



zymeworks

Research & Development Day

Accelerating the next generation of therapeutics to improve the standard of care for the most challenging diseases in cancer and autoimmune disease

December 12, 2024

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Today's Agenda

08:30 AM **Zymeworks R&D Vision**
Dr. Paul Moore

08:50 AM **Gynecological Cancer**
Dr. Susana Banerjee

09:00 AM **Lung Cancer**
Dr. Hatim Husain

09:10 AM **Gastrointestinal Cancer**
Dr. Jaffer Ajani

09:20 AM **Solid Tumor Program**
Dr. Jeff Smith
Dr. Paul Moore

09:50 AM **Q&A Session #1**

10:20 AM **Beyond Solid Tumors**
Dr. Paul Moore
Dr. Alexey Berezhnoy

10:50 AM **Next Generation Technologies**
Dr. Jamie Rich
Stuart Barnscher
Dr. Nina Weisser
Dr. Thomas Spreter Von Kreudenstein

11:20 AM **Closing Remarks**
Kenneth Galbraith

11:30 AM **Q&A Session #2**

12:00 PM **Networking Session**



ZYMEWORKS R&D STRATEGY

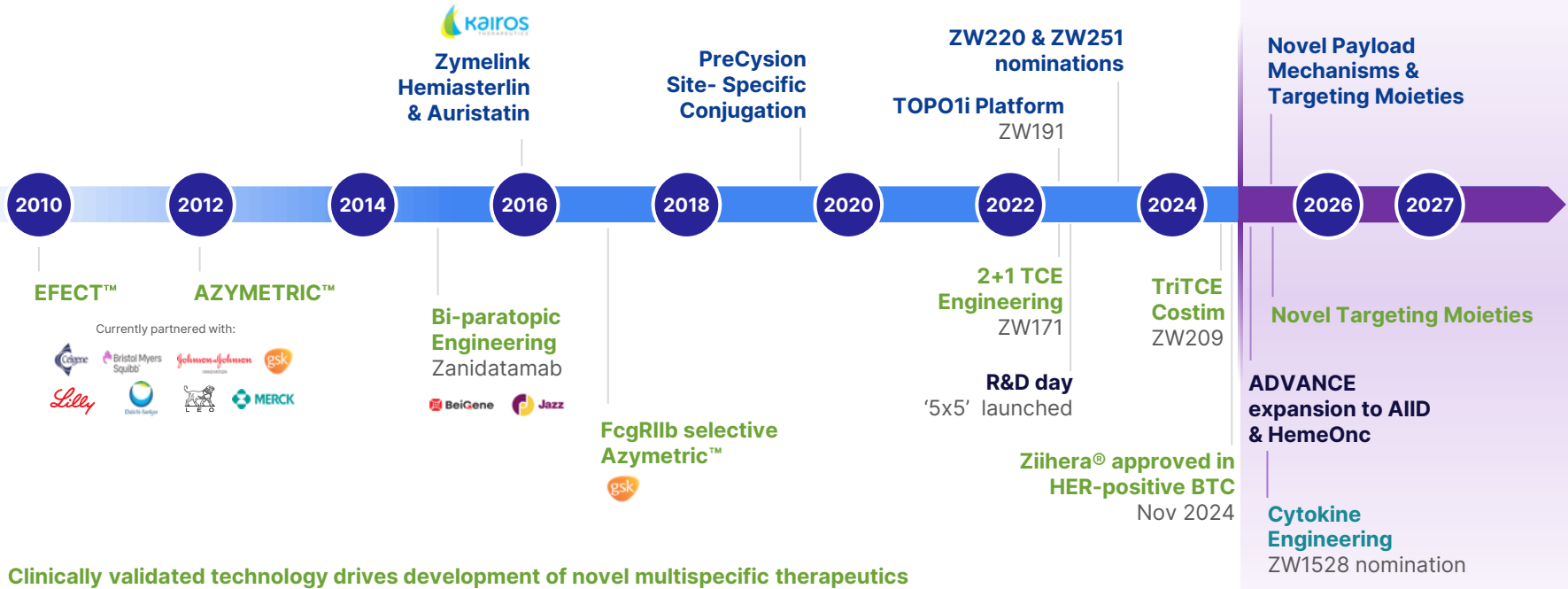
Zymeworks R&D Strategy

Paul Moore, PhD
Chief Scientific Officer



10+ Years of Pioneering Multi-Functional Antibody Development

Leading the development of next generation antibody-drug conjugates



Clinically validated technology drives development of novel multispecific therapeutics

Dedicated to Advancing Targeted Therapies that Address Some of The Most Challenging Diseases, Including Aggressive Cancers and Autoimmune Disorders

5+ Strategic Partnerships

Collaborating with industry leaders to accelerate impact

Extended the reach of therapeutic candidates, while **validating our innovative approach** through strategic partnerships with companies including Jazz, BeiGene, J&J, and others.

1 Internally Developed Approved Drug

Ziihera® (zanidatamab-hrii) (HER2 bispecific antibody)

Licensed to Jazz and BeiGene

2L BTC (IHC3+) U.S. FDA Approval

1L BTC confirmatory trial ongoing

Phase 3 GEA top-line PFS readout estimated 2Q25

6 Wholly-Owned Candidates

Multiple Modalities and Therapeutic Areas

2 Clinical Stage Assets in Phase 1 Trials: ZW171 & ZW191

2 INDs Planned in 2025: ZW220 & ZW251

2 INDs Planned in 2026: ZW209 & ZW1528

Azymetric™ – Adaptable to Different Formats and Applications

Engineering

Set of transferable mutations supporting pure and stable Fc heterodimer formation with exclusive chain pairing during co-expression

Libraries of constant domain Fab mutations available for kappa/kappa, kappa/lamda and lambda/lambda bispecific LC combinations

Flexibility

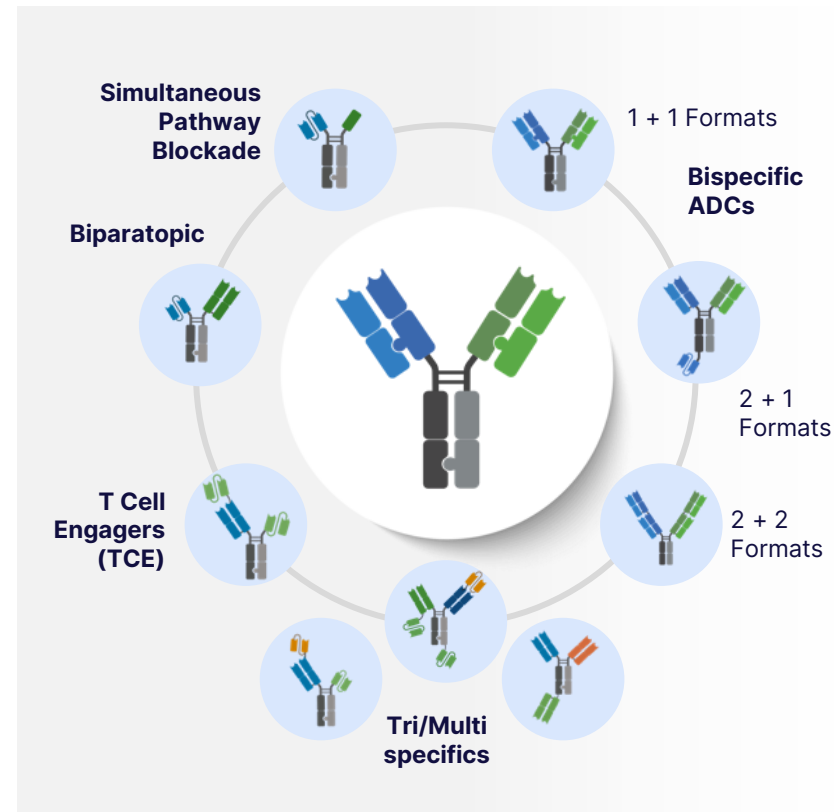
Can employ novel or existing antibody paratopes; human (IgG1, IgG2A, IgG4) and mouse frameworks; other CH2 and glyco-engineering approaches (eg YTE). Compatible with linker/payload conjugation

High-throughput Screening

Best-in-class activity requires screening of alternative targets, epitopes, sequences, target engagement geometries, and mechanisms of action (blocking, lytic, ADC)

Highly Manufacturable

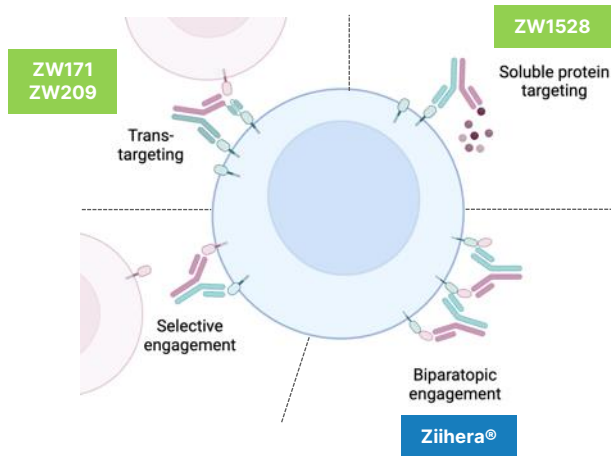
Antibody like yields/stability; leveraged by multiple pharma/biotech with various clinical stage programs in development



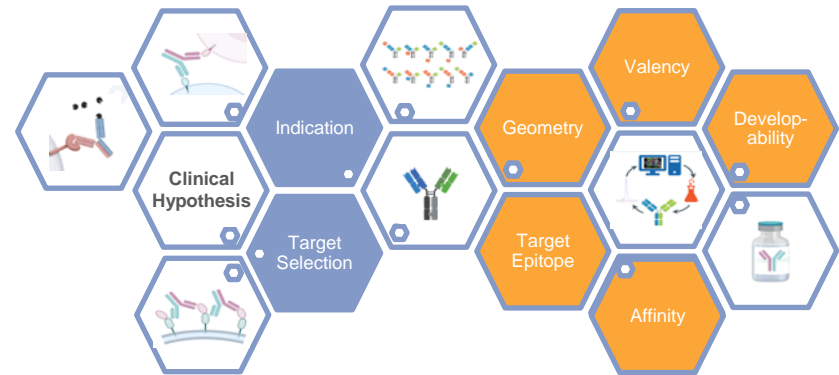
Multispecific Antibody Development Requires Optimization of Multiple Parameters Specific to Desired MOA

Understanding the interplay of antibody geometry with optimal paratope affinity, valency, and target epitope is critical to identifying best-in-class multispecific antibody therapeutics

Clinical Hypothesis and Mechanisms of Action



Biology



Zymeworks' Multispecific Engineering Approach – Key Expertise in Format and Geometry Screening to Identify Differentiated Activity

- **Potential best-in-class activity** requires screening of epitopes, affinities and target engagement geometries
- **Unique flexibility of Azymetric™** enables format and affinity optimization for potential best-in-class attributes
- **Discovery of unique biology** and differentiation to combination approaches

Biparatopic

Zanidatamab

- Optimization of affinity and format for highest biparatopic activity
- Unique biparatopic MOA
- Superior activity to combination



2+1 TCE

ZW171 (2+1 MSLN TCE)

- Avidity optimization to prevent normal tissues tox
- Avidity and format optimization to not bind shed MSLN
- Synapse optimization for high activity with minimal cytokine release



Multi-Cytokine Blocker

ZW1528 (IL4Rα – IL-33)

- IgG-like format, manufacturability and PK
- IL4Rα and IL-33 blockade equivalent to bivalent benchmarks
- Unique bispecific activity, potentially superior to combination



Trispecific T Cell Engager

ZW209 (CD28 TriTCE)

- Discovery of novel format to prevent non-specific T cell activation
- Conditional CD28 activation
- Synapse optimization for balanced Signal 1 plus Signal 2



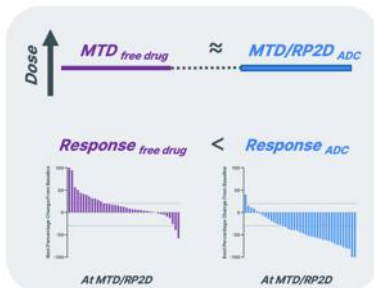
Increased Complexity



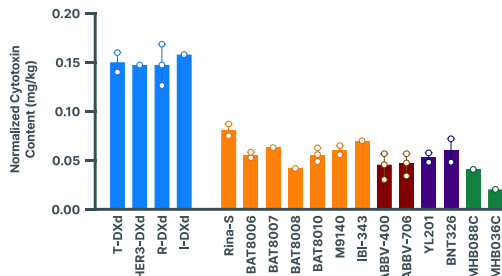
5X5

Historical Observations Guide Our Approach to ADC Design

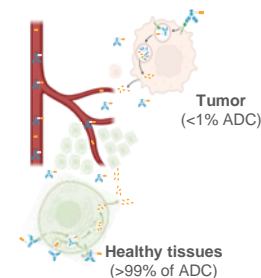
1 Conjugation does not improve payload MTD¹



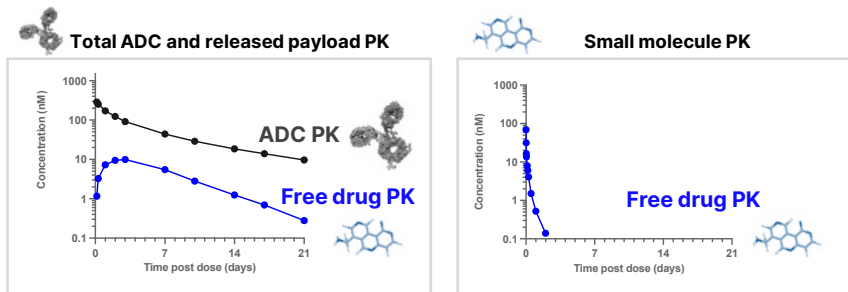
2 More potent payloads limit protein dose²



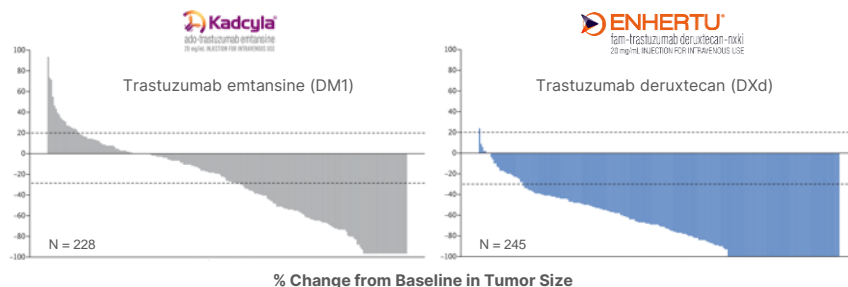
3 Most ADC catabolism occurs in normal tissue³



4 Bystander activity is a key payload feature²



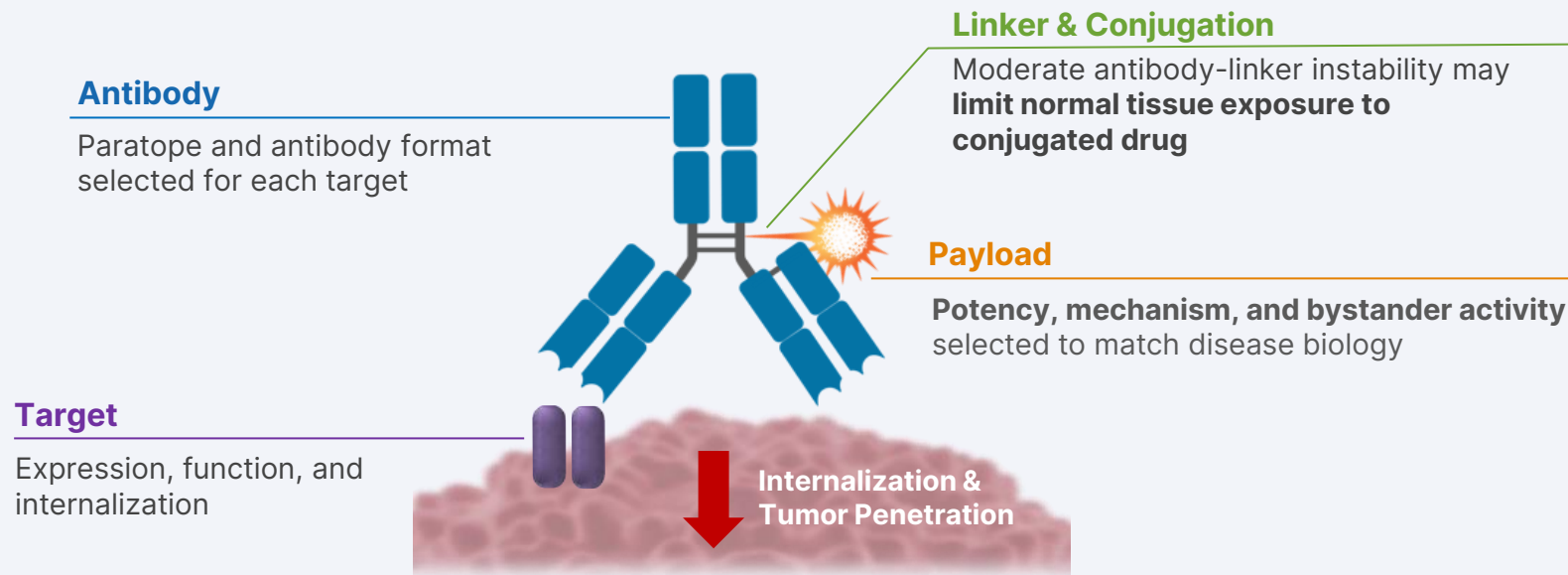
5 The right payload mechanism matters⁴



1. R. Colombo and J.R. Rich, Cancer Cell 2022, 40(11):1255-1263; 2. R. Colombo et al, Cancer Discov 2024, 14(11):2089-2108; 3. A.T. Lucas et al, Antibodies 2019, 8(1):3; 4. J. Cortés et al, N Engl J Med 2022, 386:1143-1154.

Building Clinically and Commercially Relevant ADCs Requires Careful Selection of Target, Antibody, Linker/Conjugation, and Payload

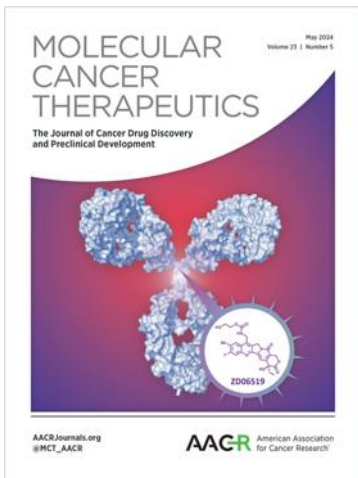
Historical Observations Guide Our Approach to ADC Design




1. Colombo R, Rich JR. Cancer Cell 2022 (40), 1255-1263; 2. Colombo R, Barnscher SD, Rich, JR. Cancer Res 2023, 83 (7). Abstract #1538 presented at AACR 2023.



Zymeworks Topoisomerase ADC Platform Exemplifies Our Philosophy and Enables Our Pipeline



Payload synthesis & screening



~100 payloads prepared and tested in vitro

ADC in vitro potency




In vitro potency: target-dependency and bystander activity

Conjugation of select payloads




Payloads conjugated as DAR4 and DAR8, multiple mAbs

In vivo efficacy & PK



Robust efficacy in multiple CDX and PDX models

ADC characterization



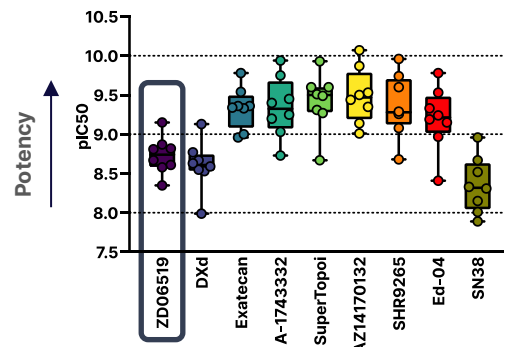
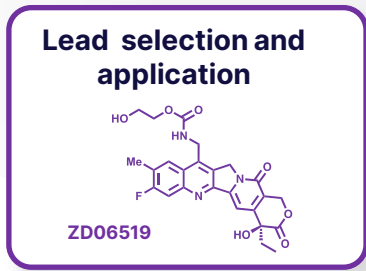
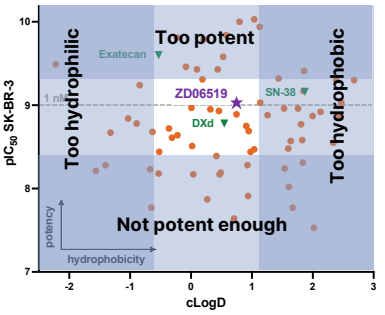
ADC properties: monodispersity, plasma stability, hydrophilicity

NHP toxicology & TK



MTD in NHPs: DAR8: ≥ 30 mg/kg, DAR4: ≥ 120 mg/kg

- Moderate potency to enable higher ADC dose
- Bystander active
- **ZW191** first in human trial (NCT0655574)
- **ZW220** and **ZW251** expected to enter clinic in 2025



M.E. Petersen, M.G. Brant et al, Mol Cancer Ther 2024, 23(5):606-618.

Zymeworks' TOPO1i ADC Assets Have Potential to Address Multiple Diverse Patient Populations

ADVANCE

	ZW191	ZW220	ZW251
Target	FR α	NaPi2b	GPC3
Payload mechanism	TOPO1i	TOPO1i	TOPO1i
Antibody	Mono	Mono	Mono
Potential Indications	Ovarian cancer, endometrial cancer, and NSCLC	Ovarian cancer, NSCLC, CRC	Liver cancer
Stage	Phase 1	IND on track for 1H 2025	IND on track for 2H 2025

Novel targets in digestive tract tumors and heme-onc

Novel mechanisms

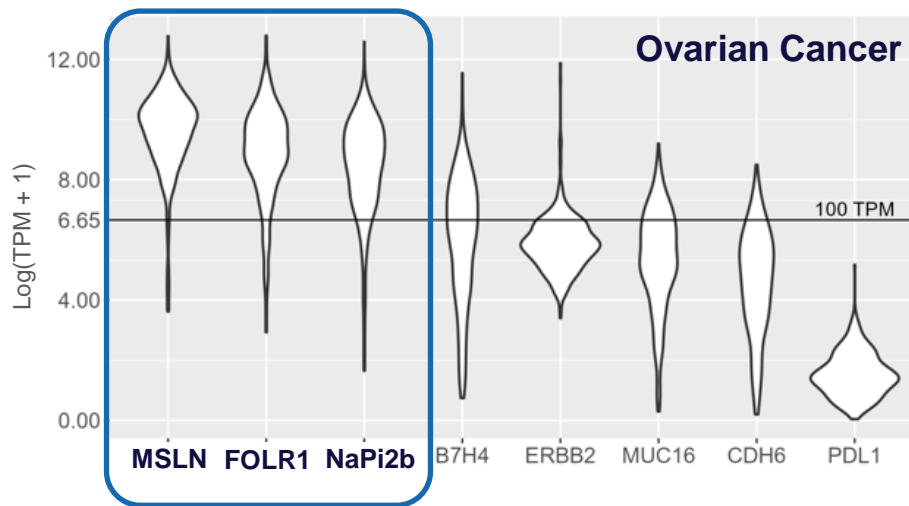
Novel formats

Discovery; INDs anticipated in 2027+

Target Selection Driven by Expression Profile, Biology and Clinical Precedence

Selection of an ADC or TCE strategy is driven by target expression, biology including internalization rate, clinical precedence and differentiation to prior therapeutic programs

mRNA Expression Profile of Select Cancer Target in Ovarian Cancer (N=421)



A balanced portfolio of ADCs targeting clinically validated FR α and NaPi2b, along with a T cell engager targeting MSLN, ensures comprehensive coverage and risk mitigation for ovarian cancer and NSCLC, **providing a diversified therapeutic focus on ovarian and lung cancers.**

MSLN, FOLR1 and NaPi2b are each expressed at higher level than other targets pursued in ovarian cancer or NSCLC

TCGA bulk RNA-sequencing data were obtained from TCGA-OV, workflow STAR – Counts from <https://portal.gdc.cancer.gov/repository>. The median TPM (Transcript per Million) for each gene in each patient was plotted on a violin plot using ggplot2. This dataset contains 421 samples (patients) from Ovarian Serous Cystadenocarcinoma (OV) and 521 sample from lung adenocarcinoma. The width of the shape/violins indicates the density of samples

TPM: transcripts per million 1. Wickham H (2016). ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag New York. ISBN 978-3-319-24277-4, <https://ggplot2.tidyverse.org>. ADC: antibody-drug conjugate; TCE: t cell engager; NSCLC: non-small cell lung cancer

