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**

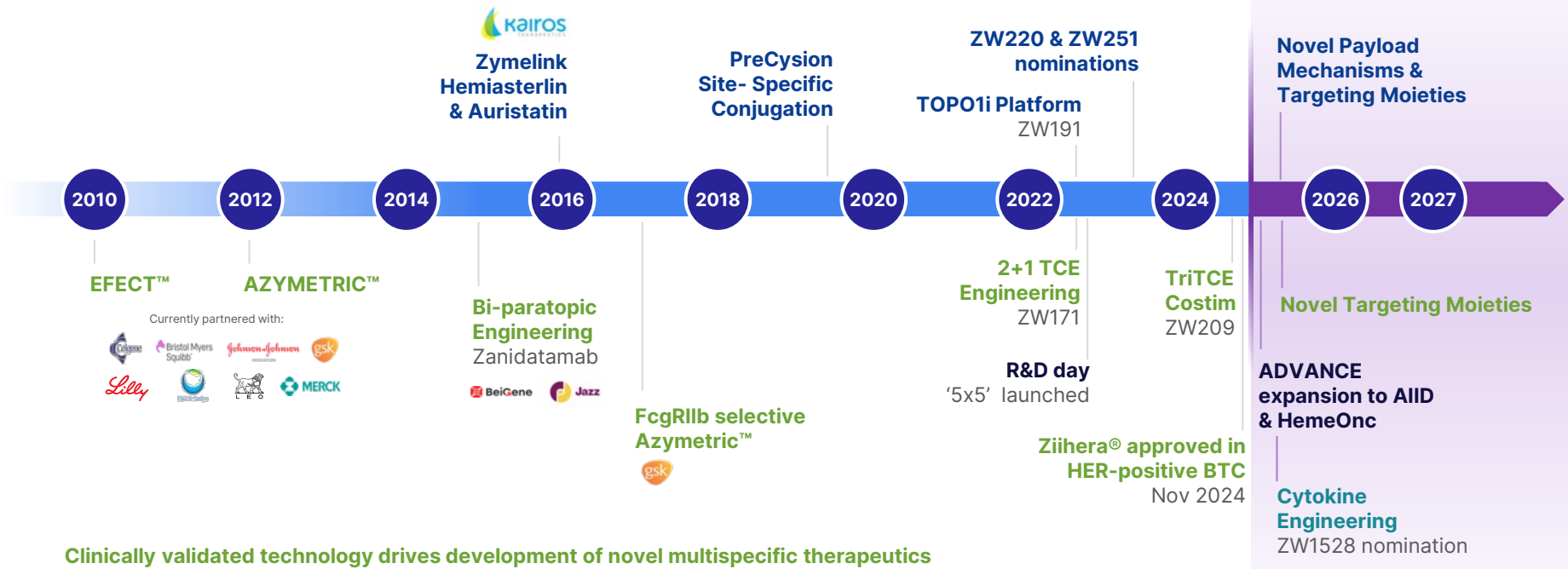
ZYMEWORKS R&D STRATEGY

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

zymeworks

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

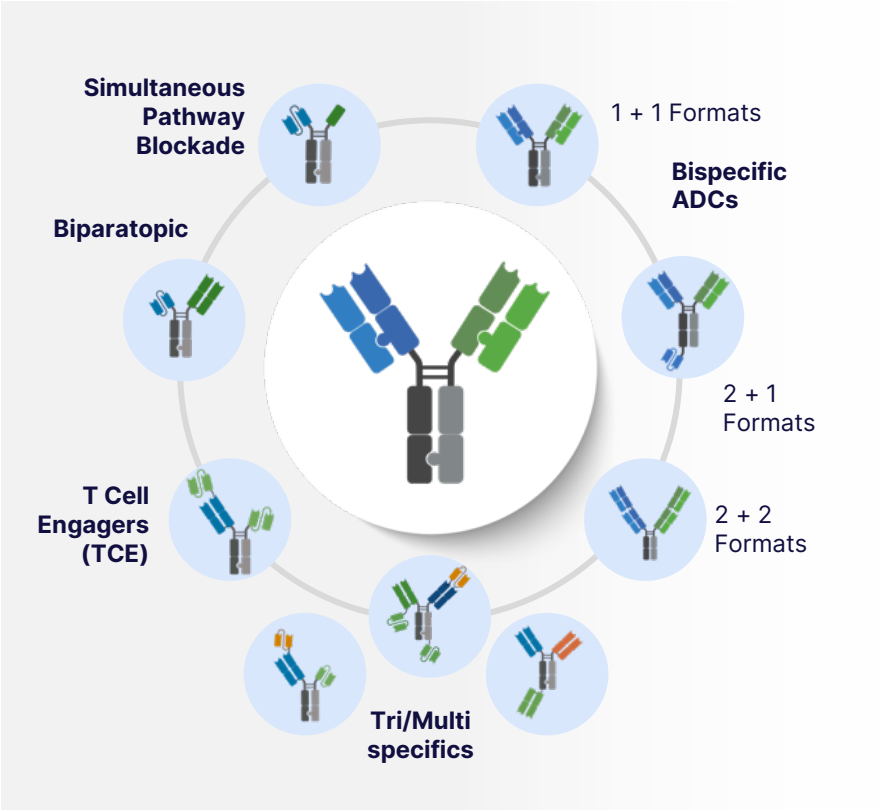
Can employ novel or existing antibody paratopes; human (IgG1, IgG2A, IgG4) and mouse frameworks; other CH2 and glyco-engineering approaches (eg YTE). Compatible with linker/payload conjugation

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

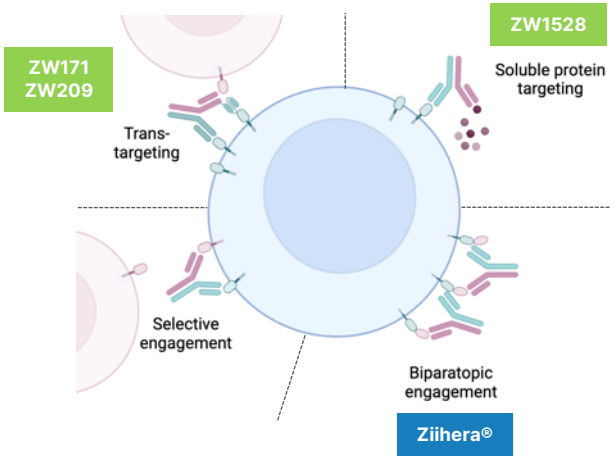
Antibody like yields/stability; leveraged by multiple pharma/biotech with various clinical stage programs in development

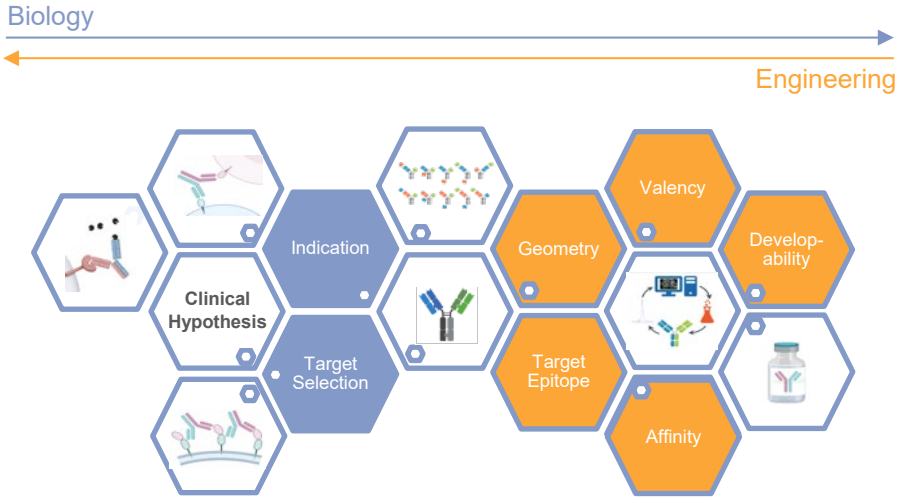


Multispecific Antibody Development Requires Optimization of Multiple Parameters Specific to Desired MOA

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





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

ADVANCE

Biparatopic

Zanidatamab

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

Multi-Cytokine Blocker

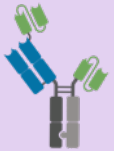
ZW1528 (IL4Rα – IL-33)

- IgG-like format, manufacturability and PK
- IL4Ra and IL-33 blockade equivalent to bivalent benchmarks
- Unique bispecific activity, potentially superior 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



Trispecific T Cell Engager

ZW209 (CD28 TriTCE)

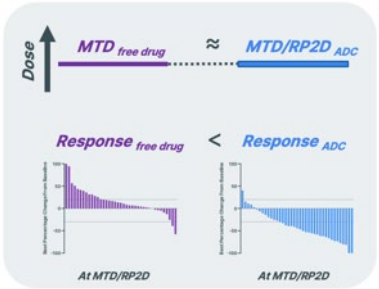
- Discovery of novel format to prevent non-specific T cell activation
- Conditional CD28 activation
- Synapse optimization for balanced Signal 1 plus Signal 2

Increased Complexity

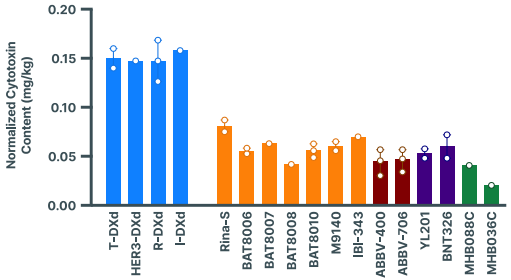
5X5

Historical Observations Guide Our Approach to ADC Design

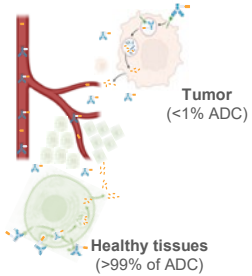
1 Conjugation does not improve payload MTD[1]



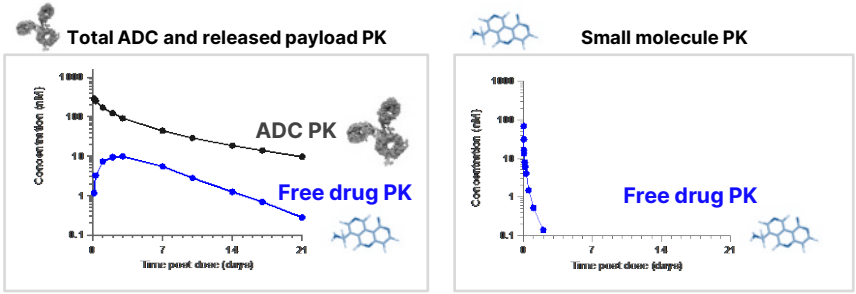
2 More potent payloads limit protein dose[2]



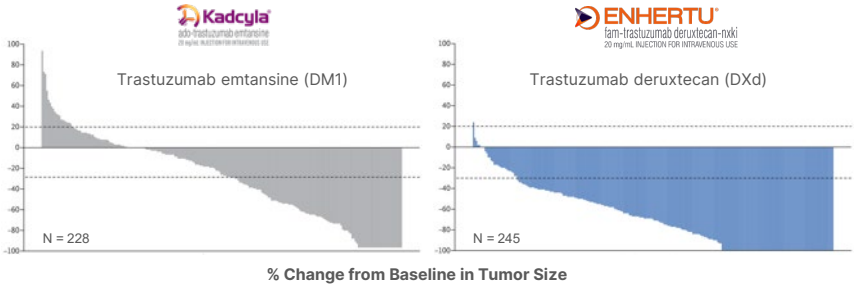
3 Most ADC catabolism occurs in normal tissue[3]



