell technology, trained to predict the outcome of virtual CRISPR knockout assays, to identify subtype-specific genetic dependencies. We then ran a genome-scale virtual combination screen evaluating over 200 million [cell line – dependency – co-dependency] relationships, prioritizing candidates by effect size, subtype specificity, pan-essentiality and drug availability.

Results: Our analysis revealed that many commonly used NSCLC cell lines poorly represented patient subtype biology, whereas several developmentally related cancer models, including pharyngeal and esophageal, more closely recapitulated specific subtype states. The Simulated Cell reproduced 75% (17/21) of the subtype-specific dependencies observed in the Dependency Map (DepMap) dataset while predicting more than 300 additional candidate vulnerabilities by exploring a broader biological space. The Simulated Cell's interpretability further enabled derivation of gene-expression signatures predictive of in vitro response heterogeneity. The combination screen based on the identified subtype-specific dependencies yielded 100–500 filtered and ranked candidate strategies per subtype, including previously reported co-dependencies, such as KRAS and PTPN11(SHP2) as well as many novel co-dependency hypotheses.

Conclusions: Taken together, our results demonstrate how Turbine's subtype-aware Virtual Cell modelling and target discovery workflow can bridge patient biology and therapeutic hypothesis generation, enabling systematic discovery of clinically actionable combination therapies in NSCLC at a scale unmatched in wet lab.

Conflict of interest: Ownership: Daniel Veres is a shareholder of Turbine Simulated Cell Technologies Ltd.

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271 - PB-063 **Poster**

Molecular evidence of tumour ancestry in cancer of unknown primary patients with previous malignancies

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Background: Cancer of unknown primary (CUP) is a biologically heterogeneous entity. In patients with prior malignancies, metastatic disease may represent true CUP or late recurrence with altered morphology. The clinicopathological and molecular features of this subgroup remain poorly explored.

Materials and Methods: We performed a retrospective descriptive analysis of CUP patients with prior malignancies who had circulating tumour (ct) DNA based next-generation sequencing (NGS) with Foundation One CDx at the Christie NHS Foundation Trust. Clinical, pathological and molecular data were extracted from electronic records. Analysis was descriptive using RStudio.

Results: From June 2021 to June 2026, among 84 patients who had NGS testing, 14/84 (16.7%) had prior malignancies. These included prostate cancer in 4/14 (28.6%), urothelial/bladder/ureter

cancer in 3/14 (21.4%), basal cell carcinoma in 3/14 (21.4%), seminoma in 2/14 (14.3%), and melanoma, cervical small cell carcinoma, triple-negative breast cancer, and renal cell carcinoma in 1/14 (7.1%) each; 2/14 (14.3%) had >1 prior malignancy.

Median age at CUP diagnosis was 70.5 years (IQR 64.3-75.5), 11/14 (78.6%) were male, and median interval from prior cancer to CUP diagnosis was 9.2 years (IQR 4.1-13.2). CUP histology included adenocarcinoma in 5/14 (35.7%), carcinoma in 3/14 (21.4%), squamous carcinoma in 3/14 (21.4%), and squamous differentiation, high-grade serous adenocarcinoma, and mucinous carcinoma in 1/14 (7.1%) each. Histopathology was concordant with the previous malignancy in only 2/14 (14.3%) cases; in 12/14 (85.7%), morphology and immunophenotype did not support an association with the previous malignancy. All patients underwent molecular tumour board review. Lineage-associated genomic features were identified in 6/14 (42.9%) cases, including TMPRSS2–ERG fusions in 3/14 (21.4%) cases with previous prostate cancer, and UV-associated signatures in 3/14 (21.4%) in cases with previous cutaneous malignancies, characterised by high tumour mutational burden (37-57 mut/Mb) and PTCH1/NOTCH1/TP53 alterations. In these 6 cases, primary tumour was reassigned in 4/14 (28.6%), 2/14 (14.3%) were managed as favourable CUP. The remaining 8/14 (57.1%) were treated as unfavourable CUP.

Conclusion: CUP in patients with prior malignancy represents a previously under-recognised biological subgroup. In selected cases, genomics revealed molecular associations with prior malignancies despite marked histological discordance. These findings warrant further study and integrated multidisciplinary interpretation involving molecular oncology, pathology and radiology.

No conflict of interest

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272 - PB-064 **Poster**

A two-stage single-cell copy number variation clustering framework: reconstructing tumor evolution with high-confidence backbones and cell reassignment

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Background: Single-cell sequencing is increasingly utilized in studying cancer evolutionary, where copy number variations (CNVs) serve as crucial evolutionary footprints for revealing tumor dynamics. However, the inherent sparsity and high technical noise of single-cell sequencing data pose significant challenges, often leading to ambiguous CNV profiling and erroneous cell clustering. Conventional clustering algorithms typically treat all filtered cells equally, overlooking the substantial variation in signal quality across individual cells and risking the misalignment of cells with noisy profiles, thereby compromising the precise identification of high-confidence regions and clusters.

Material and Methods: We developed a copy number-based single-cell clustering tool that deciphers the chronological sequence of these genomic alterations based on CNV pattern data. First, it aggregates bin-level data to perform p/q-arm clustering; second, it consolidates clusters by comparing consensus sequences inferred from regions with divergent arm states; finally, it smooths copy numbers across segments to define CNV profiles during subclone clustering to yield absolute high-confidence clusters and CNV regions. While this stringent filtering ensures the accuracy of high-confidence clustering, each step unavoidably drops cells, potentially wasting valuable biological information. To prevent this information loss, we developed a reassignment extension that builds on this core framework. It systematically evaluates and reattaches initially dropped "less confident" cells to their optimal high-confidence clusters. This reassignment is executed by calculating similarity scores based on CNV profiles, specifically leveraging the weights of high-confidence CNV regions and key driver mutations derived from the core clusters.

Results: Applying this copy number clustering pipeline to single-cell data from high-grade serous ovarian carcinoma (OV2295) and gastric carcinoma (NCI-N87) samples, our reassignment approach demonstrated significant efficacy. Under default parameters, the extension successfully rescued 73.6% (656 of 891) and 41.2% (411 of 1005) of the initially dropped cells, respectively, effectively mapping them back to their evolutionary lineages. Furthermore, our workflow demonstrated high concordance with previously published findings for these datasets.

Conclusions: By reattaching the less confident cells to clusters, the extension not only preserves valuable sequencing signals but also maintains high confidence in the derived clusters and CNV regions. Successfully balancing the recovery of dropped cells with the strict accuracy of high-confidence clustering, this extension paves the way for a new vision in studying cancer evolutionary history with single-cell sequencing data.

No conflict of interest

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274 - PB-066 **Poster**

Genetic dissection of DNA damage tolerance pathways shaping tobacco-carcinogen-induced mutagenesis

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Background: Tobacco carcinogens generate characteristic mutational signatures in cancer genomes, but the pathways that modulate their accumulation remain incompletely defined. Benzo[a]pyrene diol epoxide (BPDE), a reactive metabolite of benzo[a]pyrene (BaP), forms bulky DNA adducts that block replicative polymerases. Translesion synthesis (TLS) allows replication across such lesions and has been linked to COSMIC single-base substitution signature 4 (SBS4). We aimed to define how individual TLS/DNA damage tolerance polymerases shape carcinogen-induced mutagenesis at the whole-genome level.

Material and Methods: We used hTERT-immortalized RPE-1 *TP53*-deficient cells lacking *POLI*, *POLQ*, *POLK*, *POLH*, *REV1*, or *REV3L*, with a TLS-proficient control. Cells were chronically exposed to BPDE and propagated for approximately 20 population doublings before whole-genome sequencing (WGS). Most genotypes received 20 nM BPDE, whereas *REV3L*-deficient cells received 5 nM because of severe growth impairment at 20 nM. Matched BPDE-treated and vehicle-treated endpoint pairs were analyzed by mutation-burden analysis, mutational-signature assignment, and sequence-context comparison. In parallel, tissues from BaP-exposed mice (100 mg/kg gavage, four times weekly for 8 weeks starting at mice16-week age) and untreated 12-month-old mice from *Poli*, *Polq*, *Polk*, *Polh*, and *Rev1* knockout models are being analyzed by duplex sequencing to quantify exogenous and endogenous mutational processes and tissue specificity *in vivo*.

Results: In the cell-based BPDE exposure model, preliminary WGS analyses revealed genotype-dependent differences in mutation accumulation and sequence-context spectrum. Among genotypes exposed to 20 nM BPDE, polymerase-deficient cells showed higher

mutation burdens than the TLS-proficient control, ranging from 1.93-fold in *POLI*-deficient cells to 4.79-fold in *POLH*-deficient cells. *REV1* deficiency caused a 4.11-fold increase and the strongest divergence from the expected BPDE-associated profile. SBS4 remained the predominant assigned signature in *POLI*-, *POLQ*-, *POLK*-, and *POLH*-deficient cells, whereas its relative contribution decreased to 38.6% in *REV1*-deficient cells. *POLQ*-deficient cells retained the profile most similar to the control, with a cosine similarity of 0.981. *REV1*- and *REV3L*-deficient cells also showed marked proliferative impairment during BPDE exposure.

Conclusions: These data indicate that TLS/DNA damage tolerance polymerases have non-redundant roles in controlling tobacco-carcinogen-induced mutagenesis. Loss of *POLH* or *REV1* produced strong mutator phenotypes, whereas *POLK* inactivation caused a more moderate increase in mutation burden, consistent with a protective role in BPDE lesion bypass. This work links DNA damage tolerance pathways to smoking-associated mutational processes in cancer and extends this framework to tissue-specific effects *in vivo*.

No conflict of interest

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275 - PB-067 **Poster**

Identification of Early Differentially Expressed Genes and Dysregulated Molecular Pathways in Non-Metastatic Triple-Negative Breast Cancer Following a Single Pre-Neoadjuvant Chemotherapy Dose Using RNA Sequencing in a Window-of-Opportunity Design

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Background: Triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype, and early transcriptomic changes after chemotherapy may reflect tumour chemosensitivity. This study aimed to identify early differentially expressed genes and dysregulated pathways in non-metastatic TNBC following paclitaxel-carboplatin exposure during a window period.

Material and methods: This clinical interventional biomarker study used a window-of-opportunity design. Thirty-eight newly diagnosed patients with non-metastatic TNBC planned for neoadjuvant chemotherapy received a single dose of paclitaxel (80 mg/m^2) and carboplatin (AUC 2) during a 2-week window period. Fresh tumour tissue was collected before and after chemotherapy, followed by RNA extraction, quality assessment, Illumina NovaSeq 6000 sequencing, and differential gene expression and pathway analyses.

Results: The median age of the cohort was 46 years (range, 33–68), and 55% were premenopausal. Most tumours were grade 3 (68.4%), with cT3 disease in 52.6% and cN1 nodal status in 68.4% of patients. RNA sequencing identified 40 protein coding, significantly differentially expressed genes following chemotherapy exposure, using thresholds of log2 fold change ≥ 2 or ≤ -2 and false discovery rate (FDR) < 0.005. Notable differentially expressed genes included *FGF4, PLA2G2A, TFF1, CLCA2, VGLL1, TNFRSF11B, FABP7, SCGB2A2,* and *CCND1*, which were associated with pathways related to tumour proliferation, epithelial differentiation, lipid metabolism, cell-cycle progression, and tumour–stromal interactions.

Conclusions: Early transcriptomic alterations occur in non-metastatic TNBC following short-term chemotherapy exposure and may serve as potential biomarkers of treatment response, warranting further validation against pathological outcomes.

Table 1. Selected DEGs after short-term chemotherapy in non-metastatic TNBC.

Sl. No.	Gene Symbol	log2FC	FDR	Biological Role	Relevance in TNBC / Breast Cancer
Sl. No.	**Gene Symbol**	**log2FC**	**FDR**	**Biological Role**	**Relevance in TNBC / Breast Cancer**
1	**FGF4**	-29.8922	0.000248	Growth signalling	Proliferation/invasion
2	**PLA2G2A**	-2.62977	0.038406	Lipid/inflammatory signalling	Tumour microenvironment
3	**TFF1**	4.632957	0.030927	Epithelial differentiation	Luminal/epithelial phenotype
4	**CLCA2**	2.635234	0.042572	Cell adhesion/differentiation	Reduced invasiveness
5	**VGLL1**	-2.89717	0.011334	Transcriptional regulation	Aggressive TNBC biology
6	**TNFRSF11B**	-2.46997	0.045751	RANK/RANKL signalling	Survival/stromal signalling
7	**FABP7**	-2.06577	0.029484	Lipid transport/metabolism	Tumour aggressiveness
8	**SCGB2A2**	5.2338	0.014263	Mammary epithelial function	Epithelial differentiation
9	**CCND1**	2.969101	0.006482	Cell-cycle regulation	Proliferation

No conflict of interest

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Poster Session: Combination Therapies

276 - PB-068 **Poster**

Targeting mRNA processing to overcome resistance in melanoma

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Despite significant advancements in treatment strategies that have greatly improved outcomes for melanoma patients, Australia still witnesses one melanoma-related death every six hours. Clearly, there is an urgent need for novel therapeutic options to enhance the prospects of melanoma patients.

Recent insights from clinical and experimental settings have shed light on how MAPK targeted therapies trigger a sequence of cell state transitions, enabling cells to persist and survive without acquiring new mutations. These resilient cells, known as drug-tolerant cells, appear to exploit altered mRNA processing as a major mechanism for orchestrating the regulation of cellular processes that lead to drug tolerance. Accordingly, we hypothesis that melanoma cells hijack this altered mRNA processing to facilitate adaptation and survival, and targeting this mechanism may thwart the development of resistance. Consequently, testing the clinically available RNA processing inhibitors in combination with targeted therapies could swiftly progress to clinical trials, ultimately improving the overall outcome for melanoma patients.

To investigate whether altering mRNA processing can effectively disrupt the emergence of drug tolerance, we have assessed inhibiting the RNA binding protein RBM39 using the two clinically relevant inhibitors (Indisulam and E7820), in combination with MAPK targeted therapies. RBM39 plays a pivotal role in governing mRNA translation, stability, splicing, and transport. Importantly, our observations have shown that targeted therapies induce alternative splicing of RBM39 in both melanoma cell lines and patient samples. We tested a panel of melanoma cell lines with RBM39 inhibitors in combination with targeted therapies and consistently observed a robust synergy in all cell lines tested. Remarkably, RBM39 inhibitors rescued the expression of drug-tolerant biomarkers and inhibited the invasive phenotype switching observed after MAPK targeted therapies.

In summary, our findings support that altered RNA processing plays a crucial role during the adaptive response to targeted therapies in melanoma. Importantly, targeting this mechanism impede therapy-induced plasticity, offering new hope for improved outcomes in the treatment of melanoma patients.

No conflict of interest

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277 - PB-069 **Poster**

Chloroquine driven autophagy blockade – context based modulation of metformin induced PARP inhibitor synthetic lethality in BRCA wild type Triple Negative Breast Cancer: An in vitro study

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Background: Approximately 85% of triple-negative breast cancer (TNBC) cases in India are BRCA-wildtype, severely limiting PARP inhibitor utility in this population. Autophagy-dependent survival and metabolic reprogramming represent emerging vulnerabilities in this context. We investigated whether metformin-induced metabolic stress could sensitise BRCA-wildtype TNBC cells to olaparib, and whether chloroquine-mediated autophagy blockade could modulate this synthetic lethality in a passage-dependent manner.

Methods: MDA-MB-231 cells (BRCA-wildtype, p53-mutant) were cultured to late passage to model drug-adapted cancer phenotypes. Following mycoplasma confirmation, a $3\times3\times3$ dose matrix of olaparib (10–40μM), metformin (5–20mM) and chloroquine (2.5–10μM) was evaluated by CCK-8 viability assay and colony formation assay (CFA). Colony formation assay was analysed by ImageJ software (minimum size 50 pixels). Bliss synergy scores were calculated using SynergyFinder 3. One-way ANOVA with Tukey post-hoc and Kruskal-Wallis with Dunn correction were performed. CCK-8/CFA concordance was assessed by Spearman correlation, Lin's concordance correlation coefficient (CCC) and Bland-Altman analysis. p62 ELISA was conducted.

Results: Olaparib and chloroquine singlet showed negligible clonogenic inhibition, confirming PARP inhibitor resistance while Metformin produced moderate inhibition with a clonogenic survival of 35.6%. The triple combination showed near complete clonogenic ablation(0.15% clonogenic survival). Chloroquine dose dependent increase in synergy of the triple combination was noted(Bliss score - 37.3 – 42.81). CCK-8 demonstrated poor concordance with CFA (Spearman $\rho = 0.434$; Lin's CCC = 0.269; Bland-Altman bias 16.7%), attributed to metformin-mediated Complex I suppression of dehydrogenase activity. P62 showed significantly increased autophagic flux in the triple combination as compared to the metformin-olaparib doublet($p = 0.034$).

Conclusion: Olaparib-metformin-chloroquine synthetic lethality is achievable in BRCA-wild type TNBC. CCK-8 systematically underestimates metformin combination efficacy, with important implications for trial design.

No conflict of interest

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278 - PB-070 **Poster**

First-in-class switch-control SRC/YES1 inhibitor NXP900 demonstrates potent synergy with KRAS inhibitors in drug-sensitive and resistant NSCLC models in vitro and in vivo

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Background: RAS inhibitors are transforming the treatment of highly aggressive cancers. First-generation G12C mutant-selective KRAS inhibitors (KRASi) were approved by the FDA and several mutant-selective, pan-mutant-KRAS, and pan-RAS inhibitors have shown promising activity in clinical trials. However, KRASi monotherapy results in rapid development of acquired resistance. Mediated by SRC/YES1, YAP1 activation promotes the survival of drug-tolerant persister cells and is associated with drug resistance to KRASi. In a first-in-human study, the novel switch-control, potent and selective SRC/YES1 family (SFK) inhibitor NXP900 (IC_{50} YES1 = 0.47nM) is the first SFK kinase inhibitor to demonstrate potent on-target PD activity at well tolerated doses (Falchook et al. *Cancer Res.* 2025, 85, CT153). The key feature differentiating NXP900 from first generation SFK inhibitors entails locking its target into its native "closed" conformation, inhibiting both kinase and scaffolding properties (Temps et al. *Cancer Res.* 2021, 81, 5438-5450). In constrast, dasatinib or bosutinib induce an active "open" conformation that promotes the association with signaling partners via allosteric facilitation (Higuchi et al. *Cell Rep.* 2021, 34, 108876). Notably, a recent clinical drug-drug interaction study demonstrated no CYP3A induction by NXP900, indicating its potential to be combined with KRASi to overcome primary and acquired resistance in patients with KRAS mutated cancers.

Materials and methods: Proliferation assay: Lung adenocarcinoma cells resistant and sensitive to the KRASi sotorasib were treated with KRASi and/or NXP900 and viability measured at day 5. Combination effects were studied using SynergyFinder+ software. In vivo efficacy: CDX and PDX sotorasib-sensitive and resistant models were treated with either vehicle, NXP900, sotorasib or NXP900 + sotorasib.

Results: Sotorasib induces rapid SRC activation in sensitive and resistant cells. NXP900 inhibited SRC activity and YAP1 nuclear localization at low nM concentrations, and demonstrated synergy in

combination with sotorasib in both sensitive and resistant cell lines. In vivo, the combination of sotorasib and NXP900 was strongly synergistic and well tolerated.

Conclusions: Novel, tolerable combination therapies are needed to improve the clinical benefit of KRASi. The combination of NXP900 and sotorasib exhibits potent synergy in vitro and in vivo, both in KRASi sensitive and resistant NSCLC models. Currently in a Phase1b monotherapy expansion in patients with *FAT1, YES1* and other genomic alterations in solid tumors (NCT05873686) and in combination with osimertinib (NCT07315113), our data indicates that NXP900 is an attractive combination partner that could synergize with KRASi in cancer patients.

Conflict of interest: Ownership: A.U.-B. and N.O.C. declare that they are inventors of the patent that protects NXP900, which is licensed to Nuvectis Pharma Inc. E.P. is an employee and shareholder of Nuvectis Pharma Inc.

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279 - PB-071 **Poster**

Discovery of novel combination strategies to target SWI/SNF mutant lung cancers

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Background: Genomic studies have identified frequent mutations in subunits of the SWI/SNF chromatin remodeling complex, particularly in SMARCA4 and ARID1A, in non-small cell lung cancer, with mutations occurring in up to 33% of advanced cases. Previously we have shown that SMARCA4-mutant lung cancers are highly dependent on oxidative phosphorylation (OXPHOS). However, OXPHOS inhibitors as single agents have failed to show substantial efficacy in clinical trials. Thus, like other therapeutics aimed at cancer metabolism, the most feasible route for further development of OXPHOS inhibitors is through rational combination strategies.

Materials and Methods: To this end, we undertook a functional genomics screen to identify combination strategies by utilizing a CRISPR-Cas9 library targeting genes with FDA approved therapeutics in genetically defined lung cancer models. Importantly, we utilized very low doses of the OXPHOS inhibitor IACS-10759 that are known to be well-tolerated in patients.

Results: Among our top hits was ROCK1/2. We show that Belumosudil, a clinically-utilized ROCK inhibitor known for its robust safety and tolerability profile, exhibits profound synergistic anti-tumor activity when combined with IACS-10759 in cell lines as well as in multiple mouse xenograft and human PDX models. Mechanistically, metabolic profiling reveals that the combination of ROCK and OXPHOS inhibition triggers bioenergetic stress and cell cycle arrest. This is primarily attributed to the inhibition of the adaptive increase in glycolysis that occurs following OXPHOS inhibition by ROCK, via suppression of GLUT1-mediated glucose uptake.

Conclusions: We identified the mechanistic underpinnings of a highly synergistic combination strategy that overcomes adaptive metabolic reprograming which has been a central challenge in the successful development of therapeutics targeting cancer metabolism.

No conflict of interest

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280 - PB-072 **Poster**

Vepugratinib-induced receptor tyrosine kinase (RTK) rewiring sensitizes FGFR3-altered urothelial cancer cells to HER2-targeted therapies

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Background: Vepugratinib is an oral, highly potent, isoform-selective FGFR3 inhibitor, designed to limit off-target toxicities associated with pan-FGFR inhibitors, with promising early clinical activity in urothelial carcinoma (UC). HER2-directed antibody-drug conjugates (ADCs) are active in UC: trastuzumab deruxtecan (T-DXd) received accelerated approval and disitamab vedotin (DV) is in clinical evaluation. We report in vitro and in vivo studies in UC models showing vepugratinib-mediated modulation of RTK expression and signaling, which could be therapeutically targeted through combinations with HER2-targeting ADCs.

Materials and methods: TCGA bladder cancer data was interrogated for correlations between FGFR3 alterations and HER2/HER3 expression. FGFR3-altered and wild-type (wt) UC cell lines and tumors treated with vepugratinib at clinically equivalent doses were profiled by RNA-seq, immunoblotting, flow cytometry, or IHC. Viability was measured by CellTiter-Glo. In vivo, FGFR3-altered patient-derived xenograft (PDX) models, including an enfortumab vedotin (EV)-resistant PDX, were treated with vepugratinib plus afatinib, T-DXd, or DV. Combinations were assessed by Bliss Independence.

Results: In TCGA bladder cancer data, HER2 and HER3 expression were significantly elevated in FGFR3-altered tumors compared to FGFR3 wt, identifying a potential subgroup with enriched HER2/HER3 expression. In models harboring FGFR3 S249C or FGFR3-TACC3 fusion, vepugratinib drove rapid, FGFR3-dependent upregulation of HER2/HER3 at mRNA, total, phosphorylated, and cell-surface protein levels (up to 3-fold), an effect absent in FGFR3 wt models and sustained during vepugratinib + EV co-treatment. Pan-HER inhibitors (afatinib, sapitinib) synergized with vepugratinib and abrogated NRG1- and EGF-mediated viability rescue observed with FGFR3 inhibition alone. Vepugratinib-resistant cells acquired rewiring and growth advantage through the NRG1/HER2/HER3 axis which was effectively reversed by afatinib co-treatment. In vivo, vepugratinib + afatinib produced greater-than-additive tumor growth inhibition, but responses were not deep or durable. In contrast, vepugratinib + T-DXd delivered deep, durable regression in two PDX models with HER2-low and HER2-high expression (4/6 CR and 4/4 PR; −88.8% and −80.3% regression, respectively), preserved at subtherapeutic T-DXd doses. Comparable efficacy and durability occurred with DV (−74%). Vepugratinib + T-DXd also overcame resistance in an EV-resistant PDX (−87.2%).

Conclusions Vepugratinib-induced HER2/HER3 upregulation is a clinically actionable vulnerability in FGFR3-altered UC, positioning HER2-targeting ADCs as combination partners. Co-targeting HER2 and FGFR3 elicited complete, durable responses in HER2-high/low and EV-resistant models, supporting clinical development

of this combination following EV + pembrolizumab in FGFR3-altered UC.

Conflict of interest: Other Substantive Relationships: All authors are employees and shareholders of Eli Lilly and Company

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281 - PB-073 **Poster**

Combination of ERAS-0015 and ERAS-4001 Targets Active and Inactive KRAS and Displays Synergy in Nonclinical KRAS G12X-Driven Models

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KRAS is the most frequently mutated oncogene in human solid tumors, with mutations occurring in approximately 86% of pancreatic adenocarcinomas (PDAC), 43% of colorectal adenocarcinomas (CRC), and 32% of lung adenocarcinomas (LUAD), based on AACR Project GENIE data. KRAS functions as a molecular switch that cycles between inactive GDP-bound and active GTP-bound states to regulate RAS/MAPK signaling. Oncogenic KRAS mutations shift the protein toward the active, GTP-bound state, resulting in aberrant pathway activation. Across PDAC, CRC, and LUAD, these mutations are dominated by G12 substitutions (~69–92% of KRAS mutations), with G13 most frequent in CRC and Q61 present at lower frequencies across tumor types. ERAS-0015 is a molecular glue pan-RAS inhibitor that binds GTP-bound RAS, blocks effector engagement and promotes GTP hydrolysis, which converts active RAS to the inactive GDP-bound state. ERAS-4001 is a selective, noncovalent pan-KRAS inhibitor that binds the allosteric switch-II pocket and blocks the transition of KRAS from the inactive to the active state. Given these complementary mechanisms, we explored whether ERAS-0015 + ERAS-4001 would enhance inhibition of KRAS-driven RAS/MAPK signaling and improve antitumor activity. Subsequent disclosures showing synergy between daraxonrasib, another pan-RAS molecular glue, and either pan-KRAS inhibitors or KRAS G12C inhibitors further support this hypothesis.

In cell-based target engagement assays, ERAS-0015 + ERAS-4001 synergistically disrupted KRAS binding to RAF, a key effector protein of the RAS/MAPK pathway. In antiproliferative assays, fixed concentrations of ERAS-0015 potentiated ERAS-4001 activity across a broad panel of KRAS G12X cell lines. Synergistic antiproliferative effects were accompanied by deep suppression of pharmacodynamic markers of RAS/MAPK pathway activity, including ERK1/2 and RSK phosphorylation. Consistent with the in vitro findings, ERAS-0015 + ERAS-4001 inhibited tumor growth in KRAS G12X cell line-derived xenograft (CDX) models in vivo. A combination benefit was observed when lower doses of ERAS-0015 were combined with ERAS-4001, relative to either agent alone.

Collectively, these in vitro and in vivo nonclinical data support a mechanistic rationale for combining ERAS-0015 and ERAS-4001 to inhibit KRAS-driven RAS/MAPK signaling. ERAS-0015 converts active KRAS to its inactive form, whereas ERAS-4001 locks KRAS in the inactive state. The combination demonstrated synergistic antiproliferative activity in vitro and enhanced antitumor activity in vivo across multiple KRAS G12X models, supporting further clinical evaluation.

Conflict of interest: Ownership: Erasca stock options

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282 - PB-074 **Poster**

Synergistic targeting of histone deacetylases (HDACs) using class- and isoform-selective HDAC inhibitors

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Background: Epigenetic dysregulation involving histone deacetylases (HDACs) has led to the development of both selective and pan-HDAC inhibitors (HDACis). However, selective HDACis may induce compensatory activation of alternative HDAC isoforms and signalling pathways, whereas pan-HDACis, despite their broad activity, are associated with high toxicity and unpredictable cellular responses. Therefore, this study evaluates whether combining different class- and isoform-selective HDACis can achieve synergistic and precise modulation of HDAC activity while reducing the off-target toxicity associated with pan-HDAC inhibition.

Material and methods: Cancer cell viability following HDACi treatment was assessed using the CellTiter-Glo 2.0 assay to determine IC_{50} values and identify synergistic HDACi combinations. Synergistic interactions between HDACis were quantified using the Loewe synergy model. Annexin V/propidium iodide apoptosis assays and cell cycle analysis by flow cytometry were performed to evaluate apoptosis induction and cell cycle perturbations following combination treatment. Western blotting was used to assess epigenetic and apoptotic markers and investigate the molecular mechanisms underlying the effects of combined class- and isoform-selective HDACis.

Results: Combinatorial treatment strategies were designed based on IC_{50} values by pairing compounds with relatively high IC_{50} values with those exhibiting lower IC_{50} values. Among the screened HDACis, trifluoromethyl-1,2,4-oxadiazolyl (TFMO)-based class IIa HDACis significantly reduced the IC_{50} values of selective HDAC1/2 inhibitors in multiple myeloma and leukaemia cell lines. In contrast, TFMO-based class IIa HDACis did not enhance the reduction in cell viability induced by the pan-HDAC inhibitor vorinostat, which was used as a control. Selective HDAC1/2 inhibitors also exhibited synergistic interactions with TFMO-based class IIa HDACis, as demonstrated by the Loewe synergy model. Combination treatment significantly increased apoptosis and induced S-phase arrest, suggesting replication stress, whereas individual treatments predominantly induced G1-phase arrest. Furthermore, TFMO-based class IIa HDACis enhanced histone H3 acetylation at lysine 9 and lysine 14 when combined with selective HDAC1/2 inhibitors. The combination also increased Bax expression without noticeable changes in Bcl-2. In addition, elevated γH2AX expression was observed following combination treatment, indicating enhanced DNA damage.

Conclusions: These findings indicate synergistic interactions between selective HDAC1/2 inhibitors and TFMO-based class IIa HDACis, supporting their potential as a more effective and potentially less toxic alternative to pan-HDAC inhibition.

No conflict of interest

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283 - PB-075 **Poster**

Novel pan-TEAD inhibitor ODM-212 Demonstrates Broad Combination Potential with KRAS and Pan-RAS Inhibitors in Preclinical Models of Multiple Tumor Types

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Background: The Hippo signaling pathway is fundamental to the regulation of cell proliferation. Central to this pathway are YAP/TAZ, and their nuclear translocation and co-activation of TEAD1-4. Dysregulation of this pathway, leads to sustained activation of YAP/TAZ and TEAD and transcription of TEAD target genes that support cancer cell survival and progression. Furthermore, activation of YAP/TAZ and TEAD has been associated with therapeutic resistance to certain anti-cancer therapies, including KRAS inhibitors, highlighting TEAD as a potential target for combination strategies. ODM-212 is a novel, orally bioavailable, small-molecule pan-TEAD inhibitor with a safety and drug-drug interaction profile suitable for combination with other anticancer agents. It is currently being evaluated in phase 1/2 clinical trials as a monotherapy (NCT06725758) and in combination regimens (NCT07563738).

Methods: The combinatorial effect of ODM-212 with RAS inhibitors on cell viability were assessed across a panel of 105 cancer cell lines spanning lung (53), pancreatic (29), and colorectal (23) models with diverse KRAS alterations. Apoptosis induction was evaluated in KRASˆG12C NSCLC cell lines treated with ODM-212 in combination with KRAS G12C inhibitors. To validate the in vitro observed combinatorial effects, NSCLC patient-derived xenograft (PDX) and cell line-derived xenograft (CDX) models were treated with ODM-212 in combination with KRASˆG12C inhibitors.

Results: ODM-212 demonstrated synergistic activity in 9/12 KRASˆG12C NSCLC models (75%) when combined with sotorasib or adagrasib, and this was associated with increased apoptosis. Synergistic effects were also observed with the RAS(ON) inhibitor daraxonrasib in 30/56 lung (53%), 18/29 pancreatic (62%), and 14/25 colorectal (56%) models. In addition, the combination with zoldonrasib was synergistic in 5/10 KRASˆG12D mutated PDAC models (50%). ODM-212 enhanced the in vivo efficacy of the KRASˆG12C inhibitors adagrasib and sotorasib in NSCLC CDX models. In PDX models, where only adagrasib was evaluated, the combination provided the greatest benefit in tumors showing an incomplete response to adagrasib monotherapy, thereby supporting the combinatorial effects observed in vitro. Notably, in the PDX model, ODM-212 combinations significantly prolonged response duration after treatment discontinuation compared with single-agent KRAS inhibition.

Conclusions: Preclinical studies demonstrate that ODM-212 is an orally bioavailable, potent, and selective pan-TEAD inhibitor with single-agent anti-cancer activity and the ability to enhance the efficacy of multiple RAS-targeted inhibitors, including RAS(ON) inhibitor daraxonrasib, across diverse preclinical models. These findings support the potential of ODM-212 in combination strategies aimed at improving the efficacy of RAS inhibitors and addressing therapy resistance.

Conflict of interest:

Ownership: Riikonen and Moilanen own company stocks, Rantala is founder of Misvik Biology Oy

Corporate-sponsored Research: All authors are employees of Orion Pharma

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284 - PB-076 **Poster**

JP9441, a Novel SOS1 Inhibitor, Demonstrates Broad Activity across RAS-Driven Tumors and Synergistic Efficacy with KRAS Inhibitors

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Background: Despite the clinical success of KRAS G12C inhibitors in patients with KRAS-mutant cancers, acquired resistance frequently limits the durability of clinical benefit. Reactivation of RAS signaling through receptor tyrosine kinase (RTK)-mediated feedback is a common resistance mechanism, providing a rationale for vertical inhibition of the RAS pathway. We evaluated the preclinical pharmacological profile of JP9441, a novel SOS1 inhibitor, with emphasis on its pan-RAS activity, combination efficacy with KRAS inhibitors, and activity in KRAS inhibitor-resistant models.

Materials and Methods: JP9441 binding to SOS1 was characterized using biophysical assays. Activity against multiple KRAS, HRAS, and NRAS variants was evaluated using biochemical assays. Combination efficacy with KRAS inhibitors was assessed in 3D spheroid models, KRAS inhibitor-resistant cell lines, and KRAS-mutant xenograft models. Pharmacodynamic modulation of MAPK signaling was also evaluated.

Results: JP9441 directly bound to SOS1 and broadly inhibited SOS1-RAS interactions across multiple KRAS, HRAS, and NRAS variants, demonstrating broad pan-RAS activity. JP9441 exhibited synergistic antiproliferative activity with KRAS G12C inhibitors in pancreatic, non-small cell lung, and colorectal cancer models. Importantly, JP9441 maintained strong synergistic interactions with KRAS G12C inhibitors in KRAS inhibitor-resistant pancreatic and lung cancer cell models (CI < 0.9), supporting its potential utility in acquired resistance settings. Across pancreatic, lung, and colorectal xenograft models, JP9441 in combination with KRAS G12C inhibitors demonstrated robust antitumor activity across pancreatic, lung, and colorectal xenograft models and showed greater tumor growth inhibition and higher partial response rates than the comparator SOS1 inhibitor under identical treatment conditions. Combination treatment also produced enhanced suppression of ERK and AKT signaling, supporting effective inhibition of RAS pathway reactivation. JP9441 further demonstrated favorable in vitro DMPK properties and pharmacologically relevant systemic and tumor exposure following oral administration.

Conclusions: JP9441 demonstrated broad pan-RAS activity and synergistic combination efficacy with KRAS inhibitors in preclinical models. Synergistic activity was maintained in KRAS inhibitor-resistant cell models, and enhanced antitumor activity was observed across multiple xenograft models compared with a comparator SOS1 inhibitor. GLP toxicology studies are currently underway to support IND-enabling development.

Conflict of interest:

Corporate-sponsored Research: This study was sponsored by Jeil Pharmaceutical Co., Ltd.

Other Substantive Relationships: All authors are employees of Jeil Pharmaceutical Co., Ltd.

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286 - PB-078 **Poster**

Targeting Tumor Progression with Cabozantinib and Anti-PD-1 Therapy: Enhanced Efficacy in the 4T1 Breast Cancer Model

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Background: Triple-negative breast cancer (TNBC) is often resistant to immune checkpoint blockade due to an immunosuppressive tumor microenvironment (TME) rich in myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs), which suppress $CD8^+$ T-cell activity and promote tumor progression. The 4T1 syngeneic mouse model closely mimics human TNBC, including PD-L1 expression, metastatic behavior, and a myeloid-dominant TME, making it a valuable platform for immuno-oncology studies. Cabozantinib, a multi-targeted inhibitor of vascular endothelial growth factor receptor (VEGFR), mesenchymal epithelial transition (MET) receptor, and AXL, exhibits anti-angiogenic, anti-metastatic, and immunomodulatory effects, providing a strong rationale for combination with anti-PD-1 therapy. This study evaluates whether Cabozantinib enhances the antitumor efficacy of anti-PD-1 treatment by overcoming immune suppression and promoting antitumor immunity in the 4T1 TNBC model.

Material and methods: Female BALB/c mice were orthotopically implanted with 4T1-Luc2 tumor cells. Upon tumor establishment, animals were randomized into four groups (n = 8/group): G1: Vehicle control, G2: Cabozantinib monotherapy, G3: anti-PD-1 monotherapy, and G4: Combination therapy.

Cabozantinib dosing: (20 mg/kg, oral, QD x 21), Anti-PD-1 dosing: (10 mg/kg, intraperitoneal, biweekly; 4 doses). Study duration: 3 weeks.

Results: Combination therapy with Cabozantinib and anti-PD-1 demonstrated superior anti-tumor and anti-metastatic activity compared with either monotherapy alone ($p < 0.01$). Importantly, this combination significantly reduced the burden of lung metastases, with a marked decrease in metastatic nodule formation relative to both control and single-agent treatment groups, indicating effective suppression of tumor dissemination and metastatic progression. These benefits translated into an improvement in median survival ($p < 0.05$), suggesting that the reduction in metastatic spread contributed substantially to the overall therapeutic outcome. In addition to controlling primary tumor growth, the combination therapy favorably remodeled the tumor microenvironment, evidenced by increased $CD8^+$ T-cell infiltration, an elevated $CD8^+$/Treg ratio, reduced immunosuppressive myeloid populations.

Conclusions: Cabozantinib's action with PD-1 blockade prevents tumor growth and reduces metastatic burden in the 4T1 TNBC model. The combination therapy shows growth inhibition of immunologically cold tumors is possible by targeting different growth pathways used by tumors that are suppression of immune cells, angiogenesis and metastasis. These preclinical findings support the rationale for the clinical evaluation of Cabozantinib in combination with immune checkpoint inhibitors as a potential therapeutic strategy for patients with TNBC.

No conflict of interest

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287 - PB-079 **Poster**

MEVALONATE PATHWAY INHIBITION BY STATINS POTENTIATES THE ANTITUMOR ACTIVITY OF ADAGRASIB IN KRASG12C-MUTANT LUNG CANCER CELLS

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Background: In non-small cell lung cancer (NSCLC), $KRAS^{G12C}$ is the most prevalent mutation and is associated with poor prognosis and treatment resistance. Mutant KRAS constitutively activates oncogenic signaling, including the MAPK and PI3K/AKT pathways. $KRAS^{G12C}$-targeted therapies represent a major clinical advance, but efficacy remains limited by acquired resistance. Statins inhibit HMG-CoA reductase (HMGCR), the rate-limiting enzyme of the mevalonate pathway (MVA), which is required for proper KRAS membrane localization and function, and have been extensively studied for their anticancer properties. The aim of this study was to investigate the effect of MVA pathway inhibition on KRAS signaling and to evaluate the synergistic effect of statins combined with the $KRAS^{G12C}$ inhibitor adagrasib in NSCLC cells.

Materials and methods: HMGCR protein levels were assessed by western blot across a panel of NSCLC cell lines with different KRAS mutational status, compared with the normal bronchial epithelial cell line BEAS-2B. H358 and CALU-1 cell lines ($KRAS^{G12C}$) were treated with simvastatin and atorvastatin, alone and in combination with adagrasib. Cell viability was evaluated by the MTT assay, and drug synergism was analyzed using Combenefit software under the Loewe additivity model. The effect of statin treatment on p-ERK and total KRAS levels was assessed by western blot. MVA pathway dependency was confirmed through mevalonolactone (MVL) rescue experiments. The antiproliferative effect of the most synergistic combinations was validated by the clonogenic assay.