Development Pipeline

Program	Technology	Target	Indication	Discovery	Preclinical	Phase 1	Phase 2
Solid Tumor Oncology: Antibody-Drug Conjugates (ADC)							
ZW191 Topo1i ADC DAR 8 Fc WT	ZD06519 Payload	FR α	Gynecological Thoracic	NCT06555744			
ZW220 Topo1i ADC DAR 4 Fc Mut	ZD06519 Payload	NaPi2b	Gynecological Thoracic			IND 1H 2025	
ZW251 Topo1i ADC DAR 4 Fc WT	ZD06519 Payload	GPC3	Digestive System (HCC, PDAC)			IND 2H 2025	
Solid Tumor Oncology: T Cell Engagers (TCE)							
ZW171 Trivalent TCE 2+1 Format	Azymetric™ Novel anti-CD3	MSLN x CD3	Gynecological Thoracic	NCT06523803			
ZW209 Trispecific TCE Tri-TCE Costim	Azymetric™ Novel anti-CD3 Conditional CD28	DLL3 x CD3 x CD28	Thoracic			IND 1H 2026	
Autoimmune and Inflammatory Disease							
ZW1528 Dual Cytokine Blocker	Azymetric™ Hetero-Fab YTE	IL4R α x IL-33				IND 2H 2026	

Fc WT: Fast continuous wavelet transform; Mut: Methylmalonyl-CoA mutase; HCC: hepatocellular carcinoma; PDAC: pancreatic ductal adenocarcinoma

SOLID TUMOR PROGRAM

ZW171 and ZW191

Jeff Smith, MD, FRCP
Executive Vice President and Chief Medical Officer



Zymeworks' Pipeline has an Opportunity to Address Unmet Needs Across Indications

	Ovarian Cancer	Endometrial Cancer	NSCLC	SCLC	Pancreatic Cancer	Hepatocellular Carcinoma
ZW171 MSLN x CD3 TCE	✓	✓	✓		✓	
ZW191 FRα TOPO1i ADC	✓	✓	✓			
ZW220 NaPi2b TOPI1i ADC	✓	✓	✓			
ZW251 GPC3 TOPO1i ADC						✓
ZW209 DLL3xCD3xCD28 TCE				✓		

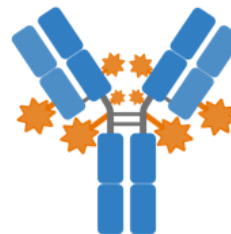
ZW171



MSLN x CD3 bispecific T cell engager

- 2+1 format
- Designed for enhanced therapeutic window
- Tumor selective binding and cytotoxicity
- Maintains potency in presence of soluble MSLN
- Reduced T cell binding to mitigate risk of CRS

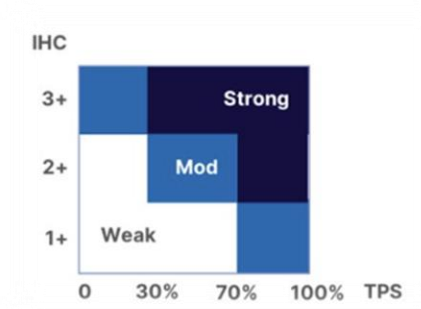
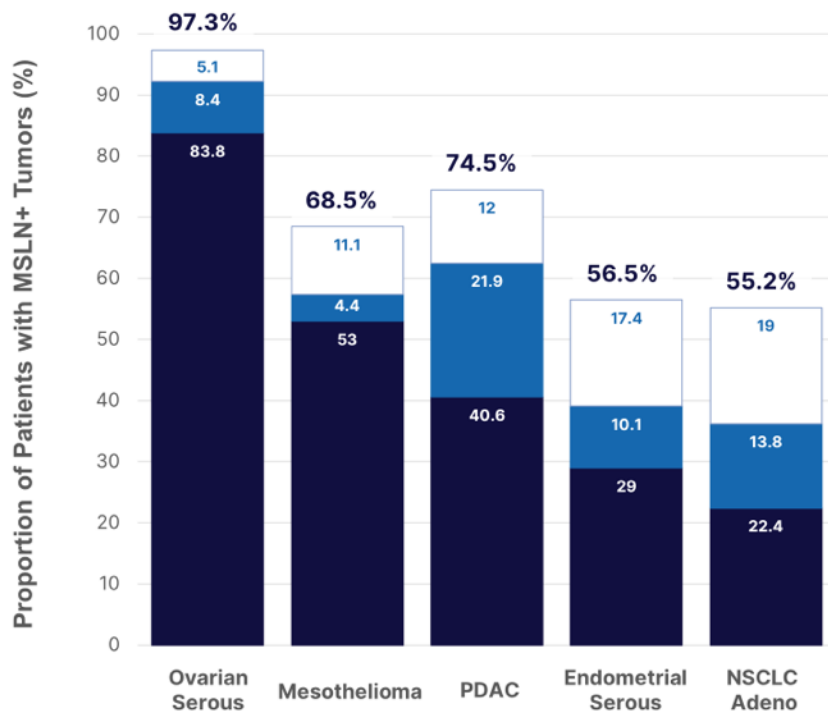
ZW191



FR α -targeting ADC

- Antibody selected to improve upon current in-clinic models
- Proprietary TOPO1i payload selected for gynecological cancer tissue response
- DAR 8 selected for protein dose vs protein expression

ZW171: Mesothelin Expression Is Frequent in Ovarian Cancer, Endometrial Cancer, NSCLC, PDAC and Other Malignancies

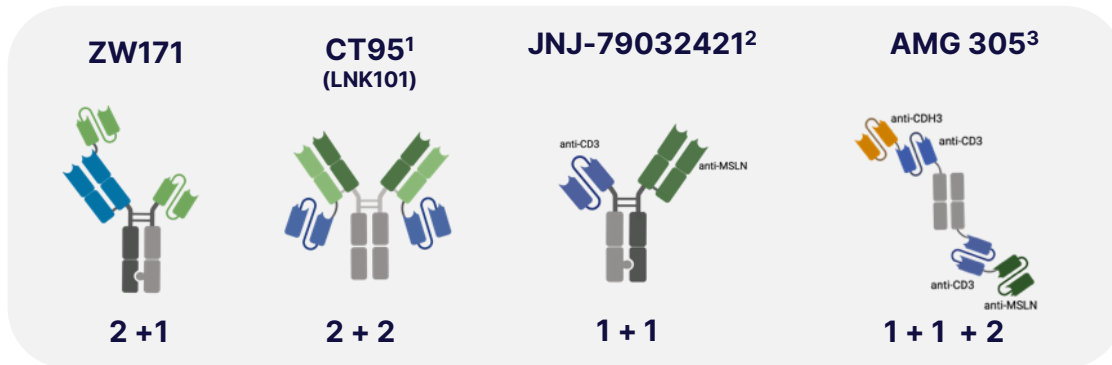


Adapted from Weidemann S, et al Biomedicines. 2021;9(4):397.

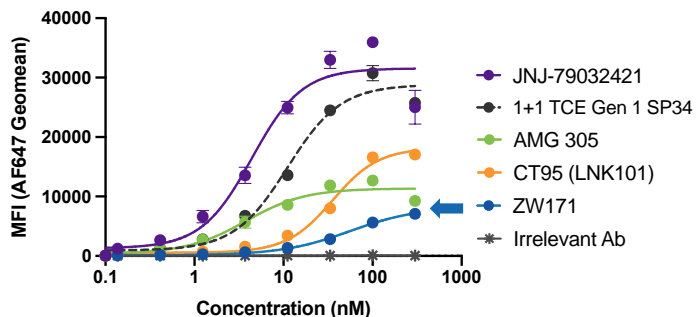
CRC: colorectal cancer; FR α : folate receptor alpha; GEA: gastroesophageal adenocarcinoma; IHC: immunohistochemistry; Mod: moderate; MSLN: mesothelin; NSCLC: non-small cell lung cancer; PDAC: pancreatic ductal adenocarcinoma

ZW171 Exhibits a Wider Therapeutic Window Compared to Next Gen MSLN TCEs

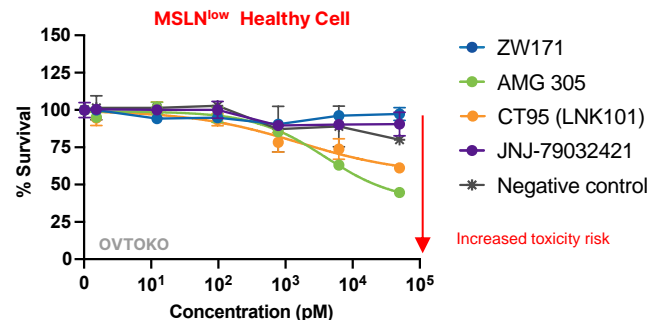
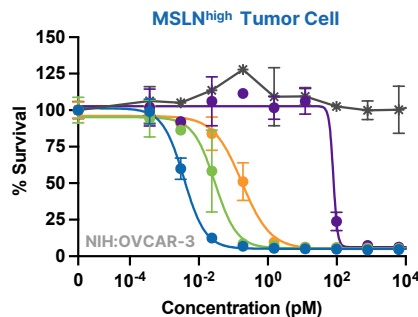
- Enhanced tumor selective cytotoxicity
- No targeting of normal tissues
- Low affinity CD3 binding to mitigate peripheral T cell binding and cytokine release
- Maintains potency in the presence of soluble MSLN



Low Binding to T cells



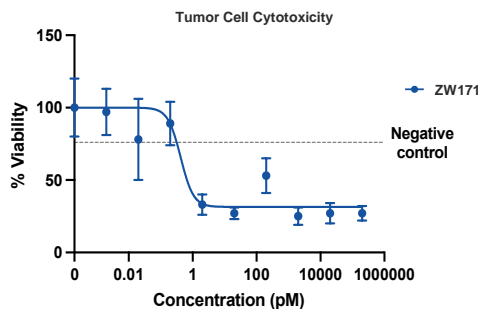
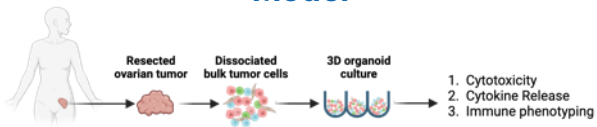
Potent Cytotoxicity in MSLN^{high} Tumor Cells but not Normal Cells



Tumor cell lines were cocultured with human PBMCs at an E:T ratio of 5:1. Test articles were titrated and added to wells in duplicate. After 72hr, tumor cell survival was assessed by high-content imaging. Negative control= HAxCD3
 1. CT95: Context Therapeutics Corporate Presentation Dec 2024; 2. JNJ-79032421: <https://clinicaltrials.gov/study/NCT06255665?term=JNJ-79032421&rank=1>; 3. AMG 305: Pham L et al AACR 2023; <https://clinicaltrials.gov/study/NCT05800964>;

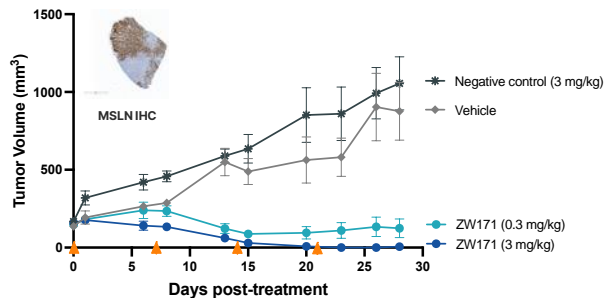
ZW171 Mediates Strong Anti-Tumor Activity in Patient-derived *Ex Vivo* and *In Vivo* Models

Ovarian Adenocarcinoma Organoid Model



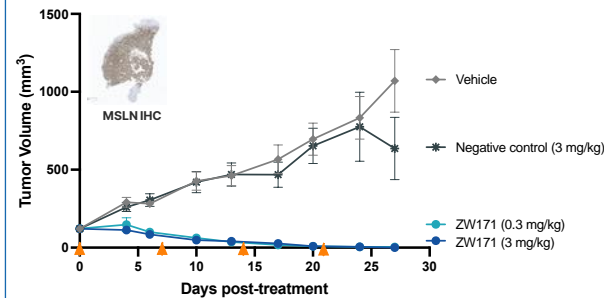
3D patient-derived ovarian carcinoma organoids were generated, and ZW171 activity assessed using Kiyatec proprietary technologies (Lassahn, 2023). Following incubation of organoids with ZW171 for 72hr, tumor cell viability was assessed using a CellTiter-Glo 3D (Promega) assay.

Patient-derived NSCLC Humanized Mouse Model



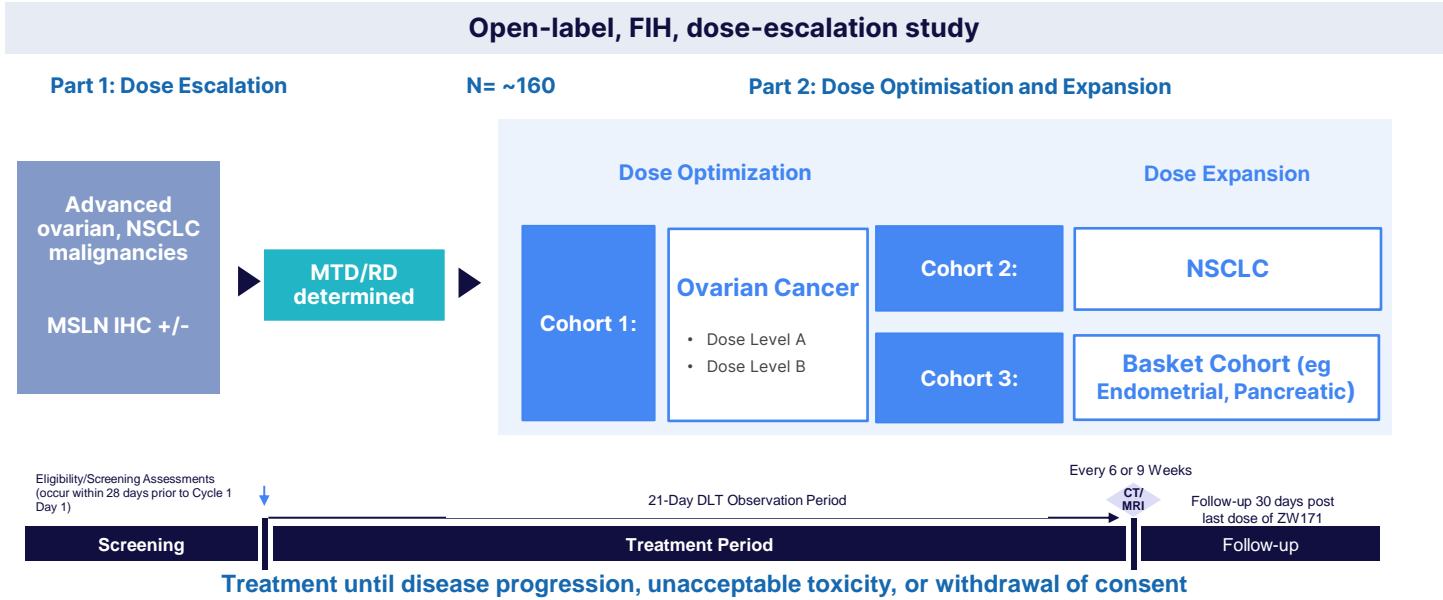
CD34 engrafted mice were engrafted with CTG-2579. When tumors reached 100-200 mm³, mice were dosed i.v. QW x4 with ZW171 at 3 or 0.3 mg/kg, the neg control (HAXCD3) at 3 mg/kg, or vehicle (H6Su).

Patient-derived Pancreatic Cancer Humanized Mouse Model



CD34 engrafted mice were engrafted with CTG-1375. When tumors reached 100-200 mm³, mice were dosed i.v. QW x4 with ZW171 at 3 or 0.3 mg/kg, the neg control (HAXCD3) at 3 mg/kg, or vehicle (H6Su).

ZW171 Global Phase 1 Study in MSLN-Expressing Solid Tumors (NCT06523803)



ADA: anti-drug antibodies; cORR: confirmed objective response rate; DL: dose level; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; FIH: first in human; GEA: gastrointestinal adenocarcinomas; IHC: immunohistochemistry; MTD: maximum tolerated dose; MSLN: mesothelin; mTPI: modified toxicity probability interval; NSCLC: non-small cell lung cancer; OBD: optimal biological dose; OS: overall survival; PFS: progression-free survival; PK: pharmacokinetics; pts: patients; PS: preferred status; Q3W: every 3 weeks; RD: recommended dose; SOC: standard of care; TBC: to be confirmed

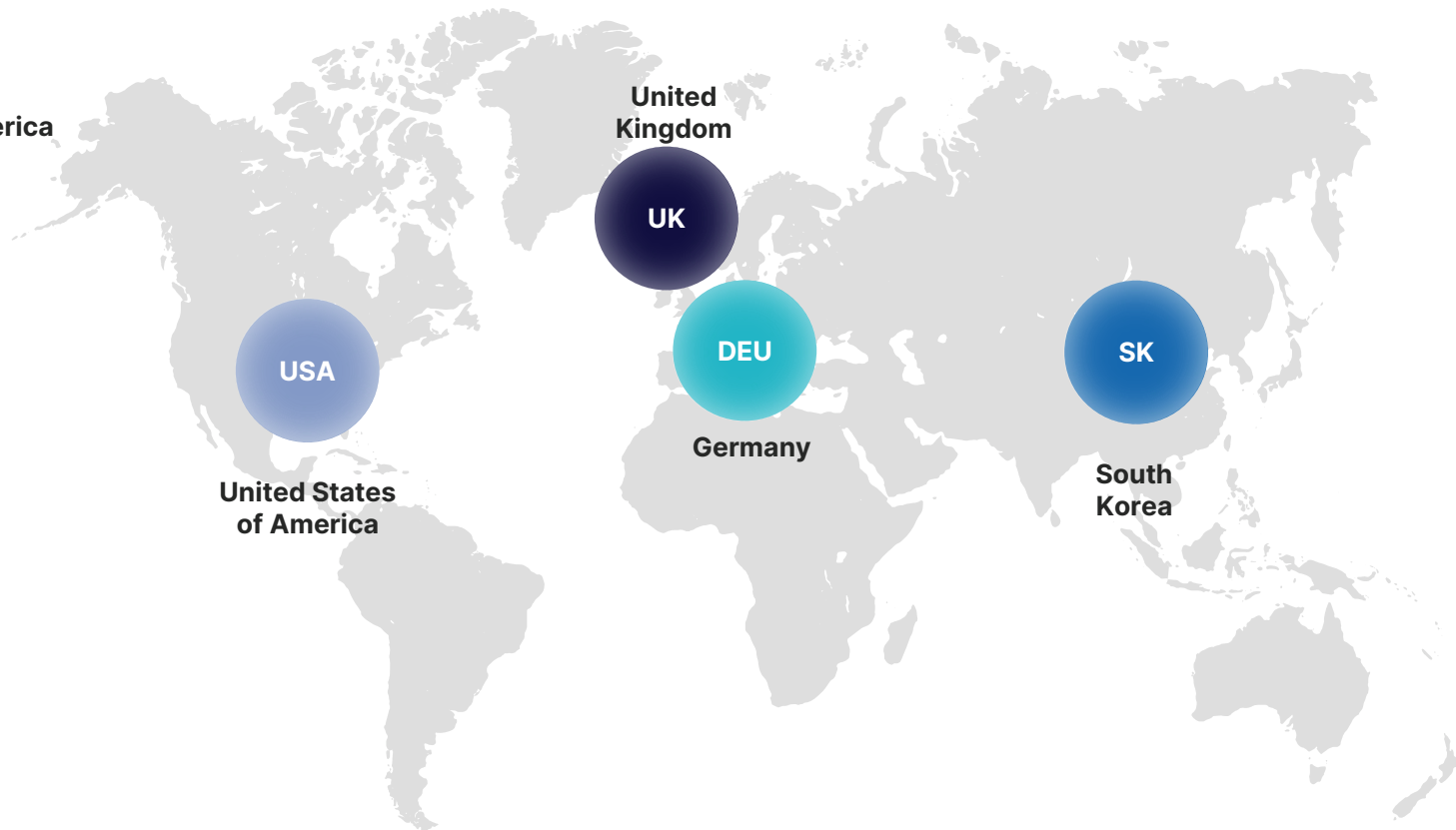
ZW171 Clinical Development Progress – Dose Escalation Territories

USA
United States of America
US FDA Approval
First Site Activated

UK
United Kingdom
UK MHRA Approval
First Site Activated

DEU
Germany
Pending Approval

SK
South Korea
MFDS Approval

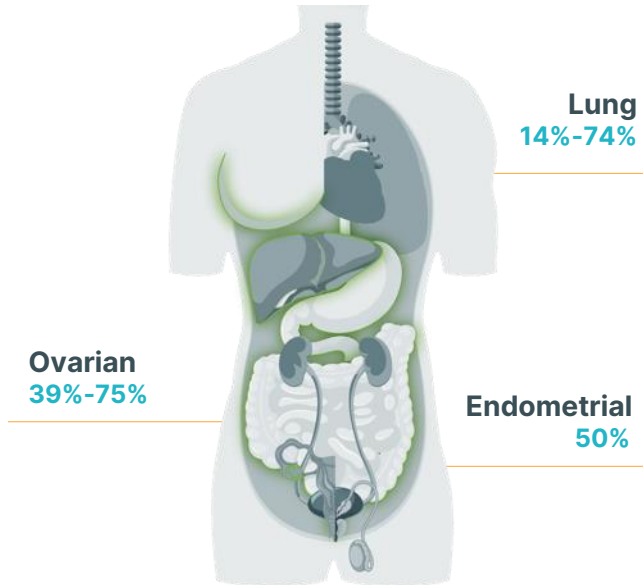


US FDA: U.S. Food and Drug Administration; MFDS: Ministry of Food and Drug Safety.

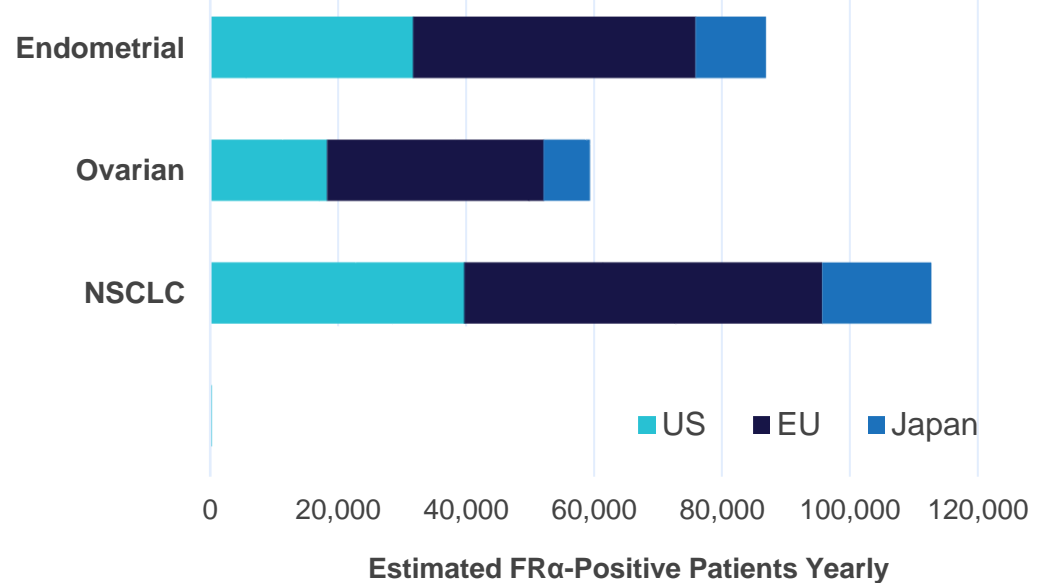
FR α -expressing Cancers Represent a Significant Commercial Opportunity¹⁻⁷

- Potential first and best-in-class in FR α -high endometrial, NSCLC and FR α -mid/low solid tumors
- Potential best-in-class opportunity in FR α -high ovarian cancer

FR α -EXPRESSING CANCERS



ESTIMATE OF NEWLY DIAGNOSED FR α + PATIENTS IN KEY INDICATIONS

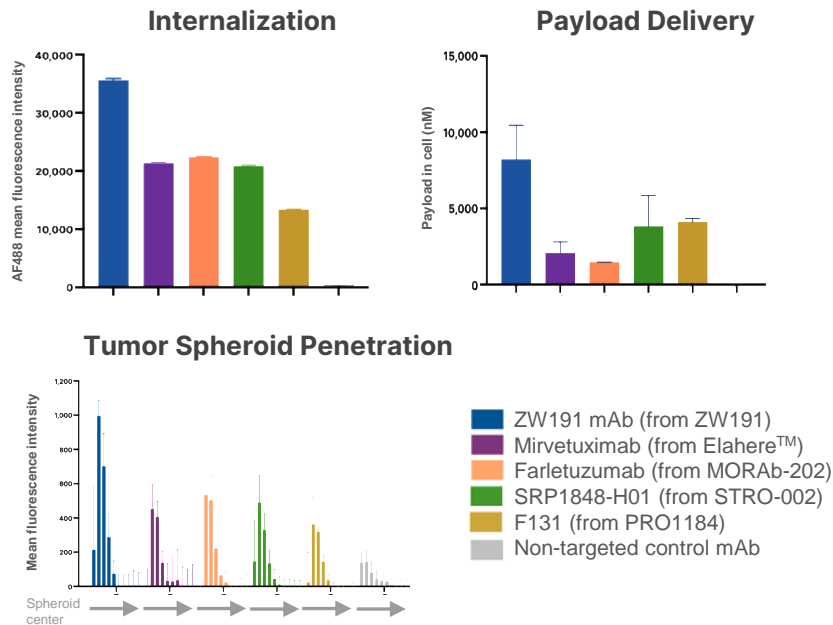


FR α : folate receptor alpha; NSCLC: non-small cell lung cancer; TNBC: triple negative breast cancer

1. Senol S, et al. Int J Clin Exp Pathol. 2015;8(5):5633-5641; 2. Omote S, et al. Med Mol Morphol. 2018;51(4):237-243; 3. Oza AM. SGO. 2021; 4. O'Shannessy DJ, et al. Oncotarget. 2012;3(4):414-425; 5. Nunez MI, et al. J Thorac Oncol. 2012;7(5):833-840; 6. D'Angelica M, et al. Mod Pathol. 2011;24(9):1221-1228; 7. Scaranti M, et al. Nat Rev Clin Oncol. 2020;17(6):349-359.