4 Bystander activity is a key payload feature[2]



5 The right payload mechanism matters[4]



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

Antibody

Paratope and antibody format selected for each target

Linker & Conjugation

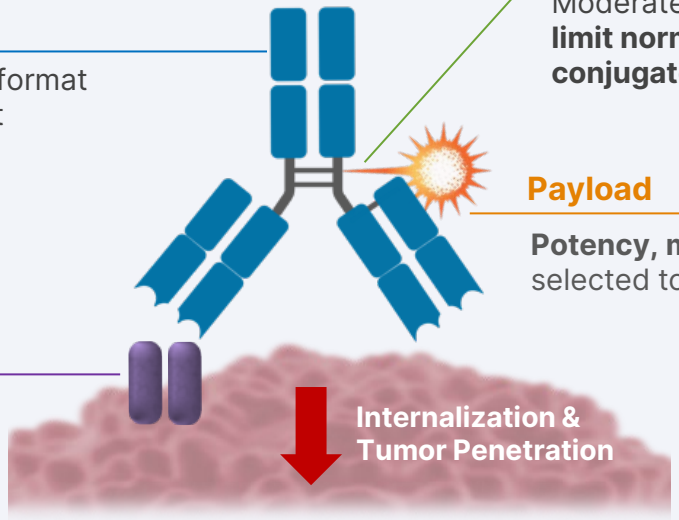
Moderate antibody-linker instability may **limit normal tissue exposure to conjugated drug**

Payload

Potency, mechanism, and bystander activity selected to match disease biology

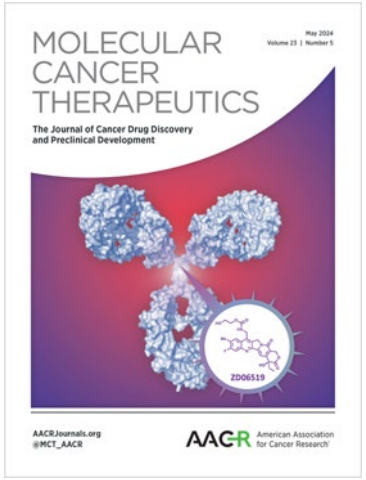
Target

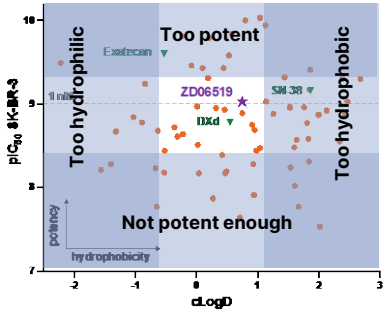
Expression, function, and internalization



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





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

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

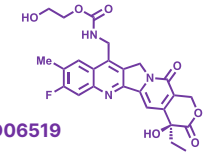
ADC characterization

ADC properties: monodispersity, plasma stability, hydrophilicity

NHP toxicology & TK

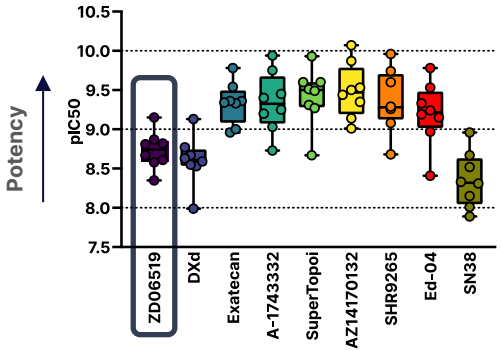
MTD in NHPs:
DAR8: ≥30 mg/kg
DAR4: ≥120 mg/kg

Lead selection and application



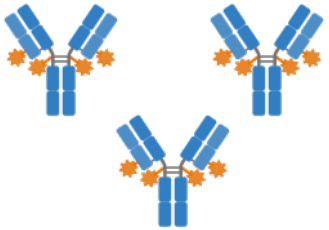
ZD06519

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



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

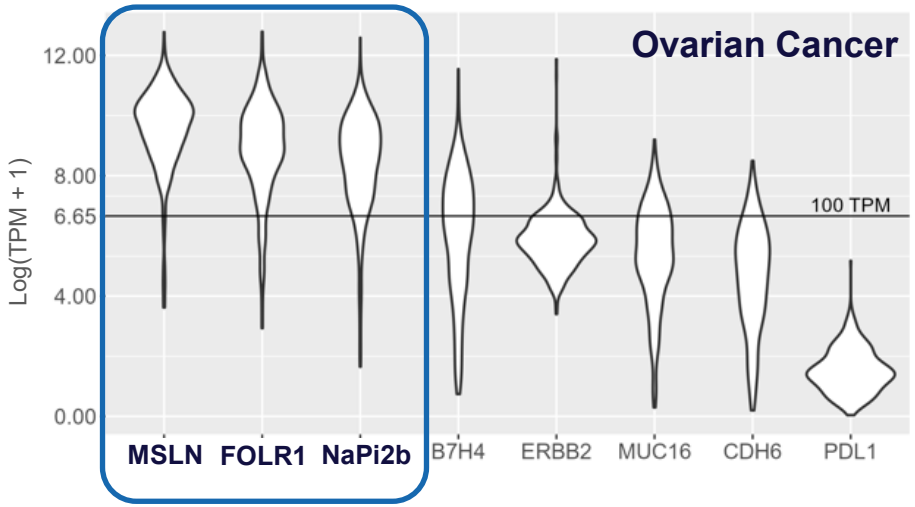
ADVANCE

	 ZW191	 ZW220	 ZW251	
Target	FRα	NaPi2b	GPC3	Novel targets in digestive tract tumors and heme-onc
Payload mechanism	TOPO1i	TOPO1i	TOPO1i	Novel mechanisms
Antibody	Mono	Mono	Mono	Novel formats
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	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 FRα 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 ggplot21. This dataset contains 421 samples (patients) from Ovarian Serous Cystadenocarinoma (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	FRα	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	IL4Rα 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

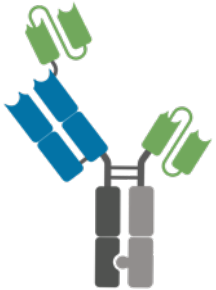
Jeff Smith, MD, FRCP
Executive Vice President and Chief Medical Officer

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				✓		

Zymeworks' Therapies Actively Enrolling into Phase 1 Clinical Studies

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

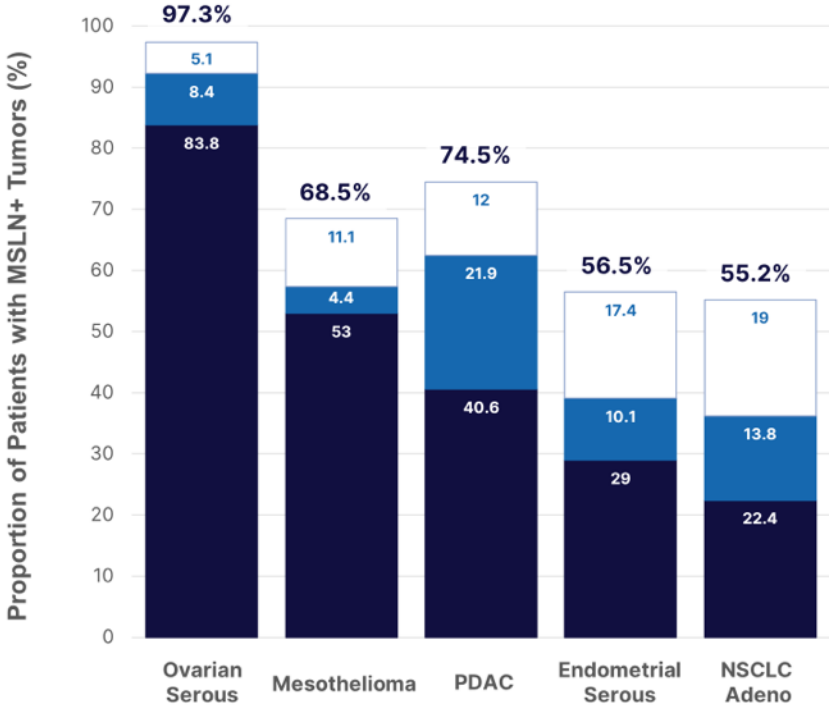
ZW191

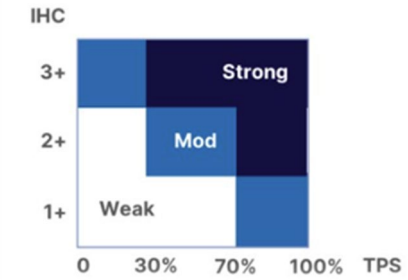
FRα-targeting ADC

- 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

ADC: antibody-drug conjugate; CD3: cluster of differentiation 3 protein complex and T cell co-receptor; CRS: cytokine release syndrome; DAR: drug-to-antibody ratio; FRα: folate receptor alpha; MSLN: mesothelin; TOPO1i: topoisomerase-1 inhibitor

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

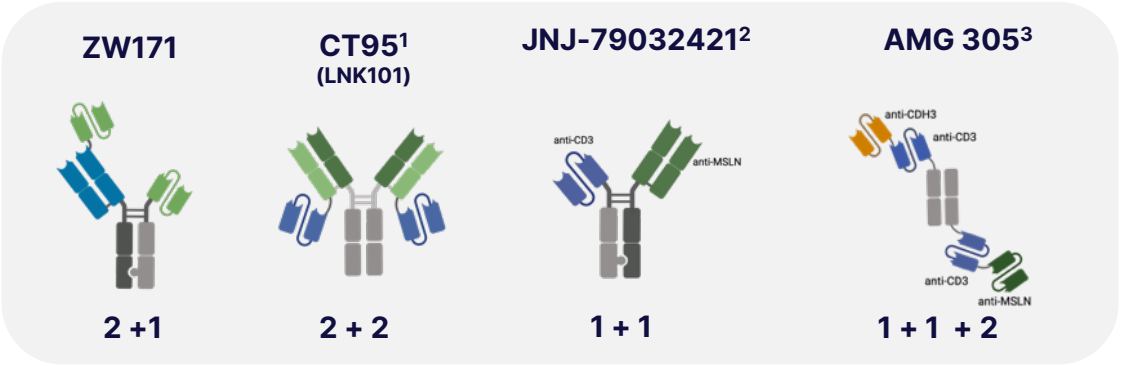




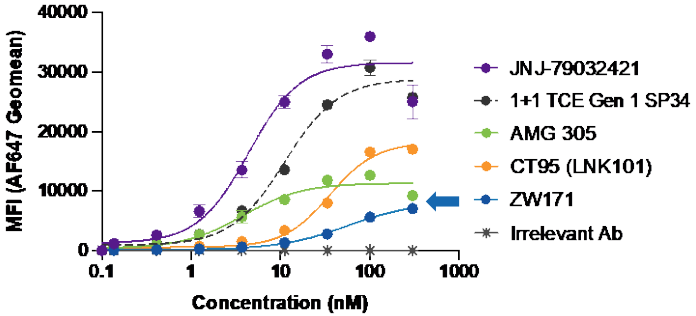
Adapted from Weidemann S, et al Biomedicines. 2021;9(4):397.
CRC: colorectal cancer; FRα: folate receptor alpha; GEA: gastroesophageal adenocarcinoma; IHC: immunohistochemistry; Mod: moderate; MSLN: mesothelin; NSCLC: non-small cell lung cancer; PDAC: pancreatic ductal adenocarcinoma