Results: Basal HMGCR levels were higher in NSCLC cell lines compared with BEAS-2B, reaching statistical significance in H358. Simvastatin (simv) had the greatest effect on viability in CALU-1 cells (IC50 1.04 μM) compared with H358 cells (IC50 14.93 μM), whereas with atorvastatin (ator), CALU-1 (IC50 11.41 μM) was more sensitive than H358 (IC 50 20.13 μM). Treatment with simv and ator (10–50 μM) induced a significant reduction in p-ERK levels ($p < 0.05$) and a significant accumulation of total KRAS ($p < 0.05$) in both cell lines, effects that were reversed by MVL, confirming MVA pathway dependency. The adagrasib-statin combination showed synergy in both lines, with greater synergism in CALU-1 (Loewe score: simvastatin 29.2, atorvastatin 32.22) than in H358 (Loewe score: simvastatin 14.95, atorvastatin 11.59). The clonogenic assay confirmed a reduction in colony number with the most synergistic combinations relative to the individual agents.

Conclusions: HMGCR inhibition by statins modulates KRAS-associated signaling and potentiates the antitumor effect of adagrasib, with CALU-1 displaying the highest degree of synergism. These findings suggest that combined KRAS–HMGCR blockade may constitute a promising therapeutic strategy in $KRAS^{G12C}$-mutant NSCLC.
FUNDING: FONDECYT Grant 1241400 – ANID Chile

No conflict of interest

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288 - PB-080 **Poster**

Adaptive cell-cycle rewiring through Cyclin A2–CDK2 promotes a replication stress–tolerant proliferative state underlying platinum–PARP inhibitor cross-resistance in ovarian cancer

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Background Platinum-based chemotherapy followed by PARP inhibitor maintenance is the standard treatment for ovarian cancer. However, clinical benefit is frequently limited by bidirectional cross-resistance between these sequential genotoxic therapies. We hypothesized that adaptive cell-cycle rewiring establishes a replication stress–tolerant proliferative state underlying platinum–PARP inhibitor cross-resistance.

Material and methods Paired platinum-resistant and PARP inhibitor-resistant ovarian cancer models were generated by stepwise chronic drug selection in homologous recombination–proficient and –deficient backgrounds. Cross-resistance was assessed by dose–response assays. DNA damage signaling, cell-cycle dynamics, and molecular alterations were analyzed by immunoblotting, immunofluorescence, flow cytometry, RNA sequencing, and bioinformatic analyses. Cyclin A2–CDK2 signaling was interrogated using CDK2 inhibition and shRNA-mediated Cyclin A2 depletion, with effects evaluated by clonogenic assays, three-dimensional spheroids, and intraperitoneal xenografts.

Results Platinum-resistant and PARP inhibitor-resistant models developed reciprocal cross-resistance across distinct homologous recombination backgrounds. Resistant cells exhibited persistent endogenous DNA damage and sustained proliferation under chronic genotoxic stress. Notably, they failed to mount effective G2/M checkpoint arrest following treatment, consistent with a replication stress–tolerant proliferative state.

Cyclin A2 was consistently upregulated across resistant models. CDK2 inhibition, but not CDK4/6, restored sensitivity to platinum and PARP inhibitors. Combined CDK2 inhibition significantly reduced clonogenic survival compared with monotherapy. Cyclin A2 depletion recapitulated these effects, restoring drug sensitivity, impairing spheroid growth, and reducing intraperitoneal tumor burden.

RNA sequencing and bioinformatic analyses identified HMGB2 and CPT1A as candidate mediators of the resistant phenotype. Immunoblotting confirmed increased HMGB2 and CPT1A expression across resistant models. Cyclin A2 depletion reduced HMGB2 expression both in vitro and in vivo. Combined CDK2 and CPT1A inhibition produced greater cytotoxicity than either agent alone.

Conclusions Adaptive cell-cycle rewiring represents a shared biological program associated with platinum–PARP inhibitor cross-resistance in ovarian cancer. Cyclin A2–CDK2 acts as a central regulator of a replication stress–tolerant proliferative state enabling continued cell-cycle progression under persistent genotoxic stress. HMGB2-associated chromatin remodeling and CPT1A-dependent metabolic adaptation are linked to this state and may contribute to therapeutic resistance. These findings provide a mechanistic framework for cross-resistance and support translational evaluation of CDK2-based combination strategies in ovarian cancer.

No conflict of interest

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289 - PB-081 **Poster**

Preclinical Efficacy of ARV-806, a PROTAC KRAS G12D Degrader, in Combination with Chemotherapy in KRAS G12D–Mutated Pancreatic Cancer Models

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Background: ARV-806, a potent and selective PROteolysis TArgeting Chimera (PROTAC) KRAS G12D degrader, forms a trimer complex with KRAS G12D and an E3 ubiquitin ligase to induce KRAS G12D ubiquitination and subsequent proteasomal degradation. ARV-806 targets both ON (active GTP-bound) and OFF (inactive GDP-bound) forms of KRAS G12D. In preclinical models, ARV-806 showed >25-fold higher potency in cell proliferation inhibition vs investigational KRAS G12D OFF and ON inhibitors or other KRAS G12D degraders. Based on promising preclinical activity, ARV-806 administered weekly or every 2 weeks is being evaluated in the phase 1 portion of a clinical trial in patients with *KRAS* G12D–mutated advanced solid tumors (NCT07023731). First-line treatment options for pancreatic ductal adenocarcinoma (PDAC) are limited, with standard-of-care (SOC) chemotherapy yielding modest clinical benefit, supporting evaluation of novel combination approaches to enhance efficacy. Here, we assessed ARV-806 combined with SOC chemotherapy, gemcitabine plus nab-paclitaxel (gem-nabP), in preclinical models of *KRAS* G12D–mutated PDAC.

Materials and methods: In vitro synergy between ARV-806 and gem-nabP was assessed in the *KRAS* G12D–mutated PDAC cell lines AsPC-1 and PANC-1. Apoptosis was evaluated by measuring cleaved caspase-3 activity following treatment with ARV-806, gemcitabine, or the combination of ARV-806 plus gemcitabine. Antitumor activity was assessed in the AsPC-1 cell line–derived xenograft (CDX) model following treatment with ARV-806, gem-nabP, or the combination of ARV-806 plus gem-nabP.

Results: Synergistic interactions between ARV-806 and gem-nabP were observed in the *KRAS* G12D–mutated PDAC cell lines AsPC-1 and PANC-1 via multiple models tested. The combination of ARV-806 and gemcitabine in vitro led to increased apoptosis compared with either agent alone. In the *KRAS* G12D–mutated AsPC-1 PDAC CDX model, ARV-806 2 mg/kg combined with gem-nabP at 50/8 or 75/12 mg/kg showed greater tumor growth inhibition (TGI; 74% and 75%, respectively) compared with either ARV-806 (66% TGI) or gem-nabP doublet (22% and 26% TGI, respectively) alone. Furthermore, after 1 week of treatment withdrawal, mice treated with ARV-806 plus gem-nabP had significantly prolonged tumor growth delay ($P < 0.01$) vs mice treated with ARV-806 alone.

Conclusions: These data demonstrate the preclinical benefit of combining ARV-806 with gem-nabP and support evaluation of this

combination regimen as first-line treatment for patients with *KRAS* G12D–mutated PDAC.

Conflict of interest: Ownership: All co-authors are Arvinas employees and own Arvinas stock

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290 - PB-082 **Poster**

Preclinical Efficacy of ARV-806, a PROTAC KRAS G12D Degrader, in Combination With Epidermal Growth Factor Receptor (EGFR) Monoclonal Antibodies (mAbs) in KRAS G12D–Mutated Colorectal Cancer (CRC) Models

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Background: ARV-806 is a potent, selective PROteolysis TArgeting Chimera (PROTAC) KRAS G12D degrader. ARV-806 forms a trimer complex with KRAS G12D and an E3 ubiquitin ligase, which induces ubiquitination of KRAS G12D and its subsequent degradation by the proteasome. ARV-806 engages both the ON (active GTP-bound) and OFF (inactive GDP-bound) forms of KRAS G12D. ARV-806 exhibited >25-fold higher potency for inhibition of cell proliferation vs investigational KRAS G12D OFF and ON inhibitors or other KRAS G12D degraders in preclinical models. In the clinical setting, efficacy of KRAS mutant inhibitors in patients with CRC is frequently limited by feedback activation of EGFR. Improved overall response rates and duration of response when EGFR mAbs were administered with KRAS G12C inhibitors in patients with *KRAS* G12C–mutated CRC have led to the FDA approval of sotorasib/panitumumab and adagrasib/cetuximab combinations. There are currently no approved therapies that target *KRAS* G12D, which is among the most common *KRAS* alterations in patients with CRC. Here, we examined the effects of ARV-806 as a single agent and in combination with EGFR mAbs in *KRAS* G12D–mutated CRC models.

Materials and methods: The effects of ARV-806 alone or in combination with the EGFR mAbs cetuximab or panitumumab were evaluated in the *KRAS* G12D–mutated CRC cell lines GP2d and LS180. Synergy was assessed using multiple models. Antitumor activity was assessed in GP2d and LS180 cell line–derived xenograft (CDX) models following treatment with ARV-806, cetuximab, or panitumumab alone, or the combination of ARV-806 plus cetuximab or panitumumab.

Results: In GP2d and LS180 cell lines, we observed induction of phospho-EGFR and rapid reactivation of phospho-extracellular signal-regulated kinase (ERK), respectively, with single-agent ARV-806 treatment. Combinatorial targeting with ARV-806 plus either cetuximab or panitumumab overcame the EGFR-mediated adaptive resistance and led to robust synergy in vitro via multiple synergy models tested. The synergistic interaction was coupled with sustained phospho-ERK inhibition and induction of apoptosis. In vivo, single-agent EGFR mAb did not lead to significant tumor growth inhibition as expected; however, greater antitumor activity was observed when ARV-806 was combined with cetuximab or panitumumab vs ARV-806 alone in both GP2d and LS180 *KRAS* G12D–mutated CRC CDX models.

Conclusions: Taken together, these combination data indicate robust synergistic effects between ARV-806 and EGFR mAbs and support future investigation of this combination in patients with *KRAS* G12D–mutated CRC.

Conflict of interest: Ownership: All co-authors are Arvinas employees and own Arvinas stock

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291 - PB-083 **Poster**

Preclinical Efficacy of ARV-806, a PROTAC KRAS G12D Degrader, in Combination With the RAS-ON Multi-Selective Inhibitor Daraxonrasib in KRAS G12D–Mutated Models

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Background: ARV-806 is a potent, selective PROteolysis TArgeting Chimera (PROTAC) KRAS G12D degrader that targets both the ON (active GTP-bound) and OFF (inactive GDP-bound) forms and has shown >25-fold higher potency in cell proliferation inhibition vs investigational KRAS G12D OFF and ON inhibitors or other KRAS G12D degraders in preclinical models. In contrast, the RAS-ON inhibitor daraxonrasib and KRAS G12D inhibitor zoldonrasib bind to RAS and KRAS G12D, respectively, and cyclophilin A (CYPA) to form inhibitory trimer complexes that suppress downstream RAS signaling. Concurrent targeting of mutant KRAS and pan-RAS is thought to deepen pathway inhibition in KRAS mutant cells while overcoming adaptive and acquired mechanisms of resistance observed in the clinic. Given the potentially complementary mechanisms of action of ARV-806 and daraxonrasib, we evaluated the activity of this combination in *KRAS* G12D-mutated pancreatic ductal adenocarcinoma (PDAC) and colorectal cancer (CRC) preclinical models.

Materials and methods: In vitro synergy between ARV-806 plus daraxonrasib vs zoldonrasib plus daraxonrasib was evaluated in multiple *KRAS* G12D–mutated PDAC and CRC cell lines. Antitumor activity and KRAS G12D protein levels were evaluated in the AsPC-1 cell line–derived xenograft (CDX) model following treatment with ARV-806 plus daraxonrasib vs zoldonrasib plus daraxonrasib.

Results: ARV-806 plus daraxonrasib demonstrated robust synergy in *KRAS* G12D–mutated PDAC and CRC cell lines, whereas zoldonrasib plus daraxonrasib showed only additive to modestly synergistic effects across multiple models. Computational modeling suggested that ARV-806 binds within the switch-II pocket, while daraxonrasib binds at the KRAS-CypA interface, potentially allowing concurrent binding on KRAS G12D, unlike competitive binding predicted for zoldonrasib and daraxonrasib. Consistent with these in vitro data, ARV-806 (1 mg/kg) combined with a subtherapeutic dose of daraxonrasib (3 mg/kg) produced greater tumor growth inhibition (TGI) compared with either agent alone and induced robust tumor regressions in the AsPC-1 CDX model. Furthermore, the combination of ARV-806 and daraxonrasib showed greater efficacy compared with the zoldonrasib (30 mg/kg) plus daraxonrasib (3 mg/kg) combination in the AsPC-1 CDX model (TGI: 122% vs 102%). Consistent with the enhanced antitumor activity observed, ARV-806 plus daraxonrasib induced greater reductions in KRAS G12D protein levels in tumors compared with ARV-806 alone, despite upregulation of KRAS G12D protein with daraxonrasib monotherapy.

Conclusions: Taken together, these preclinical data suggest that the combination of ARV-806 plus daraxonrasib is highly synergistic and demonstrated greater efficacy compared with the zoldonrasib plus daraxonrasib combination, warranting investigation in patients with *KRAS* G12D–mutated PDAC.

Conflict of interest: Ownership: All co-authors are Arvinas employees and own Arvinas stock

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292 - PB-084 **Poster**

NUC-7738 alters Functional Proteasome Activity and Enhances Carfilzomib Sensitivity in Multiple Myeloma

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Background: Adaptive upregulation of proteasome gene expression is a key mechanism by which multiple myeloma cells maintain protein homeostasis under therapeutic stress. This adaptive response is mediated by the transcription factor NFE2L1, which undergoes sequential processing from its ER-associated precursor to its active nuclear isoform. Inhibition of this adaptive pathway may increase myeloma-cell vulnerability to proteasome inhibition. NUC-7738, a phosphoramidate modification of 3′-deoxyadenosine, generates high intracellular levels of 3′-dATP, with downstream effects on RNA processing, ATPase-dependent proteins and their regulatory pathways. Proteasome function, and recovery from proteasome-inhibitor (PI) stress, are also dependent on ATPase-regulated processes; therefore, accumulation of 3′-dATP may affect proteasome function both through modulation of proteasome subunit expression and through potential inhibition of ATPase-dependent proteasome activity. Here, we show that NUC-7738 impairs adaptive NFE2L1 processing, alters functional proteasome recovery, and enhances sensitivity to carfilzomib in multiple myeloma cell lines.

Material and Methods: Human multiple myeloma cell lines, MM.1R, ANBL6 and U266B1, were treated with NUC-7738, carfilzomib, or combinations using 10 × 10 dose matrices. Viability was assessed after 96 h by alamar Blue, and combination effects were analyzed across the response surface. NFE2L1 processing was assessed in MM.1R cells by immunoblotting of p140 and p95 isoforms over 24–96 h. Proteasome catalytic activity was measured in MM.1R lysates using fluorogenic substrates for chymotrypsin-like, trypsin-like and caspase-like activity. Experiments were performed in biological triplicate.

Results: NUC-7738 demonstrated single-agent activity across ANBL6, MM.1R and U266B1 cell-lines, with IC_{50} values of 6.42, 15.4 and 1.70 μM, respectively. Carfilzomib IC_{50} values were 1.92, 0.938 and 3.02 nM, respectively. At concentrations where each single agent retained approximately 40–60% viability, the corresponding NUC-7738/carfilzomib combinations reduced viability to near-complete loss in all three cell lines. NUC-7738 treatment led to a progressive decrease in the processed nuclear NFE2L1 isoform p95, accompanied by increased accumulation of the ER-associated precursor p140, consistent with impaired NFE2L1 processing. NUC-7738/carfilzomib combination also produced sustained suppression of proteasome catalytic activity from 24 to 96 h, with activity >50% lower than carfilzomib alone.

Conclusion: NUC-7738 impairs proteasome stress adaptation by reducing nuclear NFE2L1 p95 and increasing ER-bound p140 in myeloma cell lines. Together with ATPase-linked open-gate trapping of the proteasome, this deepens carfilzomib-mediated inhibition and supports NUC-7738 as a combination partner for PIs in PI-sensitive malignancies.

Conflict of interest: Other Substantive Relationships: Mustafa Elshani. and David J. Harrison are part time employees of NuCana Plc

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293 - PB-085 **Poster**

ClpP Agonist-Induced Cellular Senescence Promotes Vulnerability to Apoptosis and Ferroptosis in Triple Negative Breast Cancers

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Background: Mitochondrial metabolism is widely reprogrammed in cancers to meet energy demand. Caseinolytic mitochondrial matrix protease (ClpP) plays a crucial role in mitochondrial protein quality control. ClpP agonists (e.g., ONC201, TR compounds) are a new class of anti-tumor drugs which induce hyperactivation of ClpP, resulting mitochondrial dysfunction and impairment of cell viability. While ClpP agonists suppress tumor growth of triple negative breast cancer (TNBC), they also induce cellular senescence. We hypothesized that targeting the senescence cells will improve the therapeutic effect.

Materials and Methods: TNBC cell lines and Patient Derived Cells (PDCs) obtained from NCI Patient-Derived Models Repository were used as *in vitro* model systems. TR compounds (TR-57, TR-107) were provided by Madera Therapeutics, LLC. National Center for Advancing Translational Sciences (NCATS) drug combination screen was conducted to identify drugs that are synergistic with ClpP agonists. Identified candidates and TR-107 were combined *in vitro* and the synergistic effect on cell viability (CellTiterGlo 2.0) and cell lethality (propidium iodide uptake) was analyzed with SynergyFinder 2.0. siRNA was used to evaluate the role of specific genes on the drug effect. Flow cytometry was used to assess cellular senescence and cell death. Protein levels were analyzed with Western blotting. Intracellular iron levels were analyzed with fluorescent probes using plate reader and confocal microscopy.

Results; A drug combination screen identified Navitoclax (an inhibitor of BCL2, BCLxL and BCLw) as a synergistic drug with ClpP agonists. When combined, TR-107 and Navitoclax showed a synergistic effect in multiple TNBC. Additionally, Navitoclax acted as a senolytic and caused apoptosis when senescence was induced by a TR-107 in TNBC cell lines and PDC. Targeting specific BCL2 family members by siRNA or specific pharmacological inhibitors revealed that loss or inhibition of BCLxL, but not BCL2 or BCLw, phenocopied the effects of Navitoclax in ClpP agonist-treated cells. Further, TR-107 induced the anti-ferroptosis protein glutathione peroxidase 4 (GPX4) and iron accumulation at the lysosome, while downregulating mitochondrial iron. RSL3, an inhibitor of GPX4, caused ferroptosis in cells pre-treated with TR-107, especially in the senescent cells. RSL3-induced senolysis of cancer cells is not previously reported. When Navitoclax and RSL3 were combined, significant senolysis was observed in TNBC cells pre-treated with the TR-107.

Conclusions: TR-107-induced senescence in TNBC cells increases the sensitivity to apoptosis and ferroptosis. Therapeutic efficacy of

the combination of TR-107, Navitoclax and Ferroptosis inducer *in vivo* is currently under investigation.

Conflict of interest: Ownership: Dr. Ed Iwanowicz is President and Founder of Madera Therapeutics, LLC.

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294 - PB-086 **Poster**

Zanidatamab plus PI3K-pathway inhibition as a rational strategy for therapy-resistant HER2-positive breast cancer

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Background: Resistance to HER2-targeted therapies remains a major challenge in HER2-positive breast cancer (HER2+ BC), including after trastuzumab deruxtecan (T-DXd). Zanidatamab is a biparatopic HER2-targeting antibody that engages two distinct HER2 epitopes (ECD2 and ECD4), but its effects on HER2-HER3 interactions and rational combination strategies in therapy-resistant models remain incompletely defined. We assessed zanidatamab-mediated disruption of HER2-HER3 proximity and used a mechanism-guided drug screen to identify combination strategies.

Materials and Methods: HER2 and HER3 expression were evaluated in parental and T-DXd-resistant HER2+ BC cell lines by flow cytometry and immunoblotting. HER2-HER3 proximity was quantified by proximity ligation assay (PLA) after treatment with zanidatamab, trastuzumab, pertuzumab, or trastuzumab plus pertuzumab. A 179-agent FDA-approved oncology drug screen was performed with or without zanidatamab. Selected PI3K pathway, DNA damage response (DDR), and cell-cycle checkpoint inhibitors were further evaluated using antiproliferative activity, Bliss synergy, and pathway analysis.

Results: Compared with matched parental controls, baseline HER2 surface expression was reduced in T-DXd-resistant HER2+ BC models, whereas HER3 expression was relatively preserved. Baseline HER2 median fluorescence intensity was 37.7%, 1.1%, and 10.7% of parental levels in HCC1954-, KPL4-, and SUM190-derived T-DXd-resistant cells, respectively. Despite HER2 loss, HER2-HER3 proximity persisted in SUM190 T-DXd-resistant cells. In this model, zanidatamab reduced HER2-HER3 PLA signal to 32.5% of IgG control, compared with 97.0% for trastuzumab and 42.3% for trastuzumab plus pertuzumab, indicating greater disruption of residual HER2-HER3 proximity by zanidatamab. A 179-drug screen, integrated with prior pathway analyses, prioritized PI3K and DDR/cell-cycle targets. PI3K/mTOR, AKT, mTORC1, ATR, WEE1, and Aurora A inhibitors were selected for validation. T-DXd-resistant models showed greater sensitivity to PI3K-pathway inhibition: alpelisib IC50 values in BT-474-derived models decreased from 1.23-2.78 μM in parental models to 0.51-0.85 μM in resistant models, and gedatolisib IC50 in SUM190-derived models decreased from 26.94 nM to 9.94 nM. PI3K pathway inhibition enhanced zanidatamab activity in both parental and T-DXd-resistant models, whereas DDR- and cell-cycle-directed agents showed more limited combination benefit.

Conclusions: Zanidatamab disrupted residual HER2-HER3 proximity in SUM190 T-DXd-resistant HER2+ BC cells. Mechanism-guided screening identified PI3K-pathway inhibition as the leading combination strategy, while DDR and cell-cycle checkpoint inhibitors showed more limited activity in the tested models. These findings support further evaluation of zanidatamab plus PI3K-pathway inhibition for therapy-resistant HER2+ BC.

Conflict of interest: Ownership: Naoto Ueno: Stock and Other Ownership Interests: Pear Bio, Phoenix Molecular Designs.

Advisory Board:

Naoto Ueno. Consulting or Advisory Role: Carna Biosciences, Gilead Sciences, AstraZeneca,

Genentech/Roche, Exact Sciences.

Jangsoon Lee. Scientific Advisory Role: Astrion Inc., Wittgen Bio.

Corporate-sponsored Research:

Naoto Ueno, Research Funding (Individual): Daiichi Sankyo, Oncotherapeutics.

Jangsoon Lee, Research Funding (Individual): OBI Pharma, Jazz Pharmaceuticals, Duality Bio, Eisai, CytoDyn, Mondego Bio.

Other Substantive Relationships: Ankur Karmokar and Kedar Vaidya are employees of Jazz Pharmaceuticals.

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295 - PB-087 **Poster**

Combination of FMC-242, a first-in-class, covalent allosteric breaker of the PI3Kα-RAS interaction, with KRAS inhibitors drives enhanced anti-tumor activity including regression in CDX/PDX models harboring KRAS mutations

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Activation of RAS and PI3Kα are the most frequent oncogenic events in cancer, playing a key role in many aspects of tumor cell physiology, including growth, survival, differentiation, and migration. While treatment options have recently emerged for a subset of KRAS mutant patients and inhibitors of PI3Kα catalytic activity have been approved, both approaches have been limited by drug resistance and in the case of PI3Kα, hampered by poor tolerability (e.g., hyperglycemia). An alternative therapeutic strategy that addresses drug resistance with improved tolerability is needed. Application of the FrontierTM Platform, which integrates chemoproteomics, artificial intelligence, and direct-to-biology approaches to accelerate the discovery and development of precision covalent medicines, enabled the discovery of FMC-242, a first-in-class, potent, selective, and orally bioavailable covalent allosteric breaker of the PI3Kα-RAS interaction. FMC-242 is designed to inhibit downstream signaling in tumors, including those driven by RTK activation and RAS mutations, without impacting normal functions such as glucose homeostasis.

FMC-242 rapidly and selectively forms a covalent bond with cysteine 242 in the RAS Binding Domain (RBD) PI3Kα resulting in allosteric inhibition of PI3Kα-RAS complex formation. This leads to inhibition of AKT activation in tumors with mutations in KRAS or PI3Kα, and where receptor tyrosine kinases, e.g., HER2, are activated. Single agent FMC-242 treatment results in potent anti-tumor activity in xenograft models carrying HER2 amplification and/or KRAS mutation. FMC-242 is well tolerated in vivo and does not impact insulin signaling or blood glucose level. In KRAS G12C

mutation-containing xenograft models including those that are insensitive to single agent KRAS inhibitors, combination of FMC-242 with the KRAS inhibitors such as FMC-376, divarasib, olomorasib, or daraxonrasib results in enhanced efficacy and tumor regression. Furthermore, FMC-242 in combination with daraxonrasib is highly effective in multiple KRAS G12X PDX models across histologies and is well tolerated. Together, these data demonstrate the potential of FMC-242, a potent, selective, and orally bioavailable covalent allosteric breaker of the PI3Kα-RAS interaction, as a differentiated monotherapy and combination approach.

Conflict of interest: Other Substantive Relationships: Authors are employees of Frontier Medicines.

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296 - PB-088 **Poster**

Pharmacologic Inhibition of ENPP1 by AVA-NP-695 Synergizes with DNA Damage Response Inhibitors in Preclinical Models of Osteosarcoma and Ewing Sarcoma

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Background: Elevated expression of ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) correlates with unfavourable outcomes across multiple tumor types and has been linked mechanistically to metastatic spread to lung and bone, a recurring obstacle in osteosarcoma (OS), Ewing sarcoma (EWS), and triple-negative breast cancer. Since these malignancies are frequently refractory to immune checkpoint blockade (ICB), ENPP1 has emerged as an actionable node for pharmacological intervention. This study demonstrates that AVA-NP-695, a selective small-molecule ENPP1 inhibitor, alone and in combination with DNA damage response (DDR) inhibitors such as Olaparib and Ceralasertib demonstrate significant anti-tumor efficacy in pediatric solid tumor models like Osteosarcoma and Ewing Sarcoma.

Material and Methods: AVA-NP-695, a picomolar inhibitor of ENPP1, has demonstrated excellent selectivity across several biochemical substrate panels. Its ADME/PK profile has been characterized extensively in mouse, rat, and beagle dog based studies. AVA-NP-695 when combined with olaparib or ceralasertib has demonstrated strong synergy, with efficacy confirmed in vivo using orthotopic, lung-metastatic, PDX, and cell line-derived xenograft (CDX) models of OS and EWS.

Results: AVA-NP-695 has demonstrated potent, selective ENPP1 inhibition and was well tolerated in repeat-dose and dose-escalation toxicology studies. Single-agent treatment regressed tumors in both orthotopic and lung-metastatic OS models. Combinatorial screening identified strong syngery between AVA-NP-695 and both DDR inhibitors, Olaparib and Ceralasertib in OS lines. In OS PDX models and an EWS CDX model, AVA-NP-695 demonstrated superior monotherapy activity to that of Olaparib or Ceralasertib alone, while the combination produced strong synergy and significant tumor regression. In an intrapulmonary OS model, treatment reduced lung nodule burden and extended progression-free survival significantly.

Conclusions: These preclinical data demonstrate that AVA-NP-695, a highly potent ENPP1 inhibitor, is an effective therapeutic modality in ICB-refractory pediatric sarcomas. AVA-NP-695 demonstrates single-agent anti-tumor and anti-metastatic activity and synergizes with DDR inhibitors Olaparib and Ceralasertib in OS and EWS models, providing rationale for clinical development of these combinations.

Conflict of interest: Ownership: Aditya Kulkarni, Avijit Goswami, Sandeep Goyal and Princy Khurana own equity in Avammune.

Advisory Board: Alejandro Sweet-Cordero serves on the advisory board of Avammune.

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297 - PB-089 **Poster**

Lasmotinib synergizes with menin inhibition to overcome acquired MEN1 mutation–mediated resistance in FLT3-mutated KMT2A-rearranged AML

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Background: Activating *FLT3* mutations and high FLT3 expression frequently co-occur with *KMT2A*-rearranged (*KMT2A*-r) acute myeloid leukemias (AML), forming a cooperative HOX/MEIS1–FLT3 axis that drives leukemic proliferation. Although menin inhibitors have shown clinical activity in relapsed/refractory *KMT2A*-r or *NPM1*-mutant AML, acquired resistance substantially limits their efficacy. On-target *MEN1* mutations disrupt menin-mediated regulation of FLT3 expression and signaling, sustaining FLT3-dependent survival pathways. Moreover, elevated microenvironmental FLT3 ligand (FL) further amplifies these signals *in vivo*. Here, we demonstrate that combining the clinically active FLT3 inhibitor lasmotinib with menin blockade overcomes acquired MEN1-mediated resistance, producing deeper and more durable anti-leukemic responses.

Material and Methods: *FLT3*-ITD/*KMT2A*-r AML cell lines including revumenib-resistant MOLM-13, MOLM-14, and CRISPR/Cas9-engineered MV4-11 clones harboring *MEN1* mutations (M327I, T349M, G331R, E368K, and E368V), and high-FLT3-expressing MM6 cells were evaluated. Cell viability was assessed using the CellTiter-Glo assay, and drug synergy was analyzed using SynergyFinder. Apoptosis induction (Annexin V binding) was quantified by luminescence, while signaling pathways were evaluated by immunoblotting and qPCR. *In vivo* efficacy of the two-drug combination was assessed in a *MEN1* M327I-mutant MV4-11 xenograft model.

Results: Lasmotinib potently inhibited the proliferation of revumenib-sensitive (IC_{50} = 0.5-2 nM), acquired revumenib-resistant cells (IC_{50} = 3 nM), and *MEN1*-mutant MV4-11 cells (IC_{50} = 0.4-0.8 nM), demonstrating superior activity compared to the clinical-stage menin inhibitors revumenib, ziftomenib, and bleximenib. Under FL-stimulated conditions, lasmotinib achieved up to 7-fold greater growth inhibition and more potent p-FLT3 suppression than the approved FLT3 inhibitor gilteritinib. In *MEN1* M327I-mutant MV4-11 cells, lasmotinib combined with revumenib produced robust synergy (HSA score > 20) and markedly increased apoptosis, evidenced by Annexin V positivity, PARP1 and caspase-3 cleavage, and MCL-1 depletion. Mechanistically, revumenib depleted total FLT3 expression, while lasmotinib blocked residual FLT3 signaling, resulting in profound inhibition of downstream FLT3 pathways. In the *MEN1* M327I xenograft model, the combination induced rapid and durable tumor

regression with complete intratumoral p-FLT3 inhibition, whereas revumenib monotherapy showed limited efficacy.

Conclusions: Lasmotinib combined with menin inhibition effectively overcomes MEN1 mutation-mediated acquired resistance through complementary FLT3 depletion and signaling blockade. These findings provide a strong mechanistic and clinical rationale for evaluating this combination in patients with *FLT3*-ITD and *KMT2A*-r AML.

Conflict of interest: Ownership: K.Y. Nam, K.T. Kim, and J. Yoon hold stocks in Pharos iBio.

A.N. Moon, H.S. Hwang, and J. Kwon hold stock options in Pharos iBio.

Board of Directors: K.Y. Nam, J. Kwon, K.T. Kim, and J. Yoon serve on the Board of Directors at Pharos iBio.

Other Substantive Relationships: All authors are employees of Pharos iBio.

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299 - PB-091 **Poster**

Preclinical combination study of NTS071 and venetoclax for the treatment of TP53 Y220C-mutated acute myeloid leukemia

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The prognosis of acute myeloid leukemia (AML) is influenced by mutations in the tumor suppressor *TP53*, which are found in approximately 30-40% of patients with advanced AML. *TP53*-mutated AML results in an overall median survival of only 6 months, in contrast to approximately 18 months for *TP53* wild-type (WT) AML patients. Therefore, there is an urgent unmet need for novel therapeutic strategies to improve the survival of this patient population.

NTS071 is a highly potent and selective small-molecule p53 Y220C reactivator developed by Nutshell Therapeutics (Shanghai) Co., LTD., which is currently in Phase 1/2a clinical trial for treating *TP53* Y220C-mutated advanced solid tumors. Y220C represents one of the most prevalent *TP53* mutations identified across hematopoietic malignancies, accounting for 4.8% of the total *TP53* mutations within these diseases. To investigate the preclinical efficacy of NTS071 in the treatment of AML with *TP53* Y220C mutation, the *TP53* Y220C point mutation was introduced into MOLM-13 cell line via CRISPR knock-in to generate *TP53* Y220C MOLM-13 #4 clone. The reactivation of p53 and its downstream pathways by NTS071 was validated by enzyme-linked immunosorbent assay (ELISA), followed by qRT-PCR and Western blotting assay in this isogeneic cell line. Cell viability assays demonstrated that NTS071 dose-dependently inhibited the cell proliferation of *TP53* Y220C MOLM-13 #4 clone and exhibited synergistic effect in combination with the BCL-2 inhibitor Venetoclax or the DNA methyltransferase (DNMT) inhibitor Azacitidine. Moreover, a robust synergy in antitumor efficacy was also confirmed for the combination of NTS071 and Venetoclax *in vivo* in the subcutaneous xenograft mouse model derived from *TP53* Y220C MOLM-13 #4 human AML cells. Mechanism-of-action (MOA) studies revealed that NTS071 significantly enhanced cell apoptosis when combined with Venetoclax.

In summary, these studies demonstrate the synergistic therapeutic potential of NTS071 in combination with a BCL-2 inhibitor for treating AML harboring *TP53* Y220C mutation, which warrants further clinical development.

No conflict of interest

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300 - PB-092 **Poster**

Prediction of post-radiotherapy survival in patients with distant metastatic hepatocellular carcinoma

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Background: The standard treatment for hepatocellular carcinoma (HCC) with distant metastasis (DM) is systemic therapy. Recent advances in radiotherapy (RT) techniques have expanded the role of RT for the treatment of HCC from the early stage to DM. However, there is a limited data on RT for patients with DM-HCC. Therefore, we assessed the overall survival after RT in patient with DM-HCC and developed a prognostic model (CLuE model) predicting post-RT survival.

Materials and methods: We retrospectively reviewed 37 HCC patients with documented DM, who were treated with RT between February 2016 and January 2025. The Eastern Cooperative Oncology Group (ECOG) performance status was 0 or 1 in 26 patients and 2 in 11 patients. A baseline Child-Pugh (CP) score of ≤ 7 was observed in 32 patients and ≥ 8 in 5 patients. A viable liver tumor was present in 24 patients. Thirteen patients had only bone metastases. Nineteen patients had oligometastases, defined as ≤ 5 lesions. Survivals were analyzed using the Kaplan-Meier method.

Results: The overall survival (OS) rates were 78% at 1 year and 64% at 2 years, respectively. On univariate analysis, ECOG of 2, CP score ≥ 8, and viable liver tumor were significantly associated with poor OS. The CLuE model (**C**P score, **L**iver t**u**mor, and **E**COG) was developed with each significant variable weighted as 1 point. According to the CLuE model, the 1-year OS rate was 100% for a score of 0, 63% for scores of 1-2, and 0% for a score of 3 ($P < 0.001$), respectively.

Conclusions: The prognosis in patients with DM-HCC was significantly affected by liver function and primary tumor control. The CLuE model can be used to guide clinical decisions regarding the application of RT for DM-HCC. Due to the limitation of a small sample size, further validation studies with a larger patient cohort are required to confirm our findings.

No conflict of interest

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301 - PB-093 **Poster**

A CRISPR-Cas9 chemo-genetic screen reveals the synergy between CDC7 and CDK8 kinases in supporting DNA replication origin firing and cell proliferation

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Background: During tumorigenesis, oncogene activation results in dysregulation of DNA replication and transcription programmes ultimately driving the hyper-proliferative state of cancer cells. The Cell Division Cycle 7 (CDC7) kinase is a key switch for DNA replication and its depletion/inhibition causes cancer cells to stop DNA synthesis. As such, a number of CDC7 kinase inhibitors are in development.

Materials and Methods: We have performed a genome-wide CRISPR-Cas9 KO chemo-genetic screen to discover genes, that upon loss, sensitize to the anti-proliferative effects of CDC7. We have developed a bioinformatic pipeline to refine hits analysis and to cluster them into functional modules based on the concept of genetic co-essentiality. Functional validation was performed with standard molecular genetics and pharmacological approaches.

Results: We found that Cyclin Dependent Kinase 8 (CDK8) gene knock-out or CDK8 protein depletion sensitizes cells to CDC7 inhibition. CDK8 is regarded as a transcriptional kinase and is a known component of the Mediator complex which bridges transcriptional control elements, promoters, chromatin modifiers and transcription factors to RNA polymerase II. CDK8 is also considered a proto-oncogene in colorectal cancer (CRC), where high expression levels are negatively correlated with poor patient survival and were associated with advanced stage disease progression with several CDK8 inhibitors been developed as targeted agents.

We find that CDK8 functionally clusters with well-known DNA replication factors. Importantly combining CDC7 and CDK8 small molecule inhibitors strongly impair proliferation and DNA synthesis. At the molecular level CDC7 and CDK8 kinases cooperate in promoting DNA replication origin firing converging on the phosphorylation of the replicative DNA helicase.

Conclusions: This work identifies CDK8 as novel protein kinase directly involved in origin activation in human cells and indicate that the combination of CDC7 and CDK8 inhibitors has the potential for the treatment of aggressive cancers by suppressing the early steps of DNA replication.

Conflict of interest: Other Substantive Relationships: M. D. Rainey and C. Santocanale are inventors on EP4275686A1 patent assigned to the University of Galway with title "Combination therapy for cancer comprising a cdc7 inhibitor and a cdk8 inhibitor or a ccnc inhibitor".

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302 - PB-094 **Poster**

Identification of MCPH1/BRIT1 synthetic lethal partners for breast cancer treatment

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Background: Synthetic lethality (SL) is a targeted cancer treatment approach in which the combined loss or inhibition of two genes results in cancer cell death, whereas disruption of either gene alone is tolerated. By exploiting tumour specific genetic defects, SL therapies can selectively eliminate cancer cells while minimizing damage to normal tissue. Thereby reducing the side effects of chemotherapy and limiting the development of drug resistance. MCPH1/BRIT1 is a tumour suppressor gene frequently altered in multiple cancer types, including a third of breast cancers (BC). Consequently, this gene warrants investigation as specific genetic defect in SL treatment for BC.

Method: High-throughput siRNA screening was performed on 6,595 genes, followed by bioinformatic filtering using six criteria to identify candidate MCPH1/BRIT1 SL partners. To validate MCPH1/BRIT1 SL partners, colony formation assays (CFA) were performed in MCF7 and MDA-MB-468 BC cell lines following siMCPH1/BRIT1 knockdown combined with treatment of a SL partner inhibitor. Western blotting was also implemented to determine the protein expression of MCPH1/BRIT1 and SL partner. Furthermore, RNA-Seq was performed to investigate potential SL mechanisms between MCPH1/BRIT1 and SL partner. SL mechanisms were then validated using several techniques, including apoptosis assay, cell cycle analysis and senescence-associated β-galactosidase (SA-β-Gal) staining.

Results: This approach identified 24 candidate MCPH1/BRIT1 SL partners, including Bromodomain-containing protein 4 (BRD4). A significant reduction in cell number was observed in siMCPH1/BRIT1 knockdown cells treated with BRD4i compared with siNTC knockdown cells treated with BRD4i, confirming a SL interaction between MCPH1/BRIT1 and BRD4. Reduced MCPH1/BRIT1 protein expression was associated with decreased BRD4 protein levels and increased sensitivity to BRD4i as indicated by reduced IC_{50} values. Different SL mechanisms were identified in both BC cell lines. In MCF7 cells, SL treatment inhibited cell proliferation by inducing G1 cell cycle arrest and cell senescence. In contrast, the same treatment induced apoptosis in MDA-MB-468 cells.

Conclusions: This study identifies BRD4 as a novel SL partner of MCPH1/BRIT1 and supports BRD4 inhibition as a promising targeted therapeutic strategy for MCPH1/BRIT1-deficient BC. The findings also suggest that MCPH1/BRIT1 deficiency enhances the therapeutic efficacy of BRD4i as a drug and may reduce cancer cell resistance to BRD4i. The diverse SL responses may be attributed to the different p53 status in the two BC cell lines. Given the role of MCPH1/BRIT1 alterations in multiple cancer types, this approach may have broader applications in other cancers including cervical, prostate and lung cancer.