ZW191: Key Design Considerations

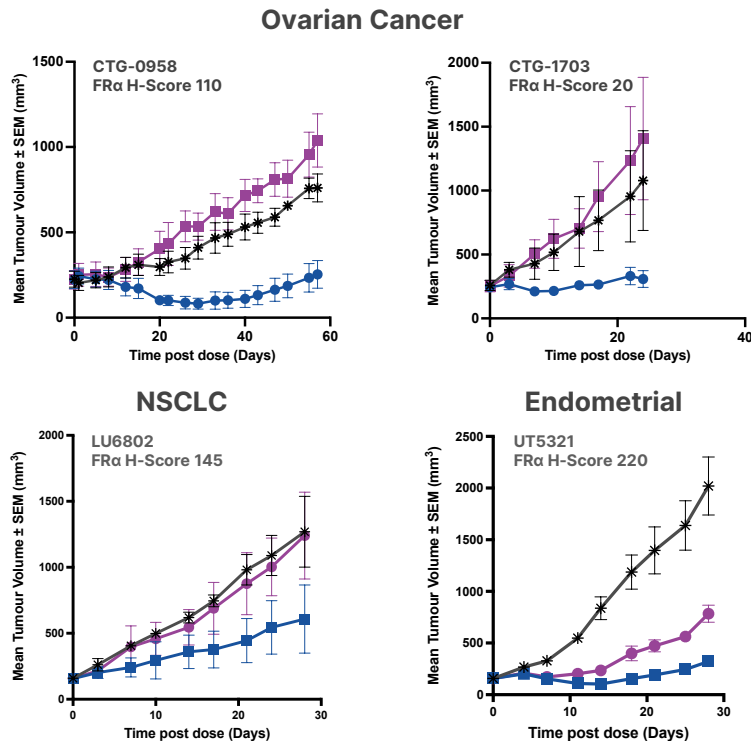
ZW191's Novel mAb Drives Superior Internalization, Payload Delivery and Tissue Penetration



Internalization of AF488 labelled antibodies to KB-Hela cells after 24 hrs at 100 nM; Mass-spec. quantification of internalized payload following 24-hour treatment of IGROV-1 cells with 10 nM of ADCs comprising ZW191 mAb or other FR α -targeted mAbs conjugated to a auristatin payload; Tumor spheroid penetration of AF488 labelled antibodies as quantified by high content imaging of spheroid layers at 24 hours post-treatment at 50 nM.

Wong J et al., Abstract #3127 presented at American Association for Cancer Research annual meeting 2024
Lawn S. et al. Abstract # 1862 presented at American Association for Cancer Research annual meeting 2024

Anti-tumor Activity Across Multiple Tumor Types and Range of FR α Expression (PDX models)



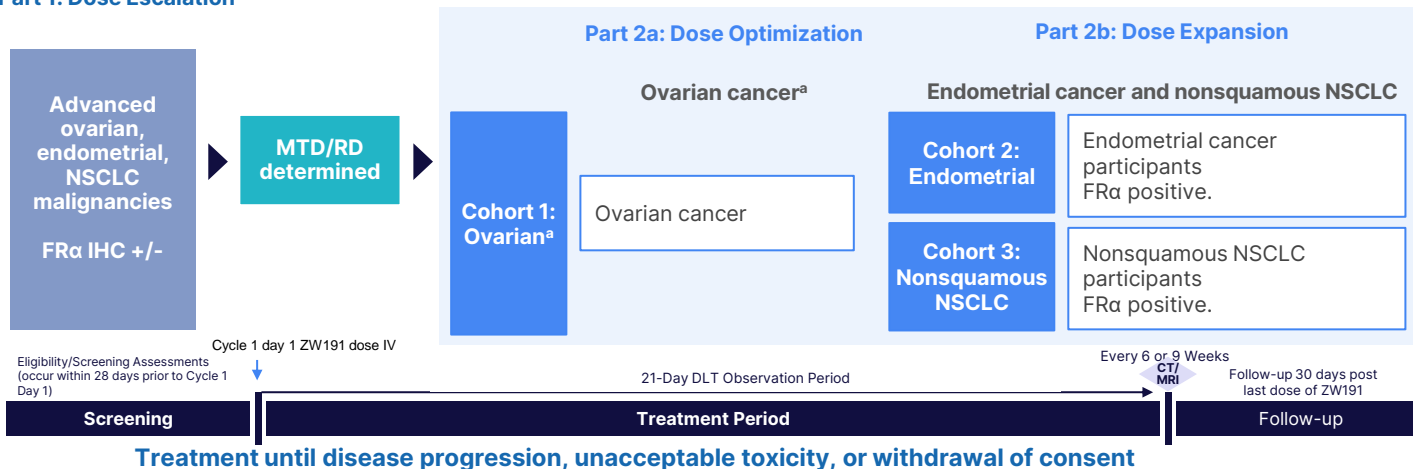
ZW191, 6 mg/kg mirvetuximab soravtansine, 6 mg/kg

ZW191: Global Phase 1 Study in FR α -Expressing Solid Tumors (NCT06555744)

Open-label, FIH, dose-escalation study N= ~145

Part 1: Dose Escalation

Part 2: Dose Expansion

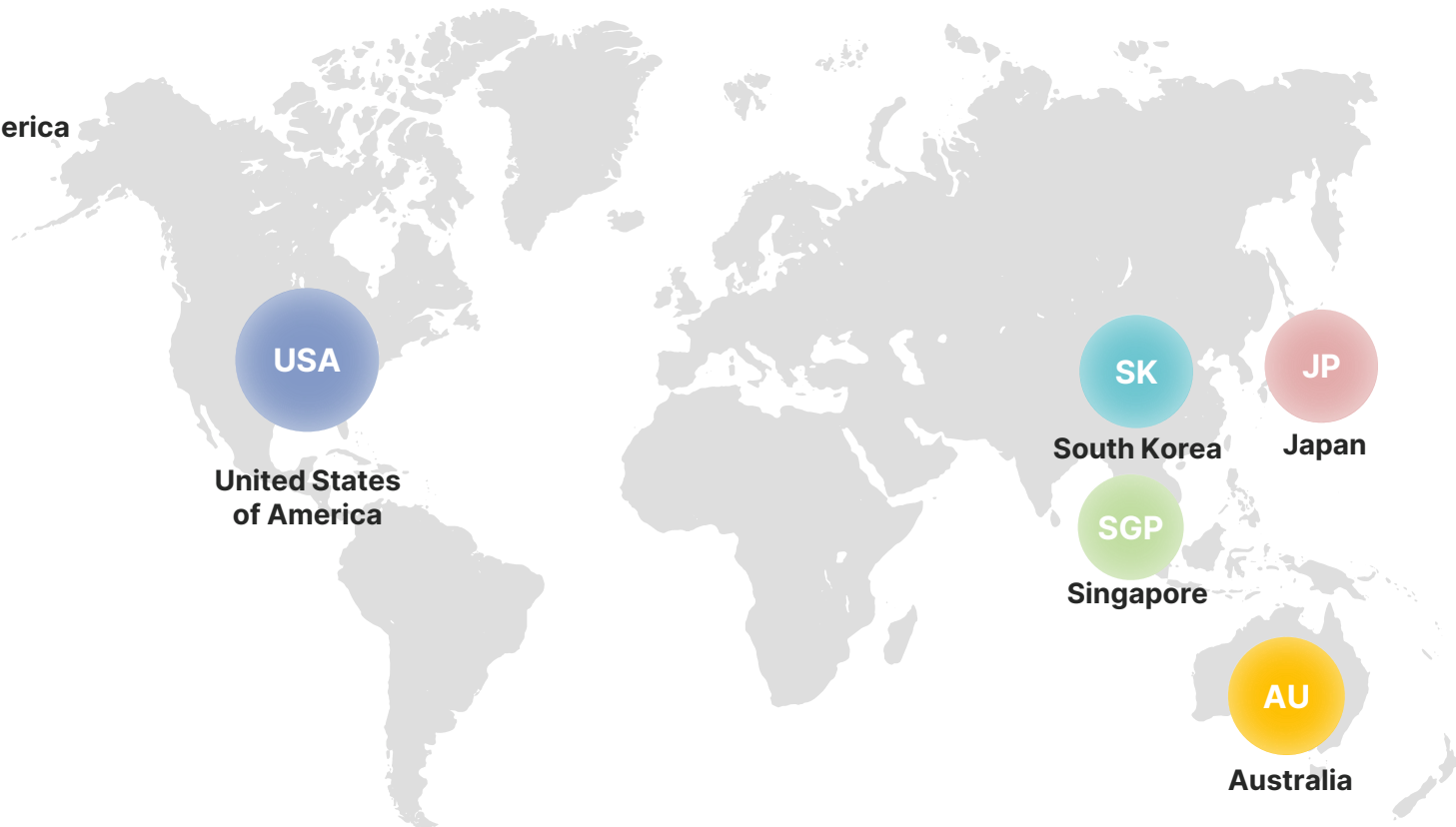


^aOvarian cancer includes primary peritoneal and fallopian tube cancers. ^bPart 2 will be initiated at dose levels (RDEs) based on the SMC's comprehensive analysis of safety, tolerability, clinical PK, PD, and preliminary antitumor activity data from Part 1. The Part 2 selected doses will be decided at SMC meetings and could be the MTD or RDEs based on comprehensive analysis of safety, tolerability, clinical PK, PD, and antitumor activity data from Part 1. The RDE dose levels may vary across the tumor types in Cohorts 1, 2, and 3. ^cTimed from cycle 1 day 1. Q6W (every 6 weeks) for the first 4 assessments and then Q9W (every 9 weeks) thereafter. ClinicalTrials.gov ID: NCT06555744.

ADA: anti-drug antibody; ADC: antibody-drug conjugate; AE: adverse event; AESI: adverse event of special interest; CNS: central nervous system; CT/MRI: computed tomography/magnetic resonance imaging; ECOG PS: Eastern Cooperative Oncology Group performance status; FR α : folate receptor alpha; IHC: immunohistochemistry; IV: intravenous; MTD: maximum tolerated dose; NSCLC: non-small cell lung cancer; ORR: objective response rate; PD: pharmacodynamics; PK: pharmacokinetics; Q3W: every 3 weeks; RDE: recommended dose for expansion; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; SMC: safety monitoring committee; SOC: standard of care; TBD: to be determined; TOPO1i: topoisomerase-1 inhibitor.

ZW191 Clinical Development Progress

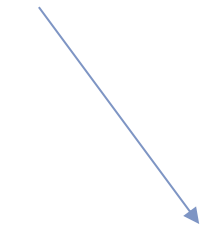
- USA**
US FDA Approval
Sites Activated
- JPN**
PMDA Approval
Sites Activated
- AU**
TGA Approval
First Site Activated
- SKr**
MFDS Approval
- SGP**
HSA Approval
First Site Activated



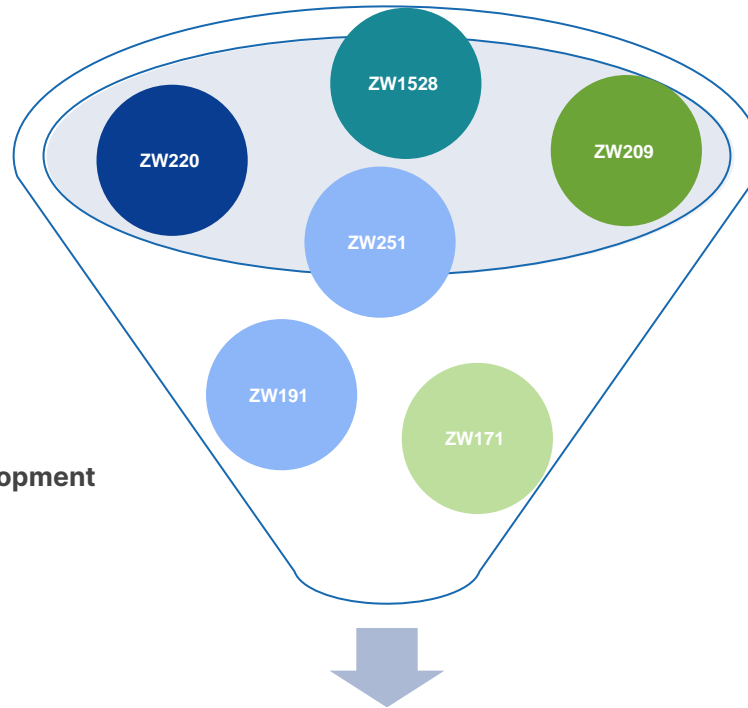
US FDA: U.S. Food and Drug Administration; PMDA: Prescription Drug Marketing Act; TGA: Therapeutic Goods Administration; MFDS: Ministry of Food and Drug Safety; HAS: Health Sciences Authority

Multiple Candidates in Development Offer Strategic Pivot Points

Preclinical Development



Phase 1 Clinical Development



Decision Pathway Factors

- Optimal dose
- Tolerability and safety
- Early signs of anti-tumor activity
- Proof of targeted therapy: strong relationship between expression levels and anti-tumor activity
- Competitive landscape

Pipeline Resource Allocation

Partnership Optionality

Combination Approaches

Accelerated Development into Phase 2/3

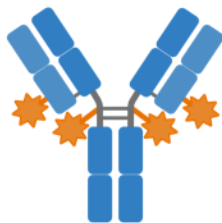
SOLID TUMOR PROGRAM

ZW220 and ZW251

Paul Moore, PhD
Chief Scientific Officer



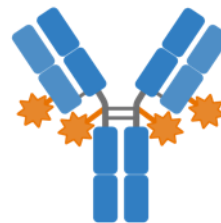
ZW220



NaPi2b-targeting ADC

- TOPO1i payload selected for gynecological and lung cancer tissue response
- DAR4 selected to balance desired antitumor activity with potential for on-target toxicities
- Fc silenced to potentially minimize toxicities driven by cellular uptake via FcγR

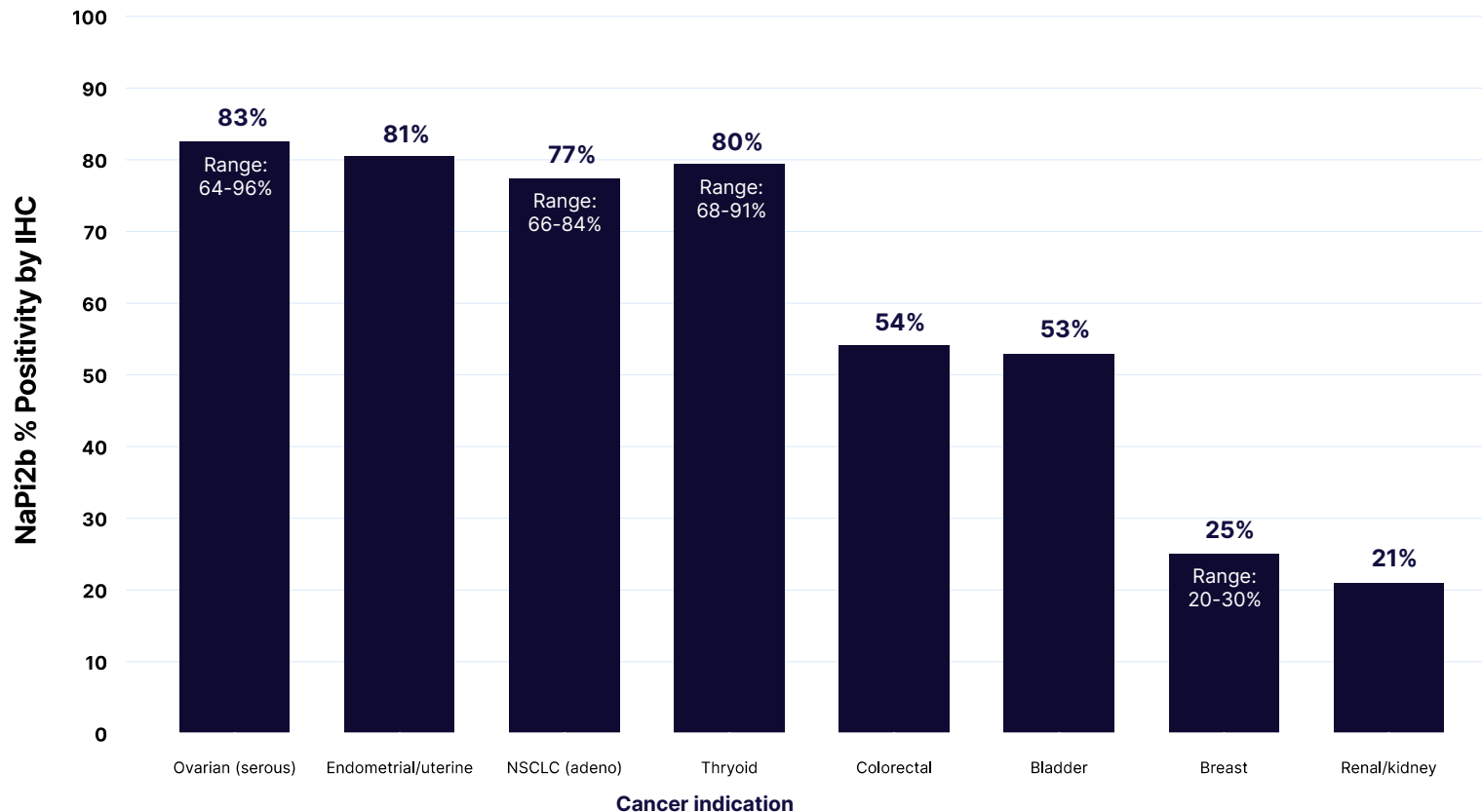
ZW251



GPC3-targeting ADC

- Designed to target GPC3 that is overexpressed in majority of Hepatocellular carcinoma patients
- TOPO1i payload with bystander activity selected for gastrointestinal cancer tissue response
- DAR4 selected for protein dose vs protein expression

NaPi2b is Overexpressed in Multiple Cancers with High Unmet Medical Need

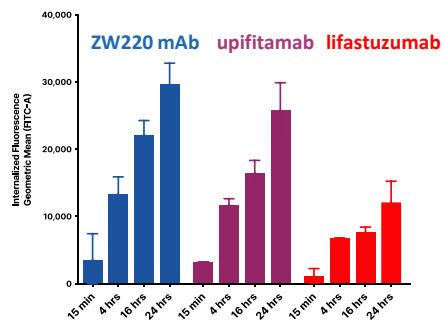


- Ovarian
- 1) Banerjee et al. 2023. ESMO #145
 - 2) Richardson et al. 2022. SGO #76
 - 3) Levan et al. 2017. BMC Cancer
 - 4) Lin et al. 2015. Clin Cancer Res
 - 5) Lopes dos Santos et al. 2013. PLoS One
- Endometrial/uterine
- 1) Horsley et al. 2024. Cancer Res #5085
- Lung
- 1) Horsley et al. 2024. Cancer Res #5085
 - 2) Heynemann et al. 2022. Clin Lung Cancer
 - 3) Yu et al. 2018. IASLC #12636
 - 4) Zhang et al. 2017. Tumor Biology
 - 5) Lin et al. 2015. Clin Cancer Res
- Thyroid
- 1) Hakim et al. 2021. Anal Cell Pathol
 - 2) Lin et al. 2015. Clin Cancer Res
- Colorectal
- 1) Liu et al. 2018. Biomed Pharmacother
- Bladder
- 1) Ye et al. 2017. Cell Death Dis
- Breast
- 1) Lopes dos Santos et al. 2013. PLoS One
 - 2) Kiyamova et al. 2011. Exp Oncol
- Renal/kidney
- 1) Lopes dos Santos et al. 2013. PLoS One

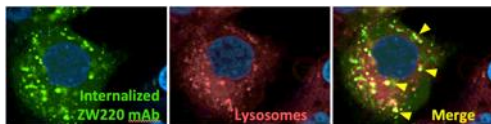
ZW220: Potential Utility in Multiple Cancers; on Track for Clinical Studies in 1H 2025^{1,2,3}

ZW220 Efficiently Internalizes and Co-localizes with Lysosomes

ZW220 (mAb) internalization in Ovarian Cancer cell line

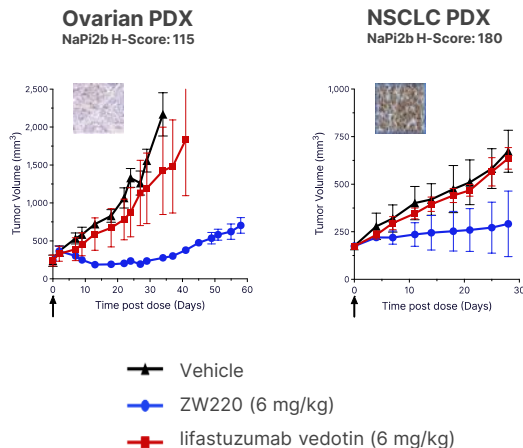


Lysosomal trafficking of ZW220 mAb



Anti-tumor Activity in Ovarian and Lung Cancer Models

Anti-tumor activity of ZW220 and lifastuzumab vedotin against ovarian and lung patient derived xenografts (PDXs) expressing NaPi2b

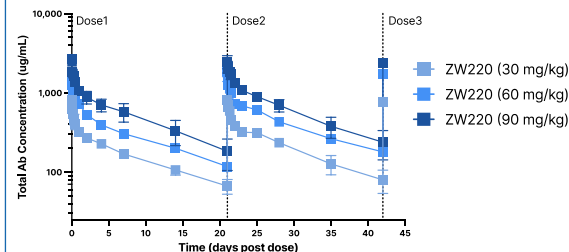


Impressive Tolerability and Dose-proportional PK in NHP

Non-GLP toxicology study in non-human primates dosed 3 times every 3 weeks

Dose	MTD	T _{1/2} (day)
30 mg/kg	≥ 90 mg/kg	10.3
60 mg/kg		9.8
90 mg/kg		8.0

Total IgG in NHP serum



*ZW220 Fc wt surrogate used in non-GLP NHP study

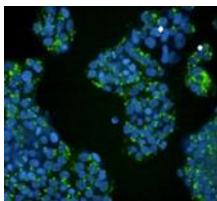
mAb: monoclonal antibody; PDX: patient derived xenograft; MTD: maximum tolerated dose; T_{1/2}: half-life; GLP: good laboratory practice

1. Hernandez Rojas A et al., Abstract #1533 presented at AACR 2023; 2. Hernandez Rojas A et al. Presentation at World ADC 2023; 3. Hernandez Rojas A et al. *Eur. J. Cancer* (2024), 211, 114535.