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

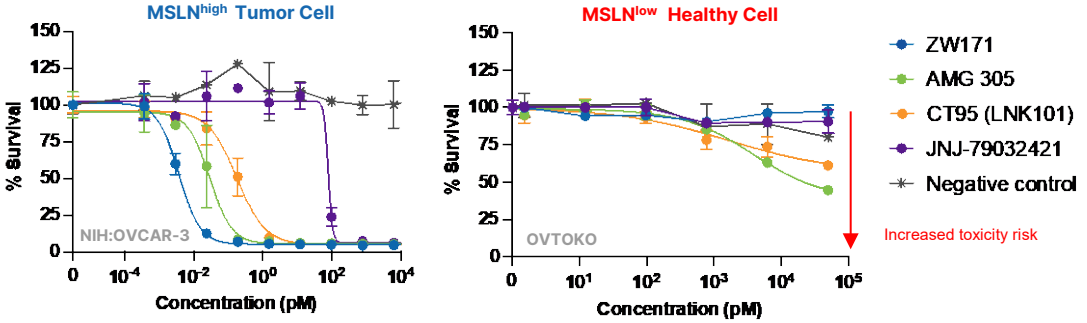
- Enhanced tumor selective cytotoxicity
- No targeting of normal tissues
- Low affinity CD3 binding to mitigate peripheral T cell binding and cytokine release
- Maintains potency in the presence of soluble MSLN



Low Binding to T cells



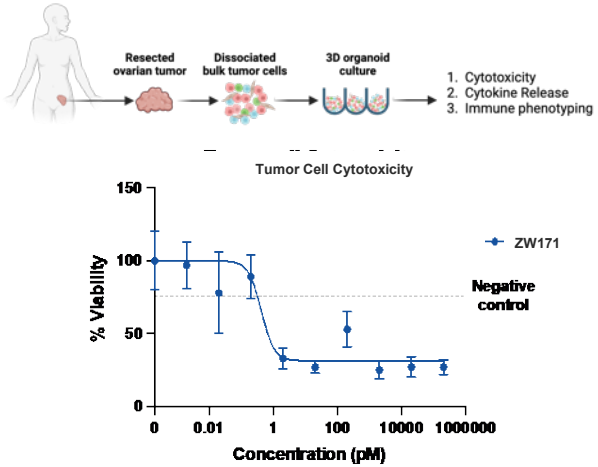
Potent Cytotoxicity in MSLN⁺ Tumor Cells but not Normal Cells



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; ;

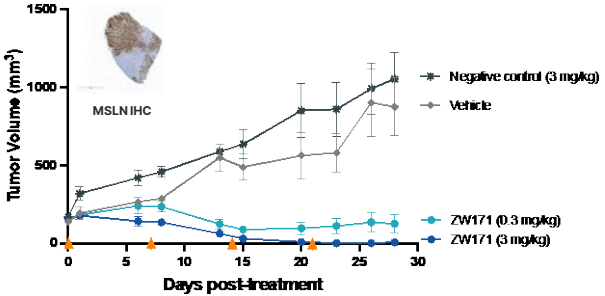
ZW171 Mediates Strong Anti-Tumor Activity in Patient-derived *Ex Vivo* and *In Vivo* Models

Ovarian Adenocarcinoma Organoid Model



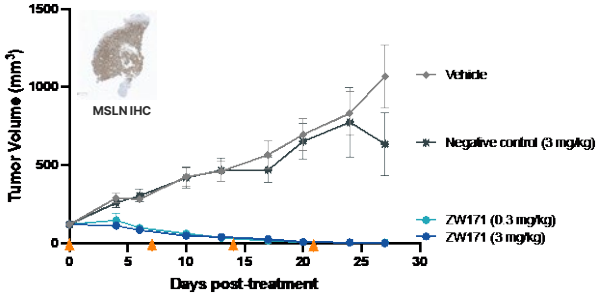
3D patient-derived ovarian carcinoma organoids were generated, and ZW171 activity assessed using KIYATEC proprietary technologies (Lassahn, 2023). Following incubation of organoids with ZW171 for 72hr, tumor cell viability was assessed using a CellTiter-Glo 3D (Promega) assay.

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).

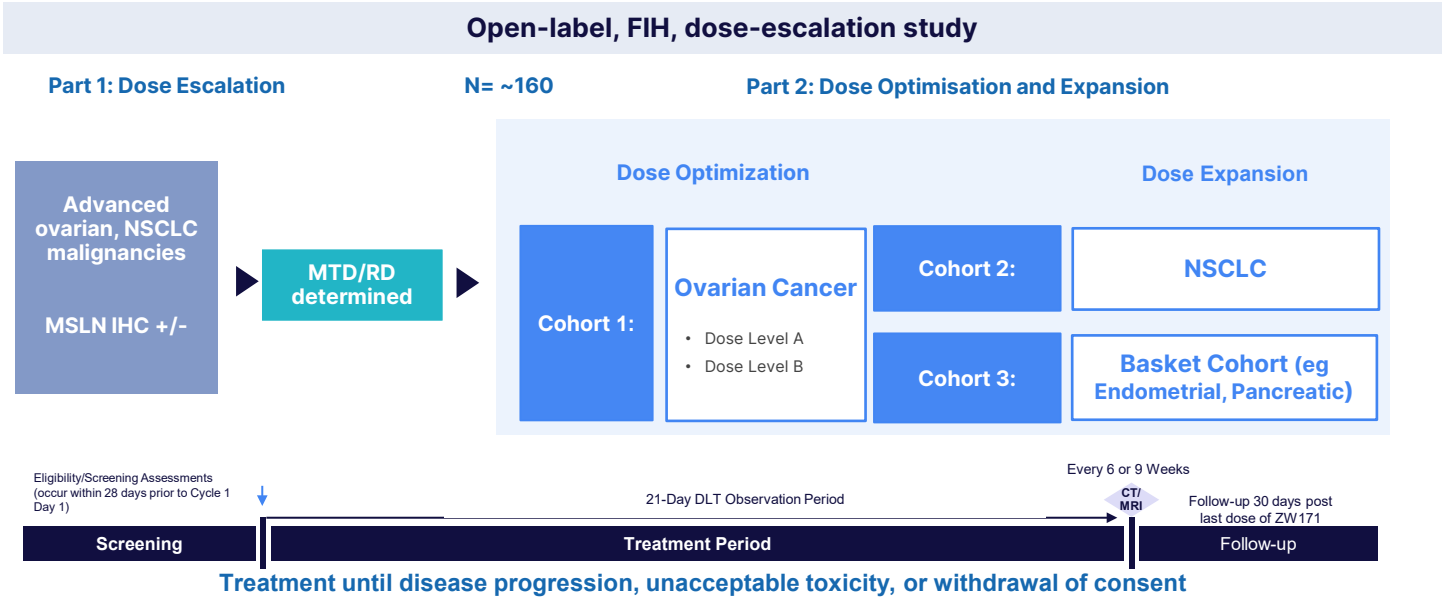
Patient-derived Pancreatic Cancer Humanized Mouse Model



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).

Lassahn et al., Abstract 2275: Preclinical testing of therapeutic biologics using patient-derived 3D spheroids. Cancer Res 1 April 2023; 83 (7_Supplement): 2275
IHC: immunohistochemistry; MSLN: mesothelin; NSCLC: non-small cell lung cancer

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

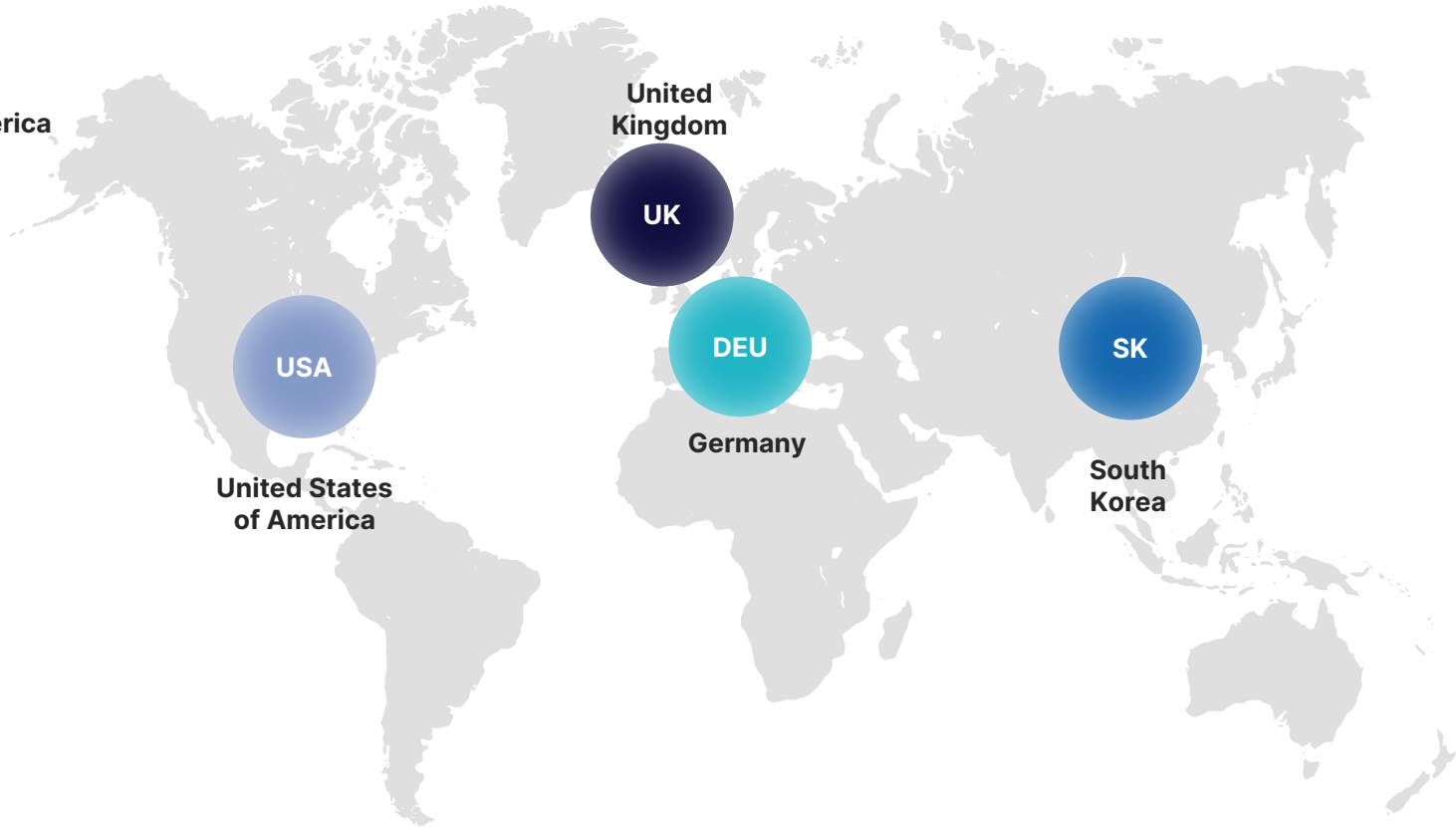
ZW171 Clinical Development Progress – Dose Escalation Territories

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

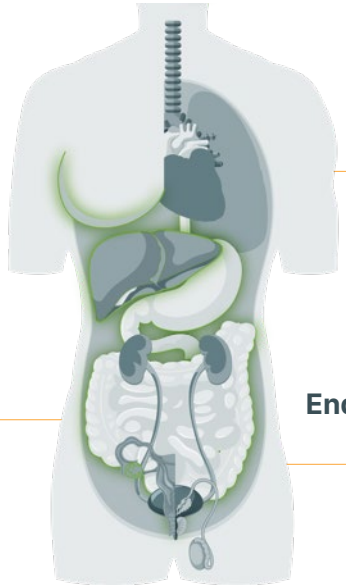


US FDA:U.S. Food and Drug Administration; MFDS: Ministry of Food and Drug Safety.