No conflict of interest

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303 - PB-095 **Poster**

Investigation of the Anticancer Effects of Dacomitinib and Curcumin on Colorectal Cancer Using In Vitro and In Silico Approaches

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Background: Colorectal cancer (CRC) is one of the leading causes of cancer-related mortality worldwide. Despite advances in treatment, therapeutic resistance and treatment-associated toxicity remain significant challenges. This study aimed to investigate the combined anticancer effects of Dacomitinib, a selective epidermal growth factor receptor (EGFR) inhibitor, and Curcumin, a naturally occurring polyphenol, in HCT116 colorectal cancer cells using *in vitro* and *in silico* approaches.

Materials and Methods: The cytotoxic effects of Dacomitinib and Curcumin were evaluated using the MTT assay. HCT116 cells were treated with Dacomitinib (15 μM), Curcumin (30 μM), or their combination. In addition, molecular docking analyses were performed to investigate the binding affinities of both compounds toward EGFR and BCL-2 proteins.

Results: Both Dacomitinib and Curcumin reduced HCT116 cell viability in a dose-dependent manner. The IC25 and IC50 values were 10.29 and 15.65 μM for Dacomitinib, and 21.69 and 49.60 μM for Curcumin, respectively. Among the four combination regimens evaluated, the combination of 15 μM Dacomitinib and 30 μM Curcumin produced the greatest reduction in cell viability. This combination significantly decreased cell viability compared with Dacomitinib alone ($p < 0.0001$), although no significant difference was observed compared with Curcumin alone. Molecular docking analysis showed favorable binding of both compounds to EGFR and BCL-2. The combination exhibited lower binding energies than either compound alone (BCL-2: −12.38 kcal/mol; EGFR: −12.46 kcal/mol), suggesting enhanced interactions with both targets.

Conclusions: The combination of Dacomitinib and Curcumin demonstrated enhanced anticancer activity in HCT116 colorectal cancer cells compared with Dacomitinib alone. These findings support further investigation of this combination as a potential therapeutic strategy for colorectal cancer.

No conflict of interest

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304 - PB-096 **Poster**

BBO-8520, a first-in-class direct dual inhibitor of GTP-bound (ON) and GDP-bound (OFF) KRAS-G12C, shows robust combination activity with anti-PD-1 at low free drug concentrations in preclinical models

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Background: Although $KRAS^{G12C}$ GDP-bound (OFF) inhibitors provide clinical benefit, adaptive increases in active GTP-bound $KRAS^{G12C}$ limit the depth and durability of pathway suppression. BBO-8520 is a first-in-class, potent, direct covalent inhibitor that targets both the GTP-bound (ON) and GDP-bound (OFF) states of $KRAS^{G12C}$, thereby blocking effector binding and providing more complete target inhibition than OFF-state $KRAS^{G12C}$ inhibitors. Dual-state inhibition enables comparable efficacy at lower free drug concentrations, potentially widening the therapeutic index for combination with immune checkpoint blockade. Here, we evaluated the efficacy and immunomodulatory effects of BBO-8520 alone and in combination with anti-PD-1 in preclinical models.

Methods: BBO-8520 and divarasib efficacy and/or mechanism of action studies were performed in the non-small cell lung cancer (NSCLC) $KRAS^{G12C}$ H358 cell line-derived xenograft (CDX) model and the engineered colorectal cancer (CRC) $KRAS^{G12C}$ CT26 syngeneic model. Cell line and/or tumor cytokine profiling and immunophenotyping studies were performed following BBO-8520 treatment alone or in combination with anti-PD-1.

Results: BBO-8520 achieved comparable efficacy at substantially lower free drug concentrations than the $KRAS^{G12C}$ (OFF) inhibitor divarasib in both the NSCLC $KRAS^{G12C}$ H358 CDX and CRC $KRAS^{G12C}$ CT26 syngeneic models. This lower free drug exposure may provide a wider tolerability margin, potentially enabling more effective combination with immune checkpoint inhibitors in the clinic. In the CT26 syngeneic model, the combination of BBO-8520 and anti-PD-1 significantly prolonged survival compared to monotherapy treatments and resulted in complete tumor regressions in 50% of the mice. In a rechallenge experiment, these cured mice showed no tumor growth following contralateral CT26 cell inoculation, indicating durable adaptive immune memory. BBO-8520 treatment resulted in a significant reduction in immunosuppressive cytokines and chemokines in CT26 cell line supernatants. Immune phenotyping of CT26 tumors demonstrated increased infiltration of CD4+ and cytotoxic CD8+ T cells following combination treatment, consistent with enhanced anti-tumor immunity.

Conclusions: BBO-8520, a first-in-class direct dual inhibitor of GTP-bound (ON) and GDP-bound (OFF) $KRAS^{G12C}$, demonstrates robust efficacy at low free drug concentrations, remodels the tumor microenvironment toward a more immune-permissive state, and enhances the efficacy of anti-PD-1 in preclinical models. These findings support the ongoing Phase 1 evaluation of BBO-8520 as monotherapy and in combination with pembrolizumab in patients with $KRAS^{G12C}$ NSCLC (NCT06343402).

Conflict of interest: Corporate-sponsored Research: The indicated authors are employees of BBOT and hold BBOT stock.

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305 - PB-097 **Poster**

Exploiting RAS-mediated resistance mechanisms in BRAF V600 mutant colorectal cancer to optimize therapeutic strategies

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Background: *BRAF* V600 mutations (*BRAFm*) occur in ~10% of colorectal cancers (CRC) and constitutively activate MAPK signaling. Although BRAF-targeted therapy induces responses in a subset of patients, most ultimately develop acquired resistance. Moreover, 25-40% of relapsed patients acquire activating KRAS and/or NRAS mutations, implicating RAS-mediated MAPK reactivation as a common resistance mechanism. However, no targeted therapies have been established for patients with acquired RAS-mutant BRAFi-resistant CRC. We therefore investigated whether targeting RAS-driven BRAF:CRAF heterodimerization with pan-RAF inhibitor combinations could overcome resistance to BRAF + MEKi.

Materials and methods: *BRAFm* CRC cells (HT29, RKO, Colo205, LS411N, CL34) with acquired resistance to BRAF + MEK or BRAF + EGFR inhibitors were generated by prolonged exposure to escalating drug concentrations. Whole-exome sequencing was performed on control and resistant pairs. Inhibitor effects on RAF dimerization, MAPK signaling, and RAS activity were assessed by co-immunoprecipitation, immunoblot, and RAS-GTP pull-down assays. Cell survival and drug synergy were evaluated by clonogenic assays and Bliss scores (SynergyFinder). CL34-resistant xenografts were treated with combination inhibitors for 21 days. Stable doxycycline-inducible cell lines expressing FLAG-tagged wild-type or mutant KRAS/NRAS constructs were generated using the pCW57 lentiviral vector.

Results: MAPK pathway reactivation was observed in all BRAF + MEKi-resistant CRC cell lines. Whole-exome sequencing identified acquired activating KRAS or NRAS mutations in 3/5 resistant cell lines (RKO, LS411N, CL34). Increased RAS activity was observed in 4/5 resistant cell lines compared with control cell lines following BRAF + MEKi treatment, suggesting that elevated RAS activity may contribute to MAPK pathway reactivation. Further investigation revealed increased BRAF:CRAF heterodimerization in 4/5 resistant vs. control cell lines. Pan-RAF + MEKi combinations exhibited synergistic growth inhibition and MAPK pathway suppression than BRAF + MEKi across all evaluated control and resistant CRC cell lines. *In vivo*, CL34-resistant tumors remained resistant to BRAF + MEKi, whereas pan-RAF + MEKi induced significantly greater tumor growth inhibition. To determine whether RAS activation was sufficient to confer resistance, inducible expression of activating KRAS or NRAS mutants was evaluated in *BRAFm* CRC models. Mutant RAS expression diminished pERK suppression by BRAF + MEKi, whereas pan-RAF + MEKi maintained effective MAPK pathway inhibition.

Conclusion: Enhanced RAS activity and BRAF:CRAF heterodimerization are key drivers of resistance to BRAF + MEK inhibition in *BRAFm* CRC. These findings support panRAF + MEKi as a promising therapeutic strategy for both treatment-naïve and -resistant settings.

No conflict of interest

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306 - PB-098 **Poster**

Optimizing p53/ISR-based cancer therapy through real-time in vivo monitoring of p53 activation

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Background: Given the limited efficacy of MDM2 inhibitors as monotherapy, we aimed to establish an orthotopic colorectal cancer (CRC) reporter mouse model for non-invasive monitoring of p53 and ISR pathway activation *in vivo* to support the development and optimalization of rational p53/ISR-targeting combination therapies.

Methods: A stable HCT116 CRC reporter cell line expressing the near-infrared fluorescent protein iRFP713 under the control of a p53-responsive promoter was generated using lentiviral transduction. Following initial validation of reporter responsiveness *in vitro* and in subcutaneous tumors, multiple MDM2 inhibitors were evaluated in the orthotopic model to compare their ability to activate p53. Reporter-based measurements were confirmed by western blotting and RT-qPCR.

Results: The reporter system enabled real-time visualization of p53 activation both *in vitro* and *in vivo*, allowing comparison of the pharmacodynamic activity of multiple MDM2 inhibitors and identification of the drug inducing the strongest p53 activation. This lead compound was subsequently evaluated in combination with an ISR activator in both acute and chronic treatment settings, demonstrating the utility of the model for assessment of therapeutic responses.

Conclusion: We established and validated orthotopic CRC reporter model that enables non-invasive, longitudinal monitoring of p53 pathway activation during therapy. This platform supports pharmacodynamic evaluation of MDM2 inhibitors and provides a robust preclinical tool for the development and optimization of p53/ISR-targeting combination therapies.

No conflict of interest

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307 - PB-099 **Poster**

Characterizing tumor intrinsic changes and elucidating mechanistic features following treatment with a neutralizing antibody targeting amphiregulin (AREG) in combination with neoadjuvant chemotherapy in both BRCA proficient and deficient high grade serous ovarian cancer (HGSOC) in vivo models

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Background: The purpose of this study was to evaluate the tumor intrinsic changes following treatment with a neutralizing antibody targeting AREG in combination with HGSOC standard of care (SOC) chemotherapy in HGSOC immunocompetent *in vivo* models and to elucidate the mechanism behind an AREG blockade.

Material and Methods: Our previous work revealed a significant reduction in tumor burden following two *in vivo* studies in ID8p53$^{-/-}$ and ID8p53$^{-/-}$BRCA2^{mut} mouse (C57/BL6) models targeting AREG in combination with SOC chemotherapy. Following these studies, tumors were submitted for comprehensive proteomic profiling and pathway analysis was performed by gene set enrichment analysis (GSEA). Apoptosis rates were evaluated across all treatment groups using TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling). Finally, siRNA was used to evaluate how tumorigenic adaptations differ following transient silencing of AREG's known receptor, EGFR. The HGSOC chemoresistant cell line, PEA2, was treated with EGFR siRNA and recombinant AREG (rAREG) stimulation. Treatment groups were as follows; scrambled control, EGFR siRNA, scrambled control + rAREG, and EGFR siRNA + rAREG, and triplicate cell lysates were submitted for comprehensive proteomic profiling.

Results: Proteomic analysis revealed that mast cell associated proteins (Cpa3, Nectin2, Rac1) were significantly ($p < 0.05$) modulated in both tumor models in the carboplatin/paclitaxel + AREG nab. group compared to saline-IgG control group. GSEA analysis revealed that proteins associated with G2M checkpoint signaling and oxidative phosphorylation were enriched in the control group compared to the carboplatin/paclitaxel + AREG nab group in both tumor models. One way ANOVA with Tukey's multiple comparison test revealed that TUNEL counts per mm^2 were significantly ($p < 0.05$) higher in the carboplatin/paclitaxel + AREG nab. group, compared to all other treatment groups in the ID8p53$^{-/-}$BRCA2^{mut} model. Proteomics analysis for the siRNA experiment revealed that silencing EGFR significantly upregulated ($p < 0.05$) WFS1 and CHEK2 proteins compared to all other treatment groups.

Conclusions: This study suggests that AREG represents a novel therapy in HGSOC with the ability to modulate proteins and signaling pathways that are pro-tumorigenic in nature. Transient silencing of EGFR revealed a distinct protein expression profile compared to EGFR siRNA + rAREG. Future directions include performing additional *in vitro* and *in vivo* mechanistic studies to continue characterizing the distinct tumor intrinsic changes following AREG blockade and to determine if AREG is acting solely through EGFR signaling.

No conflict of interest

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Poster Session: New drugs

309 - PB-101 **Poster**

AI Assisted Drug Discovery through ADMET Property Analysis and Molecular Docking Targeting the LxxLL Motif of Ubiquitin Ligase E6AP for the Inhibition of Cervical Cancer Carcinogenesis

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Cervical cancer is the leading cause of cancer in women aged 35-44, primarily driven by infection from high-risk types of human papillomaviruses [1]. Although prophylactic vaccines against the Human Papillomavirus have been utilized, a convenient pharmacological intervention against HPV's carcinogenic effects is still needed in a select population. E6AP, a host ubiquitin ligase, plays a role in cervical cancer carcinogenesis. *In silico* drug discovery, which utilizes absorption, distribution, metabolism, excretion and toxicity (ADMET) property analysis and molecular docking, offers a cost-effective method for identifying a bioavailable and effective novel compound that can inhibit cervical cancer carcinogenesis.

Drug-like compounds that fit Lipinski's rule of 5 were chosen from the ZINC15 drug database. Screening was conducted with the aid of python code, eliminating compounds based on chemical structure and ADMET properties. To assess the efficacy, the binding affinity/score of the compounds with the LxxLL motif was obtained through molecular docking by Autodock Tools (AutoDock Score) and SCIGRESS (FastDock and Molecular Dynamics Simulations). Based on the docking results, a rank test was conducted on each compound across the 3 binding data sets to identify the most promising candidate.

From the data, (3S)-1-[(S)-(6-benzamido-1H-indol-3-yl)-carboxymethyl]piperidine-3-carboxylic acid stood out as the most promising candidate, demonstrating favorable ADMET properties (ADMET score - 1.409) and strong binding (-9.4 kcal/mol through Autodock Score and -153.251 and -491.669 in FastDock and Molecular Dynamics Simulations). On average, this compound ranked the highest across the 3 binding data sets, highlighting its potential for further investigation.

These findings point to the capabilities that *in silico* drug discovery has in providing an efficient method in identifying a small molecule inhibitor for the carcinogenesis of cervical cancer.

Table 1. Compiled ADMET and molecular docking results of inhibitor candidates

Overall Rank	Compound File No.	ADMET Score	ADMET Improvement vs. Best Reference Drug (%)	AutoDock Affinity (kcal/mol)	FastDock Score	Molecular Dynamics Score	Average Docking Rank
1	44	1.409	45.029	−9.4	−153.251	−491.669	3
2	21	1.088	57.522	−8.5	−159.191	−515.642	4.67
3	32	1.298	49.348	−8.6	−176.453	−473.788	5
4	47	1.42	44.568	−9.5	−157.905	−438.401	6.33
5	43	1.405	45.158	−8.7	−139.223	−513.614	8.33

No conflict of interest

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311 - PB-103 **Poster**

EPI-326: a clinical stage mutation-independent and normal tissue-sparing bispecific antibody that degrades EGFR for the treatment of EGFR-driven solid tumors

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EGFR is an oncogenic driver in lung, head and neck, and colorectal cancers, but clinical success has been limited by EGFR having multiple oncogenic forms, acquired drug resistance, and on-target/off-tumor dose-limiting toxicities like rash and diarrhea. A therapeutic that can robustly antagonize EGFR independent of form (wild type or mutant), avoid the TKI resistance cycle, and act in a tumor-specific manner would be highly differentiated and have distinct advantages over current treatments. EPI-326 is a novel therapeutic for wild type and mutant EGFR-driven cancers that is designed to drive deep, prolonged, tumor-enriched EGFR degradation while avoiding normal healthy tissue toxicities. Extracellular targeted protein degradation (eTPD) is a promising new drug modality that eliminates transmembrane and soluble extracellular proteins. EpiTACs are novel bispecific antibody-based eTPD therapeutics, in which one arm binds a target of interest, and the other arm binds a degrader receptor.

EPI-326 is a humanized IgG1 bispecific antibody that leverages a tumor-enriched degrader receptor identified from a novel eTPD degrader receptor atlas screen. EGFR is broadly expressed in tumors and normal tissues such as the colon and skin, bioinformatics and immunohistochemistry evaluation identified a degrader receptor enriched in EGFR-driven tumors that had limited expression in normal tissues. EPI-326 was engineered to enable tumor-enriched binding, internalization and lysosomal EGFR degradation resulting in inhibition of oncogenic signaling from EGFR and its heterodimer partners. Preclinical studies evaluating degradation and efficacy in mutant and wild type EGFR models as well as IND enabling toxicology studies were performed.

Deep and sustained tumor EGFR degradation was achieved with EPI-326 resulting in robust in vivo efficacy in classical and drug-resistant (T790M, C797S) EGFR mutant NSCLC models, as well as in wild type HNSCC and CRC CDX and PDX tumor models. EPI-326 monotherapy drove a high complete response rate in an EGFR mutant NSCLC model and activity was better than EGFR inhibition. When combined with front line standard of care therapies, EPI-326 increased the depth and duration of response. EPI-326 was well tolerated in non-human primate toxicology studies to a maximal feasible dose of 200 mg/kg, with no evidence of stereotypical EGFR-related toxicities.

eTPD represents a promising new drug modality, and EpiTACs are unique extracellular targeted protein degraders that address challenging drug targets. EPI-326 is a novel and differentiated therapeutic approach to address the limitations of current EGFR drugs. The first-in-human phase I study is enrolling and will assess the safety, tolerability, pharmacokinetics, and preliminary anti-tumor activity of EPI-326 in patients with advanced/metastatic EGFR mutant NSCLC and HNSCC (NCT07462377).

Conflict of interest: Ownership: Epibiologics
Corporate-sponsored Research: Epibiologics

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313 - PB-105 **Poster**

Novel fourth-generation ALK inhibitor TQB5410 demonstrates potent activity against ALK-positive cancer

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Background: ALK fusions are oncogenic drivers in various adult and pediatric cancers, including ~3-7% of NSCLC. Emerging resistance mutations and increasing central nervous system (CNS) involvement limit utility of approved therapies. The emergence of compound mutations in the ALK tyrosine kinase domain presents a significant challenge in treating ALK-positive cancers, especially in patients who have received sequential therapy with 2nd and 3rd-generation ALK tyrosine kinase inhibitors (TKIs). Concurrently, inhibition of TRK-family kinases (TRKA, TRKB, and TRKC) elicits broad CNS adverse effects, further limiting their utility. Therefore, there is an urgent need to develop a new generation of ALK inhibitors with improved potency, selectivity, and CNS penetration.

Material and Methods: Computational and medicinal chemistry methods were used to rationally design and synthesize TQB5410. *In vitro* kinase inhibitory potency was determined by time-resolved fluorescence resonance energy transfer (TR-FRET) assays. Cell proliferation assay was assessed via CCK-8 (Cell Counting Kit-8) assay or CellTiter-Glo luminescent assay. *In vivo* subcutaneous efficacy was conducted using tumor models generated using NCl-H3122 cells and genetically modified Ba/F3 cells stably expressing EML4-ALK fusion proteins bearing distinct driver mutations.

Results: TQB5410 exhibits robust *in vitro* inhibitory potency against EML4-ALK WT, ALK G1202R and ALK G1202R/L1196M kinases (IC_{50} = 0.12, 0.048 and 0.25nM, respectively, versus 0.16, 0.036 and 0.12nM for NVL-655) and maintains high selectivity over

TRK family member (>1000 fold versus 81 fold for NVL-655). In a panel of ALK fusion cells harboring drug-resistant mutations, TQB5410 demonstrates robust antiproliferative activity (sub-nanomolar to double-digit nanomolar IC_{50}) and achieves up to 20-fold higher potency relative to NVL-655. *In vivo*, TQB5410 induced tumor growth inhibition or regression significantly in NCI-H3122, Ba/F3-EML4-ALK^{L1196M}, Ba/F3-EML4-ALK^{G1202R} and Ba/F3-EML4-ALK$^{G1202R/L1196M}$ subcutaneous xenograft models.

Conclusion: TQB5410 is a potent, selective, and brain-penetrant ALK inhibitor as demonstrated by *in vitro* and *in vivo* studies. It is highly effective against ALK fusion WT, single and compound mutations, including G1202R/L1196M, which confer resistance to all approved ALK therapies. And it has great potential to minimize TRK-related CNS adverse events and drive more durable responses for patients. It induces significant tumor regressions in various ALK-positive NSCLC models. These results support its further development as a promising therapeutic strategy for ALK-positive cancers.

Conflict of interest: Ownership: Hongjiang Xu, Fei Liu, Wei Zhao, Xiquan Zhang are current employees of ChiaTai TianQing Pharmaceutical Group and hold stock or stock options in the company

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Other Substantive Relationships: ALL authors are employees of ChiaTai TianQing Pharmaceutical Group

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314 - PB-106 **Poster**

Highly Potent Inhibitors of RAD51, with First-in-Class potential targeting HR-proficient cancers

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Background: Targeting DNA repair pathways to selectively eliminate cancer cells has seen a huge success with multiple PARP1 inhibitors (PARPi) approved in different solid tumor indications. RAD51 is a key DNA repair gene with an important role in maintaining genomic stability by mediating homologous recombination repair (HRR) and promoting replication fork protection. Impairment of HRR reduces cell fitness in genetic backgrounds with high replication stress and sensitizes cancer cells to DNA-damaging agents and DNA Damage Response (DDR) inhibitors.

Material and Methods: A drug discovery campaign was conducted to identify novel small-molecule inhibitors of BRCA2-RAD51 protein-protein interaction (PPI). Structure-based drug design was employed to develop multiple compound series. Biochemical potency was assessed using a Fluorescence Polarization (FP) assay and an ATPase assay to measure the DNA-induced activity of RAD51, which is reliant on RAD51 self-oligomerization. A cellular reporter assay to measure HRR proficiency and a high content imaging assay to measure RAD51 foci formation were developed to assess compounds target engagement.

Results: We have identified proprietary RAD51 PPI inhibitors, orally bioavailable, with single digit nanomolar biochemical potency on RAD51 and anti-proliferative activity in a subset of cancer cell lines, including those resistant to cisplatin or PARP1 inhibitors with a sensitivity profile distinct from RAD51 genetic depletion (based on the analysis of DepMap dataset). The anti-proliferative potency correlates with biochemical potency, cellular target engagement and activation of DNA damage response, confirming the expected on-target mechanism of action.

Conclusions: The novel mechanism of action, with potential for combination with DNA damaging agents and DDR inhibitors, positions Nerviano Medical Sciences' RAD51 inhibitors as promising first-in-class candidates for further development across multiple cancer types resistant to standard of care.

No conflict of interest

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315 - PB-107 **Poster**

Deletion of Peroxiredoxin 3 (PRX3) impairs mitochondrial bioenergetics and tumor growth in mesothelioma: Results from the first in human phase 1/2 clinical trial of the PRX3 inhibitor RSO-021

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Background: Aggressive tumors, including mesothelioma, generate high levels of reactive oxygen species (ROS) to support rapid growth and proliferation. To survive under increased ROS levels, tumor cells upregulate antioxidant expression and activity, including the mitochondrial hydrogen peroxide (H_2O_2) scavenging enzyme peroxiredoxin 3 (PRX3). PRX3 is overexpressed in many cancers and promotes proliferation, survival and chemoresistance, highlighting it as a promising therapeutic target in oncology.

Methods/Results: Here we demonstrate that genetic deletion of PRX3 via CRISPR/Cas9 in the H-MESO-1 human mesothelioma cell line impairs mitochondrial bioenergetics, elevates mitochondrial ROS (mROS), and suppress mesothelioma tumor growth. PRX3 deletion decreased proliferation, colony formation and 3D spheroid growth in Matrigel. In vivo PRX3 KO cells failed to form tumors in SCID mice, whereas control cells generated substantial tumor burden. RNAseq-based gene set enrichment analysis of PRX3 KO cells supported the observed phenotypes including downregulation of oxidative phosphorylation, glycolysis and E2F and MYC targets. RSO-021 (thiostrepton) covalently inactivates PRX3, inducing oxidative stress that suppresses mesothelioma tumor cell growth. Preclinical studies report anti-tumor and immunomodulatory activity. In a first-in-human phase 1 trial treating patients via weekly local intrapleural administration with RSO-021 at 90 mgs was well tolerated leading to disease control in 67% of patients at 12 weeks and was associated with tumor reductions (NCT05278975). In the phase 2 portion of the study 45 patients received RSO-021 at 45 or 90 mg QW via indwelling intrapleural catheter until PD to further access safety and efficacy. There were 2 partial responses as assessed by modified RECIST1.1 (1 at each dose level). Durable disease control favored 90 mg with median PFS 4.1 vs 3.1 months for 90 and 45mg respectively. OS was not reached for 90mg vs 12.8 months for 45mg.

Conclusions: Collectively, these findings identify PRX3 as a key regulator of redox metabolism, mitochondrial function, and mesothelioma tumorigenesis, and establish RSO-021 as a safe novel first-in-class PRX3 inhibitor with significant therapeutic potential in oncology. Efficacy outcomes support a future pivotal study at 90mg in early-stage pleural mesothelioma prior to systemic therapy.

Conflict of interest: Ownership: B.C. is an equity holder in RS Oncology

Advisory Board: D.F. has served on the advisory board of RS Oncology

Board of Directors: B.C. is a member of the BOD of RS Oncology

Corporate-sponsored Research: B.C. and D.F. have received research funding from RS Oncology

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317 - PB-109 **Poster**

Discovery of a potent and selective first-in-class cyclin D1 degrader by targeting protein folding intermediates

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Background: Cyclin D1 is a validated oncogenic driver, but targeted protein degradation or pharmacological inhibition of Cyclin D1 has not been achieved due to the lack of accessible pockets. Protein Folding Interference is a new therapeutic modality that overcomes this issue by targeting transient ligandable pockets exposed during protein biosynthesis, thus disrupting productive folding and inducing the degradation of nascent proteins. SIB-005 is a first-in-class small-molecule degrader designed to engage Cyclin D1 folding intermediates and selectively degrade nascent Cyclin D1.

Material and methods: SIB-005 was profiled in Cyclin D1-dependent breast cancer models by evaluating Cyclin D1 degradation (HTRF and WB), cell proliferation, CCND1 RT-qPCR, nascent protein-labelling and biophysical target-engagement assays. Furthermore, its *in vitro* activity, as single agent or in combination with standard of care was assessed in breast cancer cell lines. *In vivo* efficacy and pharmacodynamic modulation of Cyclin D1 were evaluated in mice bearing MCF-7 xenografts after oral administration of SIB-005 as single agent or in combination with either palbociclib or fulvestrant.

Results: *In silico* modeling identified transient ligandable pockets along the Cyclin D1 folding trajectory. Using structure-based design, we identified and optimized small molecules that engage a folding intermediate of Cyclin D1, thus perturbing its folding process. Biophysical studies confirmed the direct interaction between SIB-005 and the target. In MCF-7 breast cancer cell line, SIB-005 induced selective degradation of nascent Cyclin D1 without affecting CCND1 mRNA, consistent with a post-transcriptional effect, and leading to significant anti-proliferative activity. This effect was confirmed across multiple Cyclin D1-overexpressing cancer cell lines. Target selectivity was confirmed by whole proteome profiling. SIB-005 showed a wider *in vitro* safety margin than palbociclib when tested in human myeloid and erythroid progenitors, consistent with the selective activity on Cyclin D1.

In MCF-7 xenografts, oral administration of SIB-005 induced significant and sustained tumor growth inhibition, comparable to the efficacy observed with palbociclib. Moreover, SIB-005 showed combination benefit when co-administered with either palbociclib or fulvestrant, with tumor regression and no adverse effects reported. *Ex vivo* immunohistochemistry analysis showed the downmodulation of Cyclin D1 in tumors, confirming *in vivo* target engagement.

Conclusions: SIB-005 is a potent, selective, orally available, first-in-class Cyclin D1 degrader with *in vitro* and *in vivo* activity in breast cancer models. These data support pharmacological degradation of Cyclin D1 by targeting folding intermediates and provide a rationale for development of SIB-005 as novel therapeutic agent for the treatment of HR+ breast cancer.

Conflict of interest: Corporate-sponsored Research: All the co-authors are employees of Sibylla Biotech

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318 - PB-110 **Poster**

TQB3142, a clinical-stage BCL-XL PROTAC, demonstrates robust in vivo antitumor activity and a favorable pharmacokinetic profile as a potential best-in-class therapeutic

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Background: BCL-XL is an attractive therapeutic target across multiple malignancies, but conventional BCL-XL inhibitors are limited by thrombocytopenia caused by platelet dependence on BCL-XL. BCL-XL-targeting PROTACs may mitigate this liability by exploiting differential E3 ligase biology in platelets, thereby improving the therapeutic index. DT2216 has established proof of concept for this strategy. TQB3142 was developed as an optimized BCL-XL PROTAC for the treatment of advanced malignant tumors. Here, we report the preclinical *in vitro* and *in vivo* activity of TQB3142, together with its pharmacokinetic (PK) and safety profiles.

Materials and methods: Computational and medicinal chemistry methods were used to rationally design and synthesize TQB3142. TQB3142 was evaluated *in vitro* for BCL-XL degradation and apoptosis in MOLT-4 cells, antiproliferative activity in resistant cell models, and platelet toxicity. *In vivo* antitumor activity was evaluated in the MOLT-4 CB-17 SCID mouse xenograft model under different dose levels and dosing regimens. *In vivo* PK was assessed in rats and dogs, including systemic exposure (AUC) and half-life ($t_{1/2}$). Data were analyzed using appropriate statistical methods.

Results: Compared with DT2216, TQB3142 showed overall comparable BCL-XL degradation and antiproliferative activity in MOLT-4 cells, with a DC_{50} of 3.7 nM and an IC_{50} of 7.0 nM. TQB3142 demonstrated faster degradation kinetics at 100 nM for 4 h (degradation rate: 40.73% vs 26.31%), stronger activity in the BCL-2 inhibitor-resistant HEL model (IC_{50}, 269 nM vs 688 nM), lower human platelet toxicity (IC_{50}, 701 nM vs 371 nM), thereby demonstrating improved selectivity.

In vivo, TQB3142 achieved higher tumor growth inhibition than DT2216 after a single intravenous dose (61% vs 33%), while both compounds showed high activity in the repeated-dose setting (92% vs 88%). In PK studies, TQB3142 showed increased exposure and longer half-life than DT2216 in both rats and dogs, with $t_{1/2}$ of 30 h versus 25 h in rats and 13 h versus 7.8 h in dogs.

Meanwhile, we have also optimized the formulation, demonstrating potential for sustained release, as evidenced by a lower C_{max}, longer mean residence time and half-life.

Conclusions: TQB3142 demonstrated a differentiated preclinical profile versus DT2216, with faster BCL-XL degradation, improved activity in a resistant model, lower platelet toxicity, stronger *in vivo* efficacy and enhanced PK properties. The formulation supports an extended dosing interval with the potential to enhance patient adherence. Together, TQB3142 is a potential best-in-class BCL-XL PROTAC for advanced malignant tumors. TQB3142 is currently being evaluated in a Phase I clinical study (NCT07338838).

Conflict of interest: Ownership: Hongjiang Xu, Fei Liu, Wei Zhao, Xiquan Zhang are current employees of ChiaTai Tianqing Pharmaceutical Group and hold stock or stock options in the company.

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Other Substantive Relationships: All authors are employees of ChiaTai Tianqing Pharmaceutical Group.

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319 - PB-111 **Poster**

Preclinical activity of TQB3125, an orally bioavailable pan-RAS (ON) molecular glue for KRAS-mutant pancreatic cancer

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Background: Many clinically relevant RAS variants still lack effective broadly applicable therapies. Clinical development of the pan-RAS(ON) molecular glue RMC6236 has validated this therapeutic strategy and established a benchmark. TQB3125 is a selective, orally bioavailable pan-RAS(ON) molecular glue that forms a ternary complex with CypA and active-state RAS, thereby blocking downstream RAS signaling. Here we report TQB3125 as a differentiated candidate for KRAS-mutant pancreatic cancer with improved preclinical potency, safety and pharmacokinetic properties.

Materials and methods: Computational and medicinal chemistry methods were used to rationally design and synthesize TQB3125. TQB3125 was evaluated *in vitro* for its binding affinity and antiproliferative activity, and *in vivo* for antitumor efficacy, tolerability and toxicology studies. PK properties were also studied. Data were analyzed using appropriate statistical methods.

Results: TQB3125 selectively bound to KRAS(ON) and showed slightly stronger binding to CypA compared with RMC6236. In cellular assays, TQB3125 demonstrated improved potency in KRAS-mutant pancreatic tumor cell lines, with IC_{50} values of 2.7 nM in AsPC-1 (KRAS G12D) and 0.62 nM in Capan-1 (KRAS G12V), compared with 5.7 nM and 1.2 nM, respectively, for RMC6236. TQB3125 was Ames negative, showed an hERG inhibition IC_{50} of 19.86 μM, and exhibited low off-target risk in a safety screening panel.

In vivo, TQB3125 showed robust antitumor activity and was well tolerated; in the Capan-1 KRAS G12V xenograft model, TQB3125 achieved a tumor growth inhibition rate of 115% without obvious treatment-related body weight loss, compared with 102% for RMC6236. In exploratory toxicology studies, the highest non-severely toxic dose was >15 mg/kg in rats, with an AUC-based safety window >12.3, and >20 mg/kg in cynomolgus monkeys, with an AUC-based safety window >2.5. No dermal toxicity or obvious abnormalities were observed.

TQB3125 also showed a favorable PK profile, including enhanced systemic exposure, prolonged half-life in rats and dogs, and absolute oral bioavailability >25%. In addition, TQB3125 showed high plasma protein binding (>98%) in both human and monkey plasma, remained stable in human, dog, and monkey plasma for up to 240 minutes, and did not significantly inhibit major CYP enzymes.

Conclusions: TQB3125 demonstrated a differentiated preclinical profile versus RMC6236, with improved activity in KRAS-mutant pancreatic cancer models, robust *in vivo* efficacy, favorable PK properties, and a wide therapeutic window. These findings support the further development of TQB3125 as a therapeutic candidate for KRAS-mutant pancreatic cancer, with IND submission anticipated in 2026.

Conflict of interest:

Ownership: Hongjiang Xu, Fei Liu, Wei Zhao, Xiquan Zhang are current employees of ChiaTai Tianqing Pharmaceutical Group hold stock or stock options in the company.

Corporate-sponsored Research: The study was supported by ChiaTai Tianqing Pharmaceutical Group.

Other Substantive Relationships: All authors are employees of ChiaTai Tianqing Pharmaceutical Group.

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320 - PB-112 **Poster**

PT0253 is a potent and selective KRAS G12D degrader for treatment of cancers

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Background: KRAS is the most frequently mutated oncogene, and G12D is the most common KRAS mutation. Although G12D selective inhibitors have reported encouraging anti-tumor activity from phase1 studies, there is significant room to improve both efficacy and tolerability. A favorable safety profile may be critical to allow for combinations with front-line chemotherapies and targeted therapies. Degraders can address key limitations of inhibitors by reducing feedback activation through KRAS, eliminating increased KRAS proteins due to *KRAS* amplification acquired during KRAS inhibition, and achieving better target coverage and safety by less frequent dosing. PT0253 was developed as a potent and selective KRAS G12D degrader specifically to address these limitations.

Methods: Degradation of KRAS, inhibition of pERK and cell growth by PT0253 was evaluated in human cancer cells harboring KRAS G12D mutation using western blotting and cell viability assay. Anti-tumor activity was evaluated in mice subcutaneously xenografted with cancer cells.

Results: PT0253 demonstrated sub nanomolar degradation potency of KRAS G12D while being less potent on wild-type KRAS (DC_{50} ≥ 33nM) and having no activity on HRAS, NRAS and KRAS G12V/C. No clinically relevant off-target activity was identified in proteomics and secondary pharmacology studies including KINOMEscan and Eurofins Cerep panel profiling. PT0253 achieved potent pERK inhibition, and anti-proliferation in multiple KRAS G12D cancer cell lines. Using an E3 dead control of PT0253, we demonstrated that the sustained pERK inhibition in GP2d cells and the remarkable efficacy in PK-59 tumor model by weekly IV injection of PT0253 were primarily driven through degradation. Consistent with better control of feedback activation by KRAS degradation, while pERK inhibition by clinical G12D inhibitor A substantially rebounded at 24h post treatment, pERK inhibition by PT0253 was sustained. Better anti-proliferation activity by PT0253 compared to two clinical G12D inhibitors (A and B) was also observed. PT0253 tumor concentrations and >90% G12D degradation were maintained for 7 days after a single dose. The good target coverage by PT0253 likely will overcome resistance caused by KRAS G12D amplification. In addition, a high dose of PT0253 at 20 mpk achieved robust and durable tumor regression in the HPAC model

without causing mouse body weight loss during the 67-day dosing period. In addition, PT0253 achieved >60% regression at 3 mpk in HPAC and GP2d tumor models.

Conclusions: The low efficacious dose of 3 mpk and weekly dosing is expected to result in good tolerability in humans and enable combinations with chemotherapies and targeted therapies. Based on this promising preclinical activity, PT0253 is currently being evaluated in a phase 1 clinical trial in participants with KRAS G12D mutated advanced solid tumors (NCT06797336).

Conflict of interest: Ownership: All authors are current or former employees of PAQ Therapeutics Inc.

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321 - PB-113 **Poster**

A next-generation AR-BRD4 RIPTAC with enhanced potency and selectivity in AR-positive tumors

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RIPTAC is an induced-proximity therapeutic modality that in which a hetero-bifunctional small molecule recruits a tumor-specific protein into proximity with an essential protein, forming a ternary complex that selectively disrupts essential protein function in target protein-expressing cancer cells. HLD-0915 is the first AR-BRD4 RIPTAC that entered clinical evaluation and showed promising efficacy in AR-expressing mCRPC. To improve tumor selectivity and reduce liability in AR-negative tissues, OTR's AR-BRD4 RIPTAC molecules were designed to further enhance ternary complex formation while reducing BRD4 binding as binary complex. Compared to HLD-0915, OTR RIPTAC compounds exhibited greater potency in inhibiting BRD4 activity and proliferation in AR-positive cells, but minimal antiproliferative activity in AR-negative cells. In vivo efficacy and safety studies further demonstrated that OTR RIPTAC has superior antitumor activity in AR-positive prostate cancers, as well as reduced BRD4-related toxicity, leading to a broader therapeutic window.

No conflict of interest

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322 - PB-114 **Poster**

Intermittent BTM-3566 in advanced solid tumors: Initial safety and pharmacokinetics

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Background: BTM-3566 is an oral small-molecule activator of mitochondrial stress signaling being evaluated in a phase 1 trial in adults with advanced solid tumors (NCT07266285). We report initial safety, pharmacokinetic (PK), and preliminary antitumor activity data using an intermittent dosing schedule. Based on potential intolerable adverse events (AEs) with a 7-days-on, 7-days-off schedule in a separate study, this trial initiated BTM-3566 orally on days 1, 4, and 7 of a 14-day cycle.

Material and methods: Eligible patients had advanced solid tumors and received BTM-3566 in dose-escalation or expansion cohorts. Safety was assessed by investigator-reported AEs, dose-limiting toxicities (DLTs), and treatment status. Plasma BTM-3566 concentrations were summarized descriptively for patients with intensive cycle 1 PK sampling.

Results: At the time of submission, 7 United States solid-tumor patients had initiated BTM-3566 on the intermittent schedule at 0.9, 1.2, 1.7, or 2.2 mg/kg with a 200 mg daily dose cap. Tumor types included colorectal cancer (n = 4), and 1 each of uterine sarcoma, mucosal melanoma, and cholangiocarcinoma. No DLT was reported at data cutoff. Reported treatment-emergent AEs included grade 1 post-dose headache without intervention, grade 2 maculopapular rash improving to grade 1 with topical therapy, grade 2 exertional flushing resolving with rest, asymptomatic grade 1 creatine kinase elevation, grade 1 fatigue, nausea, diarrhea, cheilitis, and photosensitivity. Among 6 patients with available intensive PK (0.9, 1.2 [n = 3], 1.7, and 2.2 mg/kg), exposure increased from cycle 1 day 1 to day 7: day 7/day 1 Cmax ratios ranged from 1.3-2.9. Day 7 predose concentrations ranged from 1990-7190 ng/mL, and day 9 predose concentrations ranged from 2450-15600 ng/mL, indicating sustained exposure after day 7 dosing. Cycle 2 day 1 predose concentrations remained measurable at 2190-5950 ng/mL among 5 patients with available samples. No cardiac toxicity was observed, including by ECG, NT-proBNP, and high-sensitivity troponin I testing. Two patients discontinued treatment for radiographic progression. Best response to date is stable disease, and median time on therapy was 2.27 months (range, 0.23-4.4 +).