ZW251: Potential Utility in Hepatocellular Carcinoma^{1,2,3}; on Track for Clinical Studies in 2025

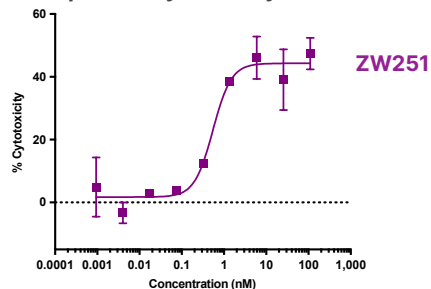
Robust ADC Internalization and Cytotoxicity

ZW251 internalized in HCC cell line



Internalization visualized after 24-hour treatment

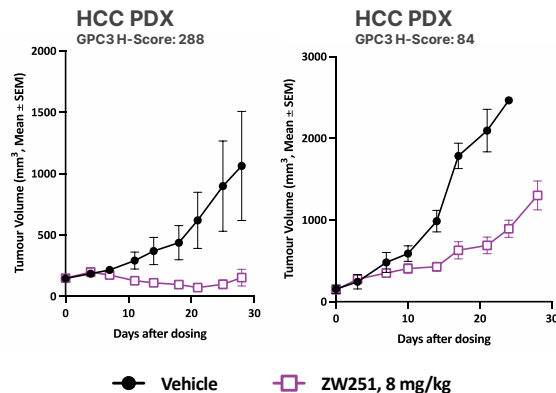
Tumor spheroid cytotoxicity in HCC cell line



Cytotoxicity assessed by cell line spheroids (treatment over 4 days)

Differentiated Modality Demonstrates Anti-tumor Activity

Anti-tumor activity of ZW251 against hepatocellular carcinoma patient derived xenografts expressing high and low GPC3

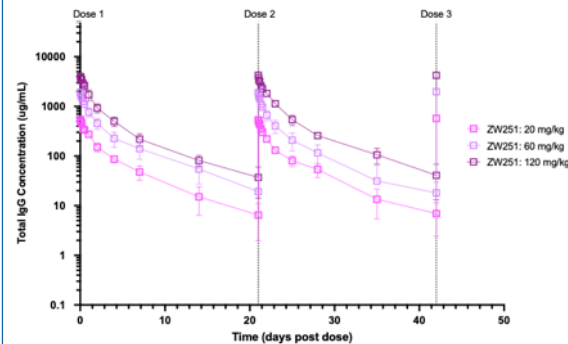


Impressive Tolerability and Dose-proportional PK in NHP

Non-GLP toxicology study in non-human primates dosed 3 times every 3 weeks

Dose	MTD	T _{1/2} (day)
20 mg/kg	≥ 120 mg/kg	4.6
60 mg/kg		4.8
120 mg/kg		5.4

Total IgG in NHP serum



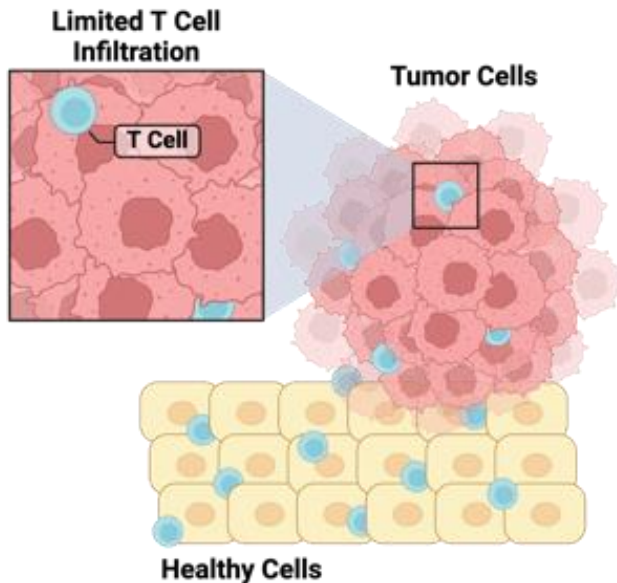
HCC: Hepatocellular carcinoma; PDX: patient derived xenograft; MTD: maximum tolerated dose; T_{1/2}: half-life; GLP: good laboratory practice
 1. Madera L et al., Abstract #2658 presented at AACR 2023; 2. Madera L et al., presentation at World ADC 2023; 3 Madera L et al., Abstract #177 presented at EORTC-NCI-AACR 2024

SOLID TUMOR PROGRAM

Product Candidate Nomination: ZW209
DLL3 x CD3 x CD28 TriTCE

Overcoming Lack of Efficacy and Durability of T cell Mediated Responses in Solid Tumors Through Incorporation of CD28 Co-stimulation

Low T cell infiltration and T cell anergy remain challenges in the treatment of solid tumors



	Expected Benefit	Opportunity
CD28	<ul style="list-style-type: none">Enhances proliferation and survival of CD8 and CD4 T cells¹Ability to expand and maintain T_{pex} and prevent T_{ex}²CD28 signaling critical for T_{eff} expansion and epitope spreading^{3,4}	<ul style="list-style-type: none">No signaling independent of TCROpportunity to engineer safe and effective conditional co-stimulation

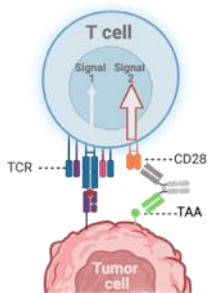
Arvedson T et al Ann Rev Cancer Biol 2022

¹ Lotze et al., Nature Reviews Immunol 2024; ² Humblin et al., 2023, Sci. Immunol.; ³ Prokhnevska et al., Immunity 2023;

⁴ Friedrich et al., Cancer Cell 2023

CD28 Co-stimulatory T Cell Engager Approaches

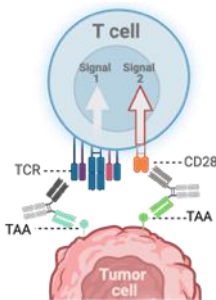
Bispecific CD28 T cell Engagers



CD28 x TAA +/- PD1

Limitations:

- Initial clinical activity for CD28-TAA +PD1, but potential toxicity due to autoreactive T cells¹

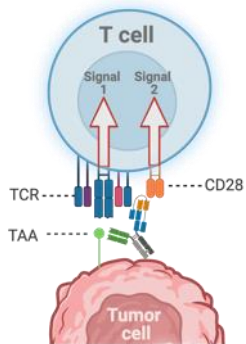


CD28 x TAA + CD3 x TAA

Limitations:

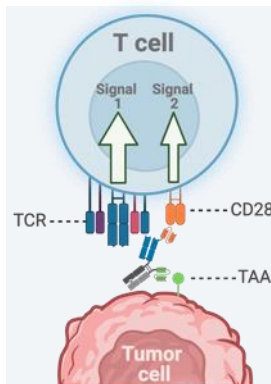
- Optimized for single agent activity and strong CD28 agonism, potential for similar toxicity to CD28-TAA and difficult to optimize by dose adjustment
- Exposure of two molecules at required dose levels potentially suboptimal

Trispecific CD28 T cell Engagers



First Generation:

- High affinity CD3 and CD28 superagonist paratopes^{2,3}
- T cell binding, activation and TMDD observed in periphery^{2,3}
- Target-independent activity and T cell activation



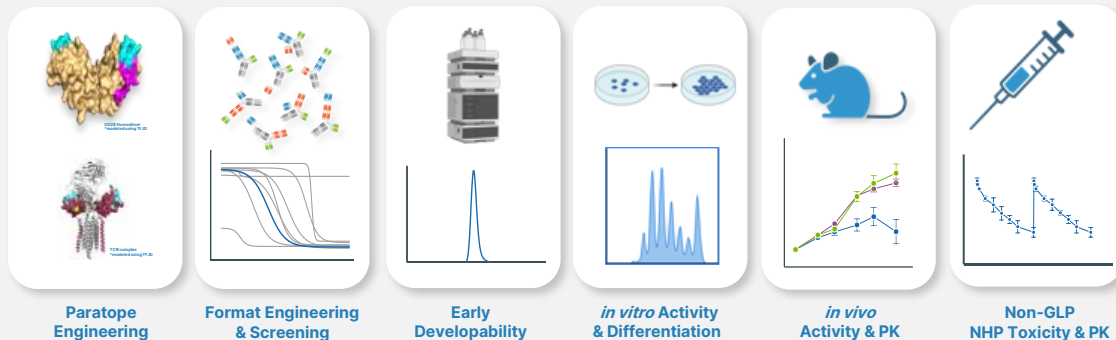
Zymeworks' Next Generation Solution:

- Balanced low affinity CD3 and CD28 engagement
- Conditional CD28 binding that only binds in cis with CD3 engagement
- Strict target-dependent activity and T cell activation
- Identified via Azymetric™ screening of various antibody geometries and CD3 and CD28 paratope affinities

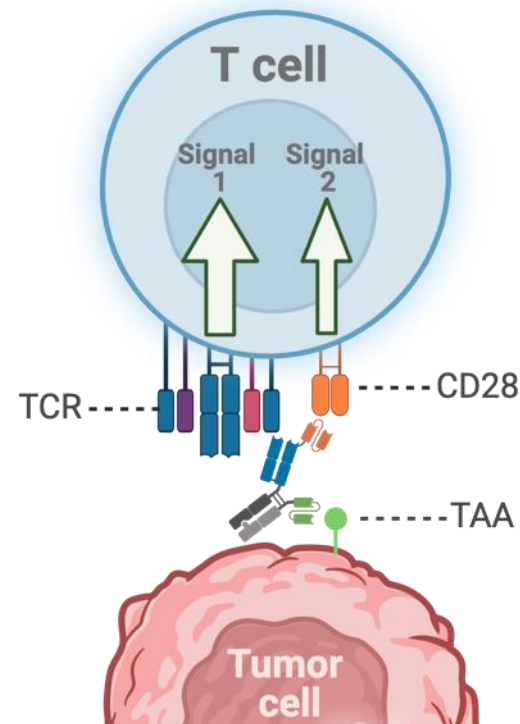
¹ Stein et al., Journal Clinical Oncology (2023); ² Seung et al., Nature (2022); ³ Promsote et al., Nature Communications (2023)

TriTCE Co-stim: A Next Generation Trispecific T Cell Engager Platform

TriTCE Co-stim Platform Workflow

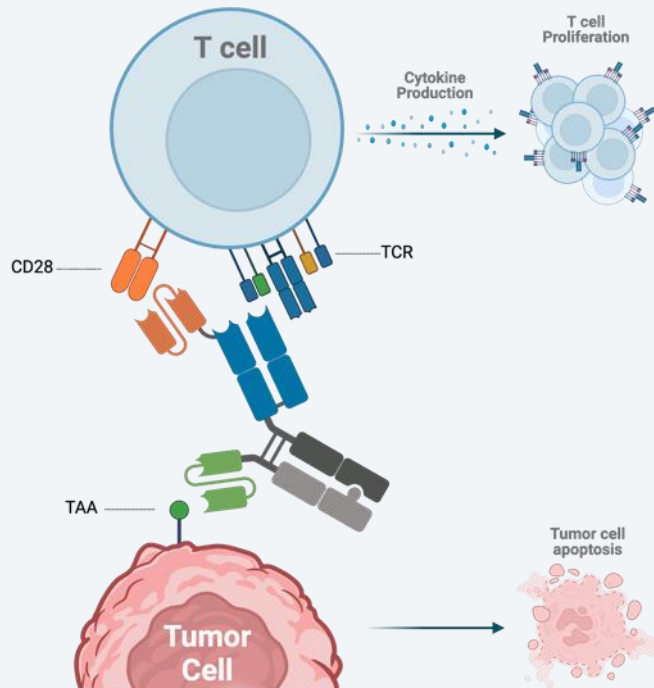


TriTCE Co-stim Lead Format Selection



TriTCE Co-stim Designed to Optimize T cell Binding, Activation and Anti-Tumor Activity

Conditional CD28 Co-stimulation and Obligate *cis* T cell Binding

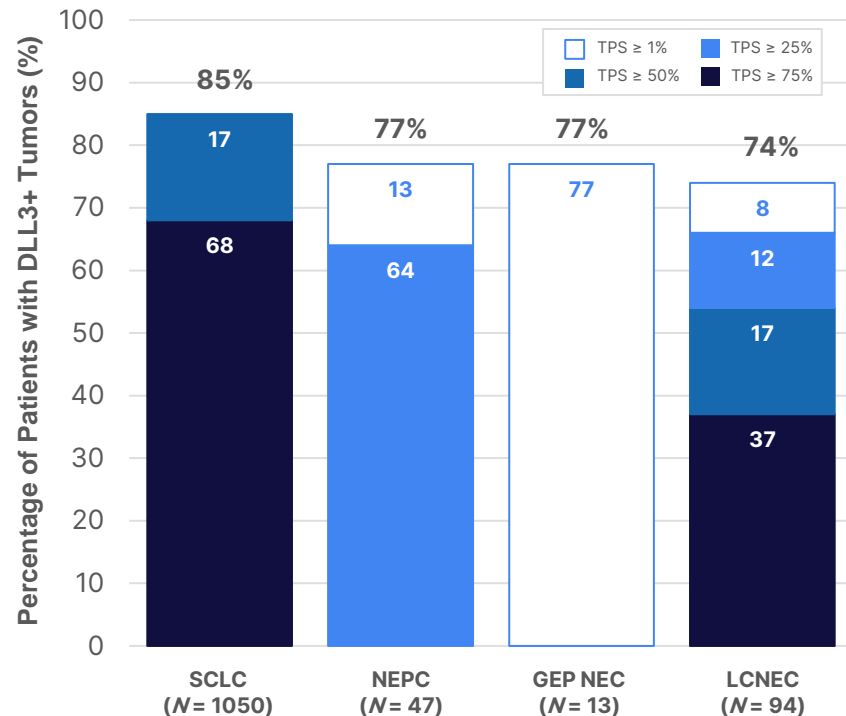


	Design Feature	Expected Benefit
1	Balanced activation of CD3 and CD28	Potential to provide more durable responses and activate T cell responses in 'cold' tumors with lower T cell infiltration
2	Low affinity CD3 and CD28 binding	Prevents overactivation of T cells and reduces risk of CRS and irAEs
3	Obligate <i>cis</i> T cell binding	No T cell-to-T cell bridging or T cell fratricide
4	Conditional CD28 engagement	Requires co-engagement of CD3
5	Enhanced target-dependent activity	Low T cell binding and no T cell activation in periphery or absence of tumor target

CRS: Cytokine release syndrome; irAEs: immune-related adverse events

DLL3 is an Ideal Target to Evaluate TriTCE Co-stim Platform, with Opportunities in Multiple Cancers

- Responsiveness of DLL3-expressing tumors to TCE modality validated with Imdeltra™ and other DLL3 bispecific TCEs; however, opportunity for improved responses remains
- DLL3 is expressed on the surface of SCLC and other neuroendocrine tumors but rarely on the surface of normal cells
- Clean expression profile and absence of on-target, off-tumor side effects observed for DLL3 x CD3 bispecifics provides ideal TriTCE Co-Stim target profile

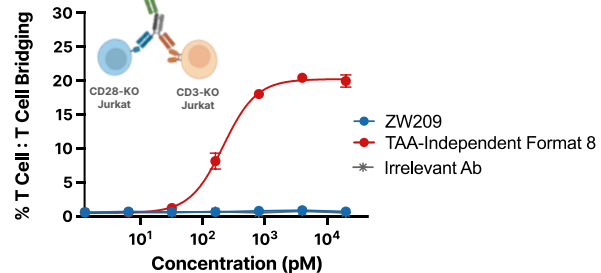
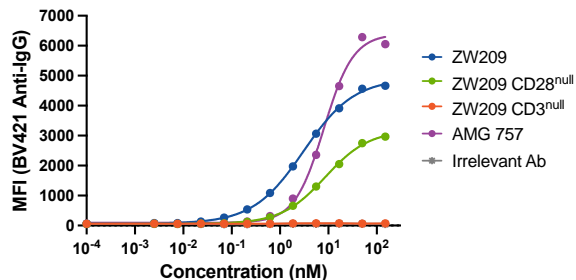


Adapted from: Rojo F et al. Lung Cancer 2020. International real-world study of DLL3 expression in patients with small cell lung cancer. Puca L et al. Delta-like protein 3 expression and therapeutic targeting in neuroendocrine prostate cancer. Sci Transl Med. 2019. 11: eaav0891. Liverani C et al. Endocrine Pathol 2021. Diagnostic and Predictive Role of DLL3 Expression in Gastroenteropancreatic Neuroendocrine Neoplasms. 32:309-27. Hermans BCM et al. DLL3 expression in large cell neuroendocrine carcinoma (LCNEC) and association with molecular subtypes and neuroendocrine profile. Lung Cancer 2019. 138:102-8. TCE, T cell engager

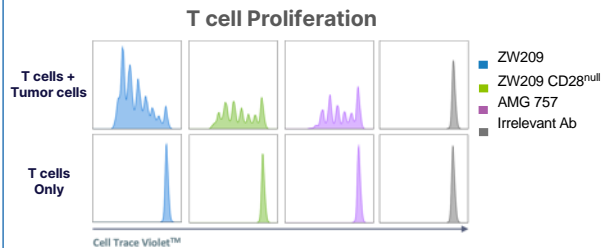
ZW209: Mediates Enhanced and Sustained Cytotoxicity

ZW209 demonstrates conditional CD28 binding and target-dependent anti-tumor activity

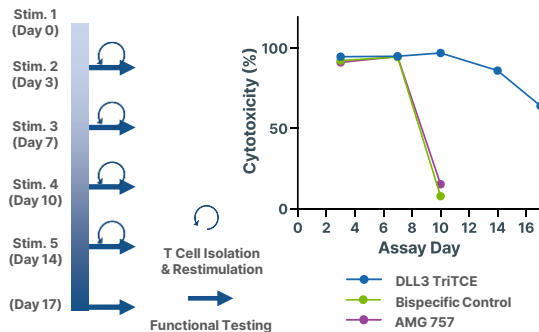
Conditional Binding of CD28, Requiring Co-engagement of CD3; Obligate Cis Binding



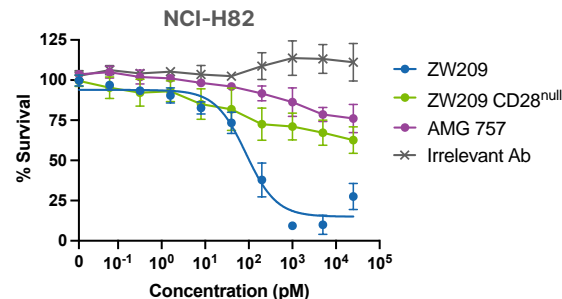
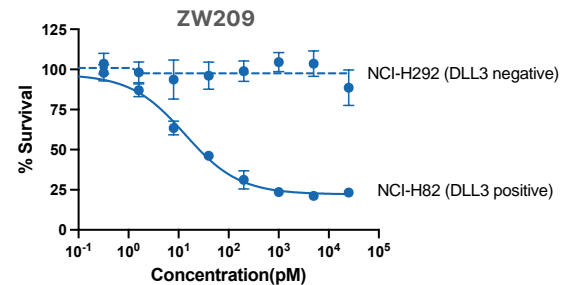
Improved T Cell Proliferation and Sustained Cytotoxicity



Repeat Challenge Assay

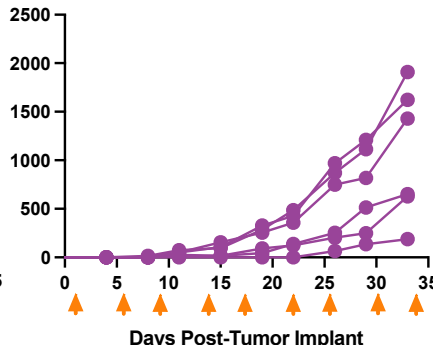
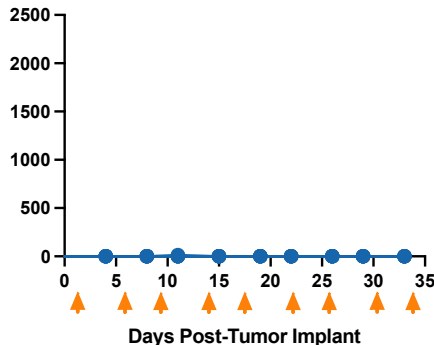
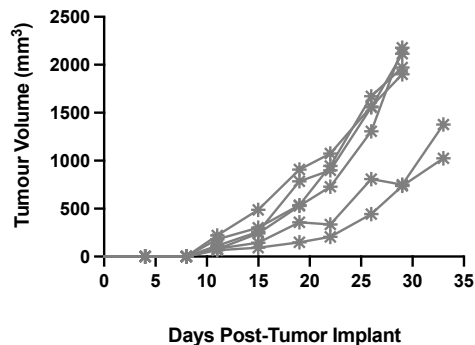


Improved Cytotoxicity Over Bispecifics in Low E:T Conditions



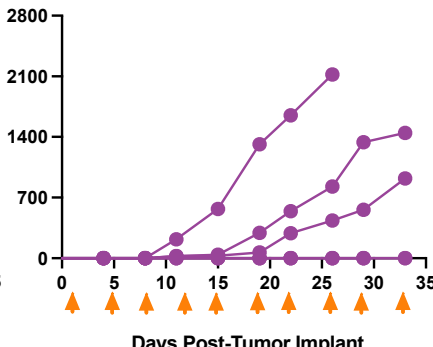
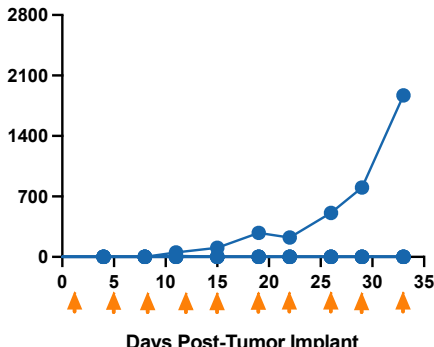
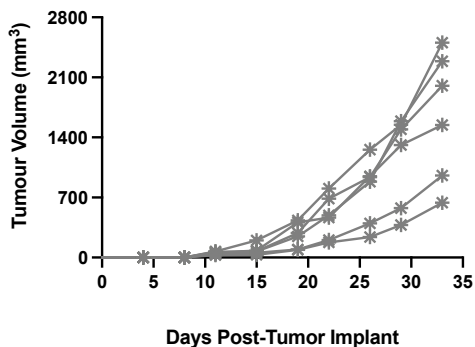
ZW209 Mediates Enhanced Anti-Tumor Activity *In Vivo* Compared to Benchmark Bispecific TCE in Humanized SCLC Models

PBMC Donor 1



- * Untreated
- ZW209 2.85 nmol/kg
- AMG 757 2.85 nmol/kg

PBMC Donor 2

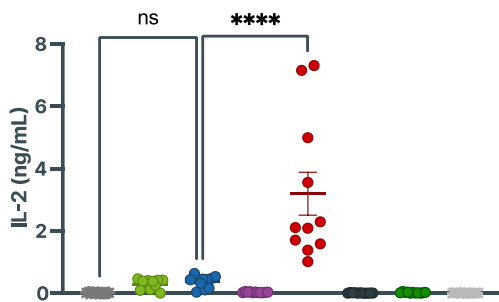


AMG 757 produced by Zymeworks for internal preclinical studies.

ZW209 has a Favorable Safety Profile in *In Vitro* and Animal Studies

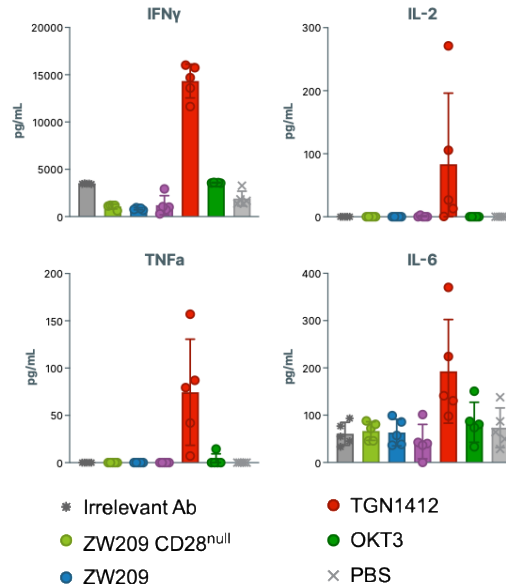
No Cytokine Activation with PBMCs Alone

Solid-Phase Cytokine Release Assay



- * Irrelevant Ab
- ZW209 CD28^{null}
- ZW209
- AMG 757
- TGN1412
- Infliximab
- Muromonab
- × No Treatment

Induces Minimal Systemic Cytokine in Humanized Mouse CRS Model

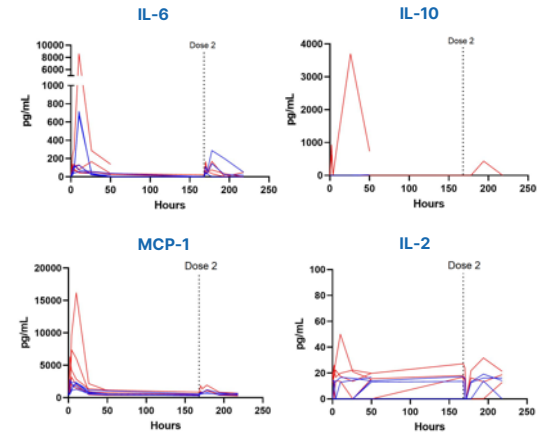


- * Irrelevant Ab
- ZW209 CD28^{null}
- ZW209
- AMG 757
- TGN1412
- OKT3
- × PBS

TGN1412 positive control
All dosed at 2 mg/kg except OKT3 (0.25 mg/kg)

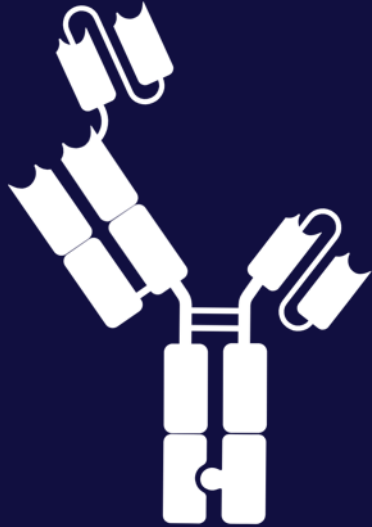
Well Tolerated in Non-Human Primate

Transient, Minor Increases in Serum Cytokine Post-Dosing



- DLL3 TriTCE (10 mg/kg)
- DLL3 TriTCE Cyno surrogate (10 mg/kg)

Note: Peak 10 mg/kg surrogate values are male with ↑ CRP



ZW209 DLL3 TriTCE Co-stim

Therapeutic Program for the
Treatment of DLL3-Expressing
Solid Tumors



Design

- Trispecific TCE with potentially optimized TAA, CD3, CD28 binding affinity and geometry using Azymetric™ and EFECT™ platforms
- Obligate cis-T cell binding with conditional CD28 engagement



Mechanism

- Targets DLL3-expressing tumor cells and CD3 and CD28 on T cells
- DLL3-dependent T cell mediated cytotoxicity prevents activation of effector T cells in the absence of TAA



Profile & Opportunity

- Differentiated long term cytotoxicity at low effector to T cell ratios, increased T cell proliferation, survival, and anti-tumor activity with reduced cytokine release
- First in class TriTCE Co-stim opportunity on validated target
- Potential to increase durability of responses in DLL3 expressing cancers
- On track for IND submission 1H 2026

SOLID TUMOR PROGRAM

Q&A Session #1

ADVANCE PROGRAM

Solid Tumors and Beyond

Paul Moore, PhD
Chief Scientific Officer



AD-VAN-CE Portfolio: Progressing “First In Class” Therapeutics

1. **Focus on novel “first in class” multi-functional therapeutics:** novelty of modality, mechanism of action, and/or targeting strategy. Disruptive therapeutics with high potential benefit to patients.
2. **Build on competitive edge in ADCs and protein engineering:** cross complementary MoA and pathway axes across Zyme portfolio.
3. **Continue to focus on select therapeutic opportunities in solid tumors:** expand portfolio coverage with GI tract and thoracic cancers.
4. **Expand technology application to Heme-Onc, Autoimmune and Inflammatory Disease:** targeted areas conducive to multi-functional therapeutic intervention; overlap with company expertise.