FRα-expressing Cancers Represent a Significant Commercial Opportunity[1-7]

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

FRα-EXPRESSING CANCERS

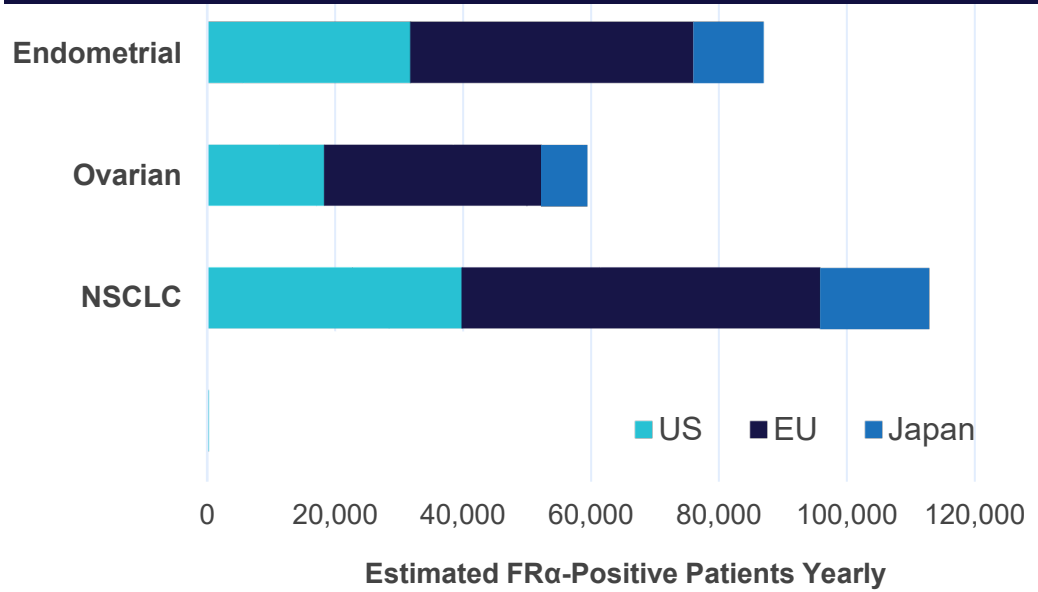


Lung
14%-74%

Ovarian
39%-75%

Endometrial
50%

ESTIMATE OF NEWLY DIAGNOSED FRα+ PATIENTS IN KEY INDICATIONS



FRα: 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.

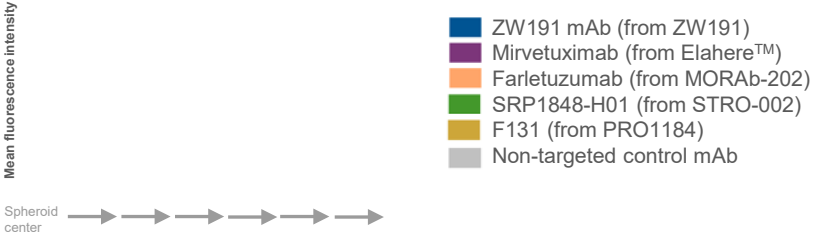
ZW191: Key Design Considerations

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

Internalization

Payload Delivery

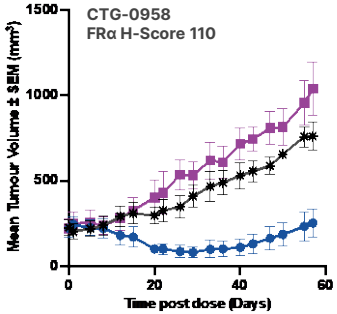
Tumor Spheroid Penetration

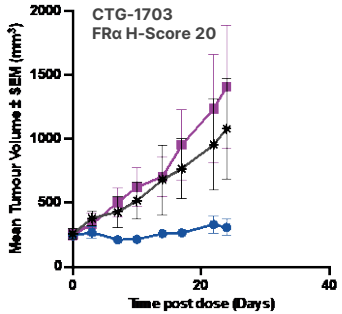


Internalization of AF488 labelled antibodies to KB-Hela cells after 24 hrs at 100 nM; Mass-spec. quantification of internalized payload following 24-hour treatment of IGROV-1 cells with 10 nM of ADCs comprising ZW191 mAb or other FRα-targeted mAbs conjugated to a auristatin payload; Tumor spheroid penetration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

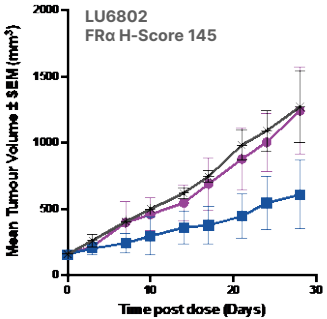
Anti-tumor Activity Across Multiple Tumor Types and Range of FRα Expression (PDX models)

Ovarian Cancer

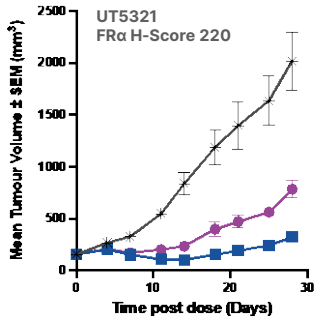




NSCLC



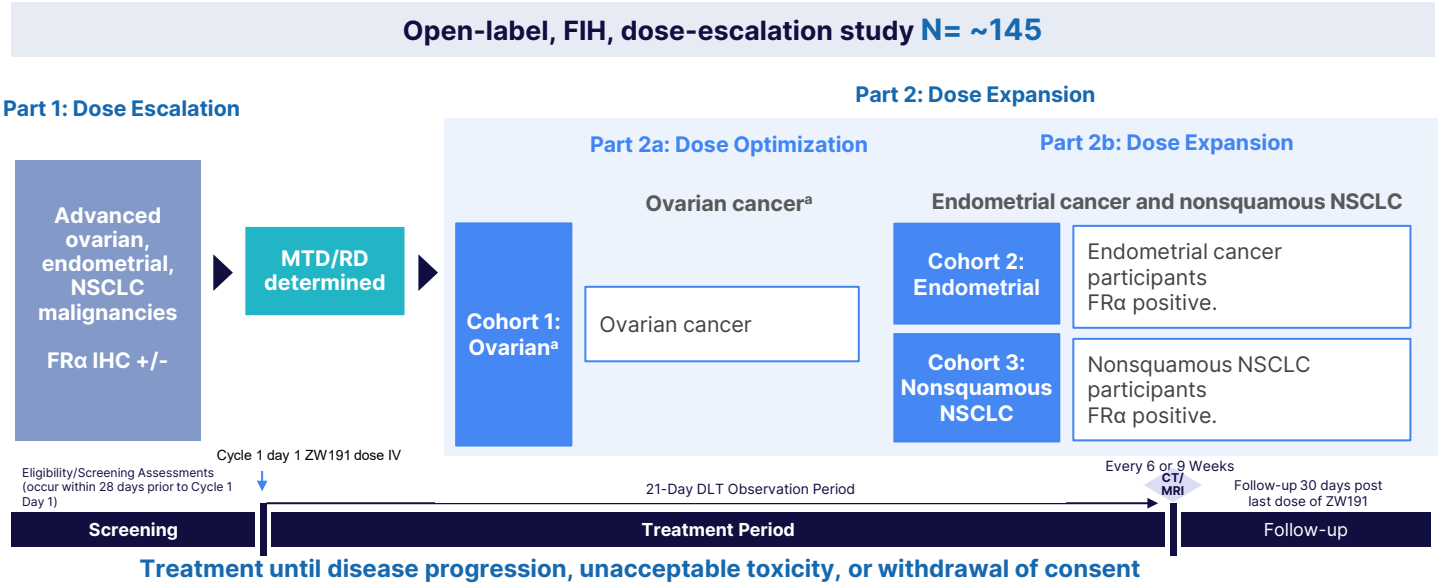
Endometrial



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

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

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



[a]Ovarian cancer includes primary peritoneal and fallopian tube cancers. [b]Part 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. [c]Timed 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; FRα: 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 — **United States of America**