Conclusions: In this preliminary solid-tumor dataset, intermittent BTM-3566 dosing on Days 1, 4, and 7 produced sustained systemic exposure with early tolerability supportive of continued dose optimization. Interpretation is limited by small sample size, short follow-up, and limited response-evaluable patients. Updated safety, PK, and preliminary activity data will be presented.

Conflict of interest: Ownership: GJW and MS Bantam Pharmaceutical

Board of Directors: MS: Bantam Pharmaceutical

Corporate-sponsored Research: JS, IIR, GJW, and LM: Bantam Pharmaceutical

Other Substantive Relationships: GJW, LM, and MS: consulting fees from Bantam Pharmaceutical.

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323 - PB-115 **Poster**

BBIT20 enhances anti-PD-1 efficacy by reshaping the tumor immune landscape in pancreatic cancer

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Background: Pancreatic cancer (PC) is one of the most treatment-refractory malignancies, due to a highly desmoplastic and 'immune-cold' microenvironment. Deficiencies in the homologous recombination (HR) DNA damage repair pathway have been shown to improve immunotherapy efficacy in PC by enhancing tumor immunogenicity. Here, we investigated the capacity of BBIT20 – a first-in-class HR inhibitor – to potentiate anti-PD-1 therapy and remodel the tumor immune landscape in a syngeneic mouse model of pancreatic cancer.

Material and methods: Murine KPC pancreatic cancer cells were subcutaneously injected into C57BL/6J mice, which were then treated with vehicle, BBIT20 (2 mg/kg), anti-PD-1 (100 μg/animal), or both. Tumor growth was monitored weekly, and tumors and vital organs were collected at the experimental endpoint. Downstream analyses were conducted to assess the levels of key molecular markers and immune cell populations.

Results: BBIT20 alone produced a stronger antitumor effect than anti-PD-1. In combination, BBIT20 further enhanced immunotherapy efficacy. Tumors treated with BBIT20 or with the combination regimen showed significantly reduced expression of PD-L-1, VEGF, and Ki-67, along with increased BAX levels compared with the other groups. Additional analyses are underway to define immune cell infiltration and activation within the tumor.

Conclusions: BBIT20 potentiated the antitumor efficacy of anti-PD-1 in PC. The increased apoptosis and reduced PD-L1 expression observed in BBIT20-treated tumors suggest that BBIT20 enhances tumor immunogenicity, contributing to improved immunotherapy responses.

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No conflict of interest

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324 - PB-116 **Poster**

BTK and BCL2 targeting with orelabrutinib (ICP-022) and mesutoclax (ICP-248): single-agent and combination activity in marginal zone lymphoma, including drug-resistant derivatives

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Background: Marginal zone lymphoma (MZL) is an indolent B-cell neoplasm, but relapse and acquired resistance to targeted agents limit long-term disease control. Combination of BTK and BCL2 inhibitors (i) is a mechanistically rational strategy. Here, we assessed the oral and highly selective BCL2i mesutoclax (ICP-248) and the irreversible BTKi orelabrutinib (ICP-022) as single agents and in combination across MZL models, including drug-resistant derivatives.

Methods: Six MZL cell lines (Karpas1718, VL51, SSK41, ESKOL, HAIR-M, and HC-1) and resistant derivatives with acquired resistance to BTK, PI3K or BCL2 inhibitors (Karpas1718-Ide, SSK41-Copa, SSK41-Ven, and VL51-Ibru) were evaluated. Antiproliferative activity was measured by MTT (72 h), and cytotoxicity by Annexin V/PI flow cytometry (24-48 h). Compounds were provided by Innocare.

Results: The BCL2i Mesutoclax showed strong dose-dependent antiproliferative activity across MZL, with a median IC50 of 1973 nM (95% CI: 6.300-3653). Karpas1718 (IC50, 1.4 nM) and HAIR-M (101 nM) were the most sensitive models. Activity was largely maintained in derivatives resistant to BTKi, PI3Ki or BCL2i (Karpas1718-Ide: IC50 5.1 nM; SSK41-Vene: IC50 4329.5 nM; SSK41-Copa: IC50 2819.1 nM; parental SSK41: IC50 3653.3 nM). The BTKi orelabrutinib reduced viability in a dose-dependent manner in all cell lines (median IC50 3931nM; 95% CI: 585.2 – 6809 nM), with Karpas1718 and SSK41 as the most sensitive models (IC50 of 585 and 483 nM, respectively), in line with previous works from our group (Arribas et al, Biorxiv 2026) identifying them as BTKi sensitive.

Annexin V/PI analysis revealed that mesutoclax induced both apoptotic and necrotic cell death in a dose- and time-dependent manner, resulting in a progressive loss of viable cells. Necrosis was particularly evident in SSK41 and VL51 cells, whereas apoptosis was most pronounced in parental and PI3Ki-resistant SSK41 models. Orelabrutinib exerted comparatively modest effects and did not induce apoptosis in Karpas1718-Ide cells. Combined orelabrutinib–mesutoclax treatment demonstrated synergistic activity in ESKOL, HAIR-M, HC-1, SSK41, and Karpas1718-Ide cells, maintaining favorable effects in the remaining resistant models.

Conclusions. Mesutoclax displayed robust in vitro activity in MZL models, whereas the antitumor effects of orelabrutinib alone were largely confined to BTKi-dependent cell lines. Notably, concurrent BTK and BCL2 inhibition consistently outperformed single-agent treatment, producing synergistic interactions in most models and additive benefits in the remainder, including those with acquired resistance to targeted agents. These results highlight the therapeutic potential of mesutoclax and support the further clinical development of mesutoclax-based combinations, particularly alongside orelabrutinib, for the treatment of MZL.

No conflict of interest

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325 - PB-117 **Poster**

Natural extracts show anti-proliferative activity in lymphoma cells with resistance to targeted agents

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Background. Marginal zone lymphomas (MZL) are among the most common types of B-cell lymphomas. Targeted agents against BTK, BCL2, and PI3K have shown clinical activity, but primary and secondary resistance are very often observed. Since plant-derived natural products are a powerful source of potentially novel scaffolds, we assessed the antitumor activity of extracts derived from *Rosmarinus officinalis* (rosemary) and *Leontopodium alpinum* (edelweiss) in MZL models, including derivatives with secondary resistance to BTK, BCL2, and PI3K inhibition, and characterized them in terms of chemotype composition.

Material and methods. Dried biomass was obtained from certified organic cultivation in Ticino, Switzerland. Plants were harvested and dried to preserve their phytochemical profile and bioactive constituents. *R. officinalis* (R0), *L. alpinum* (LA) extracts were obtained using complementary modalities: water extraction (8h, 80°C) followed by concentration and cold ethanol precipitation (1); ultrasound-assisted heating (3h, 40°C) with ethanol (2), water/ethanol 1:1 (3), ethyl acetate (4), acetonitrile/water 8:2 (5) or acetone (6); hot ethanol extraction after sonication, followed by alkaline saponification, acidification, and n-hexane recovery of free fatty acids (7). Cell viability was assessed by exposing cells to increasing concentrations of the extracts (up to 20 µg/ml). Antioxidant potential was evaluated using 3 different assays. Selected chemotypes were assigned by LC/MS-guided isolation.

Results. Extracts derived from dried biomasses of leaves and non-lignified stem portions of *R. officinalis* and flowers, leaves, and stems of *L. alpinum* were tested for their anti-tumor activity in 3 MZL cell lines (VL51, SSK41, Karpas1718) and 4 resistant derivatives (ibrutinib and copanlisib/venetoclax VL51; venetoclax SSK41; and idelalisib Karpas1718).

We observed anti-proliferative activity with 4 extracts. LA1 showed activity, reducing cell proliferation by 40% at 5 µg/ml in the parental Karpas1718. RO5 showed up to 50% reductions across all cell lines, with stronger effects in the parental Karpas1718 (75%), where the RO4 extract was also active (70% reduction). Interestingly, RO6 caused up to 75% reduction in proliferation in the VL51 with secondary resistance to PI3Ki and BCL2i. Strong antioxidant potential was observed in three extracts (RO2, LA2, and LA3), but none reduced cell proliferation. Untargeted LC-MS profiling of RO5, RO6, and LA1 identified several metabolites with previously documented antitumor activity, including carnosol (LA1, RO5/6), luteolin (RO5), and cryptotanshinone (RO5/6).

Conclusions: Selected rosemary and edelweiss extract showed anti-proliferative activity in MZL, including BTK, BCL2-, and PI3K-inh-resistant models. As proof of principle, LC-MS identified constituents with established anti-lymphoma activity.

No conflict of interest

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326 - PB-118 **Poster**

ASP5834, a novel pan-KRAS degrader, shows potent anti-tumor activity in KRAS mutant cancer models

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Background: KRAS is one of the most common oncogenic drivers of pancreatic, lung, and colorectal cancer. Although there are approved G12C-selective inhibitors, many patients with KRAS mutations harbor non-G12C mutations, including G12D and G12V mutations. Thus, significant unmet medical need remains for patients with other KRAS mutations. Here, we report the discovery and preclinical characterization of ASP5834, a novel pan-KRAS degrader that induces robust KRAS degradation and potent anti-tumor activity in preclinical models.

Materials and methods: We assessed (1) ternary complex formation with KRAS protein and an E3 ligase using homogeneous time-resolved fluorescence (HTRF) assay, (2) degradation activity of ASP5834 on multiple KRAS mutant protein using western blotting and AlphaLISA assay, (3) inhibitory effect of ASP5834 on the growth of human cancer cells harboring KRAS mutations and KRAS wild-type, (4) PK / PD profile of ASP5834 after a single intravenous administration, (5) anti-tumor activity of ASP5834 in cell line-derived xenograft models of pancreatic, lung and colorectal cancer, and (6) combination anti-tumor activity of ASP5834 with cetuximab in a cell line-derived xenograft model of colorectal cancer.

Results: ASP5834 formed a ternary complex with multiple KRAS-mutated protein and an E3-ligase protein, degraded KRAS protein with selectivity over NRAS and HRAS, and demonstrated strong growth inhibitory activity in multiple KRAS-mutated cancer cells. ASP5834 demonstrated sustained suppression of KRAS protein levels in a xenograft tumor following single intravenous administration, and significant anti-tumor activities with once-weekly dosing in pancreatic, lung, and colorectal xenograft mouse models. In addition, combination treatment with cetuximab further enhanced anti-tumor activity in a colorectal xenograft mouse model.

Conclusions: Collectively, these non-clinical data support ASP5834 as a potential therapeutic agent for tumors harboring KRAS mutations, and a Phase I clinical trial is underway (NCT07094204).

Conflict of interest: Corporate-sponsored Research: Astellas Pharma Inc.

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327 - PB-119 **Poster**

Mechanistic perspectives and clinical translation for EP102, a METTL3 inhibitor arresting plasticity and adaptive stress responses in solid tumors

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Tumor plasticity is a major driver of disease progression and therapeutic resistance, enabling cancer cells to adapt to oncogenic, microenvironmental, and treatment-induced stress. Through dynamic state transitions, tumors acquire mesenchymal, stem-like, and therapy-tolerant phenotypes that promote survival and disease persistence. Methyltransferase-like 3 (METTL3), the catalytic component of the N6-methyladenosine (m6A) RNA methylation machinery, has emerged as a key regulator of these adaptive processes, placing the epitranscriptome at the core of cancer cell adaptability.

We performed functional and genomic analyses in human cancer cell lines, patient-derived organoids, 3D spheroid models, and cancer-associated fibroblast (CAF) co-cultures representing tumor contexts characterized by oncogenic activation, replication stress, TGF-β-rich microenvironments, and radioresistant phenotypes. EP102 demonstrated robust anti-tumor activity across pancreatic, colorectal, and lung cancer models, with enhanced efficacy in TGF-β-high settings. Mechanistically, METTL3 inhibition attenuated both canonical SMAD2/3 signaling and non-canonical TGF-β pathways linked to KRAS- and EGFR-driven adaptive responses, suppressing epithelial-to-mesenchymal transition (EMT) programs and promoting reversal of mesenchymal cell states. In CAF-rich models, EP102 maintained anti-tumor efficacy while reducing CAF migration and invasion, indicating disruption of tumor–stroma crosstalk. Importantly, radioresistant tumors, typically enriched for mesenchymal, stem-like, and TGF-β-driven features, displayed particular sensitivity to METTL3 inhibition. Initial results from the dose-escalation phase of a first-in-human trial establish safety margins and set PK/PD relationships in patients with advanced solid tumors. Collectively, these data support a new therapeutic paradigm in oncology: rather than targeting individual oncogenic pathways or static biological states, EP102 targets the epitranscriptomic machinery that enables adaptation itself, transforming cancer plasticity into a therapeutic vulnerability and positioning METTL3 inhibition as a first-in-class anti-plasticity strategy for solid tumors.

Conflict of interest: Corporate-sponsored Research: Some authors of this abstract are employees of EPICS Therapeutics

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328 - PB-120 **Poster**

Mutant p53 reactivation with MANIO drives antitumour responses in ovarian cancer

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Background: Ovarian cancer (OC) remains one of the deadliest gynaecological malignancies, accounting for more than 300,000 new cases and approximately 200,000 deaths each year worldwide. Most patients are diagnosed at advanced stages, contributing to poor clinical outcomes and a 5-year survival rate of around 40%. Mutations in TP53 are present in over 90% of high-grade serous ovarian carcinomas, resulting not only in loss of tumour suppressor activity but also in oncogenic gain-of-function effects that promote tumour progression, metastasis, and therapeutic resistance. Therefore, restoration of p53 activity has emerged as an attractive therapeutic strategy. MANIO is a novel small molecule that demonstrated to activate wild-type p53 and reactivate mutant p53 and restore its tumour suppressor function.

The aim of this study was to investigate the antitumour efficacy of MANIO in preclinical models of ovarian cancer and assess its potential in combination with standard therapies.

Material and Methods: The biological effects of MANIO were evaluated in ovarian cancer cell lines carrying distinct p53 backgrounds and in patient-derived organoids. Cell viability, cell-cycle distribution, and caspase-dependent apoptosis were assessed in vitro, while combination studies with conventional treatments were also investigated. Antitumour activity was further evaluated in mutant p53 xenograft mouse models by monitoring tumour growth and performing immunohistochemical analyses. Statistical analyses were conducted using Student's t-test or one-way ANOVA, with $p < 0.05$ considered statistically significant.

Results: MANIO selectively reduced the viability of ovarian cancer cells expressing wild-type or mutant p53, whereas p53-null cells were less responsive. Treatment induced G2/M cell-cycle arrest and significantly increased caspase-3/7 activation, confirming apoptosis induction. In patient-derived organoids, MANIO triggered a dose-dependent reduction in viability, with drug sensitivity associated with p53 status. Moreover, MANIO enhanced the activity of conventional therapies, including the PARP inhibitor olaparib. In vivo, treatment significantly delayed tumour growth without evidence of systemic toxicity. Immunohistochemical analyses demonstrated reduced tumour cell proliferation and angiogenesis, increased apoptosis, and modulation of epithelial–mesenchymal transition-related markers.

Conclusions: MANIO displays potent p53-dependent antitumour activity in ovarian cancer models and potentiates the efficacy of current therapeutic strategies, supporting its further development as a targeted treatment for TP53-mutant ovarian cancer.

Acknowledgement

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No conflict of interest

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329 - PB-121 **Poster**

Rapid discovery of selective oral CDK11 inhibitors inducing complete tumor regression in acute myeloid leukemia models using Acrivon Predictive Precision Proteomics (AP3) drug discovery platform

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Background: Cyclin-dependent kinase 11 (CDK11) serves broad, critical roles in transcriptional regulation, pre-mRNA splicing, mitotic progression, and tumor cell survival. Although elevated CDK11 protein levels have been causally implicated in various malignancies, development of selective and therapeutically viable CDK11 inhibitors has remained challenging. Here, we describe the rapid discovery and characterization of highly selective oral CDK11 inhibitors uniquely designed for optimal pathway effects using the Acrivon Predictive Precision Proteomics (AP3) platform.

Methods: The AP3 platform was integrated throughout a medicinal chemistry campaign spanning multiple chemical series to characterize global pan- and phosphoproteomic pathway responses and prioritize compounds exhibiting desirable intracellular pathway effects. Compound prioritization was supported by CDK11 biochemical inhibition, CDK7/CDK9 counter-screening, cellular target engagement (NanoBRET), and viability assays in AML and genetically defined cellular systems. Prioritized compounds were subsequently evaluated for ADME/PK properties and antitumor efficacy in an AML cell line-derived xenograft model.

Results: AP3-based indication screening identified AML among the top malignancies predicted to be sensitive to CDK11 inhibition. Evaluation of multiple CDK11 inhibitor series revealed comparable low-nanomolar biochemical potency. AP3 profiling defined a CDK11-associated pathway signature characterized by early perturbation of RNA splicing and RNA processing, followed by depletion of short-lived proteins, including MCL1, MYC, and MYB, increased TP53 protein levels, activation of DNA damage response pathways, and induction of apoptosis. Collectively, these molecular changes are consistent with coordinated disruption of RNA processing, transcriptional maintenance, and survival pathways required for AML cell viability. Integration of these mechanistic insights with cellular pharmacology, selectivity, ADME/PK, and efficacy data identified a lead series exhibiting robust pathway modulation, potent activity across multiple AML models, and favorable oral exposure. Lead compounds achieved complete tumor regression following oral administration in an AML xenograft model and were well tolerated.

Conclusion: AP3-guided drug discovery identified and prioritized selective oral CDK11 inhibitors exhibiting optimal pathway modulation and profound antitumor activity in AML models. To our knowledge, this represents the first demonstration that highly selective oral CDK11 inhibitors identified using the AP3 platform can induce complete tumor regression in aggressive AML models, supporting their clinical development as potentially first-in-class therapies for AML and other transcriptionally dependent malignancies. The Acrivon CDK11 program is advancing towards IND filing, planned for H1 2027.

Conflict of interest: Ownership: All authors were employees of Acrivon Therapeutics, Inc. or Acrivon AB at the time this work was conducted and held equity interests in Acrivon Therapeutics, Inc.

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330 - PB-122 **Poster**

IAM-K2, a Novel, Brain-penetrant KIF18A Inhibitor for Targeting Chromosomal Instability in Cancer

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Background: Chromosomal instability (CIN), a hallmark of cancer linked to poor prognosis, creates a selective dependence on mitotic control mechanisms that are required to enable accurate chromosome alignment. KIF18A, a kinesin motor protein that stabilizes chromosome positioning at the metaphase plate, is critical for this process. In CIN-high tumors, KIF18A inhibition is disruptive to chromosome alignment, causing prolonged mitotic arrest, centrosome fragmentation, micronucleation, and apoptosis, while largely sparing normal diploid cells. This selective vulnerability makes KIF18A an attractive therapeutic target in cancer.

Materials and Methods: Using Iambic's AI-driven platform, IAM-K2 was identified as a potent, selective, brain-penetrant KIF18A inhibitor with favorable ADME-PK and safety profile. Selectivity was evaluated via KINOMEscan kinase profiling. In vitro potency and on-target activity were assessed by live-cell imaging, western blot, and cell growth inhibition assays. Activity in normal hematopoietic cells was evaluated via colony formation assays in progenitor cells. Xenograft models assessed efficacy, target engagement, and brain penetrance.

Results: IAM-K2 is a novel small-molecule KIF18A inhibitor with differentiated preclinical properties relative to clinical benchmarks sovilnesib (AMG650) and VLS-1488. IAM-K2 is potent in both KIF18A ATPase biochemical and cell growth inhibition assays. The selective potency of IAM-K2 is reflected in the lack of in vitro toxicity in normal dividing cells and bone marrow hematopoietic progenitor cells. Furthermore, the anti-proliferative activity in the OVCAR-3 (CIN high) cell line is correlated with increased expression of phospho-Histone H3, a mitotic phase biomarker, and with increased arrest of cells in mitosis and followed by apoptosis, confirmed by increased Caspase-3/7 activity. There is no activity in downstream signaling in MCF-7 (low CIN) cells, indicating selective activity in cancer cells with high chromosomal instability. In vivo efficacy was

assessed in a panel of cell line-derived and patient-derived xenograft models with oral once daily dosing, resulting in deep regressions in multiple models. Pharmacodynamic biomarkers, with plasma and tumor PK indicate strong correlation between drug exposure, PD response and efficacy. Furthermore, using proprietary machine learning models, IAM-K2 was optimized for CNS penetrance and achieved deep regressions in an orthotopic brain efficacy study, indicating potential for benefit in patients with brain metastasis.

Conclusion: Together, these data indicate that targeting KIF18A with IAM-K2 is expected to provide a novel anti-cancer treatment option for patients with potential to reduce tumor burden from brain metastasis. These data support the continued development of IAM-K2 as a therapeutic strategy for CIN-high cancers.

Conflict of interest: Other Substantive Relationships: All authors are employees of Iambic Therapeutics

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331 - PB-123 **Poster**

Advancing the preclinical development of ONR-001, a first-in-class TET2 activator for the treatment of cancer

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Background: Drug-tolerant persister cells are an important source of therapeutic resistance and tumor relapse. However, this can also be leveraged to target unforeseen vulnerabilities by modulating the epigenetic state of these cells through TET2 hyperactivation, which offers a new way to limit their survival. ONR-001 is an oral small-molecule allosteric activator of TET2 that increases DNA hydroxymethylation at specific loci and impairs tumor growth. Following earlier studies, we extended the preclinical evaluation of ONR-001 to better define its antitumor activity, pharmacokinetic profile and tolerability.

Our main objective was to further characterize the activity and developability of ONR-001 by assessing its mechanistic and antitumoral effects in additional models, and evaluating pharmacokinetics and safety in rodent and non-rodent species.

Materials and methods: ONR-001 was tested in an expanded panel of human cancer cell lines using cell viability and apoptosis assays. Mechanistic studies included genome-wide analyses of DNA hydroxymethylation and gene expression, together with biochemical assessment of pathways affected by TET2 activation. In vivo efficacy was evaluated after oral dosing (50 mg/kg) in mouse xenograft models. Pharmacokinetic studies were performed in mice, rats and dogs. Tolerability was assessed after acute or repeated administration (14 days) across different doses of ONR-001: 50, 100, 300 and 1000 mg/kg, using clinical observations, body weight monitoring, clinical pathology and histopathology.

Results: ONR-001 showed antitumor activity across multiple cancer models, extending the effects in melanoma and leukemia models. Treatment increased genomic 5-hydroxymethylcytosine levels, and was associated with transcriptional changes linked to cell-cycle arrest and apoptosis. In addition to modulation of the MXD1/MYC/p21 axis, further analyses suggested that p53 signaling contributes to the cellular response induced by ONR-001

Oral administration of ONR-001 resulted in antitumor activity in vivo and produced pharmacodynamic evidence of target engagement. Pharmacokinetic studies in mice, rats and dogs showed systemic exposure after oral dosing and supported the selection of ONR-001 as the lead candidate for further development. Across the species evaluated, repeated dosing up to 1000 mg/kg was generally well tolerated, with no relevant treatment-related toxicological findings observed at the dose levels tested.

Conclusions: These expanded preclinical studies support the further development of ONR-001 as an oral TET2 activator for cancer treatment. The data indicate antitumor activity across several experimental models, oral systemic exposure and an acceptable tolerability profile in the species evaluated. Together, these findings provide a rationale for continued regulatory-enabling development and future clinical evaluation.

Conflict of interest:
Ownership: HGP, IP
Corporate-sponsored Research: DAR, LC, SF, CD, EM

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332 - PB-124 **Poster**

Discovery of RPT04402, a first-in-class molecular glue activator with potent and selective anti-tumor activity in PPP2R1A mutant cancers

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Background: Uterine cancer is the only cancer type for which survival has fallen in the past four decades. Last year, uterine cancer deaths surpassed ovarian cancer for the first time, making it the deadliest gynecological cancer. Mortality from uterine cancer is primarily due to the aggressive, high-grade subtypes of endometrial cancer. Molecularly, almost every uterine serous carcinoma tumor harbors a *TP53* mutation, and 30-40% of tumors also harbor co-occurring driver mutations to *PPP2R1A*. These heterozygous mutations occur at hotspot sites, most commonly P179R and S256F. *PPP2R1A* encodes the Aα scaffolding subunit of the heterotrimeric serine/threonine phosphatase Protein Phosphatase 2A (PP2A). The PP2A heterotrimeric complex is comprised of a catalytic (C), a scaffolding (A), and a substrate-directing regulatory (B) subunit. These scaffolding mutations cause a biased pool of PP2A heterotrimers, abrogating the formation of tumor-suppressive holoenzymes while leaving tumor-promoting heterotrimers intact. We sought to target this molecular alteration using a molecular glue to correct trimer formation to the mutant scaffold.

Methods: Using the high-resolution cryo-EM structure, we designed a small-molecule library to fit into the interface pocket between Aα/B56α/Cα subunits. We tested the effectiveness of our PP2A molecular glues by cell viability, proximity ligation assays, and mouse studies.

Results: We identified RPT04402, which increases B56α affinity for the $A\alpha^{P179R}$ and $A\alpha^{S256F}$ mutant scaffolds in both biophysical and cell-based models. In multiple CDX and PDX models of *PPP2R1A* mutant uterine cancer, RPT04402 treatment drove tumor regressions and median survival extensions. Importantly, this activity was abrogated upon knockout of B56α, demonstrating target specificity. Mechanistically, we observed cMYC protein degradation, a PP2A-B56α complex canonical substrate, and apoptosis induction upon RPT04402 treatment.

Conclusions: These data demonstrate that PP2A molecular glues are a promising novel therapy for *PPP2R1A* mutant uterine cancer

patients and represent the first small molecule approach targeting a driver of this aggressive disease.

Conflict of interest:

Ownership: GN had an equity stake in RAPPTA Therapeutics and serves as a consultant for RAPPTA.

Advisory Board: DT and CO reports receiving consulting fees from RAPPTA Therapeutics. GN has served on the SAB for Hera BioLabs.

Corporate-sponsored Research: KZ received personal fees from RAPPTA Therapeutics during the conduct of this work.

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333 - PB-125 **Poster**

Safety and Preliminary Activity of MTA-Cooperative PRMT5 Inhibitors (MTA-iPRMT5) in Patients with Advanced Solid Tumors Treated in a Phase I Clinical Trials Unit

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Introduction and Objectives: MTAP loss leads to MTA accumulation and functional dependency on PRMT5, enabling a synthetic lethality strategy with MTA-iPRMT5 inhibitors. We analyzed the safety of this therapeutic class as the primary objective, and efficacy together with the clinical and molecular characterization of the population as secondary objectives.

Materials and Methods: This was a retrospective study of patients treated with MTA-cooperative PRMT5 inhibitors in phase I clinical trials, either in dose escalation or expansion, between September 2023 and April 2026. Baseline characteristics, Royal Marsden Hospital (RMH) score, molecular profile, MTAP status by NGS, response according to RECIST 1.1, survival, and treatment-related adverse events (TRAEs) were collected. ORR was defined as CR + PR and DCR as CR + PR + SD. PFS and OS were estimated using Kaplan-Meier, and follow-up using reverse Kaplan-Meier.

Results: Nineteen patients were included, with a median age of 62 years (range, 19–72); 13 were female (68.4%) and 14 had ECOG 0 (73.7%). The most frequent tumor types were biliary tract cancer and pancreatic ductal adenocarcinoma, with 7 cases each (36.8%). Overall, 78.9% had stage IV disease at diagnosis. RMH score was 0–1 in 9/18 evaluable patients (50%) and 2–3 in 9/18 (50%); 1 patient was not evaluable due to unavailable baseline LDH. Median follow-up was 13.1 months.

TRAEs of any grade occurred in 15 patients (78.9%), and grade ≥3 TRAEs in 6 patients (31.6%). The most frequent grade ≥3 TRAE was anemia (n = 5). Neurological TRAEs included optic nerve disorder (n = 2), dizziness (n = 2), blurred vision and dysgeusia (n = 1 each); grade ≥3 events were mainly optic nerve disorder. Six patients (31.6%) required dose reduction, and no treatment-related deaths were reported.

Best response was PR in 5 patients, SD in 8, and PD in 6. ORR was 26.3% and DCR was 68.4%. Median PFS was 4.1 months and median OS was 9.9 months. The molecular profile showed a median of 5 co-mutations per patient. All patients had MTAP loss: 17 cases (89.5%) by homozygous deletion and 2 cases (10.5%) by focal homozygous loss of exons 5–8. Alterations involving the 9p21 locus predominated, with CDKN2A alteration in 100% and CDKN2B alteration in 89.5%. KRAS was altered in 12 patients (63.2%), mainly G12D (n = 5), followed by G12R/G12V (n = 2 each), and isolated cases of G12C, G13D, and G10dup.

Conclusion: MTA-iPRMT5 inhibitors showed a manageable safety profile and preliminary antitumor activity in this cohort. Anemia was the most frequent grade ≥3 hematological TRAE, while optic nerve disorder emerged as a relevant neurological toxicity that may represent a potential class-related event and warrants further characterization to confirm reversibility. Regarding the molecular profile, KRAS was the most frequent associated actionable alteration.

No conflict of interest

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334 - PB-126 **Poster**

Cohort level safety and efficacy results for [212Pb] VMT-alpha-NET in advanced somatostatin receptor subtype 2-expressing neuroendocrine tumors: Cohorts 1–3

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Background: [^{212}Pb]VMT-a-NET is an alpha-particle radiopharmaceutical targeting somatostatin receptor type 2 (SSTR2)-expressing tumors. We present safety and efficacy results from the dose-escalation phase 1/2a clinical trial (NCT05636618).

Material and methods: Eligible participants (pt) for this study must have unresectable or metastatic NETs, documented radiologic progression following at least 1 prior systemic treatment, and evidence of SSTR2 expression in ≥1 lesion confirmed on an FDA approved SSTR PET scan. During the dose finding phase, pts may receive up to 4 administrations of [^{212}Pb]VMT-a-NET at their assigned dose level, and they are monitored for dose-limiting toxicities (DLTs) for 42 days and safety throughout the study. Efficacy is evaluated by investigators according to RECIST criteria v1.1.

Results: As of 03Apr2026, 67 pts have been enrolled in the study and received at least 1 dose of [^{212}Pb]VMT-α-NET: 2 pts in dose Cohort 1 (92.5 MBq; 2.5 mCi), 46 in Cohort 2 (185 MBq; 5 mCi), and 19 in Cohort 3 (222 MBq; 6 mCi). No DLTs, Grade 4 or 5 adverse events, treatment-related discontinuations, serious renal events,

dysphagia, or clinically significant treatment-related myelosuppression have been observed.

Efficacy evaluation was previously performed and presented for cohort 1 and a subset of pts of cohort 2 (n = 23/46) who had sufficient duration of follow up (96.4 wks and 60.1 wks, respectively) and an ORR in cohort 2 of 43.4%. The presented efficacy set will include 56 pts (n = 2 in Cohorts 1, n = 46 in 2, and n = 8 in Cohort 3). Among the DLT Cohort 3, 2 pts achieved a PR after 1 and 2 cycles. Both pts in Cohort 1 continued to exhibit stable disease after 2 years of follow up.

Conclusions: Treatment with [^{212}Pb]VMT-α-NET demonstrates a favorable safety profile across all treated pts (n = 67) and shows signs of sustained efficacy at the 92.5, 185, and 222 mCi dose levels. The therapy is well tolerated with no observed dose-limiting toxicities or serious treatment-related adverse events. This study is ongoing and enrolling into Cohort 4 to test a front-loading regimen (222/185/185/148 MBq; 6/5/5/4 mCi).

Conflict of interest: Corporate-sponsored Research: Perspective Therapeutics-sponsored study investigator:

Vikas Prasad, Thorvardur Halfdanarson, Vineeth Sukrithan, Brandon Mancini, Seyed Mosallaie, Savitha Balaraman, Gregory Sibley, Jason Starr, Lowell Anthony, Chih-Yi Liao, Samuel Mehr, Jared Weiss, Robert Ramirez, Amir Iravani, Richard Wahl,

Other Substantive Relationships: Employee at Perspective Therapeutics: Lucia Baratto, Alaa Hanna, Markus Puhlmann

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335 - PB-127 **Poster**

Novel Multi-Target-Directed Ligands for Glioblastoma Combining Sigma Receptor Modulation and Proteasome Impairment

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[2] *University of Milano-Bicocca, School of Medicine and Surgery, Monza, Italy*
[3] *University of Pavia, Drug Sciences, Pavia, Italy*

Background: Glioblastoma (GBM) is the most aggressive brain tumor,with a survival of 14 months, due to therapeutic resistance and the limited efficacy of current treatments. Therefore, the identification of innovative therapeutic strategies remains urgent. Sigma receptors include two subtypes, sigma-1 (S1R) and sigma-2 receptor (S2R), both involved in cancer-related processes. S1R antagonists and S2R agonists have shown anticancer activity. In parallel, proteasome-impairing agents have demonstrated promising activity in GBM. Based on this rationale, this study aimed to develop multi-target-directed ligands (MTDLs) combining SRs modulation and proteasome impairment as innovative agents for GBM treatment.

Material and Methods: Starting from **RC-106**, which was already identified by MedChemLab and proved to be a pan-sigma modulator with promising anticancer activity, a serie of MTDLs (**15a**, **15b**, **16a** and **16b**) were synthesized by covalently linking R**C-106** with the proteasome-impairing scaffold **IP24** through PEG-based spacers of different lengths and attachment points. Compounds were evaluated in U87 cell line to assess their cytotoxic effects using the CCK-8 assay. They were subsequently tested in a 3D spheroid model to better reproduce tumor architecture and microenvironmental conditions. In 3D experiments, the ability of the compounds to inhibit spheroid formation and promote spheroid disaggregation was investigated. To further evaluate the internal structure of treated spheroids, samples were embedded in paraffin, sectioned and stained with hematoxylin and eosin to assess cell viability and density within the spheroid core.

Results: In U87 cell line, the dimers showed markedly superior antiproliferative activity compared with the parent compounds, with **16a** emerging as the most potent derivative. These findings were confirmed in the 3D spheroid assays, where the dimeric compounds displayed a stronger inhibitory effect on spheroid growth than the parent scaffolds. Compound **16a** showed a stronger inhibitory effect than compound **RC-106**, with significant growth inhibition observed at an earlier time point. Histological analysis of treated spheroids further supported the biological activity of the most effective compounds, showing reduced cellular density and altered spheroid organization.

Conclusion: This study demonstrates that the rational covalent linking of the pan-SR modulator **RC-106** and the proteasome-impairing scaffold **IP24** into non-cleavable dimeric MTDLs provides compounds with superior antiproliferative activity in GBM models compared with the individual parent scaffolds. Among the synthesized derivatives, compound **16a** showed the most promising profile in both 2D and 3D models. Further studies will be required to clarify the mechanism of action, optimize the pharmacological profile and assess the translational potential of this strategy for GBM therapy.

No conflict of interest

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Poster Session: Novel clinical trial design

337 - PB-129 **Poster**

Bayesian benefit-risk dose optimisation of BAL0891, a first-in-class TTK/PLK1 inhibitor, plus paclitaxel: recommended phase 2 dose selection in metastatic urothelial carcinoma (TTK-CS-101)

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Background: BAL0891 is a first-in-class dual TTK/PLK1 inhibitor that promotes mitotic catastrophe; its combination with paclitaxel is mechanistically rational in chromosomally unstable urothelial carcinoma. For targeted-agent combinations the maximum tolerated dose (MTD) may not define the optimal phase 2 regimen. Consistent with project-Optimus principles, we applied a prespecified Bayesian benefit-risk framework to select the recommended phase 2 dose (RP2D) of BAL0891 plus paclitaxel for a metastatic urothelial carcinoma (mUC) expansion.

Material and methods: Substudy 3 of TTK-CS-101 (NCT05768932; sponsor SillaJen, Inc.) evaluated BAL0891 40–240 mg IV on days 1 and 15 plus paclitaxel 60 or 80 mg/m2 IV on days 1, 8 and 15 every 28 days in advanced solid tumours (16 treated; +3 preliminary backfill for sensitivity; data cut-off 01 Jun 2026). Dose-limiting toxicity (DLT)/overdose control used a 2-parameter Bayesian logistic regression model with EWOC threshold 0.25 and prespecified priors alpha~N(-1.099,4.453) and log(beta)~N(-0.267,0.433). Efficacy (objective response [ORR], disease control [DCR], tumour shrinkage > = 15%) used Bayesian logistic models

with neutral Beta(1,1) priors. Posterior medians and threshold probabilities were integrated into a weighted benefit-risk utility (efficacy 0.30; grade 4 neutropenia 0.25; duration and therapeutic G-CSF 0.10; delivery, dose modification and PK target-attainment 0.05); robustness was tested across exposure anchors, priors, weights and backfill.

Results: No protocol-defined DLT occurred at any dose and the MTD was not reached. Objective responses were observed at BAL0891 40, 80 and 160 mg but not at 200 or 240 mg, and exposure-efficacy modelling was flat (posterior P[slope > 0] 0.13–0.33), whereas grade 4 neutropenia and therapeutic G-CSF need rose with dose. Escalation above 80 mg did not improve utility under any paclitaxel scenario (P[lower dose better] ~1.00); BAL0891 80 mg + paclitaxel 80 mg/m2 ranked first across all sensitivity analyses.

Metric	BAL240/PTX60 (highest dose, n = 3)	BAL80/PTX80 (RP2D, n = 4)
ORR	0/2 (0%)	1/3 (33%)
DCR	2/2 (100%)	3/3 (100%)
Best % change, median	-5	-23
Tx duration, median wk	15.1	38.6
Grade 4 neutropenia (C1)	3/3	1/4
Utility rank	5	1

Conclusions: The prespecified Bayesian benefit-risk analysis selected BAL0891 80 mg + paclitaxel 80 mg/m2 as the RP2D — below the highest tested dose. This regimen preserved clinically relevant antitumour activity and treatment duration while reducing high-grade neutropenia burden, and advances to a phase 1b, open-label, single-arm mUC expansion (2nd–4th line, prior anti-PD-1/PD-L1; BAL0891 80 mg IV days 1,15 + paclitaxel 80 mg/m2 IV days 1,8,15 every 28 days; primary endpoint confirmed ORR by RECIST 1.1; Simon two-stage, ~29 efficacy-evaluable). Trial status: Substudy 3 complete; phase 1b in setup.

Conflict of interest: Ownership: J. Kim: founder and shareholder of Zarathu Co., Ltd. S. Han (Chief Executive Officer): shareholder of Aims Bioscience Co., Ltd.

Board of Directors: S. Han (Chief Executive Officer): Aims Bioscience Co., Ltd. J. Kim: Zarathu Co., Ltd. (founder/CEO)

Corporate-sponsored Research: Aims Bioscience Co., Ltd. (S. Han, S. Han) received research funding from SillaJen, Inc. to perform the pharmacokinetic analysis for this study. Zarathu Co., Ltd. (J. Kim) received research funding from SillaJen, Inc. to perform the statistical analysis for this study.

Other Substantive Relationships: S. Ma, S. Lee, J. Kang and H.J. Kim are employees of SillaJen, Inc., the study sponsor and developer of BAL0891. S. Han (Clinical Pharmacology) is an employee of Aims Bioscience Co., Ltd.

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338 - PB-130 **Poster**

A First-in-Human Phase 1/2 Study of SAR449336, an Oral Non-Covalent Pan-KRAS Inhibitor, in Patients With Advanced KRAS-Mutant Solid Tumors (Trial in Progress)

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Background: KRAS mutations are key oncogenic drivers in multiple solid tumors, including pancreatic ductal adenocarcinoma (PDAC), non-small cell lung cancer (NSCLC), and colorectal cancer (CRC). The effectiveness of KRAS G12C inhibitors and the multi-RAS inhibitor, daraxonrasib, has validated KRAS as a therapeutic target in these diseases. However, KRAS G12C inhibitors do not address other KRAS mutant alleles, and off-target inhibition of HRAS and NRAS by multi-RAS inhibitors may lead to toxicity and limit achievable drug exposure. SAR449336 (SAR'336) is an oral pan-KRAS inhibitor designed to inhibit multiple mutant KRAS proteins while sparing HRAS and NRAS. SAR'336 is chemically distinct from other pan-KRAS inhibitors, with preclinical studies predicting best-in-class pharmacokinetic properties. SAR'336 has also demonstrated *in vivo* efficacy in multiple KRAS-mutant xenograft models.

Material and methods: Here, we describe a multicenter, international, phase 1/2, open-label, first-in-human trial of oral SAR'336 in adults with metastatic *KRAS*-mutant PDAC, NSCLC, or CRC (NCT07629960). The trial initially evaluates monotherapy dose-escalation cohorts following a modified Bayesian optimal interval design to identify the maximum tolerated dose and/or recommended dose(s) for further evaluation of PK, safety and efficacy in indication-specific expansion cohorts (PDAC, NSCLC, or CRC). Eligible patients (≥18 years) must have metastatic disease, evidence of a *KRAS G12C*, *G12D*, *G12V*, *G12A*, *G12S*, or *G13D* mutation in tumors or in circulating tumor DNA, measurable disease per the Response Evaluation Criteria in Solid Tumors v1.1, and an Eastern Cooperative Oncology Group Performance Status of ≤1. Key exclusion criteria include prior exposure to (K)RAS-targeted therapy and the presence of additional known oncogenic driver mutations.