Antibody-Drug Conjugates

- Novel Payload(s) – beyond TOPO1i
- Bispecific/Biparatopic(s)
- Novel Targets and Target Pairs
- Payload modalities beyond cytotoxics

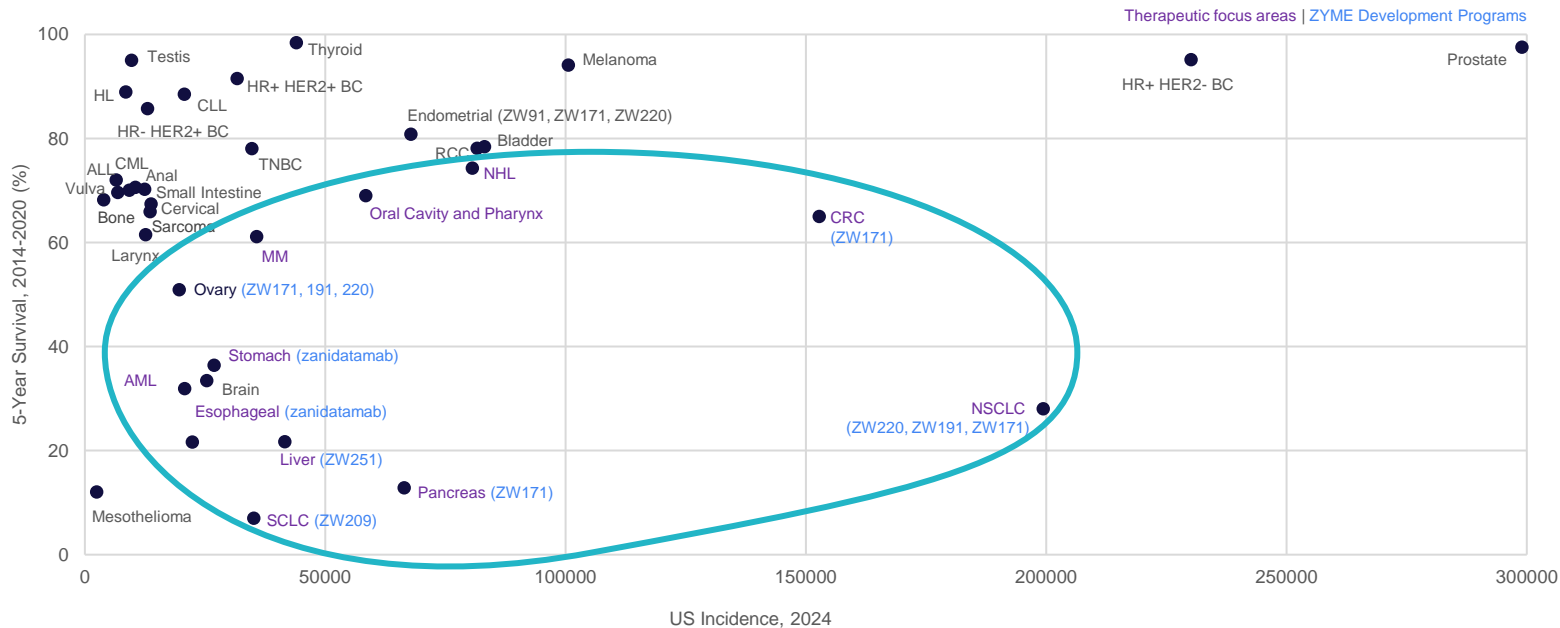
Cell Engagers

- Muti-specific T Cell Engagers
- Multi-antigen targeting
- Conditional activation
- Novel targets (e.g. proteomics)
- Intracellular antigens

Cytokine Engineering

- Tumor specific cytokine activation
- Combination Checkpoint Inhibition/cytokine activation
- Chemokine incorporation
- Multi-cytokine blockade (Autoimmune)

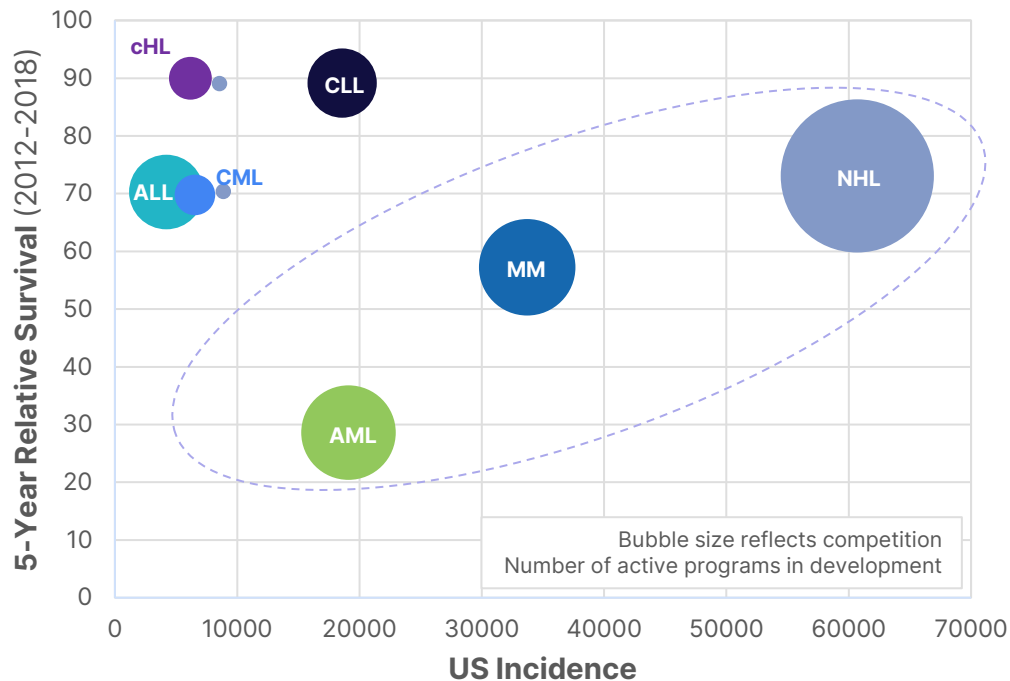
Maintain Focus on Cancers with Highest Unmet Medical Need: Increase GI Tract and Thoracic Cancer Coverage and Expand to Heme-Onc Cancers



SEER* Explorer, accessed 10 Oct 2022.

AML: Acute myeloid leukemia, CRC: colorectal cancer; MM: Multiple myeloma, NSCLC: Non-small cell lung cancer, SCLC: Small cell lung cancer, NHL: non-Hodgkin lymphoma

Opportunities in NHL, MM, AML Compatible with ZYME Technology

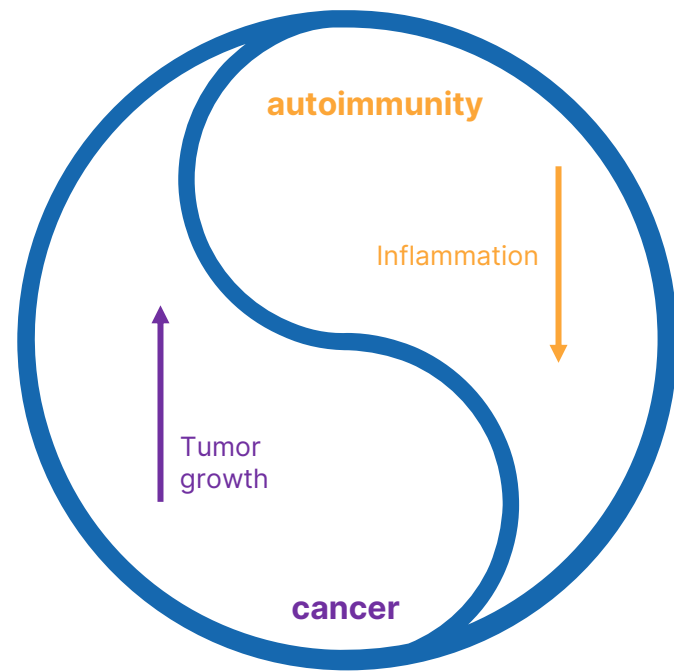


- Despite good outcomes for some, many patients with common blood cancers are not cured by frontline therapies. Patients with refractory or multi-drug resistant disease need more effective therapies.
- Outcomes for patients with AML are especially poor.
- ADCs and TCEs have proven to be important therapeutic classes to treat ALL, cHL, MM and NHLs. ZYME's differentiated technologies and next-generation multi-functional therapeutics may improve upon earlier approaches to provide better outcomes for patients.
- ZYME designed ADCs and TCEs provide opportunity for combination strategies with SOC, and potentially with each other (e.g., induction v maintenance).

Competition = program count from Cortellis filtered by indication of interest, development stage, and active development since 1 Jan 2018; US incidence is approximate – GLOBOCAN does not split leukemias or lymphomas by cell type; NHLs are diverse and comprised of B-, T- and NK cell neoplasms; CLL/SLL are considered NHLs, but are split out due to distinct treatment; chart reflects 5-year relative survival in aggregate but aggressive lymphomas e.g. DLBCL and indolent lymphomas e.g. FL, have dramatically different survival outcomes i.e. 5-Year Relative Survival for DLBCL is ~65%, 5-Year Relative Survival for FL is ~90%

Cancer Immunity and Autoimmunity are Two Sides of the Same Coin

- The resounding recent success of cancer immunotherapy has spurred rapid development in precision medicine
- Many cancer immunotherapy drugs aim to unleash endogenous cancer responses
- The regulatory mechanisms that hold back cancer immunity are often mechanisms that evolved to limit autoimmunity
- Therefore, by applying knowledge of these pathways, Zymeworks could address AIID
- **To expand the breadth of Zymeworks' pipeline, we can take advantage of significant internal expertise and existing molecules to rapidly develop programs in AIID**



AIID: Autoimmune and Inflammatory Disease

Harnessing Zymeworks' Strengths to Address AIID



Autoimmune Disease:

- Chronic immune responses
- Lymphocytes
- Self antigens
- Amenable to cell depletion approaches

- SLE
- RA
- T1D

B cell depletion and immune cell reprogramming compatible with Zymeworks' next-generation T cell engagers.



Inflammatory Disease:

- Chronic dysregulation of inflammation
- Innate immune cells
- Environmental factors
- Amenable to cytokine blockade

- Asthma
- COPD
- Atopic dermatitis
- IBD

Multispecific antibody molecules to simultaneously block multiple pathways to enhance therapeutic response.

ADVANCE Program Presenters



Alex Berezhnoy, PhD
Director
Immunology



Jamie Rich, PhD
Senior Director
*Technology
ADC Therapeutic
Development*



Stuart Barnscher
Senior Director
*Preclinical Programs
ADC Therapeutic
Development*



Nina Weisser, PhD
Senior Director
*Multispecific Antibody
Research*



**Thomas Spreter Von
Kreudenstein, PhD**
Senior Director
Protein Engineering

ADVANCE PROGRAM

ZW1528: IL-4R α x IL-33 Bispecific Blocker for COPD

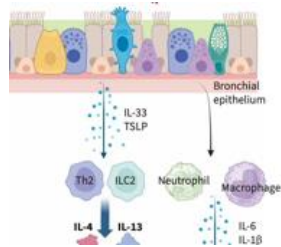
Alex Berezhnoy, PhD
Director, Immunology



Bispecific Antibody Therapeutics as the Potential Answer to Complex Biology of Autoimmune and Inflammatory Diseases

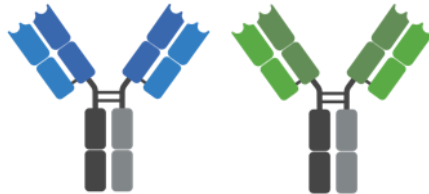
Patients

- + Serious, difficult to treat diseases
- + Large patient population
- Restricted access to advanced therapeutics



Clinical Science

- + Clinically validated targets
- + Benefits of combination
- Inconvenience and cost of clinical implementation



Technology

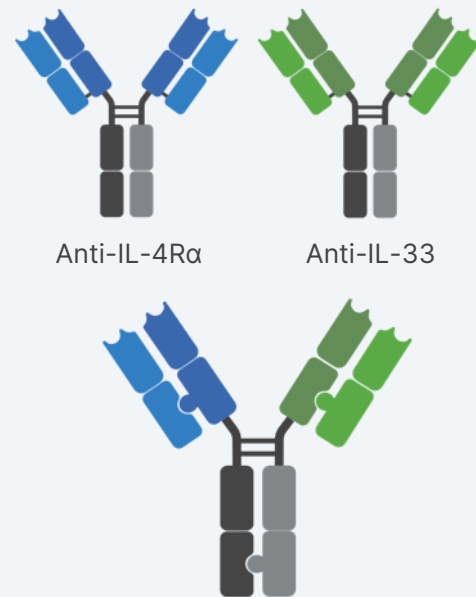
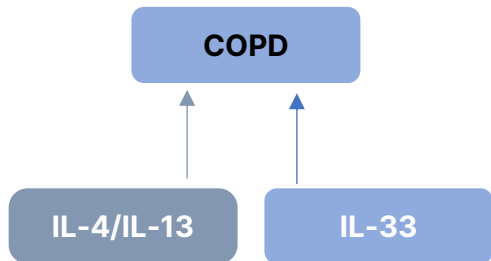
- + Clinically validated platform
- + Compatibility with Fc modifications (HLE)
- + High efficacy, convenient, cost-effective solution



Zymeworks brings a wealth of experience in this area, both within our R&D team, as well as with previous collaborations in this space.

Rationale for Anti-IL-4R α as an Anchor Arm

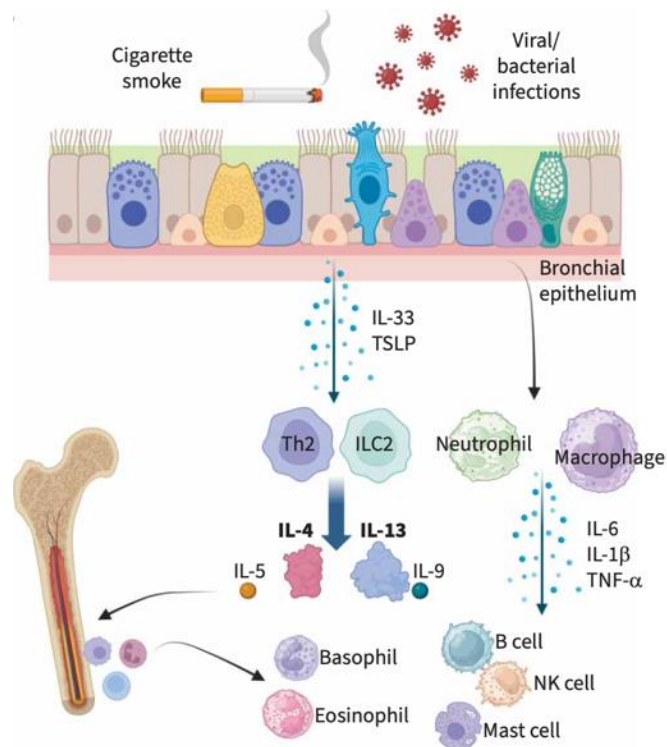
- Dupixent®/dupilumab is a highly successful mAb targeting IL-4R α
 - Approved for multiple atopic and inflammatory diseases
 - Generated revenues >\$11Bn in 2023
- Blocking IL-4R α inhibits both IL-4 and IL-13 signaling
 - Two key cytokines responsible for driving Type II inflammation
- Multiple cytokines drive pathology of respiratory inflammation
 - Add inhibition of an additional inflammatory pathway to augment or improve on monotherapy effects
 - **ZYME opportunity to develop more efficacious molecules**



- Aim at complete, prolonged blockade of IL-4R α
- Utilize potential advantages of local retention
- Take advantage of IgG-like geometry (PK, CMC)

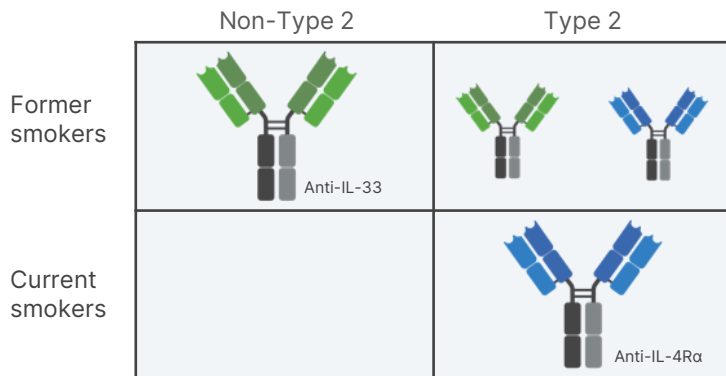
IL-33 as a Bispecific Arm for COPD and Other Respiratory Diseases

- IL-33 is a tissue alarmin released in response to epithelial damage
 - Acts on a range of cells e.g., neutrophils, Th2 cells, eosinophils, and mast cells
- Initiates and amplifies inflammatory response
 - Perpetuates chronic immune response
 - May also drive tissue remodelling in chronic inflammatory diseases e.g., COPD and asthma
- Clinical proof-of-concept for targeting IL-33
 - In former smokers with COPD, and in asthma
 - Phase III trials underway for anti-IL-33 mAbs Itepekimab [Regeneron / Sanofi] and Tozorakimab [Astra Zeneca]



IL-4R α x IL-33 Bispecific Provides Opportunity to Treat Broader Set of COPD Patients with Single Molecule

Anti-IL4R α (Dupixent[®]) and anti-IL-33 (itepekimab) are being developed to treat different COPD populations

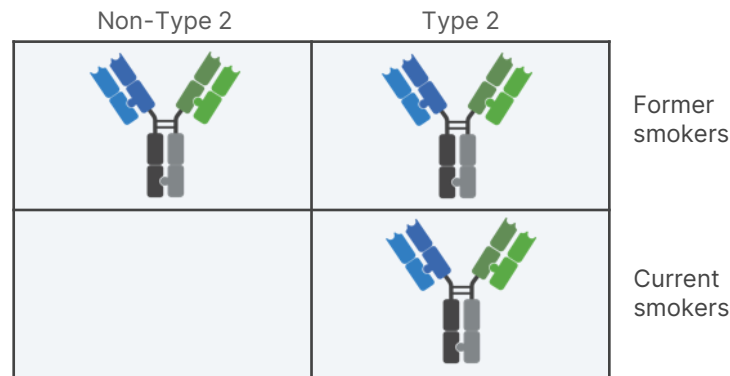


Anti-IL4R α effective in Type 2 COPD (those with eosinophilia)

Anti-IL-33 may prove to be effective in former smokers

- Post-hoc analyses of phase II data (NCT03546907)

IL-4R α x IL-33 bispecific provides opportunity to treat broader set of COPD patients with single molecule

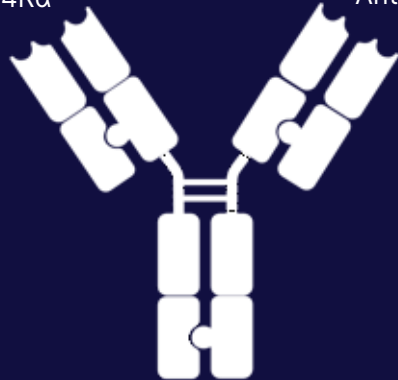


IL-4R α x IL-33 bispecific to combine the effects of two mAbs

Potential for increased efficacy in monotherapy-responsive patients

Anti-IL4R α

Anti-IL-33



IgG4 YTE

ZW1528

IL-4R α x IL-33 Bispecific

Inhibits multiple pathways within complex pathophysiology of inflammation



Design

- In-house antibody discovery of novel anti-IL4R α and IL-33 paratopes
- Native IgG-like geometry; highly manufacturable, compatible with half-life extending Fc modifications
- Clinically-validated targets; core arm mediates complete, prolonged IL-4R α blockade. Second arm adds inhibition of IL-33 - an upstream cytokine involved in perpetuating chronic inflammation.