US FDA Approval
Sites Activated

JPN — **Japan**

PMDA Approval
Sites Activated

AU — **Australia**

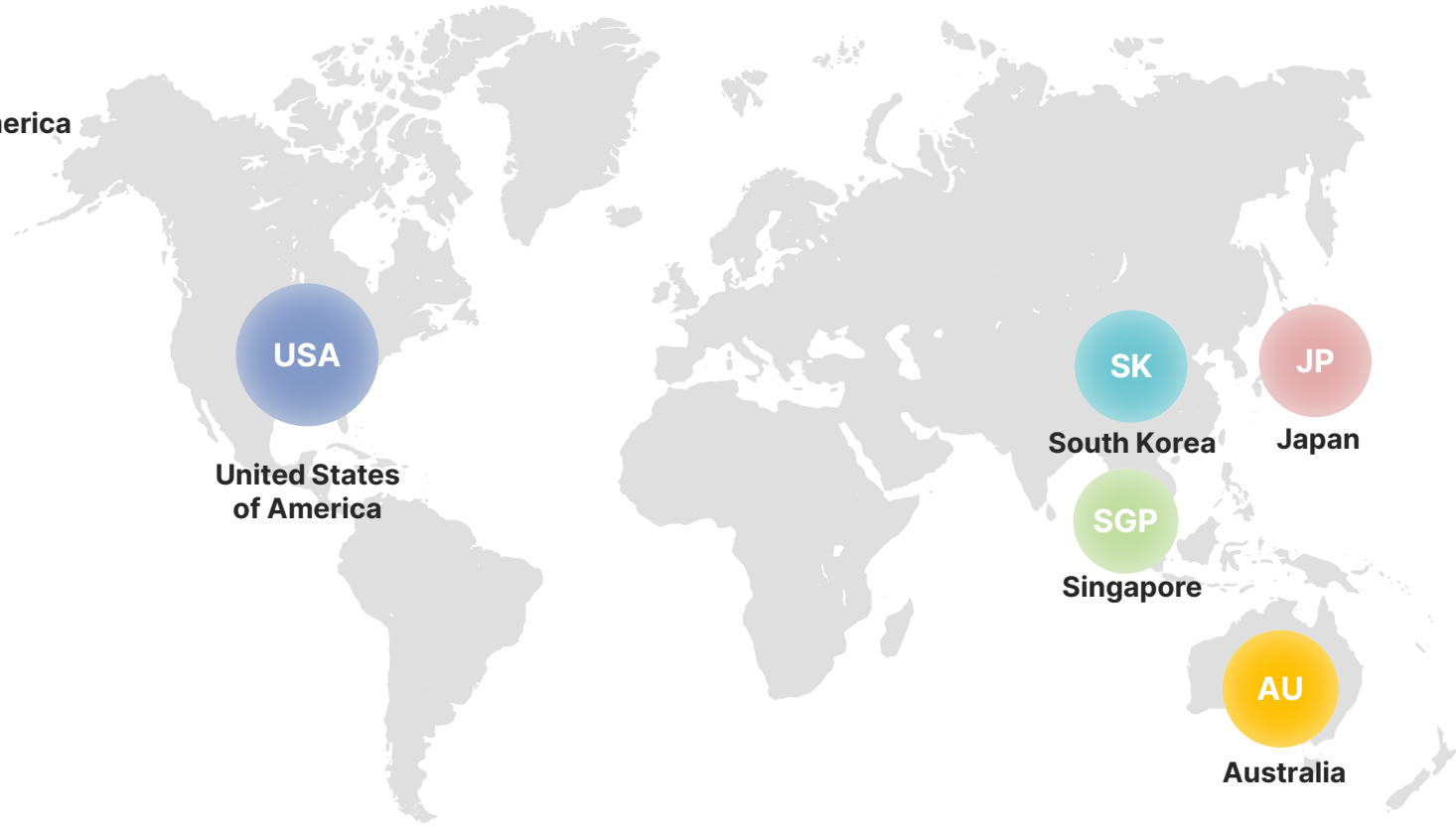
TGA Approval
First Site Activated

SKr — **South Korea**

MFDS Approval

SGP — **Singapore**

HSA Approval
First Site Activated

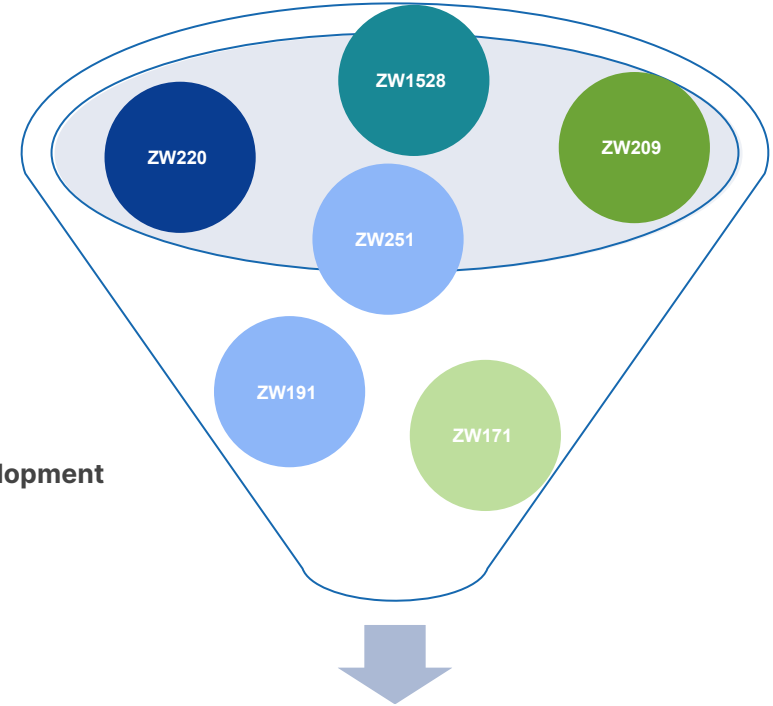


US FDA: U.S. Food and Drug Administration; PDMA: Prescription Drug Marketing Act; TGA: Therapeutic Goods Administration; MFDS: Ministry of Food and Drug Safety; HAS: Health Sciences Authority

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

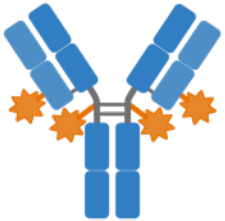
SOLID TUMOR PROGRAM

ZW220 and ZW251

Paul Moore, PhD
Chief Scientific Officer

Zymeworks' Therapies on Track for 2025 IND Submission

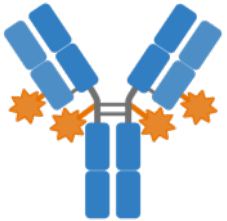
ZW220



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

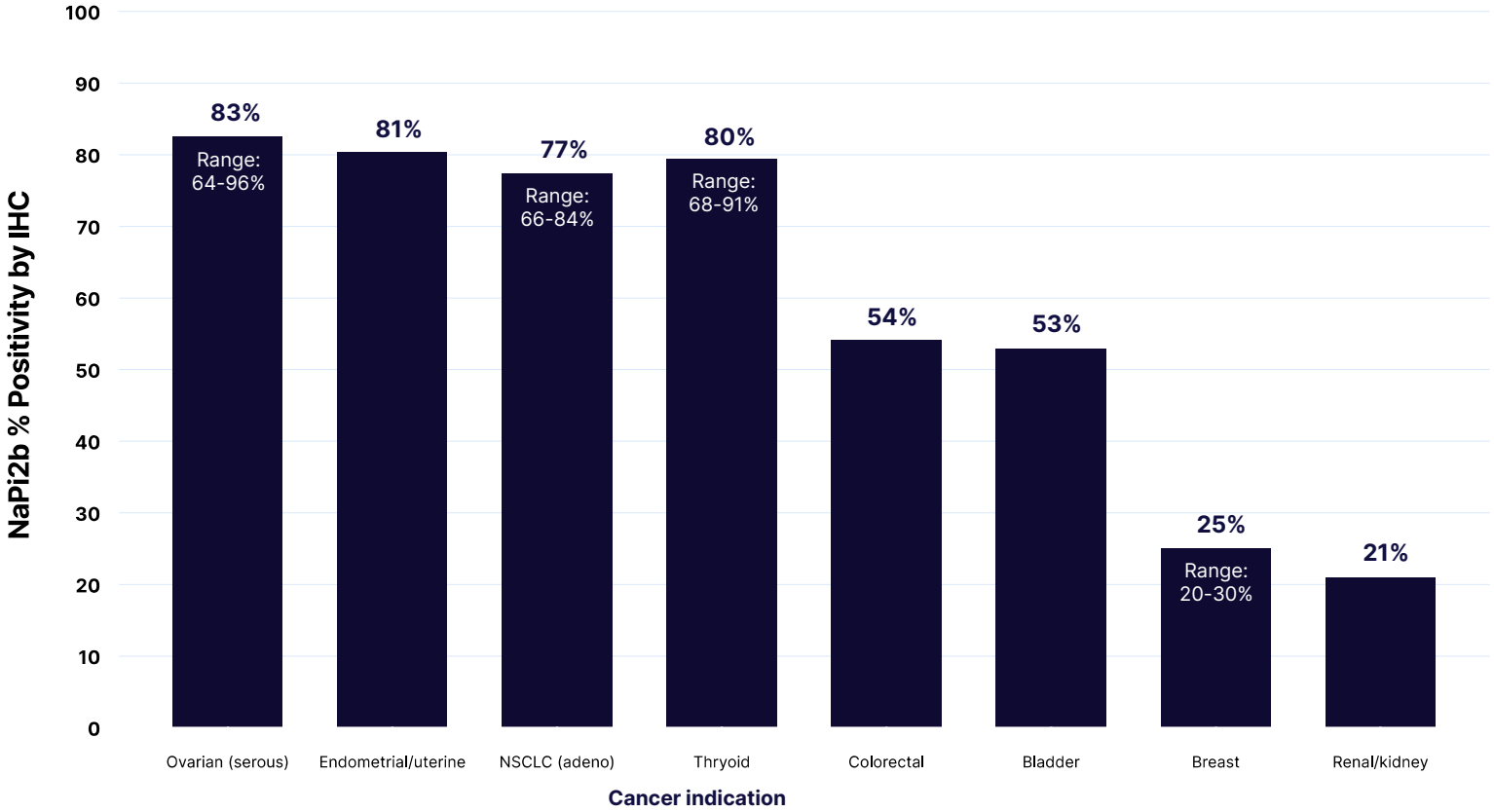


GPC3-targeting ADC

- 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

ADC: antibody-drug conjugate; DAR: drug-to-antibody ratio; FcγR: Fc gamma receptor; GPC3:Glypican-3; Napi2b:sodium-dependent phosphate transporter 2b; IND: Investigational New Drug; TOPO1i: topoisomerase I inhibitor

NaPi2b is Overexpressed in Multiple Cancers with High Unmet Medical Need

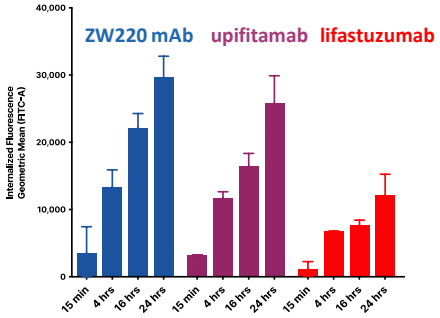


Ovarian
1) Banerjee et al. 2023. ESMO #145
2) Richardson et al. 2022. SGO #76
3) Levan et al. 2017. BMC Cancer
4) Lin et al. 2015. Clin Cancer Res
5) Lopes dos Santos et al. 2013. PLoS One
Endometrial/uterine
1) Horsley et al. 2024. Cancer Res #5085
Lung
1) Horsley et al. 2024. Cancer Res #5085
2) Heynemann 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

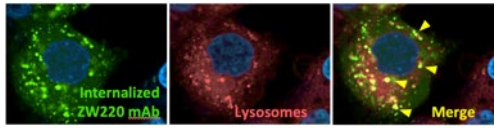
ZW220: Potential Utility in Multiple Cancers; on Track for Clinical Studies in 1H 2025[1,2,3]

ZW220 Efficiently Internalizes and Co-localizes with Lysosomes

ZW220 (mAb) internalization in Ovarian Cancer cell line

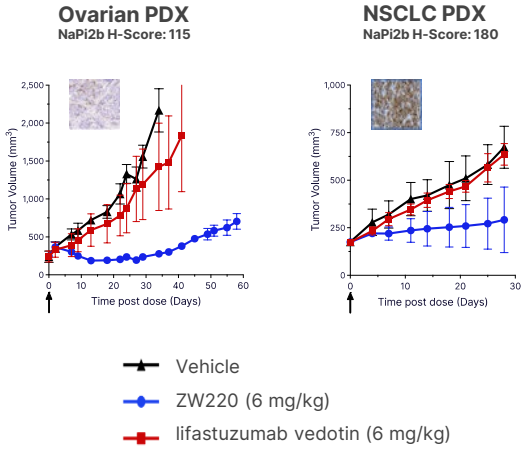


Lysosomal trafficking of ZW220 mAb



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

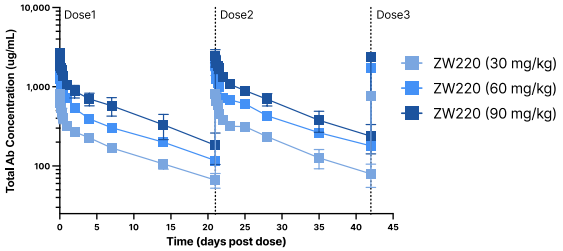


Impressive Tolerability and Dose-proportional PK in NHP

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

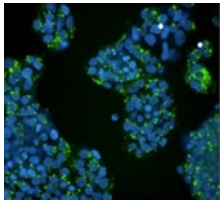
mAb: monoclonal antibody; PDX: patient derived xenograft; MTD: maximum tolerated dose; T1/2: half-life; GLP: good laboratory practice