Results: Key objectives are to determine the optimal dose and assess the safety, tolerability, PK, and antitumor activity of SAR'336. Findings will also inform future cohorts planned to investigate combination therapy.

Conclusions: The monotherapy part of the study is currently enrolling.

Conflict of interest: Ownership:

David Hong: Stock and other ownership Interests - crossbridge Bio, MolecularMatch, OncoResponse, Telperian.

Advisory Board:

Alex Spira: Consulting fees from/advisory role with Amgen, ArriVent Biopharma, AstraZeneca/MedImmune, Black Diamond Therapeutics, Blueprint Medicines, a wholly owned subsidiary of Sanofi, Bristol Myers Squibb, CRISPR Therapeutics, Daiichi Sankyo/AstraZeneca, Gritstone Bio/Oncology, GSK, Incyte, Janssen Research & Development, Jazz Pharmaceuticals, Lilly, Merck, Mersana, Mirati Therapeutics, Novartis, Regeneron, Revolution Medicines, Sanofi, Synthekine, and Takeda.

Corporate-sponsored Research:

Alex Spira: Research funding from AbbVie, ADCT, Alkermes, Amgen, ArriVent Biopharma, Astex Pharmaceuticals, Astellas Pharma, AstraZeneca, Black Diamond Therapeutics, Blueprint Medicines, a wholly owned subsidiary of Sanofi, Boehringer Ingelheim, Bristol-Myers Squibb, CytomX Therapeutics, Daiichi Sankyo, Gritstone Bio/Oncology, Ignyta, Incyte, Janssen Oncology, LAM Therapeutics, Lepu Biopharma, Lilly, Loxo, MacroGenics, Medikine, MedImmune, Mersana, Nalo Therapeutics, Novartis, Plexxikon,

Prelude Therapeutics, Regeneron, Revolution Medicines, Roche, Rubius, Scorpion Therapeutics, Synthekine, Takeda, and Tango Therapeutics.

Other Substantive Relationships:

Alex Spira is the CEO of Next Oncology; Honoraria from AbbVie, Amgen, AstraZeneca/MedImmune, Astellas Pharma, Bayer, Bristol-Myers Squibb, CytomX Therapeutics, Janssen Oncology, Lilly, Merck, Novartis, Prelude Therapeutics, and Takeda.

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339 - PB-131 **Poster**

Digital Remote Patient Monitoring in Early-Phase Oncology Clinical Trials: A Prospective Pilot Study of Feasibility and Implementation

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Background: Phase I clinical trials are crucial for evaluating the safety and determining the recommended phase II dose of new cancer therapies. In early-stage trials, understanding the toxicity and tolerability of treatments is essential. Traditionally, toxicity data have been gathered primarily through clinician assessments, which may not fully capture the patients' subjective experience of adverse events (AE). This can lead to underreporting of symptoms and a limited understanding of the real-world impact on patients' quality of life (QoL). The Resilience digital platform aims to address this gap by enabling patients to directly report their symptoms, facilitating real-time monitoring. The platform (CE-marked Class IIa medical device) uses the PRO-CTCAE framework to gather patient-reported outcomes (PROs). It offers features such as weekly symptom surveys, alerts for severe or worsening symptoms, and personalized self-management advice. By integrating these components, Resilience facilitates early AE detection and supports patient-centred toxicity management. This study aims to evaluate the feasibility, usability, and implementation of Resilience in patients enrolled in early-phase oncology clinical trials at Vall d'Hebron University Hospital (VHUH).

Methods: This is a prospective, single-centre, observational study planned to enroll 152 patients with cancer participating in Phase I clinical trials at VHUH in Barcelona. Elegibility criteria include a confirmed cancer diagnosis, age ≥ 18 years, and the ability to provide informed consent. The study will use Resilience to collect PROs using the PRO-CTCAE framework. Patients will receive weekly notifications to complete symptom surveys via the mobile app or SMS. Severe or worsening symptoms trigger automated alerts to the oncology care team and tailored self-management recommendations. The primary objective is to assess adherence to remote symptom-monitoring surveys. Secondary objectives include evaluation of platform usability, patient and healthcare professional satisfaction, and implementation outcomes including patient retention, alert rates, response times, and workflow integration. Exploratory objectives include assessment of QoL, characterization of symptom burden through PRO-CTCAE, comparison of patient-reported and clinician-reported AE, and evaluation of the influence of social and behavioral determinants of health. Statistical analyses will include descriptive and inferential methods.

Results: The study is ongoing at VHUH. Ethics committee approval has been obtained and patient recruitment has started. Recruitment progress and implementation status will be presented at the meeting.

Conclusions: This study will provide evidence on the feasibility of PRO-based remote monitoring in early-phase oncology trials in Spain and support patient-centred care in early drug development.

Conflict of interest:

Ownership:

Elena Garralda: 1TRIALSP, (stocks)

Victoria Sanchez Perez: Gilead (stocks)

Advisory Board:

Elena Garralda: Abbvie, Alentis Therapeutics, Amgen, Anaveon, Astex Therapeutics, Boehringer Ingelheim, Daiichii Sankyo, Ellipses Pharma, Genentech, GenMab, Gilead, GreyWolf, Incyte, Janssen Global Services, Marengo Therapeutics, Medpace, Pfizer, Pyramid Biosciences, Roche, Sanofi, Seattle Genetics, Skypta, Sotio, Takeda Pharmaceuticals.

Alberto Hernando Calvo: Slingshot Insights

Maria Vieito: BMS

Irene Braña: Achilles Therapeutics, Bicara Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, eTheRNA Immunotherapies, Gilead Sciences, Guidepoint, Merck Sharp & Dohme/MSD, Merus, PCI Biotech, Pyxis, Rakuten Pharma.

Guillermo Villacampa: Astrazeneca

Corporate-sponsored Research:

Hernando Calvo: Gilead

Maria Vieito: AstraZeneca, BeiGene, C4 Therapeutics, Novartis, Roche, Taiho Oncology, and Thermo Fisher Scientific

Other Substantive Relationships:

Francesco Bruzzone: Boehringer Ingelheim - Travel Grant.

Ana Matres: Roche Travel and accommodation expenses, Boehringer Ingelheim invited speaker.

Giulia Pretelli: Pierre Fabre and Roche, Travel and accommodation expenses.

Elena Garralda: NEXT Oncology, Full or part-time Employment. Lilly, Expert Testimony. Invited Speaker: AEFI, Alcura, Aran, AstraZeneca, CDDF, COR2ED, Doctaforum, Elservier Ltd, ESMO, ESO (European School of Oncology), Fundación ECO, Fundación SEOM, Horizon CME, Karger, Medscape, MeetingPharma, MSD, MSKCC, Novartis, PPD, Roche, SeaGen, Springer Nature, Swiss cancer Research Foundation, Tactics, The Ricky Rubio Fundation.

Maria Vieito: BMS, Debiopharm Group, HutchMed, Incyte, Mundipharma, Novartis, PharmaMar, Roche, Servier, and Taiho Oncology, Novocure (Speakers Bureau).

Victoria Sanchez Perez: Clinical Trials (Institutional): Adaptimmune LLC, Affimed Gmbh, Amgen SA, Anaveon AG, AstraZeneca AB, Bicycletx Ltd, BioInvent International AB, Biontech SE, Biontech Small Molecules Gmbh, Boehringer Ingelhem International Gmbh, Catalym Gmbh, Cyclacel Biopharmaceuticals, Cytovation AS, Cytomx, F.Hoffmann La Roche Ltd, F-Star Beta Limited, Genentech Inc, Genmab B.V., Hifibio Therapeutics, Hutchison Medipharma Limited, Icon, Imcheck Therapeutics, Immunocore Ltd, Incyte Corporation, Incyte, Europe Sàrl, Janssen-Cilag International NV, Janssen-Cilag SA, Laboratorios Servier SL, Medimmune Llc, Merck & Co, Inc, Merck Kgga, Novartis Farmacéutica, S.A, Peptomyc, Pfizer Slu, Relay Therapeutics, Replimmune, Ribon Therapeutics, Ryvu Therapeutics SA, Seattle Genetics Inc, Sotio as, Sqz Biotechnologies, Symphogen A/S, Taiho Pharma Usa Inc, T-Knife Gmbh, BioNTech. Boehringer Ingelheim Principal Investigator, DUKE Street BIO Principal Investigator, Eikon Therapeutics Principal nvestigator

GSK Principal Investigator British Medical Association Member, Medical Defence Union Member SEOM Member.

Irene Braña: Local PI: Adlay/Nortye, AOP Pharma, AstraZeneca, Aveo Pharmaceuticals, Bayer, Bicara Therapeutics, Bicycle Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Debiopharm, Dragonfly Therapeutics, Gilead, GlaxoSmithKline, Gliknik, Immutep, Incyte, ISA Pharmaceuticals, ISA Therapeutics, Janssen Oncology, Kura, MacroGenics, Merck Serono, Merck Sharp & Dohme/MSD, Merus, Nanobiotix, Northern Biologics, Novartis, Odonate Therapeutics, Pfizer, Pharmamar, Regeneron, Roche, Sanofi, Seattle Genetics, Servier, Shattuck Labs, Tango Therapeutics, VCN Biosciences. Invited speaker: Bristol Myers Squibb, Merck Serono, Merck Sharp & Dohme/MSD, Roche. Expert testimony: Cancer Expert Now, Merck Serono. Others: Cancer Core Europe, Principal Investigator "Basket of Baskets", ASCO member

EORTC Head and Neck Group member, SEOM member.

Guillermo Villacampa: Reveal Genomics.

Alexandre Yazigi: FTE Resilience Care.

Arnaud Ollier: FTE Resilience Care.

Charles Ferté: FTE Resilience Care.

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Poster Session: Preclinical Models

340 - PB-132 **Poster**

Radiobiological Impact of Ultrashort Pulsed Electron Beams in 3D Glioblastoma Models

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Background: Although radiobiological research is progressively moving toward more physiologically relevant 3D models, the biological effects of emerging irradiation modalities such as ultrashort pulsed electron beams (UPEB), proposed as alternatives to conventional radiation sources, remain insufficiently characterized in 3D systems. This is particularly important for glioblastoma, a highly aggressive and radioresistant brain tumor characterized by pronounced intratumoral heterogeneity and hypoxic regions that significantly influence treatment response. The aim of this study was to investigate DNA damage, oxidative stress, and cell survival in 2D and 3D glioblastoma models following UPEB irradiation.

Materials and Methods: Rat glioblastoma F98 cells were cultured under standard conditions in both 2D monolayers and 3D spheroid models. Cells were irradiated with X-rays (MultiRad 350 kV system, Precision) and UPEB (AREAL linear accelerator, CANDLE SRI, 3.6 MeV, 0.45 ps, UHPDR 1010 Gy/s) at doses of 1, 2, and 4 Gy. Post-irradiation analyses, including comet assay, γH2AX immunostaining, DCFDA-based two-photon microscopy, and clonogenic assay, were performed at 4 h, 24 h, 48 h, and 14 days.

Results: Both X-ray and UPEB irradiation induced dose-dependent DNA damage and decreased clonogenic survival in F98 glioblastoma cells, while 3D spheroids exhibited greater radioresistance compared with 2D cultures. At equivalent doses, UPEB produced a more pronounced reduction in clonogenic survival than conventional X-rays. γH2AX immunofluorescence analysis revealed heterogeneous spatial distribution of DNA double-strand breaks within 3D spheroids, with preferential accumulation in central regions following UPEB exposure, suggesting enhanced damage in hypoxic tumor areas. In contrast, X-ray-induced DNA damage displayed a more diffuse distribution with relative predominance in peripheral spheroid regions. ROS levels increased in irradiated 2D cultures following both irradiation modalities, whereas no substantial ROS elevation was detected in 3D spheroids across the investigated doses and time points.

Conclusions: UPEB showed higher biological effectiveness than conventional X-rays in F98 glioblastoma models. In 3D spheroids, UPEB caused pronounced DNA damage in hypoxic core regions, which are typically more radioresistant, suggesting potential effectiveness against resistant tumor cell populations. The lack of a corresponding ROS increase indicates that UPEB-induced effects may involve ROS-independent mechanisms. Collectively, these findings support the use of physiologically relevant 3D tumor models for assessing novel irradiation modalities, as they more faithfully reflect hypoxia-associated radioresistance and intratumoral heterogeneity influencing therapeutic response.

No conflict of interest

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341 - PB-133 **Poster**

A novel ex vivo bone metastasis culture platform for triple-negative breast cancer

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Background: Drug development for bone metastasis has been hindered by the lack of appropriate in vitro models in early testing. In such models, it would be important to include the whole bone microenvironment with bone matrix, bone and tumor cells. We have established a novel bone metastasis ex vivo culture platform that utilizes bone discs from tibiae of mice with triple-negative breast cancer (TNBC) tumors.

Material and methods: Female Balb/c mice were injected intratibially with 10,000 (10k) or 20,000 (20k) 4T1 mouse TNBC cells or PBS (control). Tumor-induced bone changes were monitored by X-ray imaging. 4T1 tumor and control bones were collected and cut into 2-3 mm thick discs, rinsed with antibiotic-containing medium, and cultured in basal medium (RPMI-1640 medium supplemented with 10% FBS) in a humidified incubator. Osteoblastic medium included ascorbic acid and beta-glycerophosphate, and osteoclastic medium included M-CSF and RANKL supplements. Culture lengths from 7-21 days were tested and analyzed for cell viability (trypan blue), proliferation (CCK-8 assay), bone resorption (Tartrate-Resistant Acid Phosphatase 5b, TRACP5b ELISA) and bone formation (Procollagen I N-terminal Propeptide, PINP EIA).

Results: Intratibial inoculation of 10k and 20k 4T1 cells induced progressive osteolytic lesions that were monitored for 13 days by X-ray imaging. Based on the extent of osteolytic lesions, days 3-5 were selected to model early bone metastasis growth with visible tumor-induced effects on bone. 20k 4T1 cells were selected for future studies due to more uniform tumor growth. In ex vivo cultures of tibia bone discs in basic medium, cell viability remained high at days 7 and 10 (88 and 91%, respectively) but dropped to 47% at day 14. Therefore, 10 days was considered maximum culture length. In discs with 4T1 tumors, cell doubling time was higher than in control discs. Discs with 4T1 tumors had higher baseline PINP and TRACP5b levels than control discs, and the values were further increased with

osteoclastic and both osteoclastic and osteoblastic supplements. Addition of osteoblastic or osteoclastic supplement to control discs increased PINP and TRACP5b levels more than in discs with 4T1 tumors.

Conclusions: We have established a novel ex vivo bone metastasis culture platform where cancer cell, osteoclast and osteoblast activities were maintained after in vivo extraction of bone discs. This indicates that the ex vivo cultures are able to maintain in vivo properties of the tumor and its bone microenvironment at least for a short period of time.

No conflict of interest

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342 - PB-134 **Poster**

Stiffness, stress, and stroma: patient-specific 3D spheroid models reveal biomechanical and cellular determinants of pancreatic cancer progression

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Background: Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy characterized by a poor prognosis, development of therapy resistance, and a dense, desmoplastic stroma produced by activated stromal cells. Extracellular matrix (ECM) production depends heavily on endoplasmic reticulum (ER)-driven proteosynthesis and the molecular response to ER stress via the unfolded protein response. This study aimed to investigate how patient-derived stromal cells interact with cancer cells, and how ER stress dynamics collectively influence 3D spheroid organization, morphology, and biomechanical variations to better recapitulate clinical PDAC heterogeneity.

Material and Methods: Tumor stromal cells (SCs) were isolated from resected human PDAC tumors, cryoarchived, and annotated with detailed clinical information. Homotypic and heterotypic 3D spheroids were generated in 2% agarose multi-well molds by combining these SCs at varying ratios with three distinct human PDAC cell lines Capan-2 (epithelial-like), and PANC-1 or MIA PaCa-2 (mesenchymal-like), while keeping total initial cell numbers constant. Spheroid area, circularity, collagen matrix invasion, and mechanical stiffness were determined using a multi-method pipeline including 3D cell culture kinetics, collagen invasion assays, high-resolution immunofluorescence microscopy, and atomic force microscopy.

Results: We show that patient-derived PDAC SCs form reproducible 3D homotypic and heterotypic spheroids, enabling the assessment of patient-specific effects on tumor architecture and biomechanical remodeling. Stromal–cancer cell interactions, ECM production, and donor-specific modulation of ER-stress signaling altered spheroid stiffness, composition, and invasive capacity within a collagen matrix. Importantly, stromal cells from different patient donors exhibited distinct interactions with cancer cells, resulting in variable effects on spheroid organization, matrix remodeling, and invasion.

Conclusions: Here we demonstrate that 3D heterotypic spheroid model successfully recapitulates cancer-stromal organization, biomechanical properties, and patient-derived stromal diversity in PDAC. This platform provides a physiologically relevant tool for studying complex tumor microenvironment dynamics, elucidating ER-stress machinery, and eventually screening stroma-targeted therapeutic strategies.

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No conflict of interest

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343 - PB-135 **Poster**

End-to-end in vitro and in vivo evaluation of radiopharmaceuticals in patient-derived models

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Background: Targeted radionuclide therapy using alpha and beta emitting agents offers a precision approach to cancer treatments, resulting in improved outcomes while minimising systemic toxicity. The development and clinical translation of novel radiopharmaceuticals depend on the integration of robust *in vitro* and *in vivo* assays throughout the drug discovery process, critical for assessing target specificity, pharmacokinetics, biodistribution and therapeutic index. Cell lines and cell line-derived xenograft (CDX) models provide fast and cost-effective means to assess drug effects, whereas patient-derived (xenograft) organoid (PD(X)O) and patient-derived xenograft (PDX) models preserve tumour genomic and gene expression profiles, heterogeneity, architecture, and enable more clinically predictive assessment of therapeutic efficacy across diverse patient populations.

In this study, the theranostic pairing of [^{68}Ga]Ga-PSMA-617 and [^{177}Lu]Lu-PSMA-617 were prepared and tested in 2D and 3D in vitro assays using CDX and PDXO, followed by *in vivo* testing in a PDX model to evaluate target expression, therapeutic efficacy, and translational relevance across heterogeneous PSMA expression profiles.

Material and Methods: PSMA-617 was radiolabelled with ^{68}Ga and ^{177}Lu using standard manual procedures. Radiochemical purity (RCP) was confirmed by RP-HPLC and TLC analysis. Viability was measured on prostate cancer cell lines and an organoid model with differential PSMA expression levels upon treatment with [^{177}Lu]Lu-

PSMA-617. DNA damage was assessed by immunofluorescence to evaluate radiobiological effects.

A prostate PDX mouse model was imaged with [^{68}Ga]Ga-PSMA-617 PET to assess target density and heterogeneity prior to therapy and monitor treatment response.

To assess anti-tumour efficacy, a prostate PDX model received a single dose of 50 MBq [^{177}Lu]Lu-PSMA-617. Subcutaneous tumour growth and body weights were monitored over time.

Results: Radiolabelling of PSMA-617 with ^{68}Ga and ^{177}Lu yielded products with an RCP ≥ 95%, as determined by HPLC analysis, with no further purification. The specific activities of [^{68}Ga]Ga-PSMA-617 and [^{177}Lu]Lu-PSMA-617 were 10 and 17.5 MBq/nmol, respectively.

In vitro prostate cancer models displayed distinct responses to [^{177}Lu]Lu-PSMA-617 treatment, and these were consistent with varying PSMA expression levels. Diagnostic PET imaging was used to image tumours in an *in vivo* prostate PDX model, and treatment of this model with [^{177}Lu]Lu-PSMA-617 resulted in tumour regression.

Conclusions: Our results highlight the feasibility of integrating radiochemistry expertise with clinically relevant patient-derived models to thoroughly characterize novel radiopharmaceuticals. This holistic approach enhances the predictive accuracy of preclinical studies and ensures that emerging therapeutic strategies are closely aligned with clinical demand.

No conflict of interest

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344 - PB-136 **Poster**

Validation framework for patient-derived 3D bioprinted tumour models for preclinical evaluation of anti-cancer therapies

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Background: Predictive preclinical models must combine biological relevance, reproducibility, and scalability to improve oncology drug development. Patient-derived three-dimensional (3D) tumour models preserve tumour complexity while generating reproducible functional drug-response data. We developed a validation framework to evaluate a patient-derived bioprinted tumour model from analytical performance through biological, functional, and translational validation.

Materials and Methods: Fresh ovarian tumour specimens were dissociated, characterised, and bioprinted into biomimetic 3D hydrogel constructs within 24 hours of surgical resection. Validation comprised four stages: (i) analytical validation through assessment of assay reproducibility; (ii) biological validation by characterising tumour epithelial, stromal, and tumour-resident immune populations; (iii) functional validation by evaluating responses to standard-of-care chemotherapies and targeted therapies across conventional 2D culture, 3D tumour cell line models, cancer-associated fibroblast (CAF) co-culture models, and patient-derived 3D bioprinted tumours; and (iv) translational validation by assessing concordance between functional drug responses in patient-derived bioprinted tumours and tumour molecular characteristics, including homologous recombination deficiency (HRD) status.

Results: Bioprinted tumour constructs demonstrated highly reproducible viability readouts (< 10% coefficient of variation), providing a robust foundation for drug-response studies. Constructs preserved key tumour epithelial and stromal populations, while emerging analyses support persistence of tumour-resident immune populations. Matched 2D and 3D models demonstrated differential responses to standard-of-care chemotherapies and targeted therapies, demonstrating the importance of the tumour microenvironment in therapeutic sensitivity. Incorporation of CAFs further modified drug sensitivity, underscoring the contribution of stromal interactions to treatment response. Patient-derived tumours demonstrated heterogeneous responses to standard-of-care chemotherapy and targeted therapies, reflecting inter-patient biological diversity. Translational validation assessed concordance between ex vivo drug response and tumour HRD status, providing an independent molecular benchmark for validation of patient-derived functional drug testing.

Conclusions: This work establishes a structured validation framework for patient-derived 3D bioprinted tumour models, providing a systematic approach for developing robust, human-relevant preclinical assays capable of generating reproducible functional drug-response data. By demonstrating analytical robustness, biological fidelity, functional relevance, and translational validation, this framework supports the use of patient-derived 3D bioprinted tumour models in preclinical therapeutic evaluation.

No conflict of interest

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345 - PB-137 **Poster**

Benchmarking Multiple Comparison Procedures for Patient-Derived Xenograft Tumor-Volume Studies: Toward Statistically Justified and Ethically Grounded Study Design

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Background: Patient-derived xenograft (PDX) efficacy studies commonly compare several treatment arms using small cohorts, such as mouse clinical trials, but the post-hoc tests used for tumor-volume endpoints are often chosen from software defaults. Because PDX studies typically have 3-10 mice per arm, skewed tumor-volume distributions, and repeated measurements that are frequently reduced to a single endpoint, the operating characteristics of common multiple comparison procedures (MCPs) remain uncertain. The objective of this study was to retrospectively analyze large data sets to determine which MCP can overcome these barriers and maximize statistical application for PDX studies.

Materials and Method: We benchmarked 15 all-pairwise MCPs, 8 many-to-one MCPs, and a longitudinal linear mixed model (LMM) using 4,123 Crown Bioscience PDX subcutaneous efficacy experiments over 10 year period comprising 124,035 animal-day tumor-volume records across more than 200 models. Endpoint analyses used raw tumor volume on the last common study day, with empirical power stratified by effect size (Hedges' g) to generate power curves suitable for prospective sample size planning. Type I error was evaluated from 3,000 simulation replicates l across designs spanning 3-7 arms and 3-10 mice per arm under normal and lognormal null distributions. We also compared raw versus log(TV + 1) tumor volume and all-pairwise versus vehicle-to-treatment testing.

Results: PDX designs were small: 30.6% of experiments had a mean group size of <= 4 mice. Fisher's LSD, Duncan's test, and Student-Newman-Keuls (SNK) failed to control false positives, with mean type I error of 12.2%, 11.4%, and 10.0%, respectively under the normal null, increasing with arm count. Tukey's HSD remained calibrated (mean type I error 3.8%) and had the highest empirical power among calibrated all-pairwise tests, reaching 11.6% at g 0.8-

1.2, 62.2% at g 1.2-2, and 90.0% at g 2-3. Conover's test was the strongest non-parametric all-pairwise option. For vehicle-versus-treatment designs, Dunnett's test outperformed all-pairwise approaches, reaching 21.7% power at g 0.8-1.2. Raw tumor volume gave higher power than log(TV + 1) for all parametric MCPs. The LMM, which used the full longitudinal record, showed substantially higher empirical power, although its null-distribution behavior was not simulated and warrants further evaluation.

Conclusions: Common software-default tests such as Fisher's LSD, Duncan, and SNK can materially inflate false-positive findings in PDX studies and should be removed from PDX analysis plans. Tukey's HSD is a practical default for all-pairwise endpoint comparisons, Dunnett's test is preferred for vehicle-versus-treatment designs, and longitudinal LMMs should be considered when complete tumor-growth trajectories and model diagnostics are available.

No conflict of interest

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346 - PB-138 **Poster**

PDX-Derived Organoids Demonstrate High Concordance with In Vivo Responses Across KRAS Inhibitors and Antibody-Drug Conjugates

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Background: Patient-derived organoids have demonstrated substantial translational value in reflecting clinical responses to chemotherapy and several targeted therapies. However, for emerging therapeutic modalities such as KRAS inhibitors and antibody-drug conjugates (ADCs), evidence supporting their translational relevance remains limited. To address this gap, we systematically evaluated drug response concordance between paired PDX-derived organoids (PDXOs) and patient-derived xenograft (PDX) models across multiple KRAS inhibitors and ADCs.

Materials and Method: Matched PDXO and PDX efficacy data were compared at the model-drug level. PDXO responses were classified as sensitive or non-sensitive based on IC50 and maximum inhibition, using thresholds of 1 μM for KRAS inhibitors, 0.1 μM for ADCs, and 50% for maximum inhibition. PDX responses were classified as sensitive or non-sensitive based on tumor growth inhibition (TGI), with TGI >= 0.7 defined as sensitive. Where multiple experiments existed for a given model-drug pair, response classification was determined by majority vote. Concordance was assessed using accuracy, sensitivity, and specificity overall and by cancer type, and drug ADC analyses were further stratified according to linker characteristics: five protease-cleavable peptide-linker ADCs and three ADCs with less stable linker systems.

Results: For KRAS inhibitors, concordance across 42 paired model-drug observations reached 76.2% accuracy, 75.0% sensitivity and 78.6% specificity. Accuracy ranged from 71.4% in pancreatic cancer to 80.0% in colorectal cancer and from 66.7% for adagrasib to 85.7% for MRTX1133.

Among 5 ADCs containing protease-cleavable peptide linkers, 46 paired observations achieved 76.1% accuracy, 66.7% sensitivity and 93.8% specificity. Lung cancer showed 100% accuracy (n = 7), whereas breast cancer showed 52.9% (n = 17). Drug-specific accuracy ranged from 66.7% for trastuzumab deruxtecan (n = 24) to 100% for BAT8006 (n = 4).

In contrast, 3 ADCs with less stable linker systems demonstrated substantially weaker concordance, with 40.0% accuracy, 92.3% sensitivity and 0% specificity across 30 pairs.

Conclusions: PDXO drug response showed substantial concordance with their paired PDX models for KRAS inhibitors and selected ADCs, although performance varied across drugs and cancer types. The high sensitivity but absent specificity observed for unstable ADCs suggests that non-specific payload release in culture may inflate apparent PDXO sensitivity. Lower concordance in breast cancer underscores the need to faithfully recapitulate organ-specific disease biology, including hormonal carcinogenesis, to maximize translational relevance. Overall, these results further support the strong translational value of organoid models and highlight the importance of drug properties and disease biology in determining predictive performance.

No conflict of interest

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347 - PB-139 **Poster**

Bone-Derived Extracellular Matrices Modulate Osteosarcoma Drug Response and Invasive Phenotypes

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Background: Osteosarcoma (OS) is a rare primary malignant bone tumor. Despite advances in treatment, outcomes remain poor for metastatic disease, highlighting the need for new drugs and better preclinical models. Conventional in vitro drug testing is typically performed on plastic surfaces that fail to recapitulate the bone tumor microenvironment. We developed human bone-derived extracellular matrix (ECM) models and investigated how it regulates osteosarcoma cell behavior and drug response.

Materials and Methods: ECM matrices were prepared from normal human bone (Bonegel) and osteosarcoma tissue (Osteogel) and were with Myogel, a human tumor-derived ECM matrix. Matrix composition was characterized by LC-MS proteomics. Long bone-derived OS cell lines (U2OS and HOS-143b), a jaw-derived OS cell line (HOSM-1), and patient-derived (long bone) OS cells were cultured on different ECM matrices. Cell proliferation, adhesion, and 3D spheroid invasion were assessed. High throughput drug screening was performed for OS cells on Bonegel, Osteogel, Myogel coated plates and sensitivity to different drugs evaluated using drug sensitivity score.

Results: ECM composition significantly influenced OS cell behavior. Myogel promoted the highest proliferation and invasion across most cell lines, whereas Osteogel consistently supported the strongest cell adhesion. HOS-143b exhibited the greatest invasive capacity, while HOSM-1 showed pronounced invasion in Osteogel. Proteomic analysis identified 306 extracellular proteins shared among all matrices, including collagens, laminins, and nidogens. Osteogel was enriched in proteins associated with bone mineralization, matrix stiffness, and cell–matrix interactions, whereas Bonegel contained proteins linked to tissue remodeling and repair. Drug responses varied among different ECM. Bonegel enhanced sensitivity

to several chemotherapeutic agents, particularly doxorubicin and cisplatin.

Conclusions: Human bone-derived ECM matrices offer physiologically relevant platforms for modeling the osteosarcoma microenvironment. Matrix composition significantly influences key cellular behaviors proliferation, adhesion, invasion and chemotherapy sensitivity. Notably, OS cells demonstrated the greatest invasive capacity on Myogel, while Bonegel-coated plates yielded heightened sensitivity in drug testing assays. These biomimetic models hold promises for improving the predictive accuracy of osteosarcoma drug screening and advancing the development of more effective therapeutic strategies.

No conflict of interest

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348 - PB-140 **Poster**

From Local Growth to Distant Metastasis: A Versatile In Vivo Imaging Platform for Modeling Cancer Progression

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Background: To gain a complete picture of neoplastic progression, experimental systems must be capable of reflecting both primary tumor expansion and the full sequence of systemic spread. Existing preclinical models, however, tend to mimic only discrete stages of this continuum, which undermines their capacity to inform clinical application.

Objective: To establish and validate an integrated in vivo platform that utilizes luciferase-based imaging to quantitatively model distinct stages of cancer progression—from primary engraftment to organotrophic dissemination.

Methods: We constructed a multifaceted in vivo platform using immunocompromised mice, with real-time monitoring of disease evolution performed via bioluminescent imaging (BLI). The model series comprised the following interventions: (a) intracardiac delivery of MDA-MB-231-Luc2 cells to establish hematogenous metastatic seeding; (b) local implantation into the tibia and cerebrum to examine breast cancer cell outgrowth within bone and neural microenvironments; (c) systemic infusion of Ba/F3 and lymphoma cells to recapitulate leukemic dissemination through the bloodstream; and (d) a topographical assessment of intracranial engraftment, wherein A375-GFP-Luc cells were deposited at stereotaxic positions 0.5 mm rostral, 1.0 mm rostral, and 0.5 mm caudal to the bregma.

Results: Using this platform, we observed diverse disease manifestations: intracardiac injection gave diffuse BLI signals consistent with widespread metastatic homing; tibial and intracranial orthotopic implants produced progressive, quantifiable local outgrowth; and intravenous hematopoietic administration led to systemic leukemic spread. Critically, deposits placed caudal to the bregma showed a statistically greater tendency for extra parenchymal dissemination than those at anterior coordinates.

Conclusion: We present a validated and versatile in vivo platform that enables the spatiotemporal quantification of tumor dynamics across multiple disease contexts. This integrated system provides a powerful tool for investigating organ-specific tumor biology and evaluating therapeutic efficacy against both primary and metastatic disease.

Key Words: In vivo imaging, Cancer metastasis, Orthotopic models, Bioluminescence, Intracranial engraftment, Preclinical platform

No conflict of interest

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349 - PB-141 **Poster**

C3PO: Complex 3D Patient Organoids for Preclinical Drug Testing in Brain Tumors

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Background: Glioblastoma (GBM) remains one of the most aggressive and therapeutically challenging brain tumors, with current treatments offering limited survival benefits. One of the major obstacles in developing effective therapies is the lack of physiologically relevant preclinical models that can accurately recapitulate the structural, molecular, and cellular complexity of the human tumor microenvironment. Conventional 2D cultures and animal models often fail to predict clinical efficacy and are associated with high variability and limited translational value.

Methods: To overcome these limitations, we have developed advanced *ex vivo* 3D glioblastoma models, termed Complex 3D Patient Organoids (C3POs), designed to reproduce the architecture, multicellular composition, and microenvironmental gradients of GBM. Each C3PO integrates patient-derived glioma stem-like cells (PD-GSCs) with astrocytes and microglia in defined ratios, generating self-assembled spheroids that mimic the tumor-stroma interactions observed *in vivo*. To ensure biological relevance, all patient-derived GSCs were also profiled for key genomic alterations commonly associated with GBM. Distinct models representing different molecular GBM subtypes were established and characterized using high-content imaging and fluorescent tracking of individual cell populations. These models have been used to evaluate both proprietary compounds and clinically used agents such as temozolomide, under conditions that more faithfully reproduce the pathophysiological features of GBM.

Results: Preliminary findings revealed subtype-specific responses to treatment, with C3POs of mesenchymal background displaying higher drug resistance and C3POs of proneural background showing higher sensitivity, consistent with a subtype-specific clinical outcome. Furthermore, 3D co-culture systems exhibited reduced drug sensitivity compared to monocultures, underscoring their higher biological fidelity. Current studies are focused on correlating *in vitro* efficacy and pharmacokinetic (PK) data from C3PO models with results previously obtained in orthotopic GBM mouse models, to quantitatively assess their predictive potential.

Conclusions: The C3PO platform provides a robust and scalable tool for *ex vivo* pharmacological testing of anti-GBM agents. By improving translational predictivity and reducing reliance on animal models, these complex 3D systems represent a promising advancement toward more ethical, cost-effective, and clinically relevant preclinical strategies for the development of new therapies targeting brain tumors.

No conflict of interest

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350 - PB-142 **Poster**

Matched Patient-Derived Xenografts and Organoids Faithfully Preserve the Molecular Landscape and Drug Response of Breast Cancer

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Breast cancer (BC) is a highly heterogeneous disease characterized by diverse genomic alterations and variable therapeutic responses. Robust preclinical models that faithfully recapitulate the molecular landscape of patient tumors are essential for translational research and precision oncology. Here, we established a mirror biobank of patient-derived xenografts (PDXs) and matched PDX-derived organoids (PDXOs) to evaluate their molecular concordance and pharmacological relevance.

Matched PDXO cultures were generated from established BC PDXs following tumor dissociation, murine cell depletion, and three-dimensional culture of human epithelial cells. Whole-exome sequencing and transcriptomic profiling were performed to compare paired PDX/PDXO models. Drug responses were assessed using standard chemotherapies, trastuzumab emtansine (T-DM1), and trastuzumab deruxtecan (Enhertu®).

Paired PDXs and PDXOs displayed a high degree of molecular conservation at both the genomic and transcriptomic levels. Whole-exome sequencing demonstrated strong mutational concordance, including preservation of key oncogenic driver alterations such as *TP53* and *ATM*. Transcriptomic analyses confirmed maintenance of tumor-specific molecular features across matched models. This molecular fidelity translated into comparable pharmacological responses to conventional chemotherapies. Likewise, T-DM1 induced significant antitumor activity in HER2-positive paired models while remaining ineffective in HER2-low counterparts, demonstrating preservation of clinically relevant biomarkers and therapeutic sensitivity. Importantly, we established a PDXO model derived from a PDX with acquired resistance to trastuzumab deruxtecan (Enhertu®). This organoid faithfully recapitulates the acquired resistance phenotype of its parental PDX, providing a valuable preclinical platform to investigate the molecular mechanisms underlying acquired resistance to HER2-targeted antibody–drug conjugates and to identify strategies for overcoming therapeutic escape.

Our mirror biobank demonstrates that PDXOs faithfully retain the genomic, transcriptomic, and pharmacological characteristics of their matched PDXs, supporting their use as scalable surrogate models for molecular and functional studies. The establishment of a trastuzumab deruxtecan-resistant organoid model further expands the value of this platform for investigating resistance mechanisms to next-generation HER2-targeted therapies. Combined with immune co-culture approaches, these complementary models provide a powerful translational framework for biomarker discovery, therapeutic stratification, and preclinical evaluation of targeted and immunotherapeutic strategies in breast cancer.

No conflict of interest

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351 - PB-143 **Poster**

A preclinical patient-derived xenograft platform to model resistance to cyclin-dependent kinase 4/6 inhibitors plus endocrine therapy in oestrogen receptor-positive breast cancer

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Background: Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) combined with endocrine therapy (ET) have become standard treatment for oestrogen receptor-positive (ER+) metastatic breast cancer (MBC) and are expanding into high-risk early breast cancer. However, understanding resistance mechanisms and identifying optimal therapeutic strategies remain major clinical challenges. We aimed to generate a clinically relevant patient-derived xenograft (PDX) platform to study both resistance mechanisms and therapeutic vulnerabilities.

Material and methods: We established and characterised 18 ER + PDX models derived from primary and metastatic tumour biopsies collected before or after exposure to CDK4/6i + ET. Models were profiled using whole-genome sequencing, PAM50 subtyping, RNA sequencing, and protein analyses. *In vivo* response was assessed using CDK4/6i + ET, selected according to prior exposure and tumour genetic background. Initially, sensitive models were chronically treated to generate acquired resistant derivatives. Whole-genome and RNA sequencing analyses were performed in matched sensitive and resistant samples.

Results: Eight models showed intrinsic resistance, whereas ten were initially sensitive. Long-term *in vivo* treatment generated acquired resistance in three models derived from both primary and metastatic tumours. In PDX244, ten independent acquired resistant derivatives were generated, enabling the study of interclonal heterogeneity within the same tumour background. In the parental sensitive model, treatment induced broad transcriptional reprogramming, with marked downregulation of proliferation, DNA replication and mitotic genes, including *MYBL2, FOXM1, TYMS, PLK1, BIRC5, CDCA5, CCNA2, CCNB1/2, AURKA and TOP2A*. By contrast, resistant derivatives showed heterogeneous and generally attenuated transcriptomic responses to treatment. Gene-set enrichment analyses identified candidate resistance-associated programmes involving altered cell-cycle regulation, immune/inflammatory signalling, extracellular matrix and cell-adhesion remodelling signatures.

Conclusions: We established a molecularly annotated PDX platform that captures intrinsic and acquired resistance to CDK4/6i + ET in ER+ breast cancer. The integration of primary and metastatic tumour models, matched sensitive-resistant pairs, and multiple

independent resistant derivatives enables the study of shared and clone-specific mechanisms of therapeutic resistance. This platform provides a resource to identify actionable vulnerabilities and guide the preclinical evaluation of novel therapeutic strategies.

Conflict of interest: Corporate-sponsored Research: Dra. Violeta Serra was previously affiliated with VHIO and is currently employed by AstraZeneca.

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352 - PB-144 **Poster**

Integrative molecular profiling of a breast cancer (BC) patient-derived xenograft (PDX) platform for biomarker discovery

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Background: Despite major advances in targeted therapies for breast cancer (BC), identifying biomarkers that accurately predict treatment response and resistance remains a major clinical challenge. Patient-derived xenograft (PDX) models retain most molecular and drug response profiles of patient tumors, providing a robust platform for biomarker discovery. Here, we aimed to integrate baseline genomic and transcriptomic data from a large BC PDX cohort with in vivo responses to multiple therapies to identify predictive biomarkers of treatment response and resistance.

Material and methods: A cohort of 79 BC PDX models (54 ER+ and 25 triple-negative [TNBC]) was characterized by whole-exome sequencing, targeted DNA sequencing, and bulk RNA sequencing. Genomic variants, copy number alterations, and gene expression profiles were integrated and correlated with in vivo therapeutic responses across 25 treatment cohorts. Treatments included conventional chemotherapies (e.g., platinum agents and microtubule inhibitors) and targeted therapies, including selective estrogen receptor degraders (SERDs) and PARP, WEE1, ATR, FGFR, PI3K, AKT and CDK4/6 inhibitors, among others. Hallmark GSVA scores were calculated and correlated with genomic alterations and treatment response. Differential expression (DE) analysis and gene set enrichment analysis were conducted across all treatment arms to identify molecular features associated with treatment sensitivity and resistance.