Mechanism

- Inhibition of 3 cytokines in single asset
- Potential advantages of local retention

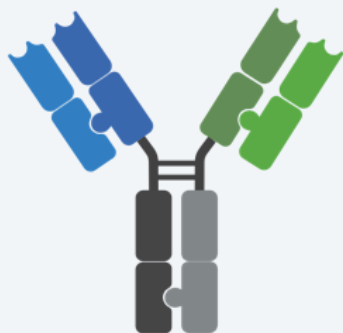


Profile

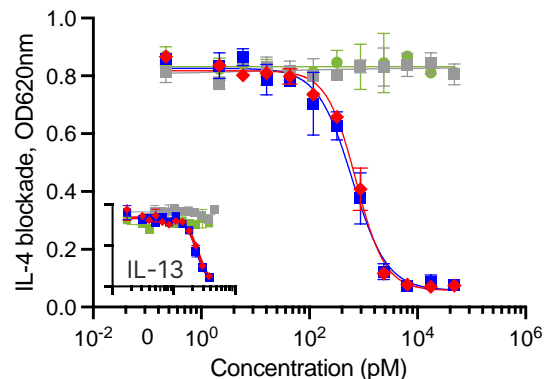
ZW1528 potently blocks of two complementary pathways of respiratory inflammation

ZW1528 Effectively Blocks of IL-4/13 and IL-33 Signaling

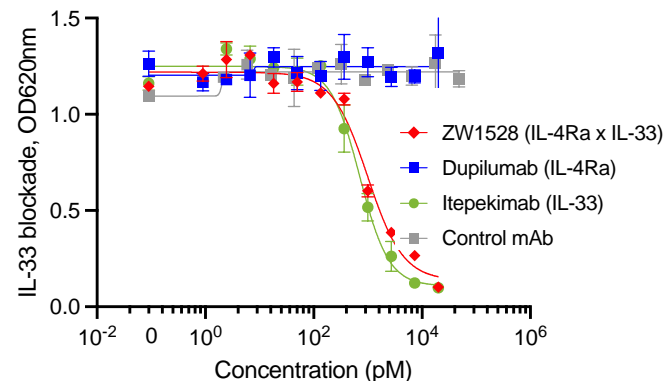
Anti-IL4Ra Anti-IL-33



Blockade of IL-4/13



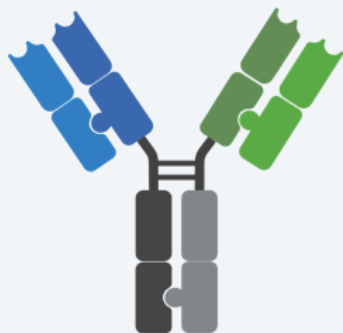
Blockade of IL-33



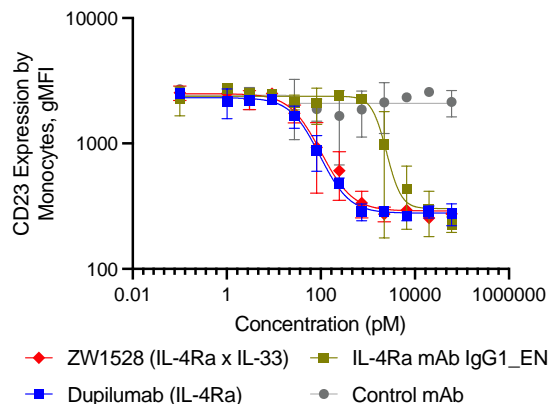
- Potency of ZW1528 similar to (bivalent) benchmark mAbs
- ZW1528 blocks both targets

ZW1528 Exhibits Favorable *In Vitro* Potency in Primary Cells

Anti-IL4Ra Anti-IL-33

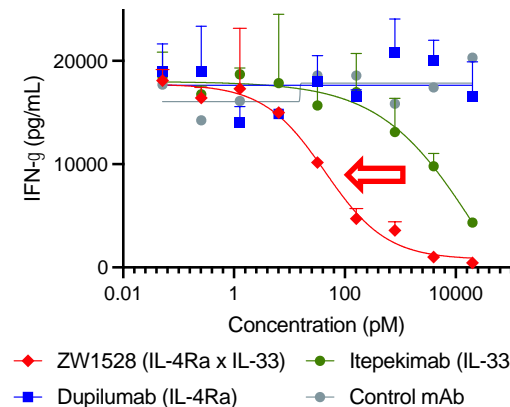


Blockade of IL-4-driven Monocyte activation



Superior potency vs
IgG1 effector-negative IL-4 α mAb

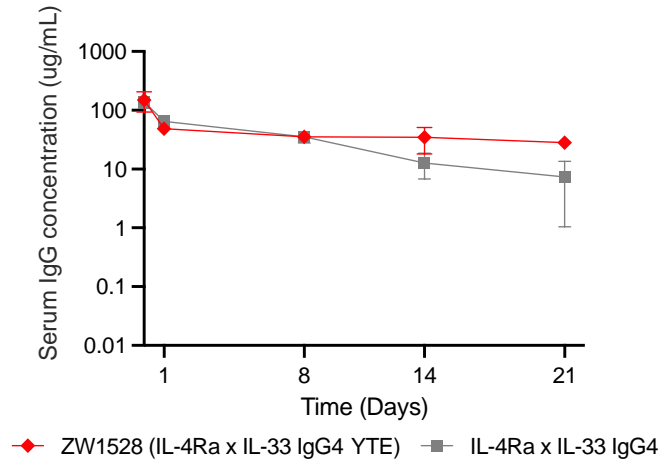
Blockade of IL-33 induced IFN- γ secretion in PBMCs



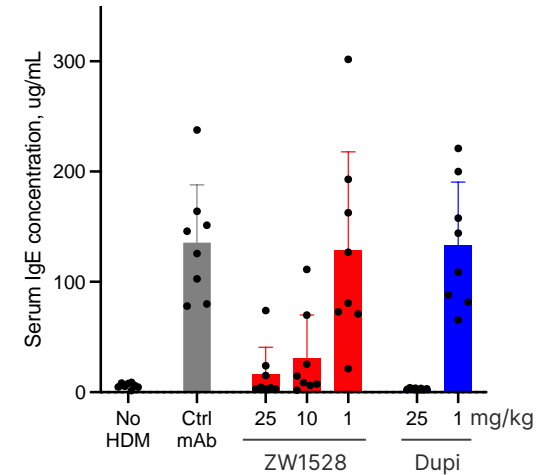
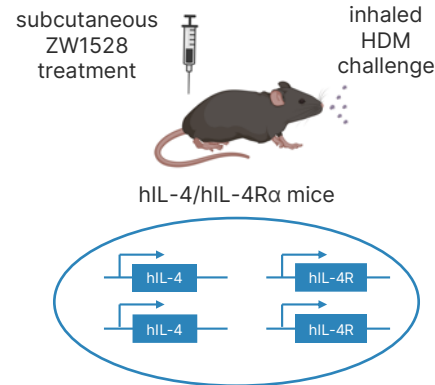
Superior potency vs
Itepekimab in PBMC (blocking IFN- γ)

ZW1528 Demonstrate IgG-like PK and Block IL-4R α *In Vivo*

IgG-like PK (Tg32 mice)



Suppression of IgE after inhaled allergen challenge

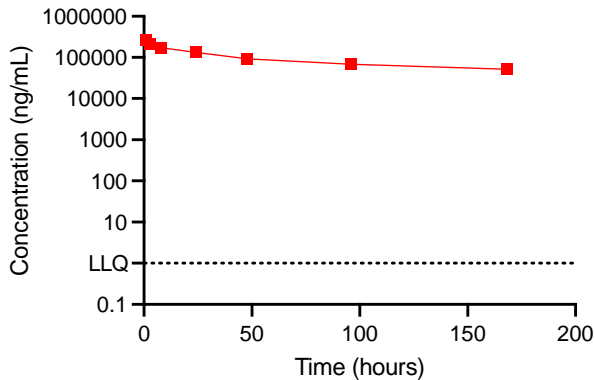


- IgG-like pharmacokinetics
- Suppression of IgE after inhaled allergen challenge

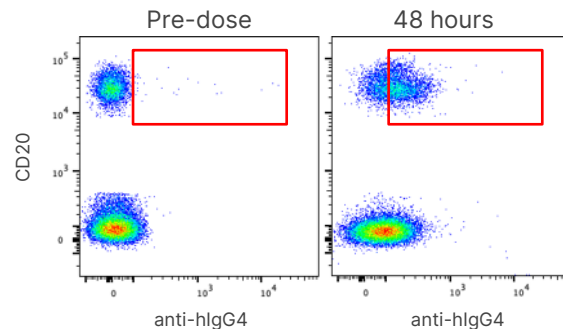
Left: PK in Tg32 mice after 5 mg/kg i.v. administration
Right: Challenge with house dust mite (HDM) inhalation

ZW1528 Demonstrates Biomarkers of IL-4R α /IL-33 Blockade in NHP

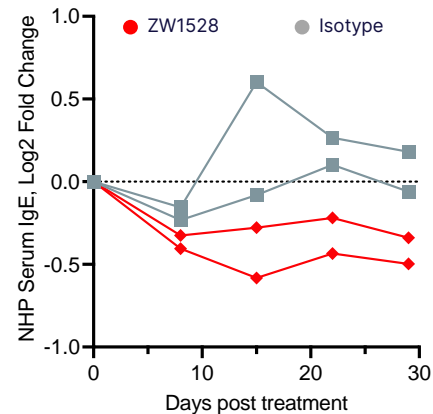
Pharmacokinetics



IL-4R α Receptor Occupancy



Reduction of Serum IgE

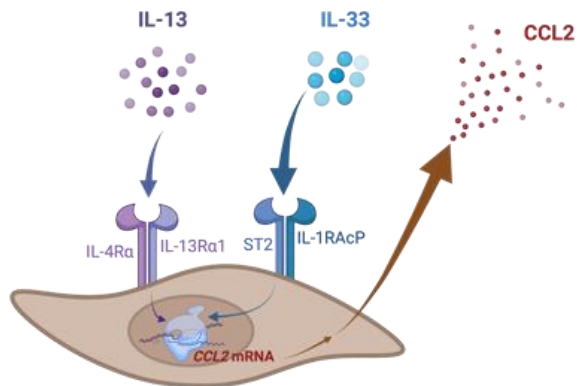


- IgG-like pharmacokinetics in non-human primates (NHP)
- Biomarkers of IL-4R α /IL-33 blockade up to **6 weeks** after single administration

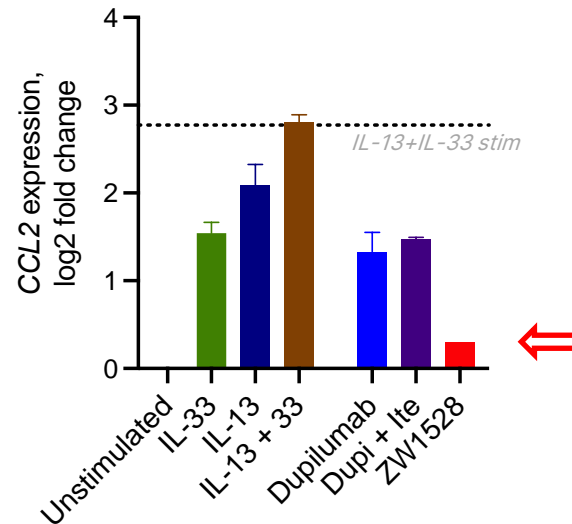
Cynomolgus monkey (N=2) were dosed with ZW1528 i.v. at 10 mg/kg

ZW1528-mediated Blockade of Primary Cell Activation is Superior to Dupilumab and Itepekimab

IL-33 and IL-13 activate human keratinocytes



ZW1528 blocks CCL2 expression

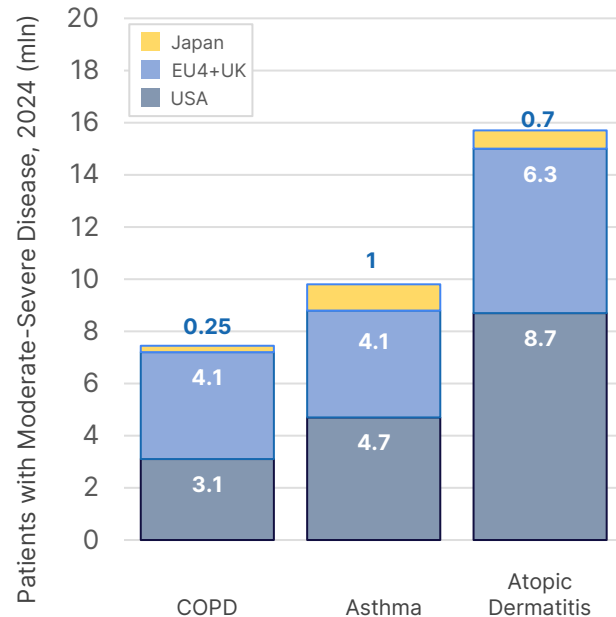
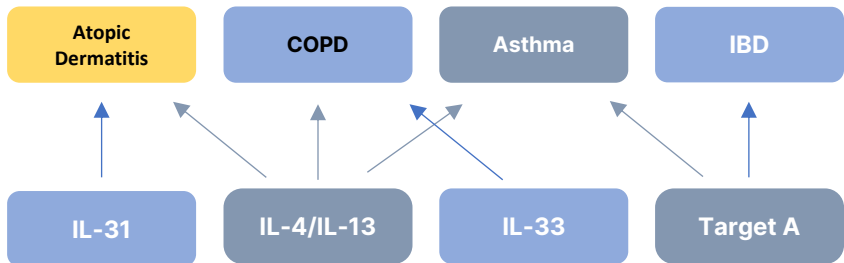


- IL-13 and IL-33 treatment induces disease-relevant genes in keratinocytes
- ZW1528-mediated blockade is superior to dupilumab, itepekimab and the combination of two antibodies

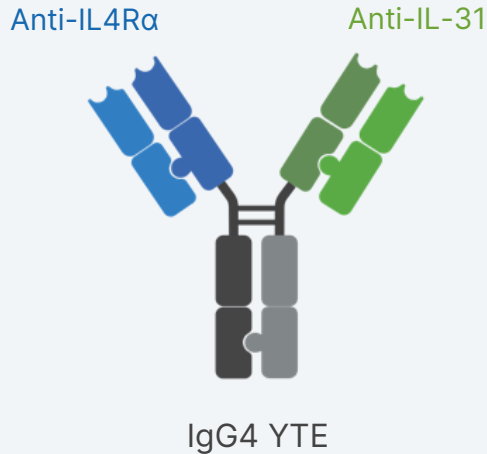
Molecules generated by Zymeworks from published sequences.
CCL2 is also known as macrophage chemoattractant protein (MCP-1) and has a role in attracting pro-inflammatory cells.

Expansion to AIID: Broadens Portfolio using Validated IL-4R α Blocker

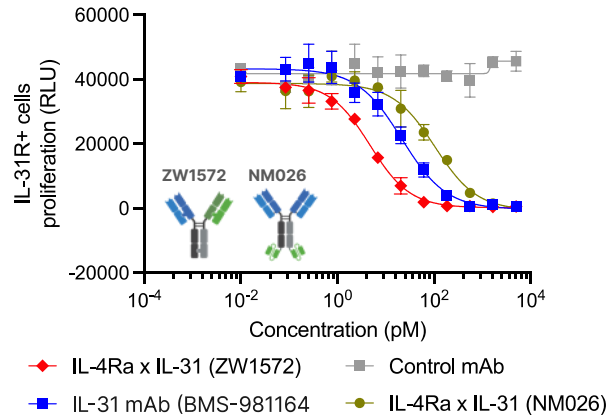
Program	Target Pair	Target Validation
ZW1528 (IND-enab)	IL4R α x IL-33	Anti-IL4R α approved in COPD Anti-IL-33 in pivotal COPD phase 3 studies
ZW1572 (Candidate nomination)	IL4R α x IL-31	Anti-IL4R α approved in Atopic Dermatitis Anti IL-31 validated clinically for itch control
Next gen (<u>ADVANCE</u>)	IL4R α x Target A	Anti-IL4R α approved in Asthma Target A efficacious in multiple AIIDs



ZW1572: Bispecific Inhibitor of IL-4R α and IL-31 for Atopic Dermatitis

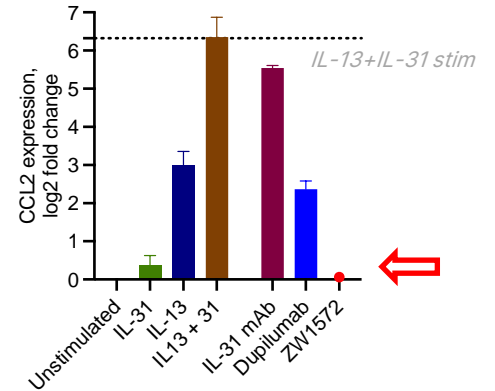


Enhanced blockade of IL-31



Superior IL-31 blockade vs. (bivalent) clinical benchmarks

Suppression of CCL2 induction in keratinocytes



Superior potency vs. individual mAbs in primary cells

Summary: ZW1528, an IL-4R α x IL-33 Bispecific Antibody

IL-33 bispecific antibody has the potential to be a significant new treatment option for patients with COPD

ZW1528 potently blocks two complementary pathways of respiratory inflammation

- Repression of Th2 driven inflammation via blockade of IL-4R α and inhibition of (non-Th2) IL-33-driven inflammation
- Favourable PK profile and biomarkers of IL-4R α /IL-33 inhibition in non-human primates up to 6 weeks after administration
- Preliminary evidence of advantages of bispecific blockade in disease-relevant cell types

ZW1528 aligns with requirements for successful AIID therapeutics

- Disease-modifying advantages of co-localized dual target blockade
- Stable IgG-like bispecific molecule (easy-to-manufacture, expected COGS advantages)
- Designed to allow for less frequent dosing (patient convenience and compliance)

Zymeworks' AIID opportunity

- Potential to benefit mixed-type COPD patients, and increase benefits for other COPD patient populations
- Clinical potential in other atopic diseases (asthma and atopic dermatitis) with established IL-4R α and/or IL-33 role
- Spearhead development of other Zyme AIID therapeutics

ADVANCE PROGRAM

Next Generation Technologies

ADVANCE PROGRAM

Antibody-Drug Conjugate Technologies



Jamie Rich, PhD
Senior Director
Technology
ADC Therapeutics



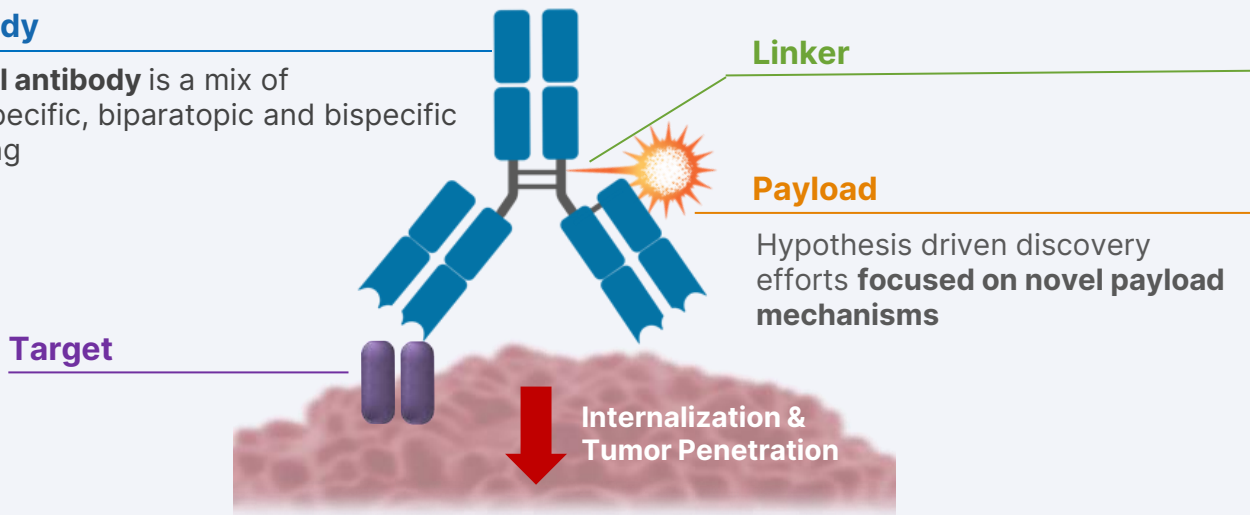
Stuart Barnscher
Senior Director
Preclinical Programs
ADC Therapeutics

ADVANCE: Novel Payloads and Optimized Antibody Formats for Next Generation ADCs

We are developing **novel payload mechanisms** & **antibody formats** to suit disease and target biology

Antibody

Optimal antibody is a mix of monospecific, biparatopic and bispecific targeting



ADVANCE ADCs will support our 2027+ IND pipeline

Therapeutic Applications

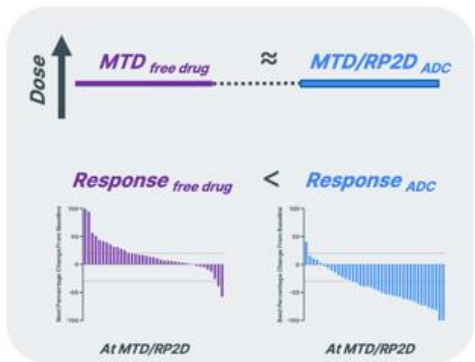
- Solid Tumors: current focus GI tumors including CRC, PDAC, esophageal, HNSCC
- Heme Onc: current focus AML

CRC: Colorectal cancer; PDAC: Pancreatic ductal adenocarcinoma; HNSCC: Head and neck squamous cell carcinoma; AML: Acute myeloid leukemia

Our Hypothesis on ADC Mechanism Guides our Approach to Novel Payload Discovery

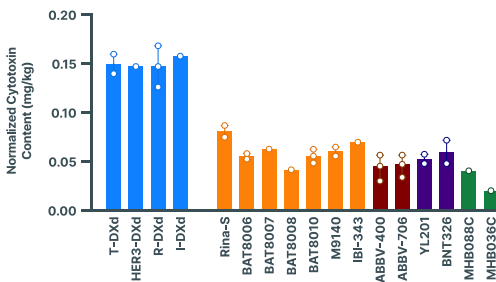
1

Conjugation does not improve payload MTD¹



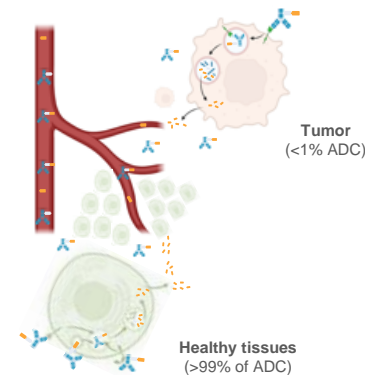
2

More potent payloads limit protein dose²



3

Most ADC catabolism occurs in normal tissue



Criteria for novel payloads:

1. Moderate potency to enable higher protein dose
2. Bystander activity
3. Evidence of activity in disease indication of interest

1. R. Colombo and J.R. Rich, Cancer Cell 2022, 40(11):1255–1263; 2. R. Colombo et al, Cancer Discov 2024, 14(11):2089–2108.

Four Novel Payload Mechanisms in Discovery to Help Drive Innovation Beyond TOP01i and Auristatin Platforms

Challenging nature of ADC Platform development necessitates multiple approaches

Cytotoxic ADCs

1 Translation Inhibitor Platform

Targeting protein synthesis pathway. Novel payloads with optimized potency

Current focus in diverse GI tumor indications

Conditionally Cytotoxic ADCs

2 Oncogene Targeting Platform

Inhibitor of key oncoprotein suited to application in ZW target indications

3 Synthetic Lethality Platform

First of kind synthetic lethal ADC approach

Biomarker driven application in solid and liquid tumors

Protein Degradation

4 Protein Degradation Conjugates

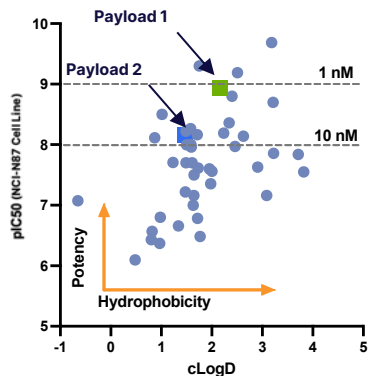
Degradation antibody conjugate modality holds significant promise across diverse diseases

Interest in AML, PDAC, and CRC targets

Protein Synthesis Inhibitor ADCs Demonstrate Preclinical Promise

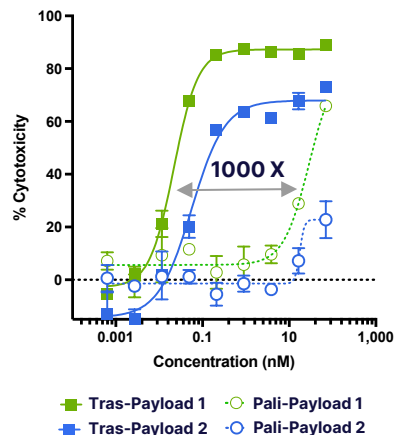
- Targeting a pathway critical to cancer cell growth enables potential first in class ADC opportunity
- Optimized ADCs demonstrate potency, selectivity, strong anti-tumor activity, and promising rodent tolerability
- Evaluation in target indications is ongoing (H&N, PDAC, CRC); planned non-human primate toxicology studies

Payload Optimization



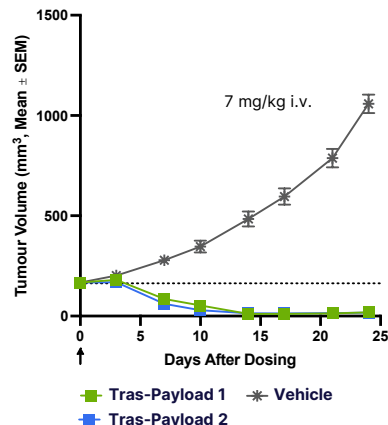
In Vitro Potency & Selectivity

SK-BR-3 Breast Adenocarcinoma Cell Line



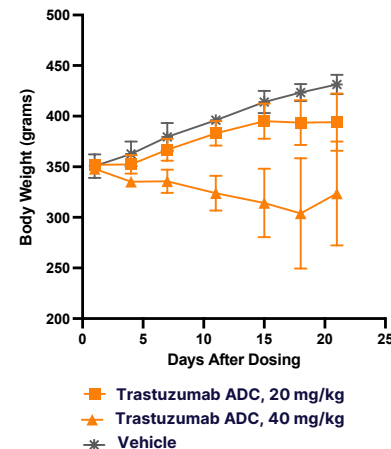
In Vivo Anti-tumor Activity

SK-OV-3 Ovarian Cancer Cell Line Derived Xenograft



Rodent Tolerability

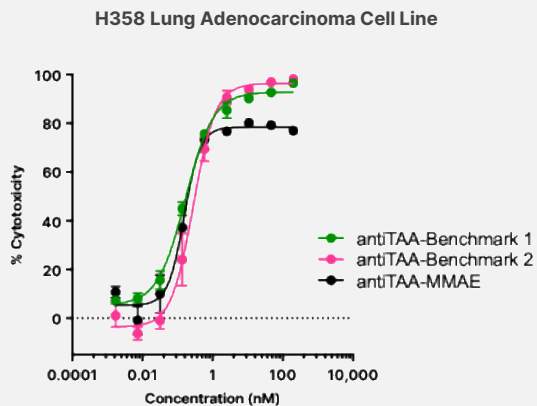
Rat Body Weight
Trastuzumab-Lead Payload, DAR8



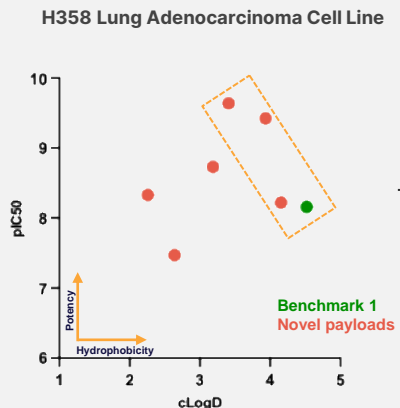
Inhibitors of Key Oncoprotein Serve as Novel ADC Payloads