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

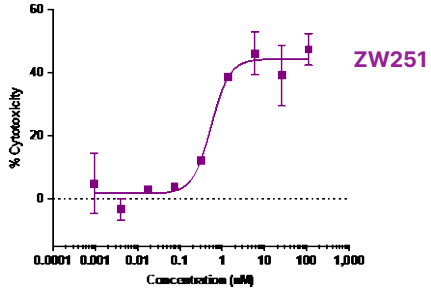
Robust ADC Internalization and Cytotoxicity

ZW251 internalized in HCC cell line



Internalization visualized after 24-hour treatment

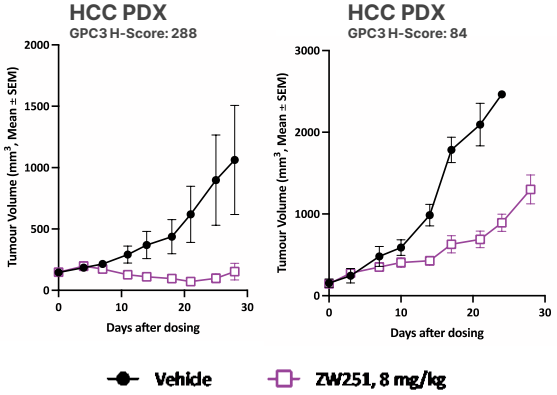
Tumor spheroid cytotoxicity in HCC cell line



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

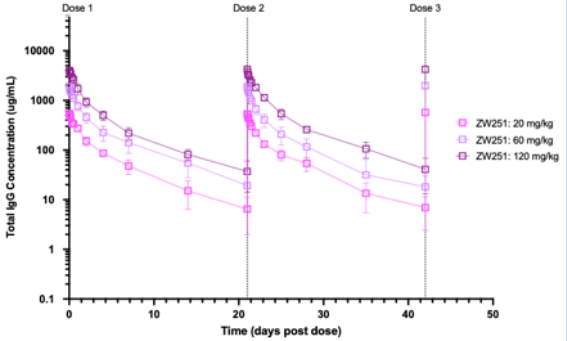


Impressive Tolerability and Dose-proportional PK in NHP

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

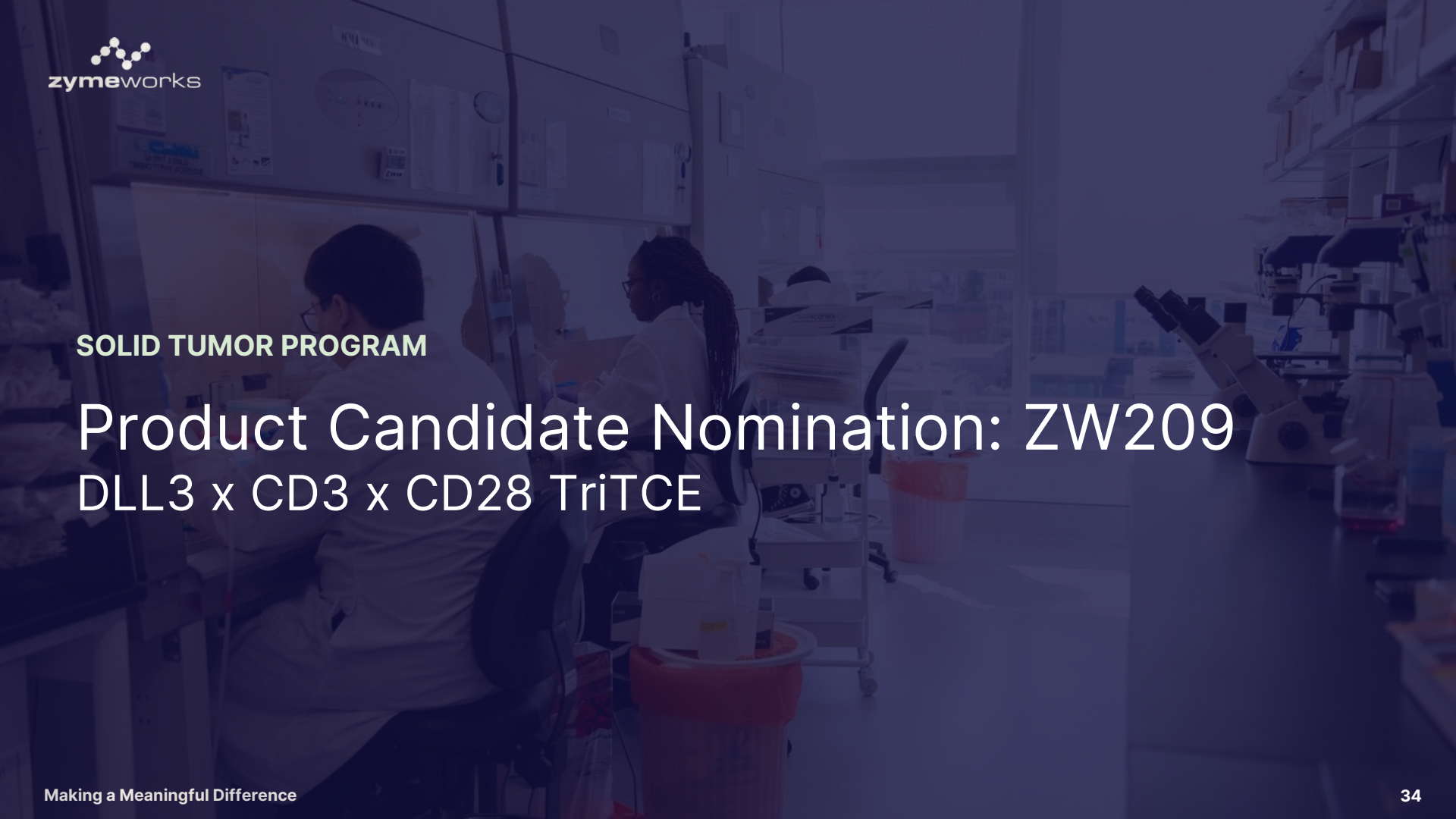
Dose	MTD	$T_{1/2}$ (day)
20 mg/kg	≥ 120 mg/kg	4.6
60 mg/kg		4.8
120 mg/kg		5.4

Total IgG in NHP serum



HCC: Hepatocellular carcinoma; PDX: patient derived xenograft; MTD: maximum tolerated dose; T1/2: 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



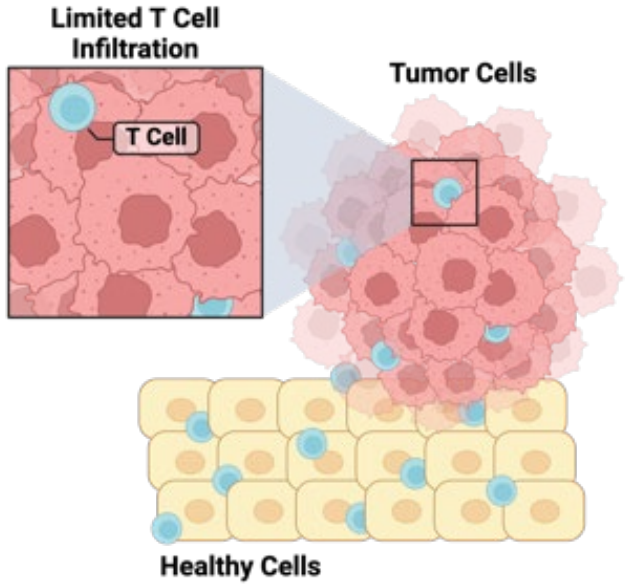
SOLID TUMOR PROGRAM

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



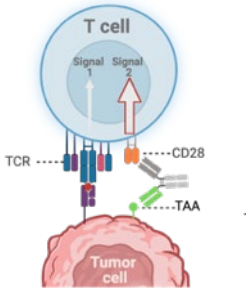
	Expected Benefit	Opportunity
CD28	• Enhances proliferation and survival of CD8 and CD4 T cells[1] • Ability to expand and maintain Tpex and prevent Tex[2] • CD28 signaling critical for Teff expansion and epitope spreading[3,4]	• No signaling independent of TCR • Opportunity to engineer safe and effective 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., Camcer Cell 2023

CD28 Co-stimulatory T Cell Engager Approaches

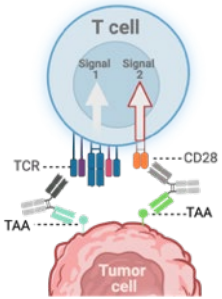
Bispecific CD28 T cell Engagers



CD28 x TAA +/- PD1

Limitations:

- Initial clinical activity for CD28-TAA +PD1, but potential toxicity due to autoreactive T cells[1]

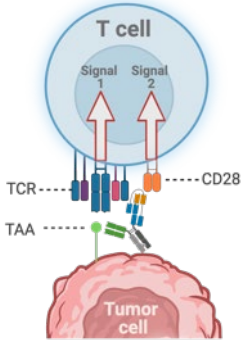


CD28 x TAA + CD3 x TAA

Limitations:

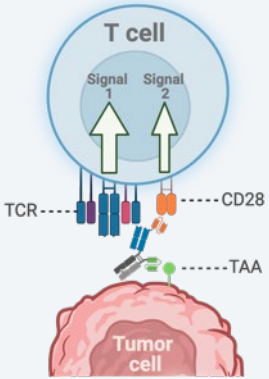
- Optimized for single agent activity and strong CD28 agonism, potential for similar toxicity to CD28-TAA and difficult to optimize by dose adjustment
- Exposure of two molecules at required dose levels potentially suboptimal

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



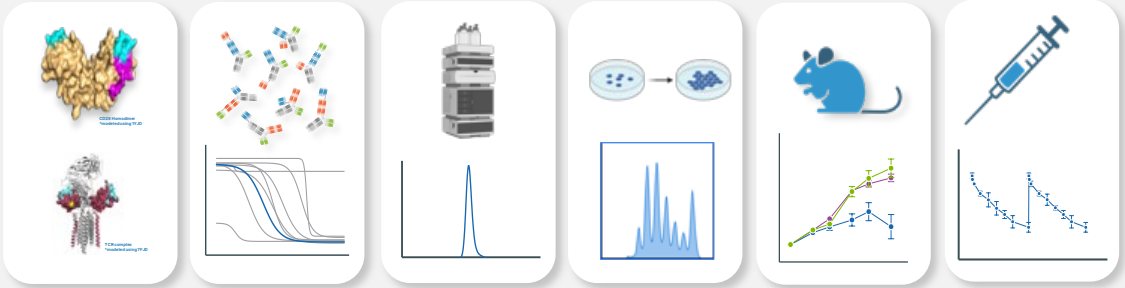
Zymeworks' Next Generation Solution:

- 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)

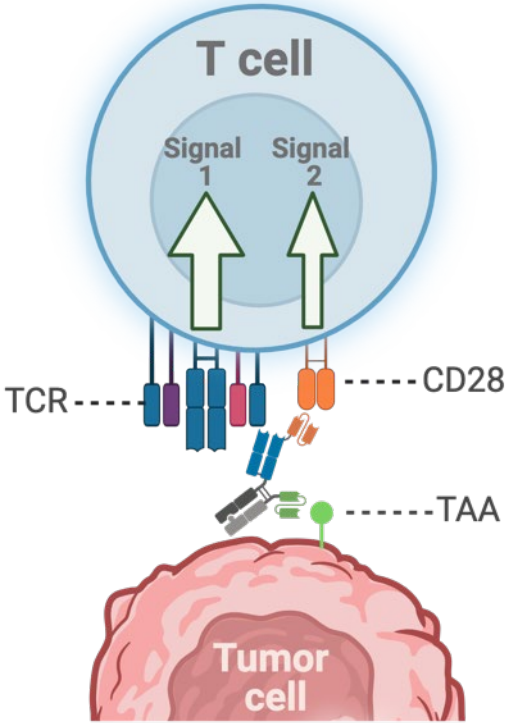
TriTCE Co-stim: A Next Generation Trispecific T Cell Engager Platform