Results: Baseline transcriptomic profiling was concordant with the genomic landscape of the PDX cohort, with expected pathway activation observed in genomically altered models. For example, ESR1-mutant models displayed significantly higher Estrogen Response Early and Late hallmark scores than ESR1 wild-type tumors (FDR = 8.98×10^{-5}). Comparison of pathway activity according to treatment response identified biologically relevant differences across therapeutic cohorts in both ER+ and TNBC models. For instance, SERD-sensitive models showed enrichment of the Estrogen Response Early and Late hallmark gene sets (NES = 1.98 and 1.62; FDR = 0.001 and 0.035), consistent with greater ER dependence. Additionally, PARPi-resistant models showed enrichment of DNA double-strand break repair gene sets (R-HSA-5693607, R-HSA-5693538, and R-HSA-5693532; NES = 2.06, 1.89, and 1.87; FDR = 0.0057, 0.0264, and 0.0260), suggesting enhanced DNA repair capacity. DE analysis further identified multiple candidate biomarkers associated with treatment response.

Conclusions: Integrative genomic and transcriptomic analyses identified biologically relevant molecular signatures associated with tumor biology and therapeutic response across multiple treatment cohorts. These findings highlight the value of this BC PDX platform for the discovery of transcriptomic signatures and predictive biomarkers with potential translational relevance.

Conflict of interest: Corporate-sponsored Research: Dra. Violeta Serra was previously affiliated with VHIO and is currently employed by AstraZeneca.

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353 - PB-145 **Poster**

Breast cancer patient-derived xenograft models reveal convergent mechanisms of acquired resistance to olaparib through homologous recombination restoration

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PARP inhibitors (PARPi), including olaparib, have substantially improved outcomes for patients with breast cancers harboring BRCA1/2 alterations or homologous recombination deficiency (HRD). However, the emergence of acquired resistance remains a major clinical challenge. Clinically relevant preclinical models are therefore essential to elucidate resistance mechanisms and identify novel therapeutic strategies.

Within our collection of 54 breast cancer patient-derived xenograft (PDX) models, 51 were evaluated in vivo for olaparib sensitivity, of which 19 were initially responsive. Selected sensitive models were subsequently maintained under continuous olaparib treatment until tumor recurrence to generate acquired resistance. Resistant tumors and their matched parental counterparts were characterized using histopathology, whole-exome sequencing, RNA sequencing, and immunohistochemical assessment of homologous recombination biomarkers.

To date, we have established a panel of 10 olaparib-resistant derivatives generated from 6 initially sensitive PDX models. These resistant models display heterogeneous molecular mechanisms converging toward restoration of homologous recombination proficiency. In BRCA1-mutated models, resistance was associated with structural BRCA1 reversion events involving exon deletions that likely restore BRCA1 function. In models lacking BRCA1 mutations, resistance was associated with marked BRCA1 transcriptional re-expression together with restoration of BRCA1 and RAD51 nuclear foci, consistent with homologous recombination reactivation. In addition, selected resistant models exhibited increased expression of drug efflux transporters, including ABCB1 and ABCG2, indicating that enhanced drug efflux may represent an additional resistance mechanism in a subset of tumors.

Overall, this unique panel of olaparib-resistant breast cancer PDX models constitutes a robust translational platform for investigating PARP inhibitor resistance mechanisms and for developing rational therapeutic strategies to overcome acquired resistance in HRD breast cancer.

No conflict of interest

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354 - PB-146 **Poster**

Pancreatic cancer-associated fibroblast-tumoroid coculture reveals morphological differences and altered drug sensitivity in functional precision medicine assays

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Background: Functional precision medicine (FPM) entails measuring drug sensitivity and resistance directly on the patient's own living cancer cells in vitro. The inclusion of cancer-associated cells from the tumor microenvironment can increase translational relevance but is challenging to standardize experimentally. Here the aim is to develop an in vitro diagnostic (IVD)-grade coculture assay to test whether the addition of fibroblasts to the experimental model improves the correlation between patient- and FPM drug response.

Materials and Methods: Fifteen primary pancreatic ductal adenocarcinoma (PDAC) patients were included. Patient-matched cancer-associated fibroblasts (CAFs) and patient-derived tumoroids (PDTs) were established in parallel from resected and biopsied tissue. One fibroblast cell line was included as a reference model. PDTs alone and PDT-CAF coculture were subject to drug screening in a standard 384-microplate and custom 16-channel microfluidic organoid-on-a-chip system. PDT drug sensitivity was assessed in mono- and cocultures. Viability and morphology were assessed at day 5 using high-content imaging and computer vision.

Results: To facilitate successful coculture on both microplate and microfluidic systems, a collagen-Matrigel combination condition was developed. For both mono- and PDT cocultures, drug screening Z'-factors were >0.4. In coculture, PDT morphology showed a subtle shift with less compact and more (non-CAF) fibroblast-like structures. Moreover, the PDTs became less dependent on culture-media supplemented mitogenic niche factors. Among 26 anti-cancer drugs tested, sensitivities for 5 were higher, and 1 was lower in PDT as compared to PDT-CAF coculture. For instance, for paclitaxel the IC50s were 2.3 nM and 4.2 nM for PDT and PDT-CAF, respectively. Similarly, for trametinib the IC50s were 0.41 nM vs 4.6 nM. In general, CAFs seem to alleviate the effect of certain compounds like RAS-ERK axis inhibitors and taxanes. Correlation between the patients' clinical response towards standard-of-care and PDT and PDT-CAF FPM assays will be compared prospectively.

Conclusion: Here we present the first data from a novel IVD coculture platform. The inclusion of CAFs had a profound effect on PDT morphology, culture media dependency, and drug sensitivities. Together, this supports the need to determine to what extent CAFs improve FPM predictive accuracy.

No conflict of interest

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355 - PB-147 **Poster**

Patient-Derived Models Reveal Distinct Molecular Mechanisms of Acquired Resistance to Trastuzumab Deruxtecan in Triple-Negative Breast Cancer

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Triple-negative breast cancer (TNBC) remains an aggressive and molecularly heterogeneous disease associated with poor clinical outcomes. Although trastuzumab deruxtecan (Enhertu®, T-DXd) has demonstrated promising clinical activity in HER2-low TNBC, acquired resistance inevitably limits its long-term efficacy. Clinically relevant preclinical models are therefore essential to elucidate resistance mechanisms and identify novel therapeutic strategies.

Within our collection of 40 TNBC patient-derived xenograft (PDX) models, 14 were treated in vivo with T-DXd, including 11 initially sensitive models. Continuous treatment until tumor relapse enabled the generation of eight resistant derivatives from five independent parental models. Resistant tumors and their matched sensitive counterparts are being characterized using transcriptomic (RNA-seq), whole-exome sequencing and histopathological analyses.

Transcriptomic analyses are performed using DESeq2-based differential expression and pathway enrichment analyses to investigate biological processes potentially involved in acquired resistance, including receptor trafficking, lysosomal function, drug transport, DNA damage response, homologous recombination and replication stress. Initial results reveal marked transcriptional remodeling, suggesting that distinct resistant models acquire different adaptive programs rather than converging toward a single resistance mechanism. Integration of genomic, transcriptomic, and histopathological data is ongoing to identify recurrent and model-specific alterations associated with resistance.

To further characterize the resistant phenotype, selected resistant PDX models were challenged with additional antibody-drug conjugates carrying either a topoisomerase I payload (sacituzumab govitecan) or a microtubule inhibitor payload (enfortumab vedotin), as well as with the free topoisomerase I inhibitor topotecan. These pharmacological studies revealed distinct patterns of cross-resistance between resistant models, suggesting that resistance may arise through either payload-specific mechanisms or broader alterations affecting ADC activity.

Overall, this expanding panel of trastuzumab deruxtecan-resistant TNBC PDX models constitutes a unique preclinical platform for deciphering both shared and model-specific mechanisms of ADC resistance and for identifying therapeutic strategies capable of overcoming resistance to HER2-directed antibody-drug conjugates.

No conflict of interest

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356 - PB-148 **Poster**

A modular mechanobiology platform for modelling clinically relevant epithelial states in colorectal cancer

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Background: Colorectal cancer (CRC) exhibits marked epithelial phenotypic heterogeneity, with clinically relevant tumour states increasingly recognized to arise through developmental and regenerative reprogramming. Conventional organoid cultures fail to capture the biochemical, mechanical and phenotypic diversity of the tumour microenvironment. We developed a modular mechanobiology platform that independently modulates extracellular matrix (ECM) composition and substrate stiffness to generate clinically relevant epithelial phenotypes for disease modelling, biomarker discovery and therapeutic screening.

Materials and methods: Patient-derived and mouse intestinal organoids were cultured in basement membrane extract (BME), collagen I, hyaluronan-collagen matrices and tunable polyacrylamide (PAA) substrates spanning physiologically relevant stiffnesses (2–20 kPa). Epithelial phenotypes were assessed by quantitative immunofluorescence, three-dimensional imaging, spatial marker analysis and nuclear morphometry. Public single-cell RNA sequencing datasets generated under comparable ECM conditions were reanalysed to complement molecular characterization.

Results: Reanalysis of public single-cell RNA sequencing datasets identified enrichment of unusual developmental epithelial signatures in collagen-based cultures, supporting ECM-driven epithelial reprogramming. Consistent with these findings, immunofluorescence of the same showed low ANXA1 expression in conventional BME cultures, increased ANXA1 in collagen I, and retained ANXA1 following transfer from collagen I back to BME. Independently, tunable substrate stiffness revealed genotype-dependent responses: wild-type organoids spread on compliant substrates, whereas APC/KRAS-mutant organoids remained organoid-like until higher stiffnesses. In mutant organoids, ANXA1 expression was inversely associated with nuclear compaction, with compact regions displaying reduced ANXA1 and peripheral regions increased ANXA1, a relationship absent in wild-type organoids. Together, these findings demonstrate that independent modulation of ECM composition and mechanics reproducibly generates distinct epithelial plasticity states.

Conclusions: Our modular mechanobiology platform enables systematic modelling of epithelial plasticity through independent control of ECM composition and mechanics. By recapitulating clinically relevant epithelial phenotypes across multiple genetic backgrounds, it provides a versatile framework for biomarker discovery, phenotype-specific drug screening, and future integration with single-cell transcriptomic and epigenomic profiling.

No conflict of interest

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Poster Session: Tumour immunology and inflammation

357 - PB-149 **Poster**

Stimulatory effect of the whole bovine thymus extract and isolated fractions on model monocytes, macrophages, dendritic, and cancer cells in vitro

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Background: The tumour microenvironment is regulated by complex interactions between cancer cells and innate immune cells, including monocytes, macrophages, and dendritic cells, mediated by inflammatory cytokines that influence tumour progression and antitumour immunity. Thymus-derived peptide preparations have been reported to enhance immune cell activation and cytokine production, but the biological activity of individual molecular fractions remains poorly understood. The identification of naturally derived immunomodulatory compounds may provide new opportunities for immune-based therapeutic strategies. Therefore, this study investigated the immunomodulatory effects of a bovine thymus extract and its size-defined fractions on human model monocytes, macrophages, and dendritic cells, together with their cytotoxic activity against representative human cancer cell lines.

Methods: A complete bovine thymus extract was fractionated by size-exclusion chromatography into four fractions (FR1 – FR4). Human THP-1 monocytes were used either directly or differentiated into macrophages (PMA-induced) and dendritic cells (defined by expression of CD40, CD80, CD83 i CD86). Cytokine secretion (IL-1β, IL-6, IL-10, IL-12, TNF-α, and IFN-γ) was assessed by ELISA following stimulation with the whole thymus extract (0 – 10 mg/mL) or individual fractions (0 – 5%) dissolved in complete culturing medium. In dendritic cells, cytokine release was evaluated after cells priming with LPS. Direct cytotoxic effect of thymus extraxt on cancer cells was assessed in A549, SK-OV-3, and SK-BR-3 lines using cell viability assays (MTT).

Results: The complete thymus extract induced concentration-dependent activation of THP-1 monocytes and differentiated macrophages, increasing IL-1β, TNF-α, and IL-10 secretion without affecting IFN-γ, IL-6, or IL-12. In dendritic cells, the highest extract concentrations restored TNF-α production following experimental stimulation. Fraction FR4 also re-induced TNF-α secretion, unlike the control stimulant LPS. The complete extract similarly enhanced IL-10 production beyond LPS-induced levels. In cancer models, the extract exhibited moderate cytotoxicity toward A549 lung carcinoma cells, reducing viability by up to 20% at 10 mg/mL, while showing no significant effects on SK-OV-3 or SK-BR-3 cells.

Conclusions: Bovine thymus extract and its FR4 fraction exhibit potent immunomodulatory activity by activating monocytes, macrophages, and dendritic cells, promoting both pro-inflammatory and regulatory cytokine production, and suggesting the presence of bioactive molecules capable of overcoming immune tolerance-like states. Together with selective cytotoxicity against lung cancer cells, these findings support further characterization of thymus-derived compounds as a natural source of immunomodulatory factors with potential applications in cancer immunotherapy.

Conflict of interest: Ownership: Magdalena Staniszewska

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358 - PB-150 **Poster**

Quantifying Immunological Synapse to Optimize Immune Cell Engagers and Cancer Immunotherapies

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Background: The immunological synapse (IS) is a key interface that regulates immune cell activation, tumor cell recognition, and immune cell-mediated tumor killing. IS plays a pivotal role in orchestrating anti-tumor immune responses for T and NK cells. Consequently, the organization and quality of the IS are key determinants of the efficacy of immune cell engagers, including T-cell engagers (TCEs) and next-generation multispecific formats. Increasing evidence highlights IS architecture and dynamics as fundamental mechanistic drivers of the potency, selectivity, and therapeutic activity of these agents.

Materials and Methods: High-content imaging and computational analytics enable deep profiling of IS structural and functional features. IS formation and quality can be quantified through metrics including receptor clustering, intercellular contact stability, intracellular signaling, and cytotoxic granule polarization. Integrating these parameters enables the establishment of quantitative relationships between IS architecture and functional outcomes.

Results: Consistent with these observations, stable and spatially organized IS are associated with effective cytotoxic responses, while weak activity correlates with transient or disorganized interfaces. TCE activity critically depends on the formation of productive and stable IS between T-cells and tumor cells. In contrast to physiological TCR signaling, TCEs impose defined geometries and binding constraints that shape IS organization. Parameters such as epitope location, valency, and flexibility influence IS topology, activation strength, and serial killing. Accordingly, optimized TCEs promote tight membrane apposition, efficient IS assembly and enhanced cytotoxic responses, whereas suboptimal formats lead to unstable contacts.

Building on these insights, modulation of key IS features through the targeting of co-stimulatory molecules represents a promising strategy to enhance the therapeutic efficacy of T-cell engagers (TCEs). In this context, the combination of a HER2 × CD2 TCE (BiTco) with an EpCAM × CD3 TCE promoted optimal IS remodeling, leading to enhanced receptor clustering and amplified T-cell signaling. These effects translated into improved antitumor activity in vivo, supporting co-stimulatory engagement as an effective approach to broaden the therapeutic window of TCEs, particularly in the setting of solid tumors.

Conclusions: IS profiling enables mechanistic differentiation of TCEs, predicts therapeutic efficacy, and facilitates the early identification of optimal design features. Integrating IS analytics into drug discovery can accelerate candidate optimization and biomarker development, ultimately enhancing the precision and clinical impact of cancer immunotherapies.

No conflict of interest

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359 - PB-151 **Poster**

Arginase-1 plays a crucial role as a novel immunotherapeutic target in tumor-associated macrophages in recurrent triple-negative breast cancer

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Triple-negative breast cancer (TNBC) is a remarkably aggressive and heterogeneous subtype, with the impaired expression of progesterone (PR), estrogen receptors (ER) and human growth factor receptor 2 (HER2), that is associated with poor prognosis, characterized by high rates of metastasis and frequent recurrence, along with inadequate therapeutic options. Tumor-associated macrophages (TAMs) constitute a predominant component of tumor microenvironment and play an essential role in modulating tumor progression, immune suppression, and therapy resistance. This study has focused on identifying the role of CD206+ TAMs in regulating TNBC recurrence and analysed the role of ARG-1 in regulating CD206+ TAMs polarization in TNBC recurrence.

In order to establish the comparative distinctions in CD206+TAMs profile between primary and recurrent TNBC, we performed flow cytometry analysis of single cells derived from tumor of primary and recurrent tissue and the data showed higher percentage of CD206+CD163+ TAMs in recurrent TNBC with similar reflection in peripheral blood. Moreover, the immunohistochemical analysis of tumor tissue sections revealed a significantly higher expression of Arginase-1, in recurrent TNBC along with the higher expression of exhaustion markers PD-1, PDL-1, CTLA-4, LAG-3, and TIM-3 and stem cell markers ALDH1 and CD44. Confocal analysis showed higher co-localization of Arginase-1 and M2 marker CD206 in recurrent TNBC. The results obtained from microscopy images confirmed the presence of a considerably higher percentage of Arginase-1 and CD206+ TAMs in recurrent TNBC, suggesting the favourability of a pronounced shift towards an immunosuppressive microenvironment, having an M2-dominant polarization phenotype. For the purpose of demonstrating the significance of Arginase-1 in regulating polarization of TAMs in TNBC, we inhibited Arginase-1 in TAMs via siRNA. The flow cytometry data revealed considerable reduction in Arginase-1 expression and induction of apoptosis in TAMs, indicating treatment efficacy. ARG1 knockdown promoted immune restoration by increasing the secretion of pro-inflammatory cytokines, i.e., IL-12 and IFN-γ, while suppressing immunosuppressive cytokines, i.e., IL-10 and TGF-β. In three-dimensional TNBC spheroids, ARG1 silencing disrupted spheroid integrity and significantly increased apoptotic and necrotic cell populations, depicting the therapeutic efficacy of ARG-1 inhibition in TNBC.

Collectively, these findings identify Arginase-1 as a critical regulator of M2 macrophage-mediated immune suppression in recurrent TNBC and demonstrate that its inhibition effectively reprograms the tumor immune microenvironment, enhances antitumor immunity, and suppresses tumor progression, supporting Arginase-1 as a promising therapeutic target for the treatment of recurrent TNBC and thus signifying the improvement of survival outcomes.

No conflict of interest

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360 - PB-152 **Poster**

Plasma complement activation is associated with favourable prognosis in luminal metastatic breast cancer

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Background: The complement system is a major component of the innate immune response, traditionally recognised for its role in host defence and homeostasis. More recently, it has emerged as a key regulator of the tumour microenvironment (TME), exerting anti- and pro-tumour effects that influence cancer progression and patient prognosis. Consequently, both complement-enhancing and -inhibitory therapies are currently under clinical evaluation, underscoring the need for complement-based patient stratification. Here, we aimed to identify complement-associated profiles in luminal breast cancer.

Material and methods: Complement activation within the TME was characterised by analysing tumour tissue using hyperplex immunofluorescence, RNAscope *in situ* hybridization and immunohistochemistry, alongside transcriptomic analysis of the TCGA-BRCA cohort. A multiplex ELISA-based *humoral complementomics* approach was then applied to plasma from 39 patients with luminal metastatic breast cancer (MBC) to quantify circulating complement proteins and activation fragments and assess their association with clinical outcomes.

Results: Complement activation was detected within the TME, with deposition of IgG, classical and alternative pathway components, and the terminal component C9 on cancer cells, indicating membrane attack complex (MAC; C5b-9) formation. Early components were partly produced within the TME, whereas terminal components were likely blood-derived, as evidenced by the absence of local C9 expression. Plasma profiling further revealed increased circulating complement activation in patients with luminal MBC. Activation fragments (C4d, Ba, Bb, C3a, C5a and sC5b-9) were elevated compared with healthy donors. Positive correlations between early activation products and downstream effectors supported progression to terminal activation, with Ba and Bb showing stronger correlations with sC5b-9 than C4d, suggesting predominant activation of the alternative pathway. Consistent with systemic inflammation, intact C3, C4 and factor B (FB) levels were increased and positively correlated with calprotectin. Importantly, intact proteins and activation fragments showed opposite prognostic associations: high C3 and FB levels predicted poorer outcomes, whereas elevated C4d, C5a and Ba/FB ratios were associated with improved outcomes.

Conclusions: Plasma complement activation markers are associated with favourable prognosis in luminal MBC and support further investigation of complement-enhancing therapeutic strategies.

No conflict of interest

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361 - PB-153 **Poster**

Complement activation is associated with distinct functional states of membrane attack complex deposition in HER2-positive breast cancer

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Background: Complement system activation leads to the cleavage of the central proteins C3 and C5, which triggers the sequential assembly of terminal proteins C5b through C9 on the cell surface, forming the membrane attack complex (MAC; C5b-9). Consequently, MAC assembly induces direct cell lysis, a process termed complement-dependent cytotoxicity (CDC). Growing evidence suggests that complement cascade can influence the tumour microenvironment and patient prognosis, however, its role in breast cancer remains poorly understood. Previous data from our group has shown that intratumoural complement expression is associated with improved prognosis specifically in the HER2-positive molecular subtype. Therefore, this study aimed to investigate the functional impact of complement activation and MAC deposition in HER2-positive breast cancer cells.

Material and methods: Treatment-naïve HER2-positive breast tumour tissues were analysed by hyperplex immunofluorescence to assess MAC deposition and its association with cell proliferation and necroptosis using C9, Ki67 and pMLKL, respectively. To further investigate this mechanism, we established an in vitro model of MAC deposition using HER2-positive breast cancer cell lines. Cells were incubated with normal human serum and treated with the anti-HER 2 antibodies trastuzumab and pertuzumab at concentrations achieving maximal complement activation measured by C3c deposition. The final stage of the cascade was determined by the deposition of C9 and C5b-9. The effect on proliferation was reached using CFSE dilution and the impact on cell death with Live/Dead staining and LDH release.

Results: On the HER2-positive tissues we characterised MAC-positive tumour cells and observed co-localisation with either pMLKL or Ki67. These findings suggest distinct functional states of MAC deposition, including lytic and sublytic forms associated with tumour cell death or survival, respectively. While neither antibody alone increased C3c deposition in vitro, combined treatment significantly enhanced complement activation in both cell lines. The combination also resulted in C5b-9 being deposited on the cell membrane in a dose-dependent manner without causing CDC, consistent with a sublytic or non-cytotoxic MAC deposition state. In addition, an extended period of treatment with the combination of anti-HER2 antibodies revealed no alterations to proliferation or cell death.

Conclusions: Anti-HER2 antibodies effectively activate complement up to the deposition of C5b-9. However, HER2-positive cells may survive through the combined action of complement regulators and membrane repair mechanisms, which convert a potentially lytic stimulus into a sublytic event. Patients with HER2-positive breast cancer may benefit from strategies that overactivate complement and enable CDC, which could help them overcome treatment resistance mechanisms.

No conflict of interest

https://doi.org/10.1016/j.ejca.2026.117771

ORAL LATE-BREAKING ABSTRACTS

Plenary Session 1: The next wave of immune engagers in cancer therapy: beyond CD3 and beyond T cells

1LBA **Oral**

Clinical activity of AT-1965, a novel CMTR2 inhibitor and B-cell activating immunotherapy, in patients with advanced solid tumors: Results from first-in-human phase 1 clinical trial

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Background: Patients with immunologically "cold" tumors, i.e low levels of immune cell infiltration in the tumor microenvironment, often exhibit limited tumor response to standard immunotherapy and have poor clinical outcomes. AT-1965, a first-in-class CMTR2 inhibitor that triggers recruitment and activation of B cell-driven innate and adaptive immunity against tumor, could address this unmet need. Here we report initial results from phase 1 clinical trial investigating AT-1965.

Methods: AT-1965-101 is a multicenter, open-label, first-in-human Phase 1/2 study evaluating AT-1965 as monotherapy in adult patients with advanced solid tumors (NCT06234098). The primary objective was to evaluate maximum tolerated dose (MTD) and/or recommended Phase 2 dose(s). Secondary objectives included safety, tolerability, and preliminary anti-tumor activity. Standard 3 + 3 design used for dose escalation based on dose-limiting toxicity (DLT). Safety assessed per CTCAE V5.0, and antitumor activity assessed per RECIST and Kaplan Meier survival analysis.

Results: As of September 2026, 27 DLT-evaluable patients were dosed with AT-1965 across nine dose levels (30 to 1000 mg/m^2). The population was heavily pretreated patients (median 3 prior lines, range: 1-7) and included advanced solid tumors (breast cancer, endometrial cancer, pancreatic cancer, sarcoma). No DLTs were observed in any cohort. Patients received a total of 411 doses (median 15.2/patient; max 46) without any grade 3/4 TRAEs or any cytokine release syndrome. Treatment-emergent adverse events (TEAEs), included fatigue, infusion related reactions, flu-like symptoms, and were all grade 1/2. Evaluable patients had Disease Control Rate of 57.7% with 39% exhibiting tumor shrinkage in at least one target lesion. Clinical activity was seen in patients with disease progression on prior immunotherapy, and the 6-month Overall Survival was 88%. Significant increase in absolute lymphocyte count (ALC) from baseline noted in 96.3% (26/27) of patients ($p = 0.00000002$), consistent with AT-1965 mechanism of action in mobilizing lymphocytes. Furthermore, in patients with baseline lymphopenia (40%), AT-1965 significantly improved time on treatment compared to prior line therapy (HR = 0.11, $p = 0.002$). Gene-expression profiling of on-treatment tumor biopsies demonstrated dominant intratumoral B-cell signature with active T- and B-cell trafficking.

Conclusion: AT-1965, a first-in-class CMTR2 inhibitor and B-cell-activating immunotherapy, demonstrated excellent safety profile with encouraging evidence of clinical activity in heavily pre-treated patients with advanced cancer, including disease progression on standard immunotherapy. Pharmacodynamic analyses support the proposed mechanism of action, i.e AT-1965 activates a B cell-mediated immune response and reverses lymphopenia in patients with solid tumors.

Conflict of interest: Advisory Board: Pfizer, Novartis, Merck, Genentech, AstraZeneca, Daiichi, Alyssum, Menarini, Gilead, Vyome, Eli Lilly, BMS.

Corporate-sponsored Research: Pfizer, Novartis, Merck, Genentech, AstraZeneca/Daiichi, Onkure, Menarini, Gilead, Eli Lilly

Other Substantive Relationships: SAB, Alyssum

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Plenary Session 2: RAS pathway: "Targeting RAS - What's Next?"

2LBA **Oral**

Tumor-selective delivery of a pan-RAS(ON) inhibitor by the novel CEACAM5-targeted ADC AN4035 expands the therapeutic window and enables potent, well-tolerated combination with EGFR blockade

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Background: Despite encouraging clinical activity, systemic pan-RAS(ON) inhibitors are limited by on-target toxicities in normal tissues, restricting dose intensity and combination opportunities. AN4035 is a first-in-class CEACAM5-targeted antibody drug conjugate (ADC) built on our RASiCA™ (RAS Inhibitor Conjugated Antibody) platform, selectively delivering a potent pan-RAS(ON) inhibitor payload to tumors to broaden the therapeutic window. Here, we characterize its pharmacokinetics/pharmacodynamics (PK/PD) profile, antitumor activity as monotherapy and in combination with EGFR antibodies, and preliminary tolerability in preclinical models.

Materials and methods: The PK/PD of AN4035 monotherapy was evaluated in the HPAC xenograft model following single-dose administration by assessing payload biodistribution in both normal tissues and tumors, and pharmacodynamic inhibition of MAPK signaling (p-ERK) and tumor proliferation (Ki67). The PK/PD of AN4035 in combination with cetuximab was also investigated in the CL-40 xenograft model. Antitumor activity was assessed as monotherapy and in combination with EGFR antibodies in colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), and non-small cell lung cancer (NSCLC) CDX and PDX models. Preliminary tolerability of AN4035 in combination with cetuximab was evaluated in cynomolgus monkeys.

Results: AN4035 demonstrated >20-fold greater target-mediated tumor retention than the unconjugated payload, resulting in markedly improved tumor selectivity over normal tissues. This translated into dose-dependent and sustained inhibition of MAPK signaling (p-ERK) and tumor cell proliferation (Ki67), supporting prolonged target engagement *in vivo*. When combined with EGFR antibodies, AN4035 produced deeper and more durable tumor regressions than either agent alone across CRC, PDAC, and NSCLC CDX and PDX models, including models resistant to RMC-6236 and a Top1 inhibitor-based CEACAM5-targeting ADC. Mechanistically, AN4035 in combination with cetuximab achieved more profound

suppression of Ki67 and ERK phosphorylation than either monotherapy alone in the CL-40 xenograft model, consistent with enhanced MAPK pathway inhibition. AN4035 combined with cetuximab was well tolerated in cynomolgus monkeys, with no evidence of additive toxicity.

Conclusions: AN4035 is a novel CEACAM5-targeted ADC that selectively delivers a proprietary pan-RAS(ON) inhibitor to tumors, broadening the therapeutic window of systemic RAS inhibition. AN4035 demonstrated tumor-selective PK/PD activity and potent, well-tolerated combination activity, supporting the ongoing Phase I study of AN4035 as monotherapy and in combination with cetuximab in patients with advanced solid tumors harboring RAS mutations and enriched for CEACAM5 expression (NCT07686445).

Conflict of interest: Other Substantive Relationships: All authors are employees of Adlai Nortye Group Ltd.

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Plenary Session 3: Proffered Papers: Clinical Trials

3LBA **Oral**

Phase 1 study of micvotabart pelidotin (MICVO) monotherapy in previously treated recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC)

F. Johnson [1], T.J. Roberts [2], W. Wong [3], D. Castellano Gauna [4], D.J. Wong [5], N.F. Saba [6], T.M. Wise-Draper [7], J.P. Machiels [8], J.C. Park [9], A. Spira [10], E. Calvo [11], D. Roda Perez [12], H. Wang [13], A. Elfiky [13], X. Qing [13], O. Bogg [13], S. He [13], S. Lewandowski [13], A.L. Ho [14]

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Background: R/M HNSCC post-platinum and anti-PD-1 therapy lacks standard of care treatment options and remains a high unmet need. MICVO is a first-in-concept antibody-drug conjugate targeting extradomain-B of fibronectin (EDB+FN), a non-cellular structural protein in the tumor extracellular matrix, comprising an IgG1 monoclonal antibody with site-specific conjugation to a protease-cleavable linker and optimized auristatin payload.

Methods: MICVO was given intravenously at 5.4 mg/kg Q3W to patients (pts) with R/M HNSCC who progressed on platinum and anti-PD-(L)1. Dose was capped at 432 mg (male ≥ 80 kg) or 378 mg (female ≥ 70 kg) during dose expansion. We report results for 35 pts whose first dose was ≤ the cap; 33/35 were efficacy evaluable. Endpoints include objective response rate (ORR) by investigator (RECIST v1.1), progression-free survival (PFS), overall survival (OS), and safety. (NCT05720117).

Results: As of 18Aug2026, among 35 pts, 51% had HPV-positive oropharyngeal cancer (OPC). 69% (24) pts had ≥ 2 prior lines of therapy for R/M disease (median 2, range 1–4). 71% had prior taxane. 57% had prior anti-EGFR agents. Confirmed ORR was 36% (12/33, including one complete response). Disease control rate was 94% (31/33). Median PFS was 6.2 months (mos) (95% CI 4.8, 8.8).12-mos OS probability was 79% (95%CI 58%, 90%). Median OS was not reached (NR) (95%CI NR, NR). Clinical benefit was observed across HPV status and prior treatment subgroups (Table 1). Among 12 confirmed responders, 75% (9) achieved response by week 6, and 83% (10) had > 50% tumor reduction from baseline.

Efficacy Evaluable	ORR, %(n)	mPFS, mos
HPV Status		
HPV+ OPC (N=17)	35% (6)	6.2
HPV-unrelated (N=16)	38% (6)	5.9
Prior anti-EGFR		
Yes (N=18)	28% (5)	5.0
No (N=15)	47% (7)	8.8
Prior novel anti-EGFR (bispecific Abs) (N=5)	40% (2)	5.8
Prior Taxane		
Yes (N=23)	35% (8)	6.2
No (N=10)	40% (4)	4.9
Line of MICVO Therapy		
2L (N=11)	45% (5)	6.7
3L (N=20)	35% (7)	6.2
4L (N=0)	NA	NA
5L (N=2)	0% (0)	Not reported*

*N=2 (actual PFS 5.0, 7.0)

Grade (Gr) ≥3 treatment-related adverse events (TRAEs) reported in ≥ 2 pts (5%) included peripheral sensory (8.6%) and motor (8.6%) neuropathy, AST increased (5.7%), GGT increased (5.7%), hyponatremia (5.7%), lymphocyte count decreased (5.7%), and neutrophil count decreased (5.7%). There was no death due to TRAE. Median time of onset for Gr3 peripheral neuropathy (PN, N=6) was 5.5 mos with 5/6 resolved/improving following dose modification. In pts with Gr3 PN, ORR was 67% (4/6) and mPFS was 8.8 mo. There was no correlation between EDB+FN expression and clinical activity.

Conclusion: MICVO addresses an unmet need in 2L+ HNSCC and demonstrates promising HPV-agnostic activity including post anti-EGFR with a manageable safety profile with dose capping. The data supports advancing MICVO monotherapy into a pivotal program in 2L+ HNSCC.

No conflict of interest

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4LBA **Oral**

A novel antibody-drug conjugate targeting urokinase plasminogen activator receptor-associated protein in previously treated patients with advanced soft tissue sarcoma: Emerging clinical results from the phase 1 ADCElerate1 study (NCT06797999)

P. Schöffski [1], J.Y. Blay [2], B. Wilky [3], S. Patel [4], R. Maki [5], S. Bauer [6], M. Wibroe [7], V. Haddad [7], E. Didier [7], L. Ottesen [7], J. Trent [8]

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Background: Urokinase plasminogen activator receptor-associated protein (uPARAP) is overexpressed across soft tissue sarcoma (STS) subtypes, a family of malignancies often affecting younger patients, with a high unmet medical need, as available post-anthracycline agents achieve objective response rates (ORR) $\leq$ 10%. ADCE-D01 is a uPARAP-targeting antibody-drug conjugate (ADC) with a topoisomerase I inhibitor payload. We report the first clinical data from an ongoing first-in-human, STS-specific phase 1 dose escalation study.

Material and methods: Adults patients (pts) with advanced STS and 1-2 lines of prior cytotoxic therapies received ADCE-D01 once weekly (Q1Wx3/ 28 days) or every 2 weeks (Q2W). Primary objectives were safety, tolerability, and determination of the maximum tolerated dose (MTD); secondary objectives included pharmacokinetics (PK) and antitumor activity. Escalation used a continual reassessment method with overdose control.

Results: Across 7 EU and US sites, 47 patients with 17 STS subtypes (most frequently leiomyosarcoma [28%], synovial sarcoma [13%], and angiosarcoma [11%]), an ECOG performance status of 0-1, a median of 2 prior lines of therapy [1-4] and a median age of 54 years [21-83] were treated with a median follow-up of 3.8 months [0.1–15.0]) of which 64% remain on treatment. The initial 18 patients received Q1W dosing (0.5–3.4 mg/kg); after PK analysis, the subsequent 29 patients had Q2W administration (3.4–6.6 mg/kg). The use of prophylactic pegylated granulocyte colony-stimulating factor (G-CSF) was mandated at doses $>$3.4 mg/kg (22/29 Q2W patients). Across all cohorts and schedules, the most common treatment related adverse events (TRAE) were nausea (66%), fatigue (45%), alopecia (45%) and neutropenia (43%). TRAEs led to dose reductions in 11% of pts and discontinuation in 2%. With mandatory G-CSF, grade $\geq$3 neutropenia decreased from 40% (10/25) to 14% (3/22), TRAEs led to dose reduction in 9%, and no TRAE led to discontinuation or death.

The ADC was stable with no major payload burst or accumulation. Terminal $T_{1/2}$ was ~2.5-3 days at 3.4-4.2 mg/kg enabling Q2W dosing. The Q2W MTD with G-CSF has not been reached yet.

Of the 23 Q2W pts evaluable for response, the ORR (RECIST 1.1) was 30% (4 confirmed, 3 pending confirmation) with responses in undifferentiated pleomorphic sarcoma, clear cell sarcoma, myxofibrosarcoma and angiosarcoma. Median duration of response has not been reached; all responses were ongoing at data cut off. The disease control rate was 88% at week 12.

Conclusions: ADCE-D01, a first-in-class uPARAP-targeted ADC, shows a manageable safety profile on the Q2W schedule with G-CSF and confirmed responses with durable disease control across multiple STS subtypes. Enrollment is ongoing. These results support further development in STS.

Conflict of interest: Advisory Board: Patrick Schöffski, Jean-Yves Blay, Breelyn Wilky, Shreyaskumar Patel, Robert Maki, Sebastian Bauer, Jonathan Trent: Adcendo Advisory Board

Other Substantive Relationships: Morten Wibroe, Vincent Haddad, Eric Didier, Lone Ottesen: Adcendo Employees

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5LBA **Oral**

Durable responses and prolonged progression-free survival with REM-422, an oral MYB mRNA degrader, in patients with biomarker-positive adenoid cystic carcinoma: Updated Phase 1 results

A. Ho [1], A. Algazi [2], M.J. Dennis [3], C. Even [4], R. Ferrarotto [5], G. Hanna [3], H. Kang [6], M. McKean [7], G. Rabinowits [8], E. Saada-Bouzid [9], J. Maag [10], J. Webster [11], C. Kung [10], M. Koneru [11], P. Swiecicki [12]

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Background: Adenoid cystic carcinoma (ACC) is characterized by dysregulation of the MYB transcription factor. There are no FDA approved systemic therapies for the treatment of ACC. Available systemic treatments (e.g. TKI, chemotherapies, immunooncology agents) demonstrate ORR of only 0-15% and median progression-free survival of approximately seven months, representing a significant unmet medical need. REM-422 is an oral small molecule that binds to a poison exon (PE) in the MYB mRNA and induces degradation of the mRNA, resulting in lower MYB protein levels.

Materials and Methods: This is a Phase 1/2 study to determine the safety, PK/PD and efficacy of REM-422 in patients with recurrent or metastatic (R/M) ACC. During Phase 1 Dose Escalation and Optimization, patients received oral REM-422 once daily (3 - 48mg) in 28-day cycles. Phase 1 enrollment was biomarker agnostic with tumor samples evaluated retrospectively for biomarker positivity (BM+, i.e. expressing MYB PE-containing mRNA transcripts or BM-, not expressing the PE).

Results: As of 24 August 2026, in the Phase 1 study, 69 patients were enrolled of which 60 patients were efficacy evaluable (as defined by measurable disease with target lesions identified in at least 1 post-treatment baseline scan): 32 BM+, 25 BM-, and 3 unknown. REM-422 was generally well-tolerated. No dose-limiting toxicities were observed. Across all dose levels tested, 10 out of 32 BM+ efficacy-evaluable patients achieved a PR with no objective responses noted in BM- patients.

At the RP2D (24 mg, n = 15), the objective response rate (ORR) was 4/7 (57%) in the efficacy-evaluable BM+ patients. All patients with starting doses >24mg underwent dose reduction to 24mg; 90% of PRs occurred at treating doses of ≤24mg. Among the BM+ patients who started at ≥24mg, the median follow-up was 8 months (m), and the time to initial PR was 7.5m (range 3-15m). Median DOR has not been reached (range up to 17m and ongoing), and time on treatment for BM+ patients for ≥24mg is up to 24m and ongoing. Median PFS has not been reached for the BM+ (n=19) and was 9m for BM- group (n=13).

MYB BM status was the consistent factor associated with both clinical and pharmacodynamic response to REM-422. Objective responses in BM+ patients were observed irrespective of mutation status, prior line of therapy, histology, ACC-subtype (type I vs II), or site of primary lesion.

Conclusions: REM-422, a small molecule MYB mRNA degrader, demonstrated durable clinical activity in BM+, R/M ACC and was generally well-tolerated with prolonged treatment at the RP2D. These findings support MYB biomarker status as a predictor of clinical benefit and continued evaluation of REM-422 in the ongoing Phase 2 study of BM+, recurrent, metastatic or unresectable ACC.

Clinical trial identifier: NCT06118086

Conflict of interest: Ownership: C Kung, J Maag, J Webster, and M Koneru are full-time employees of Remix Therapeutics and hold stock options in the company.

Advisory Board: R Ferrarotto, G Hanna, H Kang, P Swiecicki, and A Ho have participated in advisory boards for Remix Therapeutics and were compensated for their time.