- First in class ADC opportunity with cytotoxic mechanism that is well validated in our priority indications
- ADC approach may improve on small molecule drugs via increased exposure, efficacy, and tolerability
- Currently evaluating in vivo efficacy

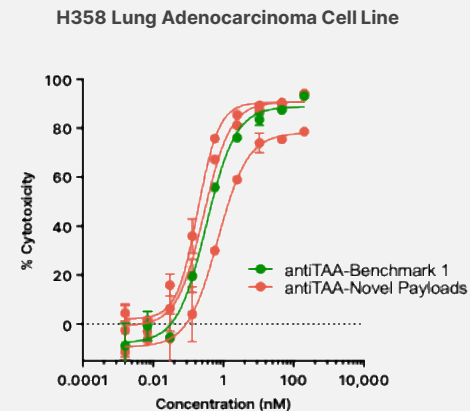
ADCs are potent and selective in vitro



Payload analogues retain potency



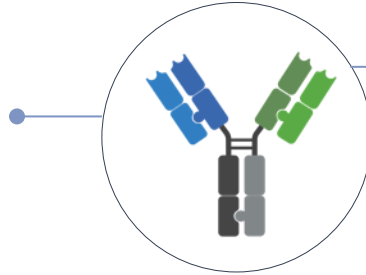
Novel payload ADCs retain potency



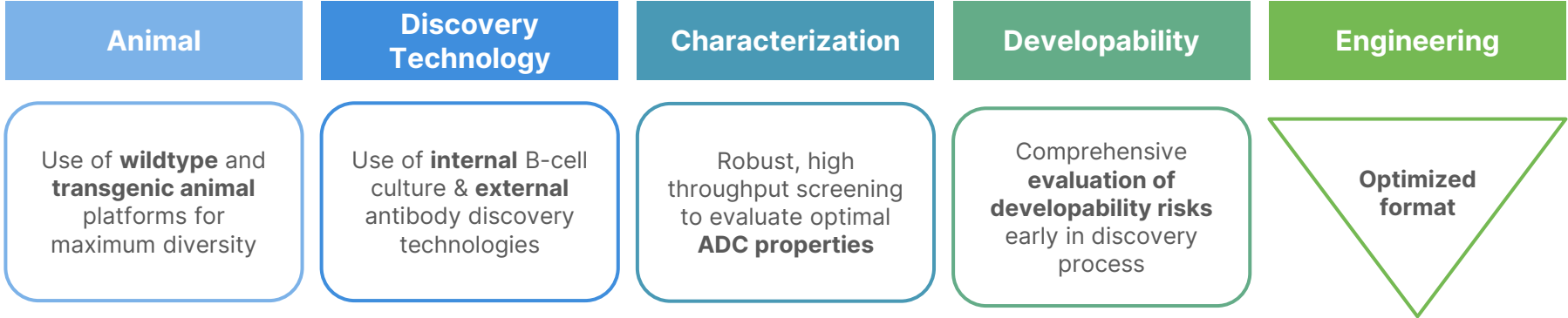
Multi-Pronged Approach to Antibody Discovery:

Seeking Optimal Antibodies for Development of Differentiated ADCs

Tailored properties to enable fit-for-purpose use as ADC



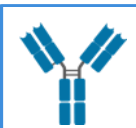
Modular discovery platform for maximum flexibility



Selection of Desired Antibody Format for ADC Assets

- Generation of differentiated fit-for-purpose ADCs is enabled by a flexible antibody discovery workflow and the Azymetric™ platform
- Target expression and biology may dictate the use of one format over another

Monospecific



Binds to single epitope on a single target

- Suitable for targets with some normal tissue expression
- May be only format available for targets with restricted epitope space
- Internalization dependent on target biology and specific epitope

Biparatopic



Binds to two distinct epitopes on a single target

- Suitable for targets with limited normal expression
- Targets with large epitope space may be most suitable
- Internalization can be enhanced via increased surface decoration and antigen clustering

Bispecific

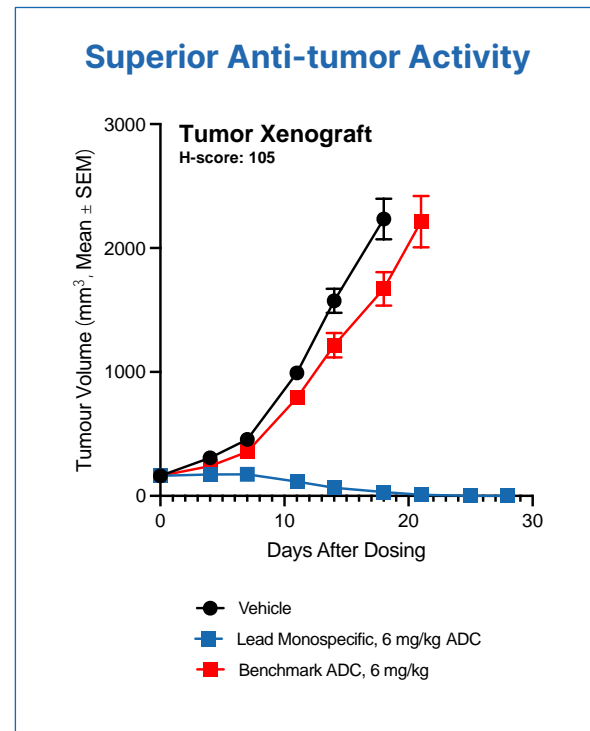
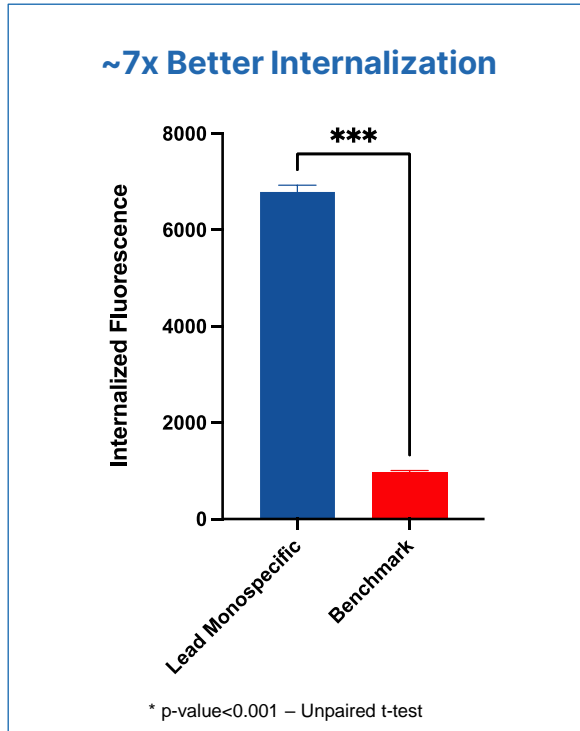
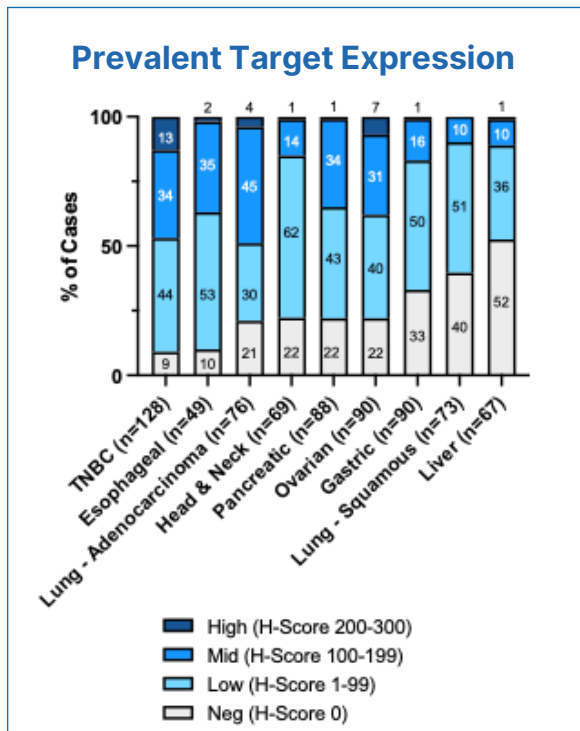


Binds to two distinct targets

- Suitable for targets with biologic association or targets with high 'tumor coverage'
- Valency can be tuned to suit tumor and normal expression of each target
- Internalization may be enhanced due to target co-engagement

Monospecific Targeting: ADVANCE Solid Tumor ADC#1

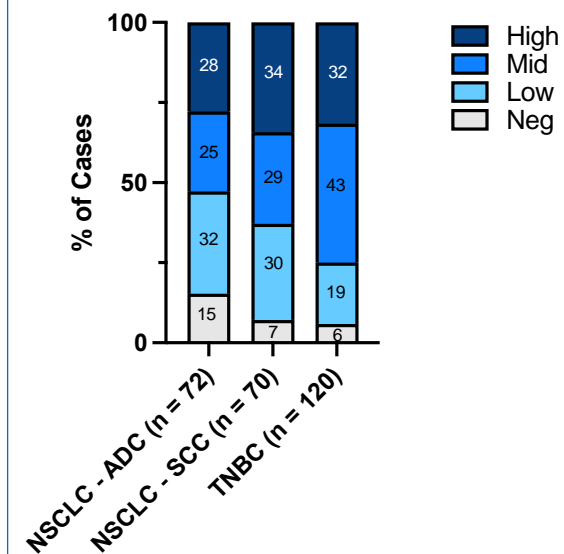
A monospecific format was selected for this program due to the small extracellular domain of the target, limited epitope diversity, and the superior characteristics of the lead monospecific over the clinical benchmark



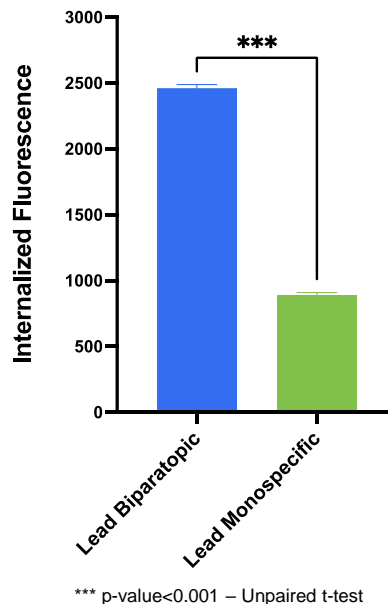
Biparatopic Targeting: ADVANCE Solid Tumor ADC#2

A biparatopic format is being evaluated for this program due to broad epitope diversity, enhanced internalization profile, and superior anti-tumor activity compared to a lead monospecific antibody

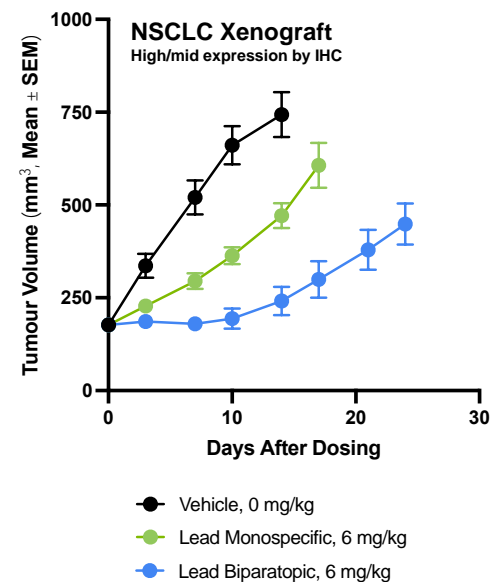
Strong Target Expression in Lung and Breast Cancer



~3x Better Internalization



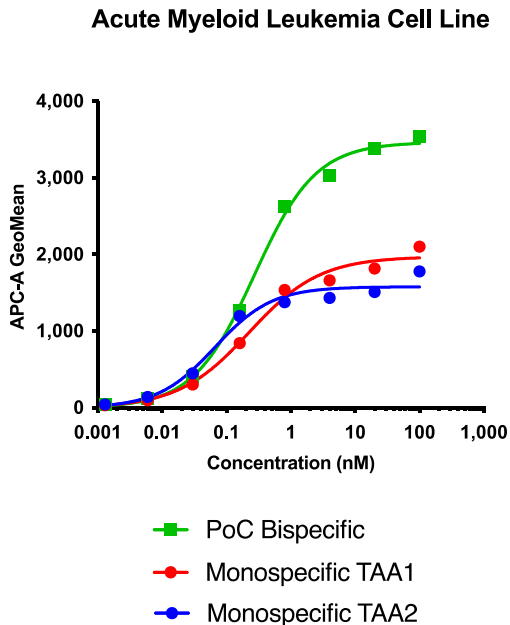
Superior Anti-Tumor Activity



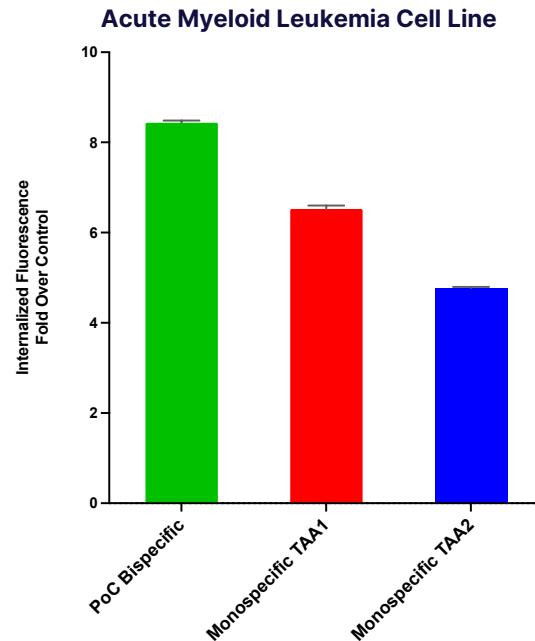
Bispecific Targeting: ADVANCE AML ADC

A bispecific format is being evaluated for this program to overcome individual target heterogeneity and to enhance functionality by co-targeting cells that express both targets

Superior Binding



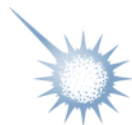
Enhanced Internalization



AML: acute myeloid leukemia; ADC: antibody drug conjugate; PoC: proof of concept; TAA: tumor associated antigen

ADVANCE Antibody-Drug Conjugates

For solid tumors (GI tract cancers) and heme-onc will help to support our 2027+ investigational new drug application pipeline



Novel Payload Discovery

- Our hypothesis on ADC mechanism guides our approach to novel payload discovery
- Four novel payload mechanisms in discovery to help innovation beyond TOPO1i and auristatin platforms



Optimal antibody formats

- Multi-pronged strategy to discover antibodies with enhanced ADC properties
- Antibody format (monospecific, biparatopic, or bispecific) dictated by target characteristics



Therapeutic Application

- Target, payload mechanism, and antibody format selected for enhanced activity in disease indication

ADVANCE PROGRAM

Multispecific Antibody Technologies



Nina Weisser, PhD
Senior Director
Multispecific Antibody
Research



**Thomas Spreter Von
Kreudenstein, PhD**
Senior Director
Protein Engineering

Driving the Forefront of Next Generation T cell Engagers

Plug and Play Platforms to Potentially Build Differentiated Therapeutic Cell Engagers

Tailored Designs



Applying flexibility of Azymetric™ to screen multiple antibody formats

Enhanced Functionality



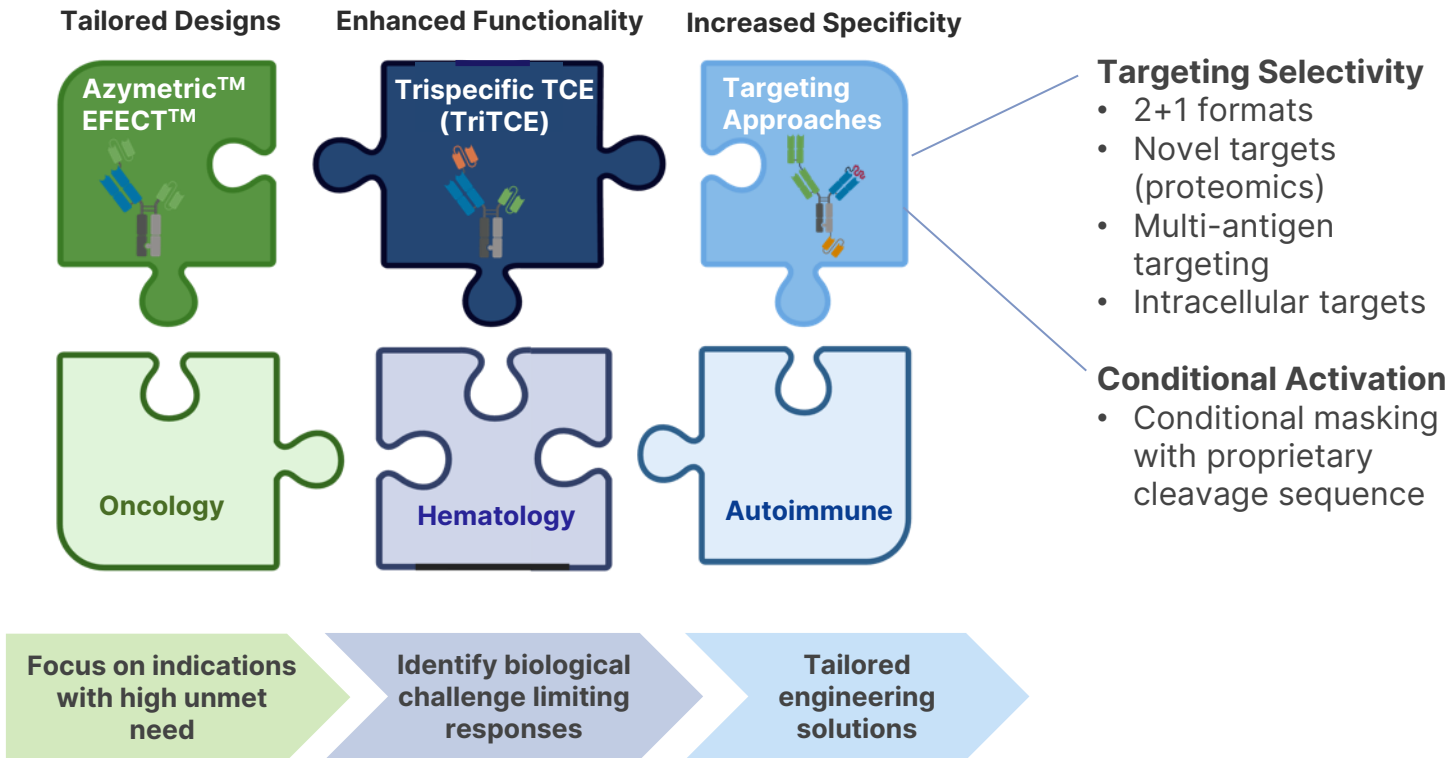
Enhance anti-tumor activity and T cell responses (e.g. TriTCE Co-stim)

Increased Specificity



Increase tumor targeting and activity within the TME

ADVANCE: Enhancing Functionality and Specificity to Help Improve Responses Across Diverse Therapeutic Areas





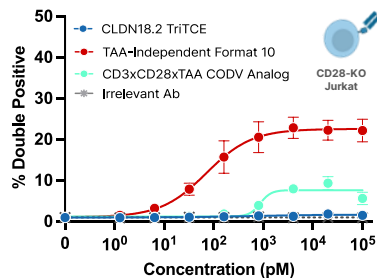
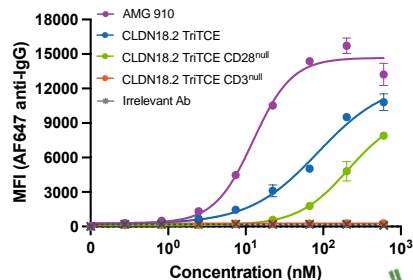
ZW239: CLDN18.2 Targeted TriTCE Co-stim to Help Improve Depth and Durability of Responses in CLDN18.2 Expressing Tumors

Focus indication of high unmet need
Gastric and Pancreatic

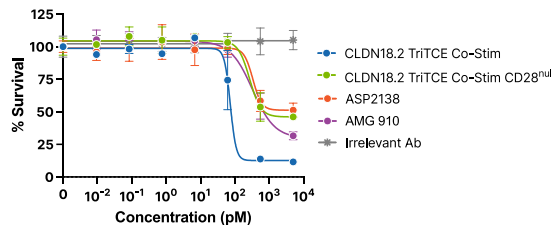
Biological challenge limiting responses
Low T cell Infiltration and T cell Dysfunction

Tailored engineering solutions
CLDN18.2 TriTCE Co-stim

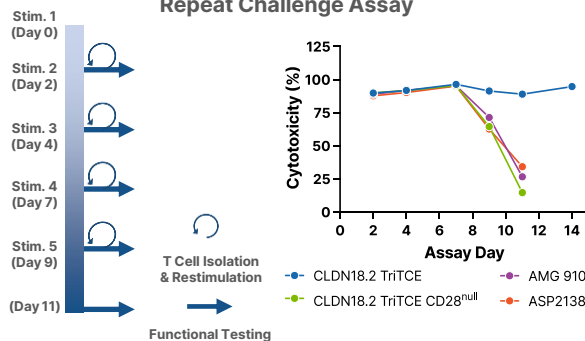
Conditional Binding of CD28, Requiring Co-engagement of CD3; Obligate cis Binding



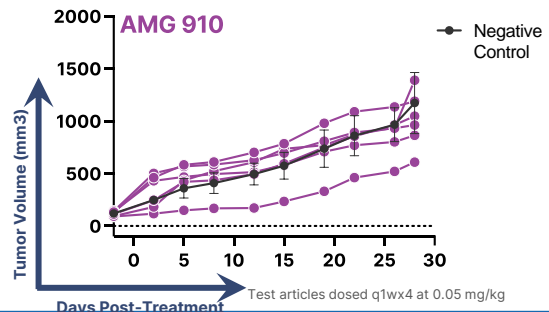
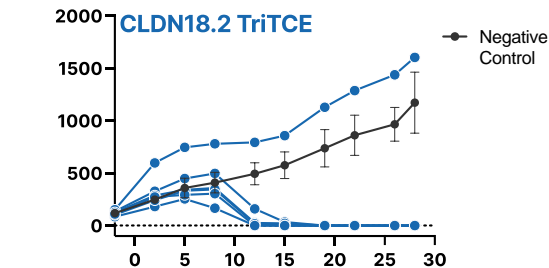
Improved and Sustained Cytotoxicity over Bispecific TCE



Repeat Challenge Assay



Superior Anti-tumor Activity in vivo





Novel Tumor Targeting to Help Improve Treatment Responses Across Diverse Solid Tumors

Focus indication of high unmet need
Multiple Solid Tumor Indications

Biological challenge limiting responses
Low T cell Infiltration & T cell Dysfunction

Tailored engineering solutions
Novel Target TriTCE Co-Stim

Multi-indication TriTCE Co-stim to novel target

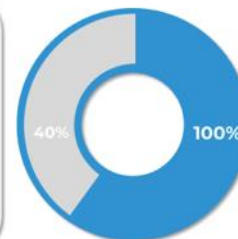
Novel proteomic approach¹ used to identify **unique membranous tumor-specific targets** with ideal TCE target profile

- No/minimal normal tissue expression
- Supportive biology and expression profile
- **Novel target** with **multi-indication potential**

× Publicly available TCGA mRNA expression dataset that everyone uses

× All targets that can be identified using this approach **have already been identified**

× 40% protein expression explained by mRNA abundance

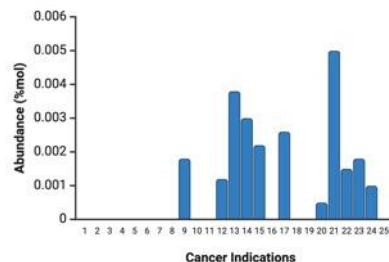


✓ OGAP[®] protein expression dataset covers **100% of the target space**

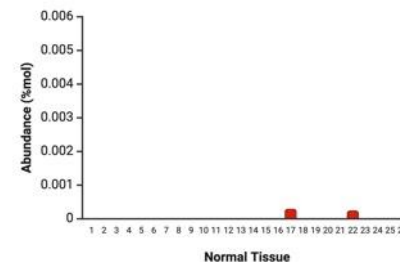
✓ 60% protein expression **only** identified by OGAP[®] and not predicted by mRNA

✓ OGAP[®] contains targets that mRNA prediction misses, as well as **first-in-class targets not previously identified / known**