TriTCE Co-stim Platform Workflow



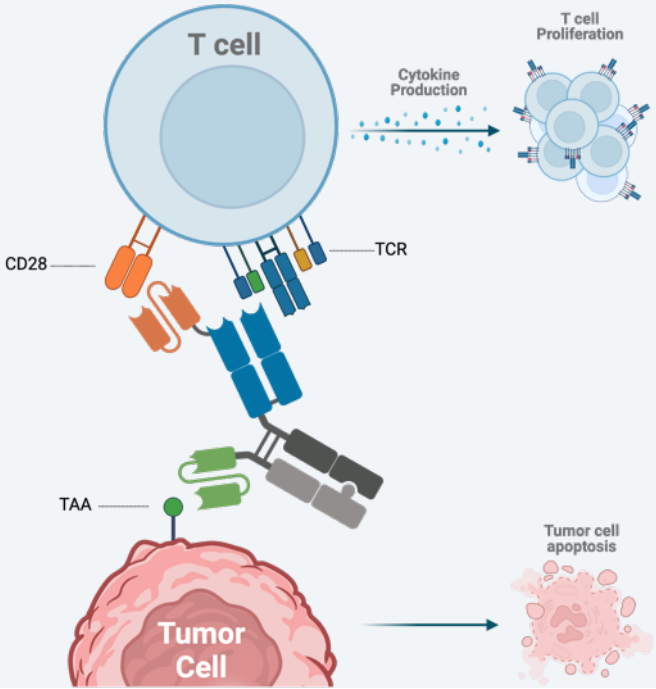
Paratope Engineering | Format Engineering & Screening | Early Developability | *in vitro* Activity & Differentiation | *in vivo* Activity & PK | Non-GLP NHP Toxicity & PK

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

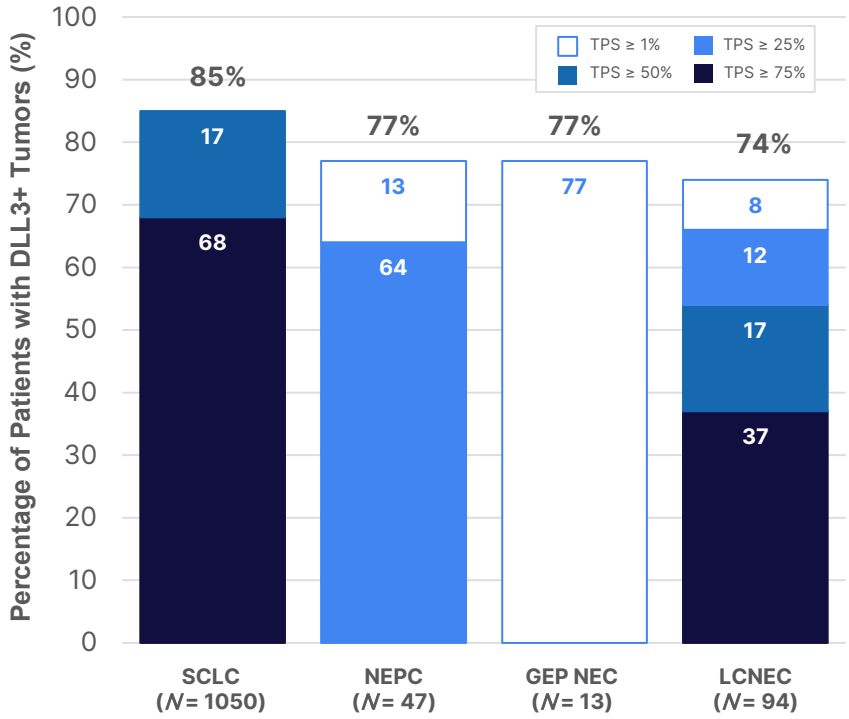


	Design Feature	Expected Benefit
1	**Balanced activation of CD3 and CD28**	Potential to provide more durable responses and activate T cell responses in ‘cold’ tumors with lower T cell infiltration
2	**Low affinity CD3 and CD28 binding**	Prevents overactivation of T cells and reduces risk of CRS and irAEs
3	**Obligate *cis* 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 Imdelltra™ 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

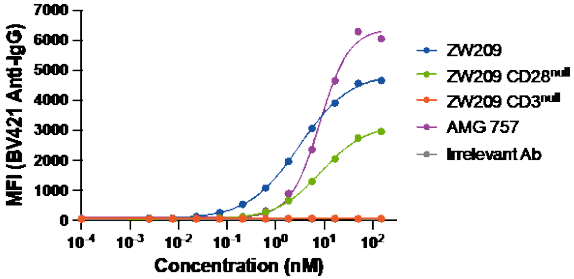


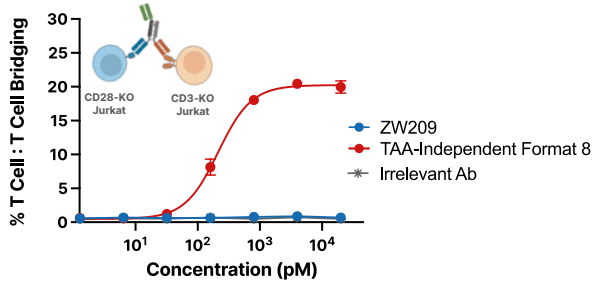
Adapted from: Rojo F et al Lung Cancer 2020. International real-world study of DLL3 expression in patients with small cell lung cancer. Puca L et al. Delta-like protein 3 expression and therapeutic targeting in neuroendocrine prostate cancer. Sci Transl Med. 2019. 11: eaav0891. Liverani C et al Endocrine 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

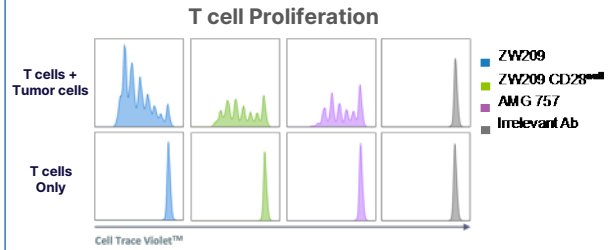
ZW209 demonstrates conditional CD28 binding and target-dependent anti-tumor activity

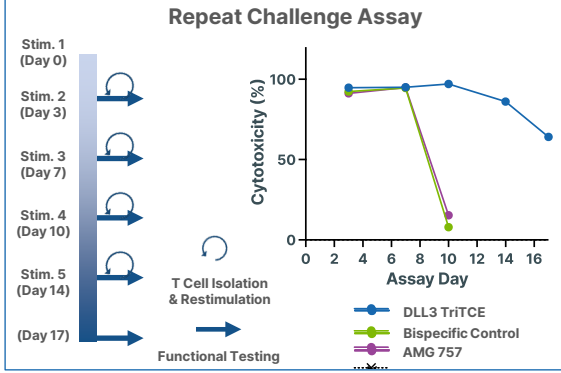
Conditional Binding of CD28, Requiring Co-engagement of CD3; Obligate Cis Binding



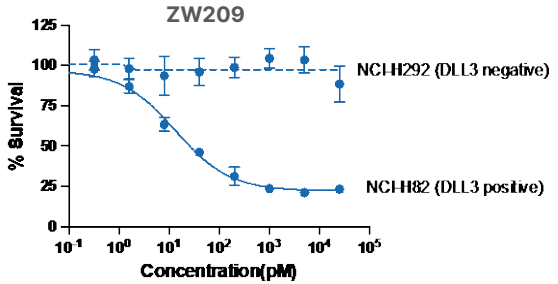


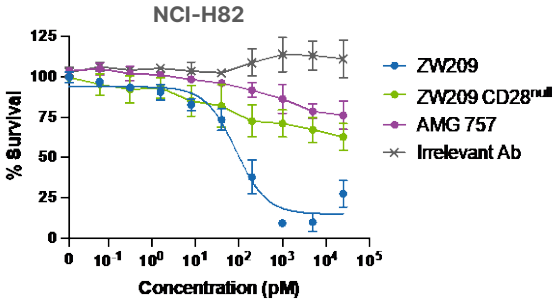
Improved T Cell Proliferation and Sustained Cytotoxicity





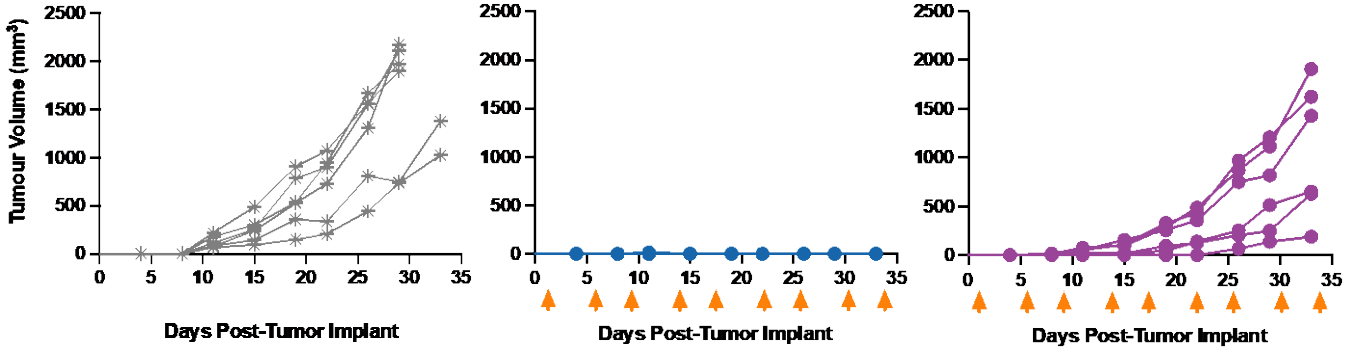
Improved Cytotoxicity Over Bispecifics in Low E:T Conditions



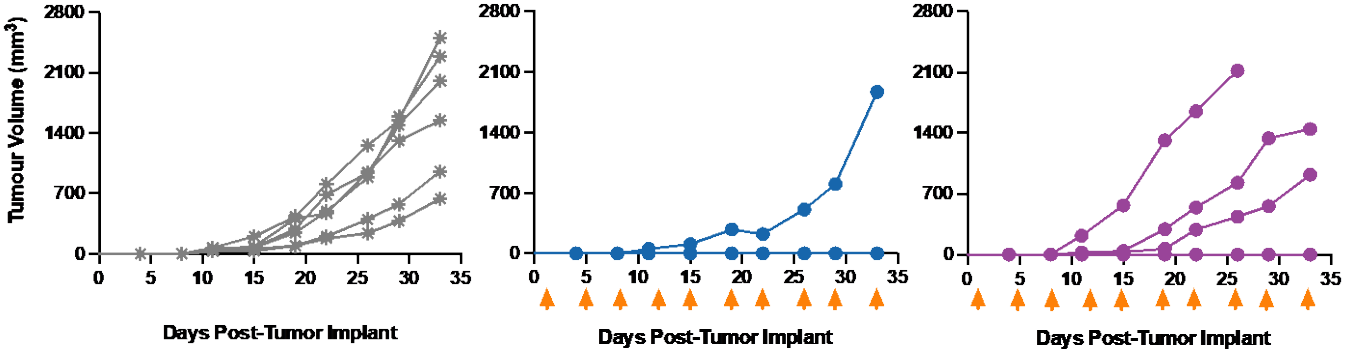


ZW209 Mediates Enhanced Anti-Tumor Activity *In Vivo* Compared to Benchmark Bispecific TCE in Humanized SCLC Models