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Plenary Session 6: Proffered papers: Advances in Targeting RAS

6LBA **Oral**

PT0253, a selective KRAS G12D degrader, shows a differentiated safety profile and antitumor activity, including after prior (K)RAS therapy, in advanced solid tumors

A. Spira [1], L. Pappas [2], W. McKean [3], D. Rasco [4], I. Rodriguez-Rivera [5], A. Tolcher [5], D.Y. Oh [6], H.J. Choi [7], J.W. Kim [8], J.O. Park [9], H.M. Chang [10], H.J. Chon [11], H. Hao [12], L. Gakhar [12], J. Donahue [12], A. Shilling [12], E. Rubin [12], N. Ji [12], A. Krivoshik [12]

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Background: PT0253 is a potent, selective degrader of KRAS G12D. Here, we report the preliminary safety and antitumor activity of PT0253 monotherapy in patients (pts) with previously treated advanced solid tumors.

Methods: In this phase 1, dose-escalation, first-in-human study, adults with unresectable or metastatic KRAS G12D-positive solid tumors were included. Pts received escalating doses of PT0253 monotherapy (10–750 mg across 10 dose levels) intravenously once weekly over a 21-day cycle. Primary endpoints were incidence of dose-limiting toxicities (DLTs) and treatment-related adverse events (TRAEs).

Results: As of 29 Sep 2026, 44 pts received PT0253 monotherapy (median [range] age: 65.5 [31-85] years; 55% male; median [range] prior lines of systemic therapy: 2.5 [0–8]). Tumor types were pancreatic ductal adenocarcinoma (PDAC) (n=21), CRC (n=13), NSCLC (n=3), and other cancers (n=7); 27% pts received prior (K)RAS therapy. At ≥120 mg (n=27), all TRAEs were Grade (Gr) 1 or 2, except one Gr3 neutrophil count decrease (4%). TRAEs in ≥10% of pts were 11 (41%) nausea, 8 (30%) fatigue, 7 (26%) rash, 6 (22%) headache, 6 (22%) infusion-related reaction, and 4 (15%) diarrhea. PT0253's differentiated safety profile showed minimal-to-no GI or liver toxicity. No DLT was observed and the maximum tolerated dose (MTD) was not reached. In (K)RAS therapy naïve patients at 120 mg and above (n=20), ORR was 30% (including 3/10 PDAC, 2/5 CRC, 1/2 NSCLC) and DCR was 95%. The DCR was 50% (6/12) in patients who received prior (K)RAS therapies, including 1 CRC PR.

Select expansion cohorts with 350 mg PT0253 were opened including combination with mFOLFIRINOX in 1L PDAC and cetuximab in 2L+ CRC. In 6 PDAC patients with at least two post-baseline scans, the confirmed ORR was 83% (5/6), including 1 confirmed complete response, and DCR was 100% (6/6). TRAEs in combination treatment with mFOLFIRINOX or weekly cetuximab were generally consistent with their respective established safety profiles.

Conclusions: The ongoing study suggests that PT0253, a selective KRAS G12D degrader, has a differentiated safety profile with promising antitumor activity, and potential ability to overcome resistance to prior (K)RAS therapies. Based on these results, additional expansion cohorts at 350 mg as monotherapy and in combination with standard of care therapies are currently enrolling.

Clinical trial identification: NCT06797336

Conflict of interest: Corporate-sponsored Research: Research funding from PAQ

Other Substantive Relationships: Several Authors are PAQ employees

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7LBA **Oral**

ALTA3263, a KRAS-selective, pan-mutant (ON/OFF) KRAS inhibitor, in patients with KRAS-mutant advanced solid Tumors: Preliminary safety, activity, and pharmacokinetics data from the 3263-001 Phase 1/1b trial

D.S. Hong [1], H. Park [2], D. Bhamidipati [3], A. Tolcher [4], C. Perez A [5], B. Huffman [6], I. Rodriguez Rivera Ismael [7], R. Heist S [2], J. Strickler H [8], M. Morse A [8], S. Punekar R [9], K. Papadopoulos P [10], C. Li [11], B. Herzberg [12], L. Faoro [13], V. Kang [13], A. Patel [13], J. Tran [14], C. Lane M [13], A. Spira I [15]

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Background: KRAS mutations occur in approximately 23% of all metastatic cancers, spanning a broad spectrum of mutation subtypes. Most patients (pts) with KRAS-mutant tumors have no approved targeted therapies. ALTA3263 is an oral, KRAS-selective, pan-mutant KRAS inhibitor that potently inhibits the ON- and OFF-state of multiple mutant forms of KRAS while sparing NRAS and HRAS. ALTA3263 has demonstrated robust antitumor activity in multiple KRAS-mutant (including G12A/C/D/V, G13 and Q61) and wild-type preclinical models.

Material and methods: 3263-001 is an open-label, multicenter Phase 1/1b trial (NCT06835569) in pts with KRAS-mutant advanced or metastatic solid tumors and ECOG ≤ 1. ALTA3263 was administered orally QD or BID starting at 25 mg QD (mTPI-2 escalation), as monotherapy (mono) or in combination with cetuximab (cetux). Study objectives include safety, pharmacokinetics (PK), efficacy and RDE/RP2D determination. Dose-escalation results are reported.

Results: As of 18 Sept 2026, 120 pts were treated across 14 dose levels: ALTA3263 mono (25 mg QD–600 mg BID; n = 80) and ALTA3263 + cetux (200–400 mg BID; n = 40). Pts had a median of 2 prior lines of therapy (range 0–9). Tumor types include PDAC (46%), CRC (42%), NSCLC (10%), and other (2%); KRAS mutations include G12V (40%), G12D (38%), G12A (8%), G13D (7%), Q61H (4%), and other (3%). The maximum tolerated dose (MTD) was not reached. ALTA3263 exposure increased approximately dose-proportionally up to 400 mg BID with no apparent accumulation after repeated dosing. Treatment-related adverse events (TRAE) occurred in 86% and 95% of pts receiving ALTA3263 mono and ALTA3263 + cetux, respectively, and grade ≥3 TRAEs in 15% and 33%. The most common TRAEs were diarrhea (51% and 83%), nausea (45% and 63%) and vomiting (46% and 45%). Dermatitis acneiform occurred in 11% and 68% of pts, with most events grade 1–2 (8% grade 3 with ALTA3263 + cetux). TRAEs led to discontinuation in 5% and 0% of pts. In response-evaluable pts dosed ≥14 weeks before data cutoff, the objective response rate ($uORR_{14w}$) was 23% and the disease control rate (DCR) was 77% in patients with PDAC on ALTA3263 400–600 mg BID mono. In pts with CRC on ALTA3263 200–300 mg BID + cetux, the $uORR_{14w}$ was 31% (5/16) and the DCR was 94%. Responses were observed across multiple KRAS mutations (G12A, G12D, G12V, G13D, Q61H).

Conclusions: ALTA3263 demonstrated strong anti-tumor activity across multiple mutations as monotherapy in PDAC and in combination with cetuximab in CRC, with a favorable safety profile. Exposure was linear and the MTD was not reached at doses up to 600 mg BID. Phase 1b cohorts are planned.

Conflict of interest: Ownership: Alterome Therapeutics, Break-Through Bio, Interact Therapeutics, IQVIA, START LP, Telperian, Triumvira Immunologics

Advisory Board: A2Bio, Aadi, AbbVie, Acuta, Adagene, Adlai-Nortye, Alpha Insights, Alterome, Amgen, Arkin, Astellas, AstraZeneca, Axiom, Bayer, BeOne Medicines (BeiGene), Biodexa, Biohaven, BioInvent, Blueprint, Boehringer Ingelheim, Boxer Capital, Bright Peak Therapeutics, Bristol Myers Squibb, BVF Consulting, Cardinal Health, Cervero, ClearView Oncology, Cogent Therapeutics, COR2ed, Cullinan Oncology, CureBio, Cytovation, Daiichi Sankyo, Ecor1, Eli Lilly, Elucida Oncology, EMD Serono/Merck KGaA, Erasca, Exelixis, Fenix Group, Fortress Biotech, Full-Life Technologies, GE Healthcare, Genentech/Roche, Gilead, GLG, Greywolf Therapeutics, GSK, Guardant Health, Guidepoint, Hexagon Bio, HuyaBio, IDEAYA Biosciences, Immunogenesis, Immunome, Incyte, Ipsen, Janssen, Jazz Pharmaceuticals, Johnson & Johnson, Kanaph Therapeutics, Kayak Therapeutics, Kestrel Therapeutics, Kivu, Kura, Leap Therapeutics, Leerink, Medscape, Merck, Mirati, Moonlight Bio, Morgan Stanley, Myricx Bio, Natera, NBE Therapeutics, Nested Therapeutics, Nextech Ventures, Parabilis Medicines, Pfizer, PharmaResearch, Pheon Therapeutics, Pre-Amp, Pyxis Oncology, Quanta Therapeutics, Qureata, Regeneron, Revolution Medicines, Sanofi, Servier, Skipta, SPARC, Spirea, Stratus Therapeutics, Sutro Bio Pharma, Syneos, Tagworks Pharmaceuticals, Taiho, Takeda, Tempus, T-Knife, Triumvira Immunologics, Turning Point Therapeutics, Verastem, Vincerx, VRISE Therapeutics, WAMBio/HighTop, WebMD, Xilio Therapeutics, Zentalis Pharmaceuticals, ZielBio

Board of Directors: None

Corporate-sponsored Research: AbbVie, Accent Therapeutics, Acendo, Adagene, Adaptimmune, Adcendo, Adlai-Nortye, Alnylam, Alterome Therapeutics, Amgen, Apollo Therapeutics, Arvinas, Astellas, AstraZeneca, Bayer, BeOne Medicines (BeiGene), Bicycle Therapeutics, BioNTech, Blueprint, Bolt Biotherapeutics, BridgeBio, Bristol Myers Squibb, C4 Therapeutics, Chong Kun, Chugai, Circle Pharma, CytomX, D3 Bio, Daiichi Sankyo, Debiopharm, Deciphera, Dewpoint, Eli Lilly/Loxo Oncology, Endeavor, Epibiologic, Erasca, Evopoint Biosciences, Exelixis, Frontier Medicine, Genentech/Roche, Genmab, GSK, Huaota, IDEAYA Biosciences, Idience, Immunogenesis, Incyte, Inhibrix, Kayak, Kestrel, Kumquat Biosciences, Kura, Leap Therapeutics, Lyell Immunopharma, MBrace, MediLink Therapeutics, Merck, Mirati Therapeutics, Modex, Monte Rosa Therapeutics, NCI-CTEP, Nested Therapeutics, Novartis, PAQ, Parabilis, Pfizer, PharmaMar, Pheast Therapeutics, Pheon Therapeutics, PMV Pharmaceuticals, Prelude Therapeutics, Quanta Therapeutics, Recursion, Regeneron, Repare Therapeutics, Revolution Medicines, Schrödinger, Sensei Therapeutics, Servier, Storm Therapeutics, Takeda,

Third Arc Bio, Tizona, Tolremo Therapeutics, VelaVagio, Verastem, VM Oncology, Yuhan

Other Substantive Relationships: AACR, AbbVie, Aclaris Therapeutics, Affinia Therapeutics, Agenus, Alterome Therapeutics (employment), Asana BioSciences, Ascentage, Astex Pharmaceuticals, AstraZeneca, Axlmmune, Bayer, BeOne Medicines (BeiGene), Blueprint Oncology, Byondis, Compugen, Coretag Therapeutics, Curadev Pharma, Cytel, Daiichi Sankyo, Day One Biopharmaceuticals, Eisai, Eli Lilly, Exelixis, FibroGen, Forbion, Gilde Healthcare Partners, HBM Partners, Horizon CME (STOP Cancer), IDEA Pharma, Ikena Oncology, Immuneering, Immunogenesis, Immunomet Therapeutics, Immuto Scientific, Impact Therapeutics US, Incyte, Indupro, Ipsen, Jazz Pharmaceuticals, Karma Oncology, Kirilys Therapeutics, Lengo Therapeutics, Link Immunotherapeutics, Lustgarten Foundation, Medicxi, Medscape, Mekanistic Therapeutics, Menarini Ricerche, Merck KGaA, Mersana, Mythic Therapeutics, Nanobiotix, Nerviano Medical Sciences, Novo Nordisk, Novo Ventures, Nurix Therapeutics, Ocellaris Pharma, Partner Therapeutics, Pfizer, Pierre Fabre, Praxis Precision Medicines, Prelude Therapeutics, Pyramid Biosciences, Qualigen Therapeutics, Roche, Ryvu Therapeutics, Seattle Genetics, Senti Biosciences, Servier, Simbec-Orion, Singzyme, SK Life Science, SOTIO Biotechnology, Sun Pharma Advanced Research Company (SPARC), Telperian, Tensegrity Pharma, Theratechnologies, Transcenta Therapeutics, Transgene, Trillium Therapeutics, Tubulis, Venus Oncology, Verastem Oncology, Vida Ventures Advisors, Voyant Bio (Ask Mendel AI)

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8LBA **Oral**

Daraxonrasib plus Gemcitabine/Nab-Paclitaxel (GnP) as First-Line (1L) Treatment for Patients (Pts) with Metastatic Pancreatic Adenocarcinoma (mPDAC)

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Background: Oncogenic RAS mutations occur in >90% of PDAC. Daraxonrasib, an oral, RAS(ON) multi-selective inhibitor targeting GTP-bound mutant and wild-type RAS, is FDA-approved for the treatment of adult pts with mPDAC who have received at least one prior systemic therapy or who are not candidates for multiagent systemic therapy. In the RASolute 302 randomized phase 3 trial, daraxonrasib demonstrated significant improvements in overall survival (OS) (hazard ratio [HR], 0.40) and progression-free survival (PFS) (HR, 0.49) compared with standard chemotherapy in pts with previously treated mPDAC. However, a high unmet need remains in 1L treatment of mPDAC, where current chemotherapy regimens provide limited clinical benefit (objective response rates: ~23%–42%, median PFS: 5.5–7.4 months, and median OS: 8.5–11.1 months), highlighting the urgency of developing more effective treatment options. Daraxonrasib plus GnP has demonstrated a manageable safety profile and encouraging antitumor activity in a cohort of pts with 1L mPDAC from an ongoing Phase 1/2 study (RMC-GI-102, NCT06445062); here, we report updated safety and more mature efficacy results, including PFS, from a larger patient population with longer follow-up.

Materials and methods: RMC-GI-102 is a multicenter study that enrolled pts who received daraxonrasib 200 mg orally once daily plus GnP (G, 1000 mg/m2; nP, 125 mg/m2; D1, D15). Pts with 1L mPDAC were eligible irrespective of RAS mutation status (including wild-type RAS tumors). Primary endpoints were safety and tolerability, and secondary endpoints included antitumor activity; PFS was estimated using Kaplan–Meier methods.

Results: As of September 28, 2026 (median follow-up, 18.3 months; range, 13.1-23.7 months), 61 pts with mPDAC had received daraxonrasib plus GnP. Safety profile was consistent with prior reports and the known safety profile of each component of the regimen; no new safety signals were identified with longer-term follow-up. The objective response rate was 60.7% (95% CI, 47.3–72.9), including complete response in 8.2% of pts. The disease control rate was 90.2% (95% CI, 79.8–96.3). Median PFS was 12.8 months (95% CI, 10.8–18.4).

Conclusions: Updated results from the Phase 1/2 study in 1L mPDAC, showed that daraxonrasib plus GnP demonstrated a clinically meaningful PFS and a consistent safety profile. These data support the continued exploration of daraxonrasib plus GnP as a potential 1L treatment option for pts in the ongoing global Phase 3 RASolute 303 study (NCT07491445).

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Conflict of interest: Ownership: J.R. Hecht: Stock option in Actym, Radical.ai, Triumvira; J. Strickler: Stock/Stock options in Triumvira Immunologics; N. Azad: Stock in Tempus; G. Botta: Shares in TumorGen; A. Parikh: Equity in C2i Genomics, Khora, OneCell, XGenomes, Cadex, and Panthera; S. Pant: Oncomed LLC and Telperian; H. Patel: Stock in Revolution Medicines; A. DeYoung: Stock in Revolution Medicines; Y. Zheng: Stock in Revolution Medicines

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W. Messersmith: Revolution Medicines. S. Pant: Ipsen, 40 Pharma, Amal Therapeutics, Arcus Bioscience, Astellas, Boehringer Ingelheim, Bristol-Myers Squibb, Elicio Therapeutics, Framewave, Immuneering, ImmunoMET, Incyte, Ipsen Biopharmaceuticals, Inc, Janssen Biotech, Jazz Pharmaceuticals, Lilly, Mirati Therapeutics, NGM Pharmaceuticals, Novartis, Pfizer, Revolution Medicines, Xencor, Zymeworks. B. Wolpin: Agios Pharmaceuticals, Inc., Amgen, AstraZeneca, Break Through Cancer, Eli Lilly and Company, Harbinger Health, Lustgarten Foundation, Mark Foundation for Cancer Research, NIH/NCI, Novartis, Pancreatic Cancer Action Network, Revolution Medicines, Stand Up To Cancer, and Stephenson Pancreatic Cancer Research

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9LBA **Oral**

Preliminary clinical results of QTX3034, an oral G12D-preferring KRAS inhibitor, in patients with KRASG12D-mutated endometrial cancer (EC)

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Background: QTX3034 is a selective, non-covalent, oral allosteric KRAS inhibitor with potency preference for G12D. QTX3034-001 is a FIH phase 1 study in patients (pts) with *KRAS*^{G12D}-mutated advanced solid tumors, including EC (NCT06227377). *KRAS*^{G12D} mutations are uncommon in EC, occurring in approximately 5-8% of patients. Initial QTX3034 dose-escalation results demonstrated a favorable safety profile with encouraging responses. Presented here are results from patients with EC treated with QTX3034 in the study.

Methods: The primary objectives were to evaluate the safety, tolerability, and maximum tolerated dose and/or recommended phase 2 dose (RP2D) of QTX3034. Part 1 enrolled cohorts at escalating QTX3034 doses. Part 2 enrolled expansion cohorts, including EC, at the RP2D of 1200 mg twice daily (BID). QTX3034 was given orally BID until PD, toxicity, or withdrawal.

Results: As of August 2026, 11 pts with EC were treated with QTX3034, including 1 patient at 800 mg BID and 10 patients at 1200 mg BID. The median follow-up was 7.9m (range 1.4-19.1). Median age was 63y (range 33-76) and 36% were ECOG 1. Known enrolled histologies were endometrioid (N = 5), serous (2), carcinosarcoma (1), and mesonephric-like adenocarcinoma (1). All were pMMR and had progressed following prior platinum-based chemotherapy and PD(L)1 inhibitors. The median number of prior lines of therapy was 4 (range 1-8). The ORR in patients with EC was 55%, including one complete response, and the median DOR in confirmed responders was 9.8m (range: 5.4+ to 11.0). Four of the 5 endometrioid patients responded. Across all patients with solid tumors enrolled in the monotherapy arm at 800-1200 mg BID (n = 31), the most common treatment-related AEs were nausea (87%), diarrhea (65%), vomiting (65%), and fatigue (23%). Grade 3-4 AEs occurred in five (16%) patients. Seven patients (23%) required dose reduction and there were no discontinuations due to AE.

Conclusions: Encouraging preliminary anti-tumor activity along with a well-tolerated safety profile were observed in patients with heavily pre-treated *KRAS*^{G12D}-mutant EC treated with QTX3034, warranting further development of QTX3034 in EC.

Conflict of interest: Ownership: Quanta Therapeutics, CrossBridge, Molecular Templates, OncoResponse, Telperian, Triumvira.

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Plenary Session 7: Proffered papers: Novel Agents and Targets

10LBA **Oral**

A first-in-human phase 1/2a study of the p53 Y220C reactivator NTS071 in patients with advanced solid tumors: Preliminary safety and antitumor activity

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Background: The *TP53* Y220C mutation occurs in ~100,000 new cancer cases worldwide annually and has no approved targeted therapies. NTS071 is a novel small-molecule designed to restore wild-type p53 function. In preclinical studies, NTS071 demonstrated superior *in vitro* potency, favorable ADME/T properties, and enhanced *in vivo* antitumor efficacy compared to other p53 Y220C reactivators in clinical development, supporting its potential as a best-in-class therapy.

Materials and Methods: NTS071-101 is an ongoing, open-label, multi-center phase 1/2a study evaluating NTS071 in patients (pts) with *TP53* Y220C-mutated advanced solid tumors following standard therapies (NCT07060989). Phase 1 employs an accelerated titration design followed by a Bayesian Optimal Interval (BOIN) design with backfilling. NTS071 is administered once daily (QD) in 21-day cycles at planned dose levels of 100–2000 mg. Primary objectives are to evaluate safety, tolerability, pharmacokinetics, and determine the recommended phase 2 dose (RP2D). Exploratory objectives include evaluation of pharmacodynamic biomarkers and their association with safety profiles and efficacy. The study is enrolling pts in the US and China.

Results: As of Sep. 24, 2026, 26 pts had been enrolled across the 100–1200 mg dose cohorts. Median age was 62 years (range, 30–80); 95% had ECOG PS of 1 and had received a median of two prior lines of therapy. Most frequent tumor types included were microsatellite-stable metastatic colorectal (MSS CRC), triple-negative breast (TNBC) and lung (NSCLC) cancers. No dose-limiting toxicities (DLTs) or Grade 4/5 treatment-emergent adverse events were observed. Grade 3 TRAEs occurred in 15.4% (4/26) of the pts. Responses were observed from the 200 mg dose level onward across multiple cancer types. Among the 18 response-evaluable pts in the efficacious dose range (200 mg QD to 800 mg QD), the objective response rate (ORR) was 66.7% (12/18) including 1 complete response (CR) in a pt with ovarian cancer (OC) and 11 partial responses (PRs) in: MSS CRC (3/4), TNBC (2/3), NSCLC (2/3), OC (2/2), gastric cancer (1/1) and sarcoma (1/1), indicating the potential of NTS071 as a tumor-agnostic therapy. Notably, among 4 pts with MSS CRC, 3 achieved confirmed PR, 1 pt had stable disease with tumor shrinkage. The overall disease control rate (DCR) was 94.4% among the 18 pts, and 13 of them were still on treatment at the data cut-off date.

Conclusions: NTS071 demonstrated a favorable safety profile and encouraging preliminary anti-tumor activity across multiple *TP53* Y220C-mutant tumor types, including MSS CRC. Responses were observed starting 200mg QD dose, supporting the continued clinical development of NTS071 as a potential tumor-agnostic treatment. The trial remains ongoing, with further evaluation in dose-expansion cohorts underway.

No conflict of interest

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11LBA **Oral**

Safety, dose optimization, and preliminary antitumor activity from a Phase 1 dose escalation study of ACR-2316, a novel WEE1/PKMYT1 inhibitor

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Background: ACR-2316 is a potentially first-in-class, oral WEE1/PKMYT1 inhibitor rationally designed using the Acrivon Predictive Precision Proteomics (AP3) platform for superior single agent activity through CDK1/2 and PLK1 activation. We report the results from the first-in-human trial.

Material and Methods: This ongoing Phase 1/2 trial (NCT06667141) evaluates ACR-2316 in adults with AP3-predicted, relapsed/refractory solid tumors. MTD was primary endpoint, safety, tolerability and PK secondary, and PD and antitumor activity

exploratory. Patients received ACR-2316 once daily in 21-day cycles (Schedule A: 3 days on/4 off; Schedule B 2 on/5 off). AEs were graded per CTCAE v5.0; CT scans obtained every 6 weeks (RECIST v1.1). Unbiased global PD assessment was done by AP3-based mass spectrometry in PBMCs. Safety, tolerability, PK/PD and antitumor activity across doses/schedules guided dose optimization and RP2D selection (FDA Project Optimus).

Results: Thirty-three heavily pretreated patients received 30-240 mg across the 2 dose escalation regimens. AP3-predicted tumor types included lung (8), endometrial (EC; 5), breast and ovarian/fallopian (4 each), colorectal and head/neck (3 each), prostate (2), and pancreatic, ampullary, urothelial, and vulvar (1 each). Median age: 63 years (35–77). Median prior lines: 3 (1–8); prior immunotherapy 25/33 (76%); prior ADCs 9/33 (27%). MTD was 160 mg and 240 mg for schedules A and B, respectively. Median treatment duration: 5.9 weeks; 3 lung cancer patients remained progression-free ≥60 weeks; two confirmed PRs in patients with squamous NSCLC and EC had PFS of 13.6mo and 6.8mo, respectively. TRAEs (1/20 Gr4 and 7/20 Gr3) were limited to primarily transient, mechanism-based hematologic including neutropenia (1 Gr4, 4 Gr3), anemia (1 Gr3), as well as 1 Gr3 ALT increase and 1 Gr3 INR increase. Only Gr3 SAEs were observed (5/20). No TRAE-based dose discontinuations were observed. C1D1 geometric mean Cmax/AUClast: 51.2 ng/mL/577 ng·h/mL (120 mg; n = 3), and 60.2 ng/mL/858 ng·h/mL (160 mg; n = 4). Schedule A was chosen for dose optimization at 120 and 160 mg.

Conclusions: ACR-2316 showed a highly differentiated, favorable safety profile, primarily limited to transient, asymptomatic, mechanism-based neutropenia. Durable activity and long-lasting clinical benefit was observed across AP3-predicted tumor types, including EC as well as lung cancer (SCLC, squamous NSCLC, adenocarcinoma), a tumor type not typically sensitive to WEE1 or PKMYT1 inhibitors. Dose optimization is ongoing in 2 selected doses to support RP2D selection and further development.

Conflict of interest: Ownership: University of Texas MD Anderson Cancer Center; where I am Vice President, Head Clinical Development in the Therapeutics Discovery Division, which has a commercial interest in DNA damage response (DDR) and other inhibitors (IACS30380/ ART0380 was licensed to Artios)

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12LBA **Oral**

Efficacy, molecular activity and safety from the pivotal PYNNACLE Phase 2 trial assessing rezatapopt, a p53 reactivator, in TP53 Y220C-positive advanced solid tumors

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Background: *TP53* Y220C mutations occur in ~1.2% of solid tumors and ~3.2% of ovarian cancers (OC). Rezatapopt is an investigational, first-in-class p53 Y220C reactivator designed to restore p53 tumor suppressor activity. Updated efficacy, molecular activity and safety are reported.

Methods: PYNNACLE (NCT04585750) is a pivotal Phase 2, global, single-arm basket trial of rezatapopt 2000mg once daily for advanced solid tumors with a *TP53* Y220C mutation and *KRAS* wildtype. Cohorts are defined by tumor type. Primary endpoint: overall response rate (ORR; RECIST v1.1; blinded independent central review) across all tumors and in OC. Other endpoints: investigator-assessed (IA) ORR; duration of response (DoR); time to response (TTR); safety; biomarkers. IA ORR is reported for all tumors and OC.

Results: By 4 Sep 2026, 180 patients (pts) had received rezatapopt (OC 113). Median age was 65 years (range 33–91). Pts had received 1–9 prior therapies (median 3). Most OC was high grade serous (95%) and platinum-resistant/refractory (PROC 97%).

IA ORR was 36% across all tumors and 45% in OC (**Table**). Median TTR/DoR were 1.3/8.1 months across tumors and 1.3/10.4 months in OC. In pts with PROC that had received standard of care (n = 65 primary analysis population), ORR was 48% (median DoR 10.4 months). Responses were seen across tumor types and in the presence of additional *TP53* alterations or other oncogenic driver mutations at baseline.

Across tumors, in pts with ctDNA data (n = 121), 80% had ≥ 50% and 57% had ≥ 90% decreases in ctDNA *TP53* Y220C variant allele frequency after 3–6 weeks of treatment.

Treatment-related adverse events (TRAEs) across tumors (n = 180) were mostly Grade 1/2; most frequent (> 20%): nausea (46%), fatigue (26%), creatinine increase (21%). Eleven pts (6%; OC 7) discontinued treatment due to TRAEs.

Conclusions: In heavily pretreated pts, rezatapopt demonstrated clinically meaningful efficacy and robust on-target activity, with substantial reductions in *TP53* Y220C ctDNA and responses in PROC and other tumor types, including in pts with additional baseline oncogenic driver mutations. Together with a manageable safety profile, these findings support rezatapopt as a promising therapeutic approach for *TP53* Y220C-positive advanced solid tumors.

Investigator assessed	All tumorsn = 168[a]	Ovarian cancer (OC)n = 101[a]	Primary analysis populationPlatinum resistant/refractory OCn = 65[a]
Overall response rate,[b] n (%) 95% CI	61 (36.3) 29.0–44.1	45 (44.5) 34.7–54.8	31 (47.7) 35.1–60.5
Confirmed response (CR)	4 (2.4)	4 (4.0)	1 (1.5)
Partial response (PR)	53 (31.5)	37[c] (36.6)	30[c] (46.2)
Unconfirmed PR (uPR)	4 (2.4)	4 (4.0)	
Median duration of response,[d] months	8.1	10.4	10.4
Disease control rate,e n (%)	130 (77.4)	81 (80.2)	52 (80.0)

Cutoff 4 Sep 2026
[a]Had first post-baseline tumor assessment or discontinued early
[b]CR + PR + uPR
[c]1 PR was unconfirmed CR
[d]Confirmed responses only
[e]CR + PR + stable disease

Conflict of interest: Ownership: David Shao Peng Tan: Ownership of stocks/shares: Asian Microbiome Library (AMiLi). Shivaani Kummar: Stock or ownership interest: Arexeon (spouse), Fortress Biotech (self), Pathomiq (self). Other: Mirati Therapeutics. Anita Schmid: Employee: PMV Pharmaceuticals, Inc. with stock options. Deepika Jalota: Employee: PMV Pharmaceuticals, Inc. with stock options. Marc Fellous: Employee: PMV Pharmaceuticals, Inc. with stock options.

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Lee: Consulting or advisory role: AstraZeneca, CanariaBio, DS, Eisai, Genmab, GII, ImmunoGen, Merk, MDS, SEagen, Sutro, Regeneron. Data Safety Monitoriing Board or Advisory board: AstraZeneca, Genmab, ImmunoGen, MSD, Merk, Regeneron, Seagen. David Shao Peng Tan: Personal fees for advisory board membership: AstraZeneca, Bayer, BioNTech, Boehringer Ingelheim, Eisai, Genmab, GlaxoSmithKline, MSD, PMV Pharmaceuticals, Inc., Daiichi-Sankyo, Roche. Geoffrey Shapiro: advisory boards: Merck KGaA/EMD Serono, Concarlo Therapeutics, Circle Pharmaceuticals, ForRx Therapeutics, Schrodinger, MycRx. Shivaani Kummar: advisory board: Springworks Therapeutics, SeaGen, Bayer, Genome & Company, HarbourBiomed, BPGbio Therapeutics, Oxford Biotherapeutics, Mundibiopharma, BPGbio, Inc., Gilead, Mirati, GI Innovation Inc, XYone Therapeutics, Genome Insight, Aadi Biosciences, MOMA Therapeutics, Daiichi Sankyo, Parabilis, Boehringer Ingelheim Pharmaceuticals, Navexio, Two Step Therapeutics. Alastair Greystoke: Consultancy and speaker fees: AstraZeneca, Amgen, Boehringer Ingelheim, BMS, Janssen/Johnson & Johnson, MSD, Novartis, Pfizer, Eli Lilly, Takeda, and Roche. Ecaterina E. Dumbrava: advisory board: BOLT Therapeutics, Mersana Therapeutics, Orum Therapeutics, Summit Therapeutics, Fate Therapeutics and PMV Pharmaceuticals.

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Previous non-renumerated role as chair of the Asia Pacific Gynecologic Oncology Trials Group (APGOT) a previous non-renumerated role as the Society President of the Gynecologic Cancer Group Singapore non-renumerated membership of the Board of Directors of the GCIG. Product samples: AstraZeneca, Eisai, MSD (non-financial interest) for research trials. Geoffrey Shapiro: Patents: "Dosage regimen for sapacitabine and seliciclib," and "Compositions and Methods for Predicting Response and Resistance to CDK4/6 inhibition." Alastair Greystoke: Other role: Clinical Director (Cancer), North East England Hull and Yorkshire Genomic Medicine Service. Ecaterina E. Dumbrava: Speaker: PMV Pharmaceuticals and BOLT Therapeutics. Travel, accommodation, expenses: ASCO, LFSA Association, Rain Oncology, Banner MD Anderson Cancer Center, Triumvira Immunologics, KSMO and Boehringer Ingelheim. Anita Schmid: Employee: PMV Pharmaceuticals, Inc. with stock options. Deepika Jalota: Employee: PMV Pharmaceuticals, Inc. with stock options. Marc Fellous: Employee: PMV Pharmaceuticals, Inc. with stock options.

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Poster Session: Late Breaking Abstracts

25LBA - PB-010 **Poster**

In vitro and in vivo evaluation of the therapeutic effect of a Melatonin-Furanochalcone hybrid on colorectal cancer

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Introduction: Colorectal cancer (CRC) is a leading cause of cancer-related morbidity and mortality worldwide. Current treatments are associated with significant adverse effects, which drives the search for more effective and safer therapeutic alternatives. Melatonin and chalcones have attracted interest because of their antioxidant, anti-inflammatory, and antitumor properties. The aim of this study was to evaluate the therapeutic potential and safety profile of a melatonin-furanochalcone hybrid (MFC) in experimental models of CRC, both *in vitro* and *in vivo*.

Materials and Methods: *In vitro* assays were first performed to assess the cytotoxicity, selectivity, and antiproliferative activity of the MFC hybrid using the SW480 (human colon adenocarcinoma), CT26 (murine colon adenocarcinoma), and NCM460 (non-tumorigenic human colon) cell lines. The oral median lethal dose (LD50) of the hybrid compound was then determined in BALB/c mice following OECD Guideline 425 for the testing of chemicals. Subsequently, mice received 50% of the LD50 orally to evaluate genotoxic effects in liver and colon tissues using the comet assay, and mutagenicity in bone marrow using the micronucleus assay. Finally, a pilot study was conducted to assess the effect of MFC on CRC progression. For this purpose, 25% of the LD50 was administered to mice with CRC chemically induced by azoxymethane and dextran sulfate sodium.

Results and Discussion: *In vitro* assays showed that MFC exerts a potent cytotoxic effect and high selectivity toward human and murine colon adenocarcinoma cells, with greater sensitivity in the human SW480 cell line. The compound also displayed marked antiproliferative activity that was dependent on both concentration and exposure time, demonstrating its ability to inhibit tumor cell growth. *In vivo*, MFC showed an LD50 above 2000 mg/kg, suggesting a favorable safety profile and low acute toxicity after oral administration. Likewise, genotoxicity and mutagenicity assays revealed no DNA damage or chromosomal alterations, indicating no adverse effects on genetic stability under the conditions evaluated. In the pilot study of chemically induced CRC, administration of MFC between weeks 4 and 8 after tumor induction delayed disease progression. This effect was evidenced by a lower tumor burden and a slower evolution of preneoplastic lesions compared with untreated animals, supporting the antitumor potential and biological safety of this compound. **Conclusion:** These results suggest that the MFC hybrid is a promising anticancer agent against CRC, owing to its antiproliferative activity, its ability to delay tumor progression, and its low toxicity. However, additional studies are required to confirm its efficacy and to elucidate its possible mechanisms of action.

No conflict of interest

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26LBA - PB-011 **Poster**

First-in-human immuno-PET validates oncofetal chondroitin sulfate as a novel druggable target across solid cancers – A Phase 0 Nuclear Imaging Basket Trial (VARTUTRACE)

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Background: Targeted therapy development is limited by the scarcity of actionable cancer targets and by the challenge of achieving therapeutically relevant antibody concentrations within tumors. Oncofetal signatures, shared by embryonic and cancer cells but absent from healthy adult tissues, offer a selective targeting strategy. One example is oncofetal chondroitin sulfate (ofCS). Tissue staining and preclinical models suggest that ofCS is tumor-specific, broadly expressed across cancer types and contributing to tumor immune evasion. However, its accessibility and true tumor specificity in patients remain unknown. We developed Vartumab C9, the first anti-ofCS human monoclonal antibody. We conducted a phase 0, first-in-human microdosing immuno-PET study to establish ofCS accessibility and tumor-specific targeting across solid malignancies.

Materials and Methods: Vartumab C9 was produced as single chain variable fragment with a genetically fused albumin binding domain for half-life extension and labelled with Zirconium 89. Following a single intravenous microdose administration of the Vartumab (1mg, 15 MBq), long axial field of view (LAFOV) PET/CT images were obtained at day 0, 1, and 3 post-injection (p.i.) for the first 3 patients and at day 3 for 13 additional patients. Standardized uptake values (SUV), quantified on standardized EARL reconstruction, of volumes of interest were compared to blood pool to calculate tumor/organ-to-background ratios (TBR/OBR) over time (NCT06645808).

Results: All injections were well tolerated, with no product-related adverse events reported. In the first three patients,

comprising two with non-small cell lung carcinoma (NSCLC) and one with rectal carcinoma, tumor uptake was evident in all patients by day 3 p.i. (mean SUVpeak 7.23; TBR 1.98). The subsequent 13 patients were scanned on day 3, also without biomarker-based stratification for patient inclusion. In total, 14 out of 16 patients demonstrated significant and specific tumor uptake of Vartumab C9 across a broad range of malignancies, including lung cancer, colorectal cancer, glioblastoma, PDAC, bladder cancer, soft tissue sarcoma, metastatic breast cancer, and esophageal cancer. Off-target accumulation was for most patients restricted to the adrenal glands and testis.

Conclusion: The VARTUTRACE study provides the first clinical demonstration that ofCS is an accessible and druggable pan-cancer target. Vartumab C9 safely achieved specific tumor accumulation across a remarkably broad spectrum of solid malignancies in non-stratified patients, including difficult-to-target tumors such as PDAC, glioblastoma and sarcoma, with acceptable off-target binding. Building on this clinical validation, we have successfully manufactured VTP-03, a Vartumab-based antibody drug conjugate that has completed GLP toxicology studies and is expected to enter clinical trials in Q2 2027.

Conflict of interest: Ownership: Ali Salanti, Thor Theander, Mads Daugaard and Thomas M. Clausen are shareholders in VAR2-Pharmaceuticals who holds the rights to use VARTUMABS to target, treat and diagnose cancer. The trial was sponsored by VAR2Pharmacueticals

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27LBA - PB-012 **Poster**

Discovery of NTS242, a highly potent and selective covalent PI3Kα–RAS PPI disruptor featuring a de novo AI-generated scaffold

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RAS binding to PI3Kα is largely dispensable in normal cells but essential for tumor formation and maintenance. Selective disruption of the PI3Kα–RAS protein–protein interaction (PPI) suppresses RAS-driven PI3Kα pathway activation, as exemplified by the pioneer molecule BBO-10203, without perturbing insulin homeostasis, in contrast to conventional PI3Kα kinase inhibitors.

NTS242 is an orally available, highly potent and selective small-molecule inhibitor of PI3Kα–RAS family interactions, with covalent binding to the Cys242 residue of p110α confirmed by co-crystal structure. Its chemical scaffold was generated using AI diffusion models within Nutshell Therapeutics' proprietary AlloStar™ platform, guided by the structure of the PI3Kα RAS-binding domain (RBD), and subsequently optimized for drug-like properties.

In the PI3Kα–RAS homogeneous time-resolved fluorescence (HTRF) assay, NTS242 exhibited more potent inhibitory activity of the PI3Kα–RAS PPI than BBO-10203, with a lower IC_{50} and substantially greater maximal inhibition (near 100% vs. <80% for BBO-10203). Consistently, NTS242 was found to be more potent than BBO-10203 in inhibiting AKT phosphorylation (pAKT) and cell proliferation as demonstrated in HER2-positive cells. Furthermore, NTS242 has superior PK properties relative to BBO-10203, with markedly higher oral exposure and lower plasma protein binding. As illustrated in the HER2-positive KYSE-410 esophageal cancer xenograft model, NTS242 achieved *in vivo* antitumor efficacy comparable to BBO-10203 at one-tenth the dose (1 mg/kg vs. 10 mg/kg for BBO-10203) and showed enhanced tumor regression at higher doses. NTS242 also displays single-agent antitumor efficacy in multiple CDX and PDX models, including HER2-positive breast and gastric cancer, HR + /HER2- breast cancer, KRAS-mutant NSCLC, and notably, Enhertu-resistant models refractory to HER2-targeted therapy. In addition, NTS242 exhibited synergistic *in vitro* and *in vivo* antitumor activities when combined with fulvestrant and ribociclib in HR + /HER2- breast cancer models, and with daraxonrasib (RMC-6236) in RAS-mutant models. Unlike alpelisib, NTS242 did not raise blood glucose or insulin levels in oral glucose tolerance test (oGTT).

Collectively, these findings warrant further development of NTS242, both as monotherapy and in combination with standard targeted agents, for the treatment of HER2-positive malignancies, HR + /HER2- breast cancer and RAS-mutant cancers.