Target Expression on Tumor



Target Expression on Normal Tissues




1.Houghton et al. 2024 , 6th Annual Targeted Radiopharmaceuticals Summit Europe

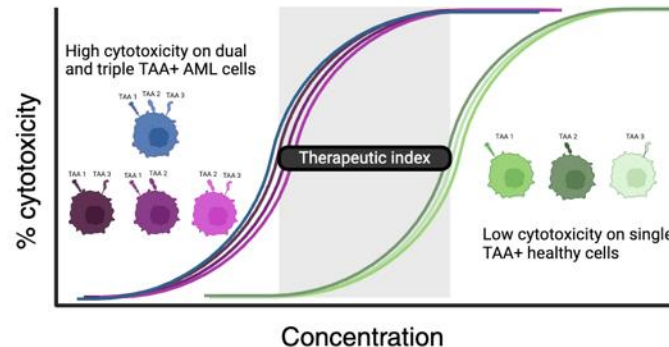


Overcoming Antigen Escape and T cell Dysfunction to Help Improve Treatment Responses in AML



Biological Challenge	Limitation of Mono-antigen Targeted Therapies	Solution
Heterogeneous intertumoral antigen expression	Antigen escape and treatment failure ¹	Multi-antigen targeting with co-stimulation  Representative potential format
Lack of a clean single target between AML blasts, LSCs and healthy cells	Narrow therapeutic window	
T cell dysfunction ²	Bispecific TCE resistance and lack of long-term responses ²	

Selective tumor cytotoxicity in presence of 3 or 2 target antigens



1. Atar 2024 Leukemia, 38; 2.Kazerani et al. 2024 Leukemia, 38. AML, Acute myeloid leukemia; LSC, leukemic stem cell; TCE, T cell engager



Multiparameter Screening using Azymetric™ Identifies Candidates with the Desired Biology

WT (TAA 1+TAA 2+ TAA 3+)
TAA 2+

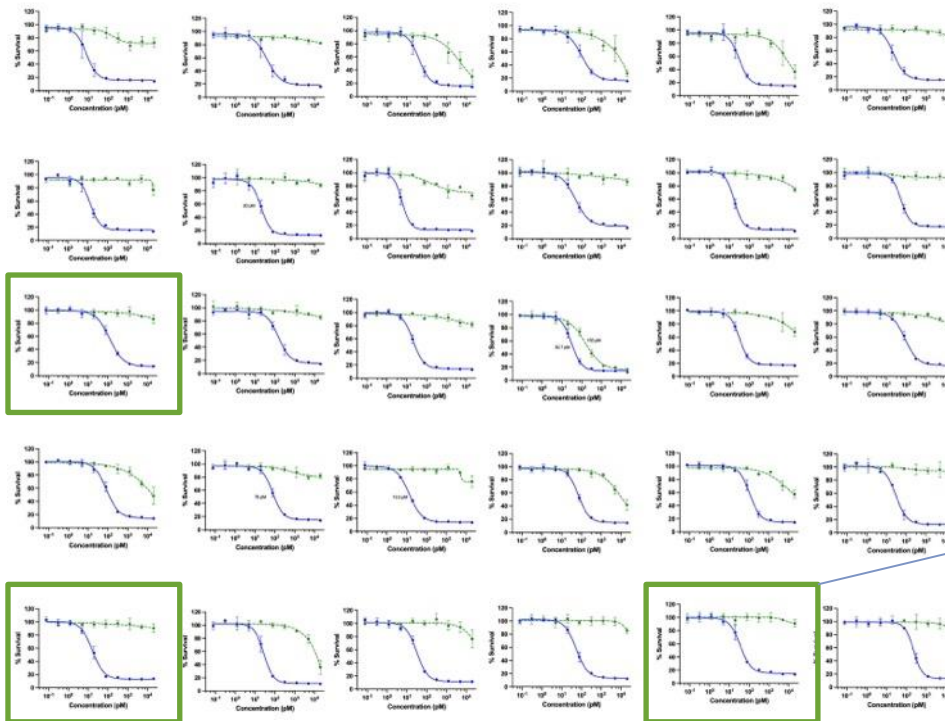
Triple positive cell

TAA 1 TAA 2 TAA 3

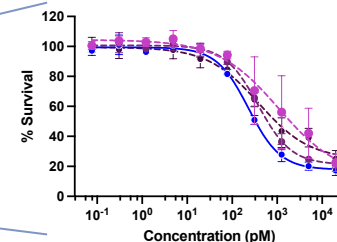


Single positive cell

TAA 2



Multiple candidates with potency in triple and dual target-expressing cells





ADVANCE Multispecific Cell Engagers

For difficult to treat tumors with complex disease biologies in oncology and hematology to support our 2027+ investigational new drug application pipeline

Advanced Protein Engineering Solutions

- FDA approved, clinically validated, and novel engineering solutions enable plug and play building blocks to address complex biological challenges
- Flexibility of Azymetric™ facilitates high throughput multiparameter antibody screening to identify molecules with the desired biology

Addressing Biological Challenges in Indications with High Unmet Need

- Focusing on indications with high unmet need and complex biological hurdles
- Designing next generation T cell engagers to overcome biological challenges not addressed with traditional bispecific T cell engagers

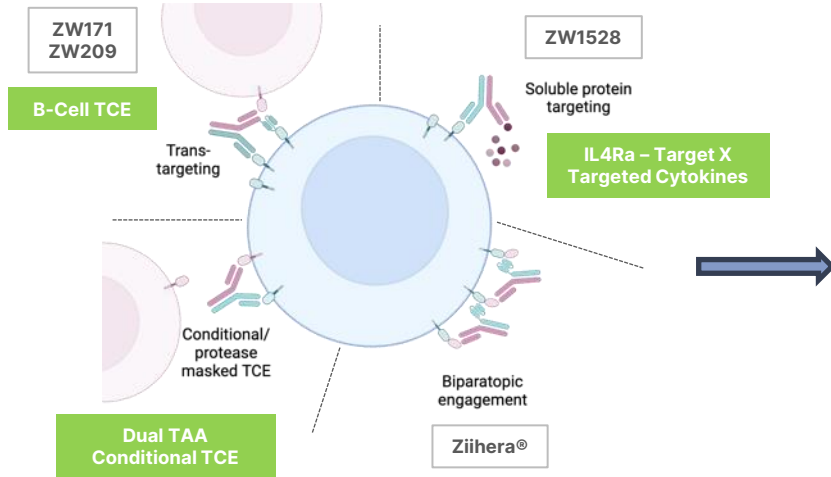
Driving the Forefront of Next Generation T cell Engagers

- Enhancing functionality and specificity to drive deep and durable responses in difficult to treat tumors
- Plug and play platforms enable fast development to rapidly address patient need

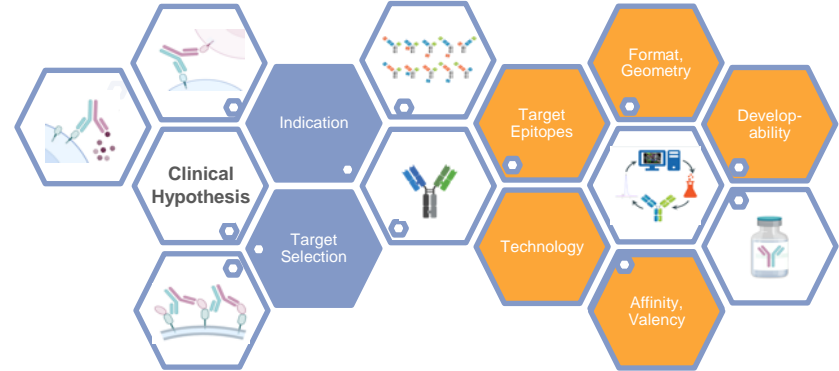
Zymeworks' Technology Development Approach: Integration of Engineering and Drug Discovery Driving Differentiation

- Cross-functional approach critical to enable 'Technology Driven' innovation and differentiation
- 10+ years of structure-based Protein Engineering and Design and in-house tool development
- Critical learnings for Multispecific Engineering and further in-house Technology Development

Clinical Hypothesis and Mechanisms of Action



Biology



Integration of AI/ML with Azymetric™ Engineering Expertise Enables Novel Technology Driven Drug Development

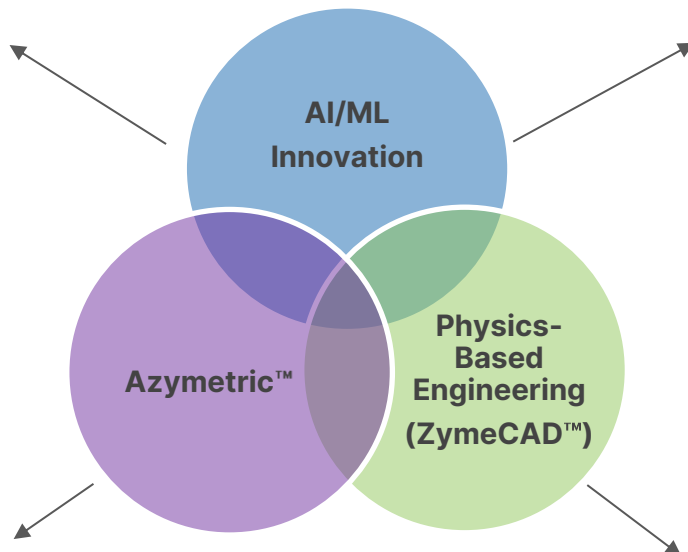
Accelerating Multispecific Discovery

Accelerating multispecific discovery through “Lab in loop” Azymetric™ HTP workflow

Screening of library in final Multispecific format

3-4x Accelerated Multispecific Discovery

Opportunities for Combining AI/ML with Multispecific Engineering Expertise



Multi-parameter Antibody Optimization

Enhanced Multispecific Engineering

- Multifactorial optimization for affinity, stability, developability
- Engineering for improved PK and s.c. formulation

Optimization for PK (Tg32 mouse PK study)

Time (Days)	Variant 1 (Red)	Variant 2 (Blue)	Variant 3 (Green)	Variant 4 (Purple)
1	~100	~50	~100	~100
8	~50	~20	~60	~40
14	~40	~15	~50	~30
21	~30	~10	~40	~20
28	~20	~8	~30	~15

2-in-1 Antibody Engineering

2-in-1 Antibody Engineering Applications for both AIID and cancer

dual target binding

2-in-1 Multispecific

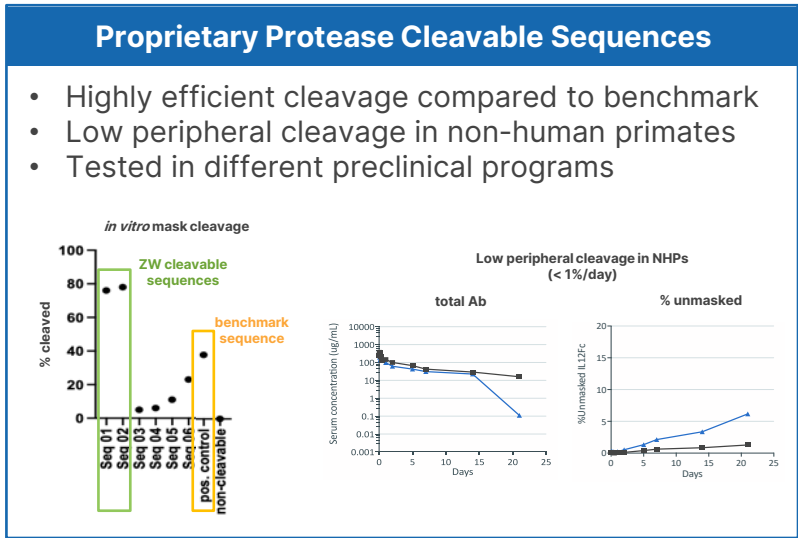
Cytokine and Receptor Engineering

Stability engineering of cytokines and natural receptors or ligands for cancer and AIID

Difficult targets (low stability, manufacturability)

Next Gen Technologies: Conditional Masking Technologies

- Internal development of highly efficient tumor specific protease cleavage sequences
- Masking technology application for TCE and TriTCE
- Internal IL-12 program using attenuated IL-12 displays higher therapeutic window than clinical competitors



Conditionally Masked TCE and TriTCE

Expanding target space for TCE and TriTCE portfolio

Potential to combine with 2+1 and CD3 engineering

Conditionally Masked Cytokines

Novel approach of conditionally masked, attenuated IL-12

Efficacy

Legend:
 ■ Untreated
 ● ZW270 mouse surrogate (1 mg/kg)
 ▲ WT mIL12 Fc (0.05 mg/kg)
 ▼ Attenuated mIL-12 Fc (1 mg/kg)

Tolerability

Next Gen Technologies: Novel Engineering for Autoimmune and Inflammatory Indications

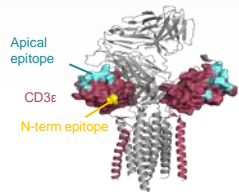
T Cell Engager Engineering for AIID

Significant opportunity for enhanced B cell depleting therapies for AIID

Critical engineering for high activity with reduced cytokine release syndrome potential

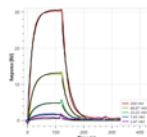
ZW has panel of anti-CD3 binders with fast Kon/off and different epitopes to fine tune activity

CD3ε structure with structural and non-structural epitopes

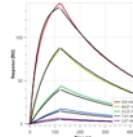


Name	Epitope	k_{on} (1/Ms)	k_{off} (1/s)	K_d (nM)
ZW1	Epitope 1	1.38E+05	3.12E-03	22.7
ZW2	Epitope 2	5.20E+05	4.08E-03	7.84
ZW3	Epitope 1	1.62E+05	1.10E-02	68.3
ZW4	Epitope 2	1.45E+05	1.26E-02	87.1
ZW6	Epitope 1	1.59E+05	2.54E-02	159.9

ZW fast Kon/off CD3



Benchmark CD3

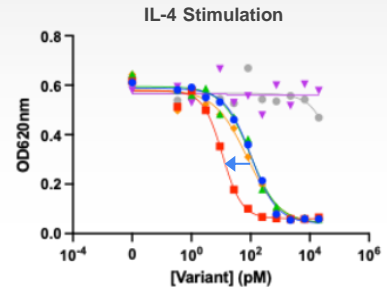


Novel Bispecific Cytokine Antagonists

Additional IL4Rα-X bispecific cytokine antagonists

Engineering for optimized PK

Bispecific engineering for superior potency to IL-4Rα comparators and bispecific advantage vs. combination

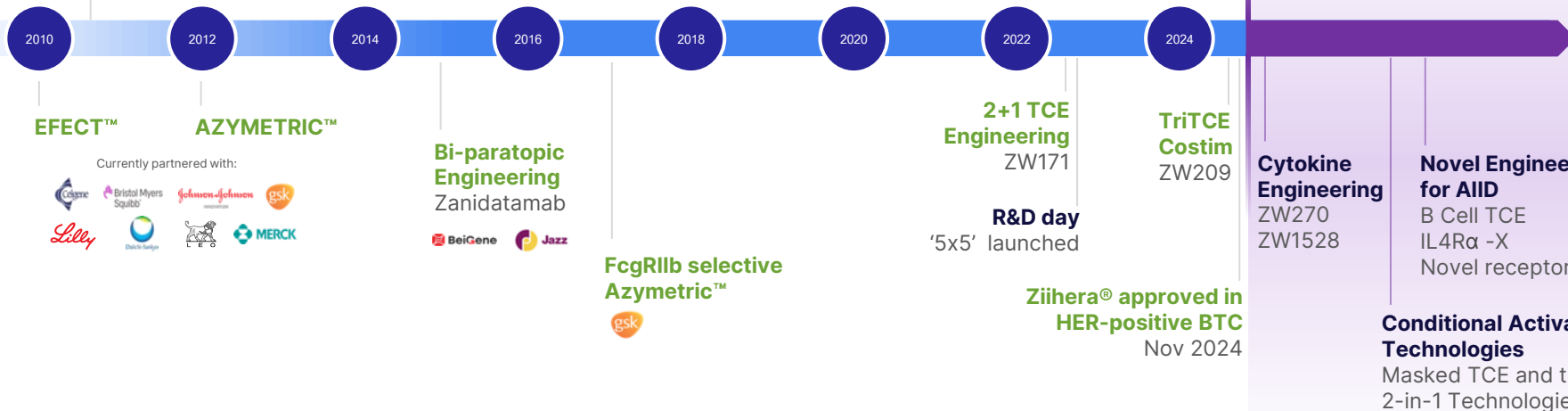


- ◆ Dupilumab
- ◆ Target A monospecific
- ◆ IL4Ra-TargetX bispecific
- ◆ Dupilumab + Target A combination
- ◆ Isotype control

Building on 10+ Years of Protein Engineering and Multispecific Development: Continued 'Technology Driven' Innovation

ZymeCAD™

In silico Protein Engineering and Design Platform



Integrated Approach of Protein Engineering and Technology Development →

RESEARCH & DEVELOPMENT DAY

R&D Strategy Summary: 2025-2027

Kenneth Galbraith
Chair and CEO





Focus

- 5 x 5 solid tumor portfolio completed 18 months ahead of original target
- Solid tumor portfolio expansion focused on mainly digestive system cancers and certain other unmet needs
- Patient populations of interest to expand beyond solid tumors to include heme cancers and AIID



Execution

- Investment in preclinical research and capabilities over 2022-24 allows for acceleration of ADVANCE strategy
- Zanidatamab experience, focused efforts and quality drives higher probability of success in portfolio
- Preclinical, clinical and TMO groups built to manage active portfolio of candidates across expanded focus areas
- R&D investment balanced across clinical candidates and preclinical research over 2025-2027



Growth

- Partnering, strong target product profiles and attrition in development will maintain a manageable portfolio of opportunities over time
- New product candidates will continue to add novelty, differentiation and value to the product portfolio through 2027

Focused Therapeutic Areas Provide Diversity to R&D Portfolio and Enhanced Optionality for Partnering and Retained Product Rights

Solid Tumors

- Gynecological cancers
- Thoracic cancers
- Digestive system cancers

Hematological Cancers

- AML
- Multiple myeloma
- Lymphomas

Autoimmune & Inflammatory Diseases

- Respiratory diseases
- Rheumatoid arthritis
- Inflammatory bowel diseases

Early Research & Development

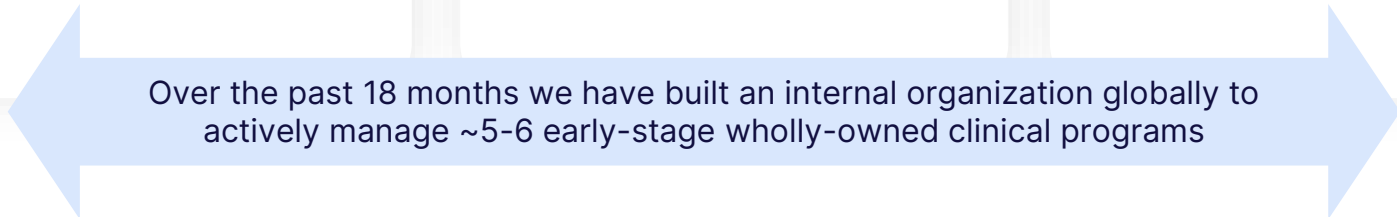
- Full internal capabilities for multi-functional therapeutics development
- 150-person group located in Vancouver laboratories
- Capacity to sustain current R&D productivity with core focus on internal development vs. in-licensing
- Building novel biology/target capabilities

Early-stage Clinical Development

- Geographically dispersed capabilities located between West Coast North America, Dublin, and Singapore
- Strong outsourcing model
- 35-person group
- Capacity to manage 5-6 early-stage clinical candidate portfolio
- Specialization between solid tumors, heme cancers and AIID

TMO & Quality

- Strong outsourcing model
- Benefit from zanidatamab experience
- 30-person group located on West Coast NA
- Capacity to manage 10-12 product candidates

A large, light blue arrow pointing from left to right, spanning across the bottom of the three main content boxes.

Over the past 18 months we have built an internal organization globally to actively manage ~5-6 early-stage wholly-owned clinical programs

Current Financial Status:

- Cash resources¹ of approx. \$375M (as of Sept 30, 2024)
- Additional development activities in AIID and ADVANCE, along with nomination of ZW1528 for COPD, was executed while maintaining cash runway
- Anticipated cash runway into 2H 2027, which includes certain anticipated regulatory milestone payments

¹cash, cash equivalents, and marketable securities

Potential sources to extend cash runway beyond 2H 2027:

- Additional regulatory approval and commercial milestones for zanidatamab from Jazz and BeiGene
- Tiered royalties between 10-20% from Jazz and 10-19.5% from BeiGene sales (up to 20% when royalty reduction of 0.5% reaches cap in the low double-digit millions of dollars)
- Additional payments from legacy technology platform collaborations
- Optionality to monetize royalties from existing partnerships
- Potential new partnerships/collaborations to provide upfront payments and committed R&D funding

Differentiated Development of Multifunctional Therapeutics

Program	Technology	Target	Indication	Discovery	Preclinical	Phase 1	Phase 2	Phase 3
Solid Tumor Oncology: Antibody-Drug Conjugates (ADC)								
ZW191 Topo1i ADC DAR 8 Fc WT	ZD06519 Payload	FR α	Gynecological Thoracic	NCT06555744				
ZW220 Topo1i ADC DAR 4 Fc Mut	ZD06519 Payload	NaPi2b	Gynecological Thoracic				IND 1H 2025	
ZW251 Topo1i ADC DAR 4 Fc WT	ZD06519 Payload	GPC3	Digestive System (HCC, PDAC)				IND 2H 2025	
Solid Tumor Oncology: Multispecifics								
Zanidatamab Bispecific	Azymetric™	HER2	Multiple indications					
ZW171 Trivalent TCE 2+1 Format	Azymetric™ Novel anti-CD3	MSLN x CD3	Gynecological Thoracic	NCT06523803				
ZW209 Trispecific TCE Tri-TCE Costim	Azymetric™ Novel anti-CD3 Conditional CD28	DLL3 x CD3 x CD28	Thoracic				IND 1H 2026	
ZW239 Trispecific TCE Tri-TCE Costim	Azymetric™ Novel anti-CD3 Conditional CD28	CLDN18.2 x CD3 x CD28	Digestive System					
AIID								
ZW1528 Dual Cytokine Blocker	Azymetric™ Hetero-Fab YTE	IL4R α x IL-33					IND 2H 2026	
ZW1572 Dual Cytokine Blocker	Azymetric™ Hetero-Fab YTE	IL4R α x IL-31						

Meaningful Catalysts Expected Throughout 2025 & 2026



1H 2025

2H 2025

2026

PIPELINE EVENTS

- Pivotal Phase 3 top-line data readout in 1L GEA for zanidatamab targeted by our partner Jazz in 2Q 2025
- Potential China approval for zanidatamab in 2L BTC in Q2 2025
- Initial royalty revenue from Jazz Pharmaceuticals
- Expected IND submission for ZW220 (NaPi2b) in 1H 2025
- Potential EU approval for zanidatamab in 2L BTC in Q2 2025

- Initial royalty revenue from BGNE Pharmaceuticals
- Expected IND submission for ZW251 (GPC3) in 2H 2025
- Potential Phase 1 clinical data readouts on ZW171 and ZW191 as soon as 2025
- Jazz Pharmaceuticals may file a sBLA for zanidatamab in 1L GEA
- Jazz potential for further development of zanidatamab in neoadjuvant/adjuvant GEA

- Expected IND submission for ZW209 (DLL3) in 1H 2026
- Expected IND submission for ZW1528 (IL4R x IL-33) in 2H 2026
- Jazz to potentially launch expanded market strategy for zanidatamab in GEA in 2026

CASH RUNWAY¹ FORECAST INTO 2H 2027 WITH RECEIPT OF CERTAIN ANTICIPATED REGULATORY MILESTONE PAYMENTS

¹ cash, cash equivalents, and marketable securities

Illustrative. Key news flow only. AACR: American Association for Cancer Research; ASCO: American Society of Clinical Oncology; ASCO GI: ASCO Gastrointestinal Cancers Symposium; BLA: biologics license application; EORTC-NCI-AACR: EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics; EMA: European Medicines Agency; ESMO: European Society for Medical Oncology; JSMO: Japanese Society of Medical Oncology; MAA: marketing authorization application; PEGS: Protein Engineering Summit; SABCs: San Antonio Breast Cancer Symposium; SITC: Society for Immunotherapy of Cancer; T-DXd: trastuzumab deruxtecan; World ADC: World Antibody Drug Conjugates Summit; WCGI: World Congress on Gastrointestinal Cancer.

Key Takeaways From ZYME R&D Day



With nomination of ZW209, 5x5 solid tumor portfolio construction is 18 months ahead of schedule with expected initial clinical data disclosures potentially starting in 2025



Recent approval of zanidatamab demonstrates our experience and abilities to develop unique and differentiated therapeutics with clinically meaningful benefits for patients



ADVANCE portfolio broadly diversified into hematological cancers and AIID in addition to solid tumors with initial IND planned for 2H-2026 for ZW1528 and more in 2027 and beyond



Clear decision-making processes to advance or cease development activities on product candidates based on clinical data generated



Enhanced optionality for partnerships and collaborations to share capital and development risk



Strong financial position to provide opportunity for retaining certain product rights



R&D organizational structure in place to drive continued progress in both '5x5' and ADVANCE portfolios



Additional solid tumor research focused on digestive system cancers, including CRC and PDAC

ADVANCE PROGRAM

Q&A Session #2



zymeworks