No conflict of interest

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28LBA - PB-013 **Poster**

NP-101 in advanced solid tumors: Early clinical experience and preliminary evidence of disease control

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Background: Immune checkpoint inhibitors have transformed cancer treatment, yet durable responses remain limited in advanced solid tumors, driving the need for novel immunomodulatory therapies. NP-101 is a first-in-class oral therapeutic derived from *Nigella sativa* containing thymoquinone and associated bioactive fatty acids. Preclinically, NP-101 demonstrated robust antitumor activity in pancreatic neuroendocrine tumor cell lines, as well as NRAS-mutant pancreatic neuroendocrine and hepatocellular carcinoma models, providing a clinical rationale for evaluation in advanced solid tumors.

Methods: This ongoing open-label Phase 1 study (NCT06563375) is investigating oral NP-101 administered twice daily in continuous 28-day cycles in patients with advanced solid tumors. The study utilizes a Bayesian optimal interval design comprising a 15-patient dose escalation across three planned dose levels (3.0, 4.8, and 6.0 g/day) to determine the maximum tolerated dose (MTD). A 10-patient dose expansion will then assess preliminary antitumor activity and recommended Phase 2 dose (RP2D). Adverse events (AEs) are graded according to the CTCAE v5.0, and tumor response is assessed using the RECIST v1.1 and iRECIST. Primary objectives are safety, tolerability, MTD, and recommended Phase 2 dose (RP2D). The secondary objective is preliminary antitumor activity. Exploratory objectives include pharmacokinetic characterization, biomarker discovery via AI-guided tumor microenvironment analysis, T-cell receptor β sequencing, and imaging, and patient-reported outcomes.

Results: As of October 5, 2026, 13 patients were enrolled across dose level 1 (n = 3) and dose level 2 (n = 10). The median age was 60 years (range, 32–78), 46% were male, 92% were non-Hispanic White, and 46% had colorectal cancer (CRC). No dose-limiting toxicities were observed. Four Grade 1 treatment-related AEs were reported in 3 patients, consisting of bloating, stomach pain, diarrhea, and constipation. Three Grade 3 serious AEs were reported in 3 patients but were deemed unrelated to treatment, including back pain, hepatic hemorrhage (secondary to biopsy), and hyponatremia. Best overall response was stable disease in 3 patients, including 1 patient with pancreatic cancer (lasting 8.2 months) and two patients with CRC (lasting 4.6 and 5.4 months).

Conclusions: NP-101 is well tolerated and exhibits antitumor activity in immunologically resistant solid tumors, including pancreatic cancer and CRC. Ongoing translational analyses will define pharmacodynamic effects, identify biomarkers associated with clinical benefit, and inform RP2D, supporting the continued clinical development of NP-101 as a novel oral immunomodulatory cancer therapeutic.

Conflict of interest: Ownership: Ahmed Kaseb: Co-founder, Novatek Pharmaceuticals, Inc

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29LBA - PB-014 **Poster**

CRISPR screens reveal MCT1-driven metabolic escape from SMAD3 inhibition as a therapeutic vulnerability

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Background: Resistance to therapy remains a critical challenge in cancer. This is exemplified by TGF-β pathway inhibitors which, despite broad clinical testing, have failed to deliver survival benefit. More precise SMAD3 targeting has shown preclinical promise, yet resistance mechanisms to SMAD3 inhibition remain entirely unknown.

Materials and methods: The study implements functional genomics tools such as genome-wide CRISPR-screening together with Oxford nanopore direct long-read RNA sequencing, Seahorse metabolic flux assay, LC-MS metabolite quantification, multi-omics analyses, functional KO-Rescue validation, multiple human cancer cell lines and mouse preclinical models.

Results: Using complementary genome-wide CRISPR activation and knockout screens, we discover that cancer cells escape SMAD3 inhibition through metabolic reprogramming. Strikingly, this escape is driven not by transcriptional bypass but by the lactate transporter MCT1, with the effect preserved across BRAF-mutated melanoma, KRAS-mutated lung adenocarcinoma, and mouse melanoma. Mechanistically, SMAD3 inhibition creates energetic stress that cancer cells exploit through MCT1. By conferring metabolic flexibility and switching toward glycolysis under drug pressure, MCT1 increases anabolic activity to drive lipid and cholesterol synthesis. Pharmacological and genetic MCT1 inhibition synergizes strongly with SMAD3 blockade to impair tumor viability in BRAF-mutated melanoma, while suppressing drug-tolerant cell emergence in BRAF inhibitor-resistant cells. Critically, this synergy extends to preclinical models, where co-inhibition of SMAD3 and MCT1 potently reduces tumor growth in vivo.

Conclusions: These findings establish metabolic escape through MCT1 as a therapeutically exploitable vulnerability in resistance to transcription factor-directed therapy and provide a new explanation for why TGF-β inhibitors have failed in the clinic. Given the additional and well-established role of MCT1 in shaping the tumor immune microenvironment via lactate transport, these results position MCT1 as both a metabolic and immunological target and provide a strong rationale for the repurposing of TGF-β/SMAD3 pathway inhibitors in a novel and efficient combination, opening a path toward overcoming the clinical limitations of this therapeutic class.

No conflict of interest

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30LBA - PB-015 **Poster**

Early Identification of Interstitial Lung Disease Risk While Measuring ADC Efficacy in a Human Systemic In Vitro Platform

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Background: Antibody–drug conjugates (ADCs) have transformed targeted oncology, but systemic toxicities such as interstitial lung disease (ILD) remain difficult to predict during preclinical development. ILD is a major safety concern for deruxtecan (DXd)-containing ADCs, including trastuzumab deruxtecan (T-DXd). Their membrane-permeable payloads enable antitumor bystander effects but may also contribute to pulmonary injury. Human-relevant models capable of assessing both antitumor activity and lung toxicity are therefore needed.

Material and methods: We established a human multi-tissue co-culture platform combining AlveolAir™, a primary human alveolar model, with encapsulated 3D tumor spheroids under shared exposure conditions. The platform enables tissue-specific assessment of drug responses within the same assay. T-DXd, free exatecan, and trastuzumab emtansine (T-DM1) were evaluated as benchmarks to characterize pulmonary toxicity and antitumor activity. The model was subsequently challenged with patritumab deruxtecan (P-DXd), a HER3-targeting ADC investigated in EGFR-mutated non-small cell lung cancer.

Results: The platform detected lung injury-associated responses following exposure to DXd-containing ADCs, while T-DM1 exhibited limited pulmonary toxicity under the tested conditions. These findings demonstrated the ability of the assay to distinguish ADCs with different pulmonary safety profiles. Evaluation of P-DXd also revealed lung injury-associated responses, consistent with the clinical ILD safety concern reported for this ADC. The combined tumor–alveolar system provides a framework to investigate tissue-specific responses under shared exposure conditions and explore potential tumor-mediated bystander effects.

Conclusions: This human multi-tissue platform provides a scalable and biologically relevant approach to investigate ADC-associated lung injury alongside antitumor activity. By integrating pulmonary safety and efficacy assessments within a single assay, it offers an opportunity to characterize therapeutic windows, explore mechanisms of systemic toxicity, and support early de-risking of emerging ADC candidates.

Keywords: Antibody–drug conjugates; Interstitial lung disease; Human multi-tissue models

No conflict of interest

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31LBA - PB-016 **Poster**

Therapeutic targeting of SUMOylation in BRAF-mutated skin cutaneous melanoma

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Skin cutaneous melanoma (SCM) is an aggressive malignancy originating from the melanocytes of the skin. SCM accounts for majority of skin cancer deaths and its incidence has been rising globally. Key genetic changes include mutations of *BRAF*, *NRAS*, *CDKN2A/B*, and *NF1*. Treatment results of SCM have improved due to development of immune checkpoint inhibitors and therapies targeting BRAF and MEK, but typically less than half of patients survive over 5 years with metastatic disease, highlighting a need for novel prognostic biomarkers and therapeutic strategies.

Several pathways and processes relevant to cancer involve regulation by the small ubiquitin-related modifier (SUMO) but little is known of its impact on melanoma pathogenesis. SUMO proteins are attached to substrates in a reversible post-translational modification termed SUMOylation that regulates the interactions, localization, stability, and enzymatic function of target proteins. SUMO-activating enzyme (SAE1/2) inhibitor TAK-981 is being evaluated in clinical trials in cancer patients as the first-in-class SUMOylation inhibitor, but the cancer types most sensitive to TAK-981 remain to be discovered.

We find that SCM has the highest overall frequency of mutations targeting SUMOylation-regulating factors based on our analyses of the TCGA pan-cancer cohorts representing 32 different cancer types, suggesting that the SUMO pathway may play a role in melanoma pathogenesis. Our *in silico* data show that expression of *SAE1* is upregulated in melanoma compared to normal tissues, and SAE1 is highly expressed at the protein level in melanoma cell lines. Survival analyses of the SCM TCGA cohort showed that high *SAE1* expression associates with poor overall and disease-specific survival in patients with BRAF-V600 mutation but not in wild type (wt) BRAF patients, suggesting for potential differences in the impact of SUMOylation on pathogenesis of BRAF-V600-mutated and BRAF wt melanoma. Our data show that patient-derived melanoma cells are sensitive to SUMOylation inhibition with TAK-981 based on *ex vivo* drug screening results using samples from our prospective PROEXMET clinical study. These results were also confirmed using organoid cultures of patient-derived cells. Patient-derived melanoma cells harboring BRAF mutation may be more sensitive to SUMOylation inhibition compared to wt BRAF-expressing cells and accordingly analysis of CRISPR data from the Cancer Dependency Map indicated that BRAF-mutated melanoma cell lines are more sensitive to CRISPR knockout of *SAE1* compared to BRAF wt melanoma cells. Preliminary data also indicates that SUMOylation inhibition may have synergistic effects with BRAF-targeted therapeutics. Overall, the data indicates that SUMOylation may be a novel therapeutic target in BRAF-mutated melanoma.

No conflict of interest

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32LBA - PB-017 **Poster**

Identification of Novel drugs for Osteosarcoma treatment

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Background: Osteosarcoma (OS) is a rare primary bone malignancy with limited treatment advances over recent decades. The extracellular matrix (ECM) and tumor microenvironment (TME) influence cancer cell growth, invasion, and therapeutic response. However, conventional drug screening on two-dimensional plastic surfaces does not adequately reflect these conditions. This study aimed to identify promising therapeutic candidates using more physiologically relevant culture models.

Materials and Methods: We screened 32 anticancer compounds across seven OS cell lines, including four patient-derived and three commercial cell lines, under normoxic and hypoxic conditions on plastic and Myogel-coated surfaces. Drug sensitivity was assessed using cell viability assays to identify candidates with consistent efficacy. Selected candidates were further evaluated in 3D Myogel-based spheroid invasion assays, with invasion quantified from microscopic images using ImageJ.

Results: Napabucasin, salinomycin, and gedatolisib emerged as promising candidates, showing consistent activity in patient-derived OS cell lines and retaining efficacy under ECM and hypoxic conditions. All three compounds suppressed spheroid invasion. Gedatolisib demonstrated the broadest anti-invasive activity across patient-derived cell lines, with the strongest inhibition observed in the jawbone OS model.

Conclusion: Our findings identify three potential therapeutic candidates for OS and demonstrate the value of incorporating TME-related conditions into preclinical drug screening. Further investigation of their therapeutic potential using an in vivo zebrafish model is ongoing.

No conflict of interest

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33LBA - PB-018 **Poster**

Preclinical evaluation of M-2552: A novel next generation menin inhibitor capable of overcoming clinically observed menin resistance mutations

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Background: First-generation small molecule menin-KMT2A inhibitors, such as revumenib and ziftomenib, have demonstrated significant clinical efficacy in KMT2A-rearranged and NPM1-mutated acute leukemias. However, the rapid emergence of acquired somatic resistance mutations in the MEN1 gene alters the drug-

binding pocket through steric clash, leading to disease progression and limiting response durability. There is an urgent medical need for next-generation, mutation-resilient therapies. We report the preclinical profile of M-2552, a structurally unique, highly potent, next generation menin inhibitor designed to retain efficacy against wild-type (WT) and mutated menin.

Methods: Binding affinity was evaluated using an FP assay against WT menin and recombinant menin proteins carrying M327I, M327V, T349M, and S160C mutations. Cell antiproliferation was assessed across a panel of KMT2A-rearranged (MV4;11, MOLM13), and NPM1-mutant (OCI-AML-3) cell lines as well as mutant MOLM13, OCI-AML-3 cell lines expressing M327I, M327V, T349M, and S160C mutations. Co-crystal structures were obtained of inhibitors complexed with wild-type and M327V mutant menin protein. Pharmacokinetics were evaluated in mice, rats, dogs, and monkeys. In vivo pharmacokinetic/pharmacodynamic (PK/PD) study was in an MV4;11 xenograft model in which drug plasma/tumor concentrations were determined and RT-PCR was used to evaluate suppression of *HOXA9* and *MEIS1* in harvested tumor. In vivo efficacy was tested in an MV4;11 xenograft model.

Results: M-2552 demonstrates potent binding affinity to the clinically observed mutant menin proteins carrying M327I, M327V, T349M, and S160C mutations. Consistent with its binding profile, it potently inhibited the cell growth of wild-type MV4;11, MOLM13, and OCI-AML-3 leukemia cell lines, as well as mutant MOLM13 and OCI-AML-3 cells expressing these mutations. The co-crystal structures of a close analogue complexed with wild-type and M327V mutant menin provided structural rationale for its activity profile. M-2552 exhibited favorable pharmacokinetics in mice, rats, dogs, and monkeys. Furthermore, in a PK/PD study using an MV4;11 xenograft model, M-2552 showed high exposure and significantly decreased the levels of the biomarkers *MEIS1* and *HOXA9*. This translated into robust antitumor activity, with daily oral dosing of M-2552 at 50 mg/kg achieving complete and lasting tumor regression.

Conclusion: These data demonstrate that M-2552 effectively disrupts the menin-KMT2A interaction despite structural binding-pocket mutations, achieving robust anti-leukemic activity where first generation inhibitors fail. These findings identify M-2552 as a second-generation menin inhibitor with the potential to overcome resistance to first-generation inhibitors in the treatment of MLL-associated leukemias.

Conflict of interest: Other Substantive Relationships: Angleo Aguilar, Liyue Huang, Jeanne Stuckey, and Shaomeng Wang are co-inventors of the disclosed menin and related inhibitors. The University of Michigan has filed several patent applications related to the disclosed menin inhibitor, which were licensed to Ascentage Pharma. Shaomeng Wang is co-founder, Non-executive Director, and Chief Science Advisor in Ascentage Pharma.

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34LBA - PB-019 **Poster**

Comprehensive preclinical in vivo oncology platform for rational drug candidate nomination

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Introduction: Robust *in vivo* pharmacology is critical to de-risk oncology drug candidates and guide translational decision-making. Evotec's integrated preclinical platform combines scientific and animal welfare expertise with AAALAC and My Green Lab accreditations to accelerate candidate nomination.

Methods and Results: Leveraging multidisciplinary capabilities such as chemistry, early formulation, ADME/DMPK (LC-MS/MS), *in vitro* biology, and translational biomarker analysis is essential to support projects at any stage of drug discovery and whatever the therapeutic modality: small molecules, degraders, ADCs, antibodies, oligonucleotides, cell therapies, vaccines, and oncolytic viruses.

Our extensive tumor model repertoire covers multiple cancer indications and includes CDX and syngeneic models implanted SC, orthotopically or as metastatic model in a variety of mice backgrounds, immunocompetent, immunosuppressed or humanized for the immune system. We describe here case studies illustrating flexible study designs that include:

- Target validation with engineered cancer cells
- PK/PD studies (single/repeated dosing)
- Tolerability for chronic dosing derisking
- Efficacy studies assessing anti-tumor activity

Readouts encompass tumor growth inhibition, PK/PD correlation, target engagement, transcriptomics, proteomics, metabolomics, and tumor microenvironment characterization.

In addition, deciphering the relationship between PK, PD markers modulation and antitumor efficacy is of great value to model and predict human dose. Experts at Evotec have access to several modeling and simulation softwares from PK, PK/PD, PBPK, statistical and mathematical analysis to optimize dosing for best efficacy while minimizing toxicity.

Conclusion: Our platform enables tailored strategies that integrate PK/PD and biomarker-driven endpoints to optimize dosing and predict efficacy.

Over 5 years, our multidisciplinary expertise delivered comprehensive *in vivo* solutions that accelerated oncology drug discovery with the nomination of nine preclinical drug candidates progressing in the clinic.

No conflict of interest

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35LBA - PB-020 **Poster**

Therapeutic targeting of SATB2 for treating hepatocellular carcinoma

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Background: Hepatocellular carcinoma (HCC) remains one of the most common and lethal malignancies worldwide, driven by chronic liver disease and limited therapeutic options. HCC represents one of the leading causes of cancer mortality worldwide. While significant advances have been made for the treatment of advanced HCC, the overall 5-year survival rate is low (about 21%).

Therefore, new treatment options are urgently needed. Special AT-rich sequence-binding protein 2 (SATB2) is a nuclear matrix-associated protein and higher-order chromatin organizer. It is markedly overexpressed in tumors, correlates with poor survival, and regulates transcriptional programs essential for CSC maintenance. There are no SATB2 inhibitor in the clinics. Therefore, targeting SATB2 may be a viable option for the treatment of HCC. The objective of this paper is to develop small molecule SATB2 inhibitor for the treatment of HCC using computational modeling, artificial intelligence, lead optimization, and biological assays.

Materials and Methods: We performed high-throughput virtual screening, biophysical hit validation, artificial intelligence (AI) assessment, and chemical optimization of SATB2 inhibitors. Cell viability and colony were measured by CellTitre Glow luminescence and colony formation assays, respectively. Epithelial-to-Mesenchymal Transition (EMT) was assessed by motility, migration and invasion assays. Protein and gene expressions were performed by Western blot and qRT-PCR analyses, respectively. Pharmacokinetics and efficacy studies were performed in mice.

Results: SATB2 is highly expressed in HCC cell lines, CSCs and primary tissues. By comparison, normal human hepatocytes did not express SATB2. Higher expression of SATB2 in HCC cells was associated with greater growth rate, cell viability, colony formation and EMT than those cells expressing low SATB2. Knockout of SATB2 in CSCs by Crispr/Cas9 technique significantly inhibited the expression of SATB2 gene, stem cell markers (CD24, CD44 and CD133), pluripotency maintaining factors (cMyc, KLF4, SOX2, Nanog and OCT4), and EMT compared with non-targeting control group. Small molecule SATB2 inhibitor selectively binds human SATB2 protein, inhibits cell proliferation, EMT and CSC characteristics. SATB2 inhibitor suppressed HCC tumor growth *in vivo*.

Conclusions: SATB2 expression can be used as a biomarker of HCC, and SATB2 inhibitor can be used to treat HCC patients.

Conflict of interest: Ownership: Authors are the employees of the company.

Advisory Board: Anju Shrivastava is in the Advisory board.

Board of Directors: Rakesh Srivastava is one of the board of directors.

Corporate-sponsored Research: National Institutes of Health

Other Substantive Relationships: Dr. Srivastava is a co-inventor in the patent.

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36LBA - PB-021 **Poster**

BCCA7693, a development candidate DNA-PK inhibitor that blocks repair of double-strand breaks and synergises with radioligand & molecular targeted therapeutics

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Background: DNA-dependent protein kinase (DNA-PK) plays a key role in non-homologous end-joining (NHEJ)-mediated DNA repair, promoting cancer cell survival following exposure to direct or indirect DSB-inducing therapies. Inhibiting DNA-PK represents a strategy to overcome therapeutic resistance and enhance precision oncology modalities. Here, we present the preclinical development and evaluation of BCCA7693, a novel, orally bioavailable DNA-PK inhibitor identified through rational, iterative, structure-based design from >1,000 synthesized structures across two distinct chemical classes.

Methods: Biochemical and cellular kinase assays were performed to assess target potency and selectivity over related PI3K family enzymes, supplemented by ADME and a commercial 44-target safety panel. A novel 3D multicellular spheroid assay was utilized to screen for extravascular distribution and predict *in vivo* activity. Efficacy was tested in cancer cell lines (varying in p53 and DNA damage response mutational status) combined with external beam radiation, PSMA-targeted ^{177}Lu-radioligands, or targeted agents (adagrasib, dabrafenib, trametinib, olaparib, and the pol-θ inhibitor ART889). *In vivo* pharmacokinetic, pharmacodynamic, and antitumor efficacy studies were conducted in murine xenograft models via dietary administration.

Results: BCCA7693 achieved sub-nanomolar IC_{50} potency with >1000-fold selectivity over PI3K enzymes and clean profile in safety panels. Preclinical PK/PD profiles across mice, rats, and dogs confirmed clinical viability. Combined with ionizing radiation, BCCA7693 demonstrated a 3- to 8-fold dose-modifying enhancement factor across diverse cancer cell lines and strong synergy with ^{177}Lu-PSMA in LNCaP cells. In $p53^{mut}$ FaDu xenografts, continuous dietary BCCA7693 (75 mg/kg/day) with 5 Gy radiation achieved a >3-fold sensitization enhancement factor. When combined with molecular therapeutics during replicative stress (KRAS, BRAF and BRCA mutant models), BCCA7693 suppressed cell survival and prevented acquired resistance. In $BRAF^{V600E}$ Colo-205 xenografts, continuous therapy (trametinib + dabrafenib + BCCA7693 at 0.1, 10, and 75 mg/kg/day) achieved complete tumor control for 8 weeks, compared to disease progression at week 3 with dual BRAF/MEK inhibition alone.

Conclusions: BCCA7693 is a highly selective DNA-PK inhibitor that substantially potentiates radioligands, radiotherapy and targeted molecular therapies. Combining BCCA7693 with targeted agents did not increase toxicity or body weight loss, highlighting its potential for clinical combination strategies.

Conflict of interest: Other Substantive Relationships: AK, JB, SO, ESH, SA, JP and AM are named as inventors on patent applications relating to DNA-PK inhibitors.

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37LBA - PB-022 **Poster**

IL-13Rα2-targeted radioimmunotheranostics: From precision imaging to tumor control in IL-13Rα2-positive solid tumors

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Background: Interleukin-13 receptor alpha-2 (IL-13Rα2) is highly expressed in several solid malignancies with limited expression in normal tissue, making it an attractive therapeutic target. IL-13Rα2-positive tumors, such as leiomyosarcoma (LMS), the most common soft-tissue sarcoma, and glioblastoma (GBM), have poor outcomes and limited therapeutic options.

We developed KLG-3, a human IgG4 monoclonal antibody targeting IL-13Rα2, and evaluated it as a radioimmunotheranostic platform across LMS and orthotopic GBM models.

Material and methods: Nude mice bearing subcutaneous LMS (SK-UT-1, RKN) or orthotopic GBM (U-87MG) xenografts underwent serial ^{89}Zr-KLG-3 PET/CT (0.9 MBq; 5 μg; n = 4) at days 1, 3, 6, 10 and 14. *Ex vivo* biodistribution of ^{177}Lu-KLG-3 (27.8 MBq; 30 μg) and ^{225}Ac-KLG-3 (37 kBq; 10 μg) was assessed at the same timepoints (n = 5/group), with representative ^{177}Lu-KLG-3 SPECT/CT (n = 1/timepoint). Therapeutic efficacy was evaluated in SK-UT-1-bearing mice following a single IV dose of ^{177}Lu-KLG-3 (22.2, 14.8 or 7.4 MBq; 30 μg; n = 10) or ^{225}Ac-KLG-3 (37, 27.8, 18.5, 11 kBq; 10 μg; n = 6-10) compared with radiolabeled IgG control. Efficacy was assessed by tumor volume and survival, toxicity by body weight, hematology and serum biochemistry.

Results: ^{89}Zr-KLG-3 showed tumor-specific uptake in both LMS models (43 ± 11 %ID/g SK-UT-1, 37 ± 7 %ID/g RKN at day 3), followed by a plateau and gradual clearance; ^{89}Zr-IgG control followed blood pool clearance. *Ex vivo* biodistribution confirmed tumor retention of ^{177}Lu-KLG-3 (118 ± 43 %ID/g SK-UT-1 at day 14, 17 ± 5 %ID/g RKN at day 3), consistent with SPECT/CT, and ^{225}Ac-KLG-3 (100 ± 31 %ID/g at day 10). A single ^{177}Lu-KLG-3 dose significantly prolonged survival compared to IgG control ($p < 0.0001$ for 22.2 MBq); at day 145, 8/10 mice at 22.2 MBq and 4/10 at 14.8 and 7.4 MBq were tumor-free. Tumors responded to single-cycle ^{225}Ac-KLG-3 in a dose-dependent way; at day 45, 6/6, 9/10, 9/10 and 2/10 were alive at 37, 27.8, 18.5 and 11 kBq, respectively. Hematological toxicity was transient and dose-dependent; liver and kidney function markers did not significantly diverge from baseline. In the orthotopic GBM model, ^{89}Zr-KLG-3 PET/CT detected tumors at early stage whereas IgG control showed no or late uptake.

Conclusions: KLG-3 shows the key features of a radioimmunotheranostic platform: ^{89}Zr immunoPET/CT delineated IL-13Rα2-positive tumors over a prolonged timeframe, including orthotopic GBM; ^{177}Lu-KLG-3 achieved durable tumor control (up to 8/10 mice tumor-free); and ^{225}Ac-KLG-3 demonstrated dose-dependent antitumor activity, both with transient hematological toxicity and no biochemical sign of renal or hepatic injury. These findings support the translational potential of KLG-3 as a radioimmunotheranostic platform in IL-13Rα2-positive solid malignancies with limited treatment options.

No conflict of interest

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38LBA - PB-023 **Poster**

ABSK192, a novel selective CDK4 inhibitor, demonstrates single-agent activity and broad combination efficacy in HR +/HER2− breast cancer models

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Introduction: Cyclin-dependent kinase 4 (CDK4) is a key regulator of G1/S transition and a critical therapeutic target in HR +/HER2− breast cancer. Although approved CDK4/6 inhibitors have demonstrated clinical benefit, CDK6 inhibition is associated with hematologic toxicity, particularly neutropenia, which may limit sustained treatment and CDK4 target coverage. Selective CDK4 inhibition while sparing CDK6 may therefore improve the therapeutic window and enable deeper CDK4 inhibition. ABSK192 is a potent, selective and brain-penetrable CDK4 inhibitor in IND-enabling development. Here, we characterized its pharmacological activity and evaluated its therapeutic potential, both as a single agent and in combination with other therapeutic agents, in HR +/HER2− breast cancer models.

Methods: The CDK4 inhibitory activity and selectivity over CDK6 were characterized using biochemical assays, cellular target engagement assays (nanoBRET), and pRB phosphorylation assays. Antiproliferative activity was assessed across a panel of HR +/HER2− breast cancer cell lines with PIK3CA-mutant or wild-type backgrounds, and cell-cycle effects were characterized following treatment. Synergistic effects of drug combinations with various therapeutic agents, including endocrine therapies, PI3K inhibitors, or CDK2 inhibitor, were assessed *in vitro* using the Chou-Talalay combination index method. *In vivo* anti-tumor activity of ABSK192 as single agent or in combinations were further evaluated in HR +/HER2− breast cancer xenograft models.

Results: ABSK192 demonstrated potent CDK4 inhibition and greater than 70-fold selectivity over CDK6. Consistent with these findings, ABSK192 showed superior antiproliferative activity across HR +/HER2− breast cancer cell lines irrespective of PIK3CA mutation status and induced pronounced G1 cell-cycle arrest. ABSK192 demonstrated synergistic activity with the endocrine therapies fulvestrant and imlunestrant, the PI3K inhibitors GDC-0077 and RLY-2608, and the CDK2 inhibitor PF-07104091 across multiple HR +/HER2− breast cancer cells, with CI values as low as approximately 0.1 at the most synergistic dose combinations. *In vivo*, oral administration of ABSK192 demonstrated robust antitumor activity as a single agent, while in combination with fulvestrant, imlunestrant, or GDC-0077 further enhanced antitumor efficacy, with > 30% tumor volume reduction from baseline at the end of treatment.

Conclusion: ABSK192 is a novel, potent and selective CDK4 inhibitor with single-agent activity and broad combination efficacy in preclinical models of HR +/HER2− breast cancer. These findings support its further development in diverse combination regimens, with the potential to improve therapeutic efficacy and tolerability.

Conflict of interest: Ownership: All authors hold stock in Abbisko Therapeutics.

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39LBA - PB-024 **Poster**

O3R-119 overcomes the limitations of first-generation SMARCA2 inhibition in SMARCA4-deficient cancers

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Background: Loss of the SMARCA4 ATPase in tumors creates a synthetic-lethal dependency on its paralog SMARCA2. Exploiting this vulnerability requires deep and sustained SMARCA2 inhibition while sparing SMARCA4 in normal tissues. The recent decision to discontinue clinical development of FHD-909, the first clinical-stage SMARCA2 inhibitor with ~30-fold selectivity over SMARCA4, emphasizes the need for greater selectivity to support a wider therapeutic window. Guided by our unique translational model defining the required SMARCA4 selectivity, we developed O3R-119, an 87-fold selective SMARCA2 inhibitor. O3R-119 combines best-in-class potency/selectivity, tailored PK, and favorable drug-like properties to fully unlock the therapeutic potential of SMARCA2 in the clinic.

Material and methods: Cellular SMARCA2 potency and selectivity versus SMARCA4 were quantified in a unique isogenic HT1080 SMARCA2 or SMARCA4 knockout model. Anti-tumor activity and tolerability following oral dosing were evaluated in SMARCA4-deficient NSCLC cell-line derived xenograft (CDX) models, with FHD-909 as benchmark. A 9-day mouse dose-range-finding (DRF) study integrated body weight, clinical pathology, histopathology and exposure to define the preclinical therapeutic window.

Results: O3R-119 inhibited cellular SMARCA2 with an IC50 of 0.6 nM and demonstrated 87-fold selectivity over SMARCA4, compared with 7 nM potency and 29-fold selectivity for FHD-909. In a large lung cancer cell line panel, SMARCA4 loss-of-function was

significantly enriched among sensitive cell lines, confirming synthetic-lethal activity. At 40 mg/kg twice daily, O3R-119 induced tumor regression in the A549 and NCI-H2126 CDX models and stasis in the less-sensitive RERF-LC-A1 CDX model, without body weight loss. At the same dose and schedule, FHD-909 only achieved tumor regression in the most sensitive NCI-H2126 CDX model and was associated with severe body weight loss. A mouse DRF study confirmed an exposure margin from the minimum efficacious dose to the maximum tolerated dose of at least 10-fold for O3R-119, compared with a maximum of 3-fold for FHD-909, demonstrating a wider preclinical therapeutic window.

Conclusions: The discontinuation of FHD-909 does not invalidate SMARCA2 as an oncology target. Our data package demonstrates that while FHD-909 is anticipated to allow limited SMARCA2 target coverage due to SMARCA4-driven toxicities, O3R-119 has sufficient therapeutic window to sustain optimal target coverage and drive maximal efficacy in the clinic. O3R-119 is advancing as a development candidate for SMARCA4-deficient cancers.

No conflict of interest

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40LBA - PB-025 **Poster**

A novel cMET-targeted ADC incorporating a first-in-class translation inhibitor payload demonstrates favorable preclinical profile supporting its clinical development

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Background: Resistance to antibody-drug conjugates (ADCs) delivering topoisomerase I inhibitor (TOP1i) payloads is an emerging clinical challenge, highlighting the need for new ADC payloads with orthogonal mechanisms of action (MOA). HEX-360, a HER2-targeted ADC pairing a first-in-class eukaryotic translation initiation factor 4A inhibitor (eIF4Ai) and a glucuronide-based linker, is on track to enter the clinic in mid-2027. Unlike TOP1i and microtubule inhibitors, eIF4A inhibition blocks translation of eIF4a dependent oncogenes, offering a differentiated approach to tumor cell killing. Given the clinical development of TOP1i-based ADCs in c-MET-expressing lung, gastric and colorectal tumors, resistance to TOP1i payloads may limit their activity in these settings. To address this potential unmet need, we developed a c-MET-targeted ADC incorporating the same linker-payload as HEX-360, with a drug-to-antibody ratio (DAR) of 8 and a Fc-silenced antibody backbone to minimize Fc-mediated toxicity. By blocking translation and depleting short-lived oncoproteins required for tumor cell survival, Hexagon's cMET-eIF4Ai ADC is designed to provide an orthogonal MOA for anti-tumor activity in cancer patients with pre-existing or acquired resistance to TOP1i-based ADCs.

Methods: Antitumor activity was evaluated in c-MET-expressing cell line-derived xenograft (CDX) models, including models that progressed on TOP1i-based ADCs. Expression of β-glucuronidase (GUSB), the enzyme that cleaves the glucuronide linker, was profiled in colorectal and lung cancer specimens spanning a range of c-MET expression levels and in normal human tissues. Tolerability and pharmacokinetics (PK) were assessed in single- and repeat-dose studies in rodents and non-human primates (NHPs), with clinical pathology and histopathology evaluations.

Results: The cMET-eIF4Ai ADC induced durable tumor regressions across multiple CDX models, with a minimum efficacious dose (MED) of 1 mg/kg. Importantly, the ADC retained antitumor activity in models that had progressed on TOP1i-based ADCs. GUSB expression was consistently high across the tumor specimens compared to normal tissues and did not appear to vary substantially with c-MET expression. In single- and repeat-dose studies in rats and NHPs, the cMET-eIF4Ai ADC was well tolerated. Pharmacokinetic analyses showed antibody-like clearance and a stable DAR, consistent with favorable conjugate stability.

Conclusions: The cMET-eIF4Ai ADC induced durable tumor regressions across multiple CDX models, with a MED of 1 mg/kg. Importantly, the ADC retained antitumor activity in models that had progressed on or exhibited resistance to TOP1i-based ADCs, alongside favorable PK and preclinical tolerability. These findings support further development of this ADC with an orthogonal payload mechanism for c-MET-expressing tumors with resistance to TOP1i-based ADCs.

Conflict of interest: Ownership: All authors are employees of Hexagon Bio and hold stock and/or stock options in Hexagon Bio

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41LBA - PB-026 **Poster**

Characterization of the antibody target CFC1 in neuroendocrine neoplasms (NENs)

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Background: NENs are malignancies that can arise in various body locations, with common primary sites in the gastroenteropancreatic tract and lungs. Despite treatment options such as surgery, systemic therapies, and immunotherapy, metastatic NENs often lack effective therapeutic options, highlighting the need for novel therapeutic approaches. The identification of tumor-specific antigens is central to the development and effectiveness of cancer immunotherapies.

Material and methods: Target identification was performed using bulk and single-cell RNA-sequencing (RNA-seq) datasets derived from human samples. Target expression was further characterized at the protein level by immunohistochemistry. The tumor-associated antigen was characterized using RNA-seq data from cell lines and functional assays, and its involvement in signaling pathways was investigated using pathway inhibitors. Therapeutic potential was evaluated using antibodies generated in collaboration with BioNTech, which were characterized for binding and internalization properties and assessed for their ability to inhibit tumor growth.

Results: In this study, we identified CFC1 as a tumor-associated antigen that is highly and broadly expressed in primary and metastatic human NENs. Given the current lack of effective therapies for NENs, CFC1 represents a potential target for immunotherapeutic approaches. Functional characterization revealed that CFC1 is associated with cancer stemness (CSC), epithelial to mesenchymal transition (EMT), as well as cell migration and invasion. Pharmacological inhibition of key components of the transforming growth factor β (TGFβ) signaling pathway identified canonical SMAD2/3 signaling as a critical mediator of CFC1-dependent processes *in vitro* and in human tumor samples. Finally, CFC1-specific antibodies were compared with respect to cell-surface binding affinity and cellular internalization. Importantly, treatment with antibodies demonstrated potent tumor cell-killing activity, highlighting their potential as therapeutic candidates.

Conclusions: In conclusion, our findings highlight the role of CFC1 in tumor progression by promoting CSC and EMT through TGFβ/SMAD2/3-dependent mechanisms. Its tumor-specific expression and surface localization make CFC1 a promising candidate for antibody-based immunotherapy, offering new avenues for the treatment of NENs.

No conflict of interest

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42LBA - PB-027 **Poster**

Discovery of PXG-P300/CBP, a potent and selective DCAF16-mediated dual p300/CBP degrader for biomarker-defined solid tumors and multiple myeloma

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Background: Induced proximity offers a powerful strategy to circumvent the limitations intrinsic to conventional pharmacology. We present PXG-p300/CBP an exceptionally potent, highly selective, orally bioavailable molecular glue degrader of p300 and CBP, key regulators of oncogenic transcription. Despite clinical validation of targeting p300/CBP, hematologic toxicities observed with inhibitors currently in clinical development such as inobrodib underscore the need for differential impairment of p300/CBP in tumor versus non-malignant cells.

Material and methods: Kinetics of p300/CBP degradation, pathway modulation and antiproliferative activity were evaluated *in vitro* in multiple myeloma, non-small cell lung cancer (NSCLC), bladder and prostate cancer models, and non-malignant human cells. Tumor and peripheral blood mononuclear cell (PBMC) pharmacodynamics and tumor growth inhibition were assessed after *in vivo* dosing.

Results: Through templated covalent engagement of the E3 ubiquitin ligase DCAF16, PXG-p300/CBP degrader induces selective and durable p300/CBP degradation. It achieves antiproliferative IC_{50} values of 0.04–0.1 nM in multiple myeloma cell lines and potently suppresses the IRF4–MYC survival pathway. Multiple Myeloma tumor cells are more than 50-fold more sensitive than non-malignant human hematopoietic and fibroblast models. Biomarker-defined CBP- or p300-mutant NSCLC and bladder cancer, and AR + prostate cancer cell lines, show antiproliferative IC_{50} values of 1–10 nM, while WT and AR-negative models are up to 500-fold less sensitive. Consistently, we observe rapid suppression of histone acetylation, MYC signaling and AR-dependent transcriptional programs, depending on the genetic context. This exceptional *in vitro* potency translates into significant tumor regression in AR-positive VCaP xenografts. Remarkably, a single 30-minute treatment induces *in vitro* degradation lasting up to seven days. *In vivo*, unbound plasma concentrations above the DC_{50} for approximately six hours lead to $>90\%$ target degradation in tumor xenografts for at least 72 hours after a single dose. In contrast, p300/CBP degradation reaches only 60% in PBMCs, with full protein recovery after 72 hours.

Conclusions: DCAF16-mediated p300/CBP degradation combines a unique mechanism of action with potent and selective antitumor activity. The exceptional pharmacodynamic durability and differential recovery in tumor versus non-malignant cells suggests the potential for a superior therapeutic window in multiple myeloma and biomarker-defined solid tumors.

No conflict of interest

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43LBA - PB-028 **Poster**

Integrated transcriptomic and regulatory analysis for robust biomarker discovery in tobacco-related lung cancer

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Background: Lung cancer is the leading cause of cancer-related mortality worldwide, with tobacco use as its main risk factor. In Costa Rica, it represented an estimated 3.9% of new cancer cases and 6.5% of cancer deaths in 2024. Artificial intelligence (AI) and bioinformatics can support biomarker discovery from public genomic data. Aligned with Costa Rica's National Plan for Science, Technology, and Innovation (PNCTI 2022-2027), this project aims to develop an accessible AI-driven platform for identifying and evaluating molecular biomarkers for early detection of tobacco-related lung cancer.

Material and methods: Candidate genes from two independent transcriptomic studies were integrated. The first analyzed lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) data from the Genomic Data Commons using AI. The second analyzed an independently collected cohort with DElite, which integrates DESeq2, edgeR, dearseq, and limma through the Lancaster method. Genes shared across studies were prioritized. Clinically relevant variants within selected candidates were assessed with AlphaGenome to predict effects on chromatin accessibility, regulatory activity, and RNA expression. Processing was performed on the Kabré supercomputer at CeNAT-CONARE, and AlphaGenome analyses used its open notebook.

Results: All six differential-expression outputs shared 76 upregulated and 39 downregulated genes, defining a high-confidence consensus signature. Gene Ontology Biological Process enrichment and gene-concept network analysis linked these genes mainly to mitotic nuclear division, chromosome and sister chromatid segregation, organelle fission, and positive regulation of cell-cycle progression. Central genes included CDC20, BUB1, TOP2A, AURKA, AURKB, BIRC5, NDC80, CCNE1, CDC25C, CDC6, SPAG5, NUF2, KIF2C, KIF14, and KIF23, indicating coordinated involvement in cell-division pathways. AlphaGenome identified chr17:43852966>A in the downregulated gene CD300LG as the variant with the highest combined effect. Negative CAGE (-0.076) and DNase (-0.027) scores predicted reduced transcription initiation and chromatin accessibility.

Conclusions: Integrating independent transcriptomic studies, consensus differential-expression analysis, and regulatory predictions provides a reproducible framework for prioritizing statistically robust biomarker candidates. These results form an initial component of the platform under development, which will expand validation across independent cohorts and analytical approaches before assessing potential clinical applications in tobacco-related lung cancer.

No conflict of interest

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