PBMC Donor 1



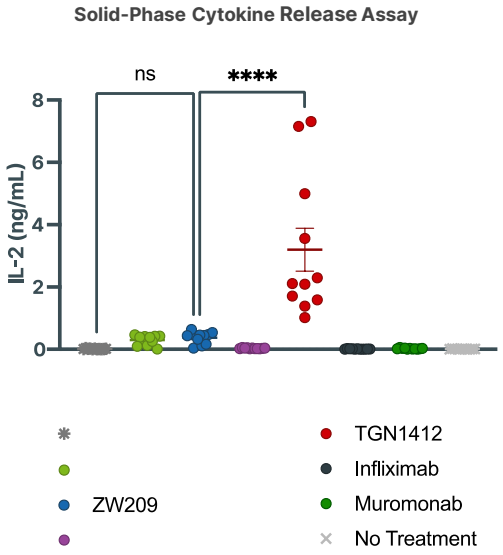
PBMC Donor 2



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

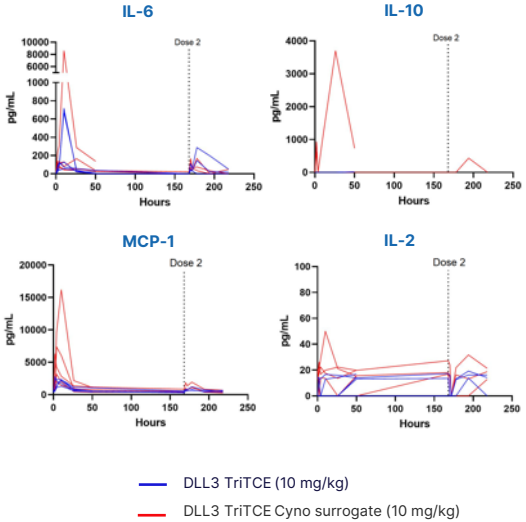


Induces Minimal Systemic Cytokine in Humanized Mouse CRS Model

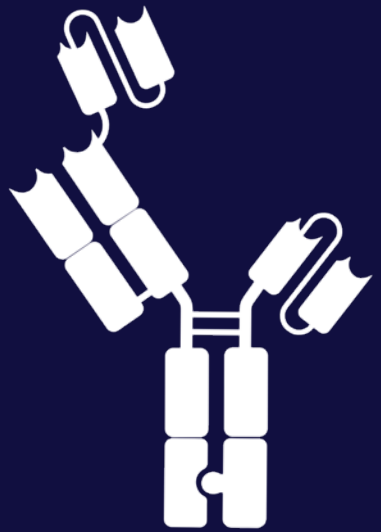
TGN1412 positive control
All dosed at 2 mg/kg except OKT3 (0.25 mg/kg)

Well Tolerated in Non-Human Primate

Transient, Minor Increases in Serum Cytokine Post-Dosing



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

zymeworks

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

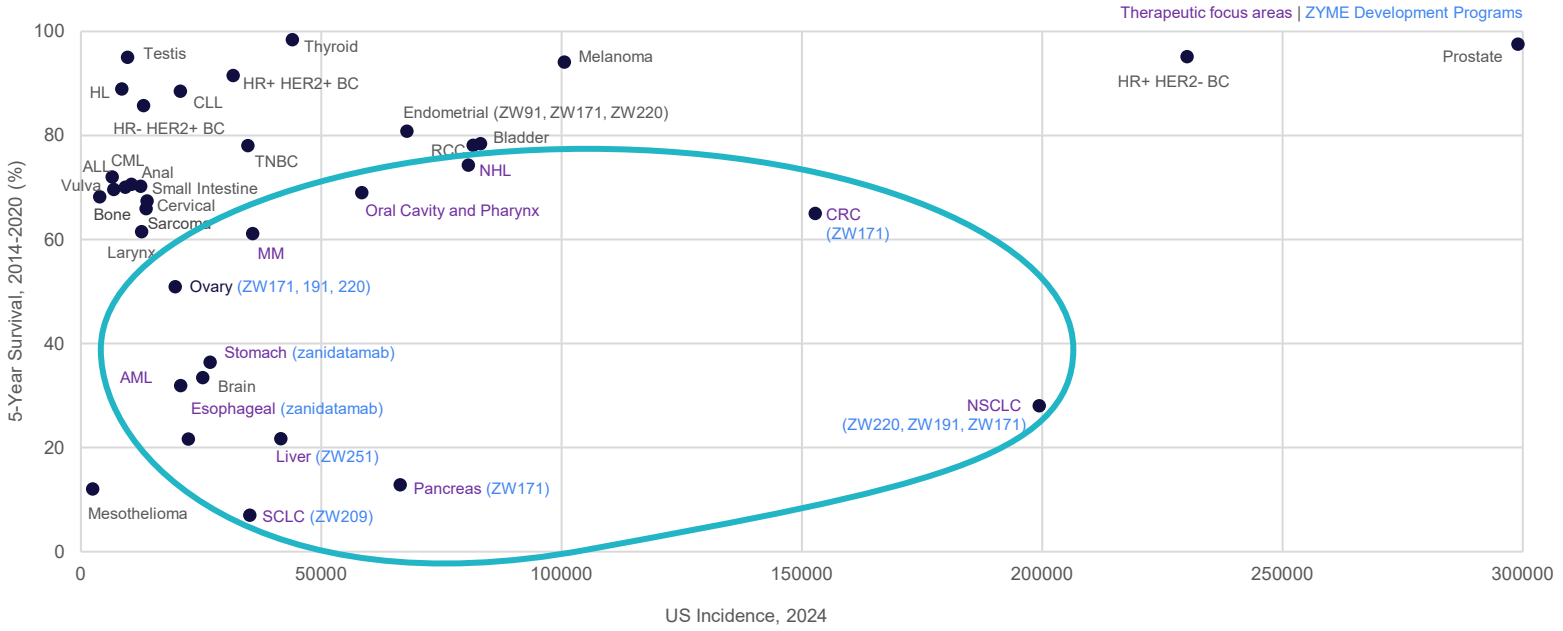
- Muti-specific T Cell Engagers
- Multi-antigen targeting
- Conditional activation
- Novel targets (e.g. proteomics)
- Intracellular antigens

Cytokine Engineering

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

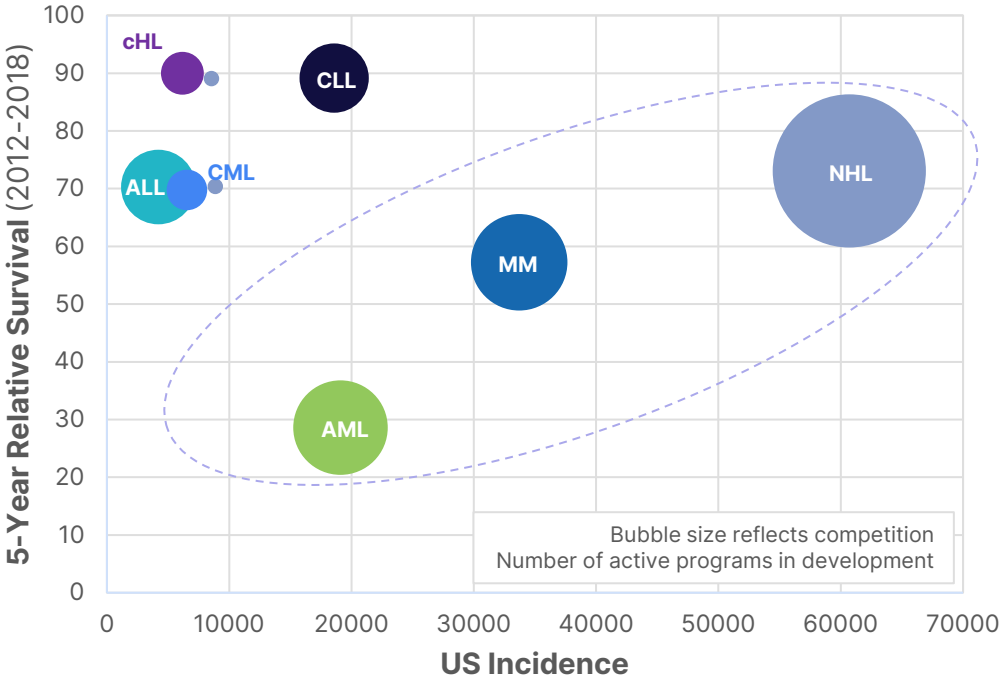
MoA: mechanism of action.

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: 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

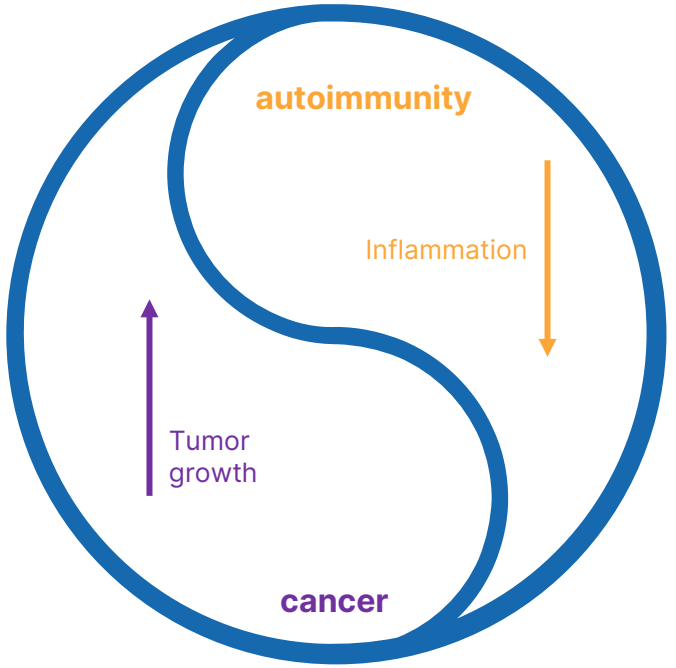


- Despite good outcomes for some, many patients with common blood cancers are not cured by frontline therapies. Patients with refractory or multi-drug resistant disease need more effective therapies.
- Outcomes for patients with AML are especially poor.
- ADCs and TCEs have proven to be important therapeutic 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%ç√ç

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-4Rα x IL-33 Bispecific Blocker for COPD

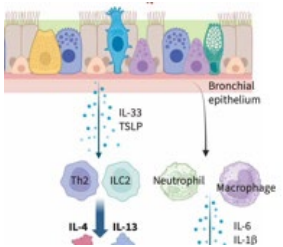
Alex Berezhnoy, PhD
Director, Immunology

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

zymeworks

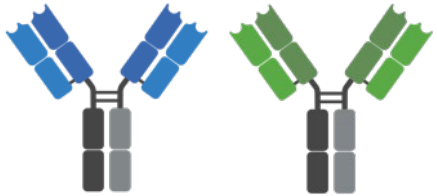
Patients

+ 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



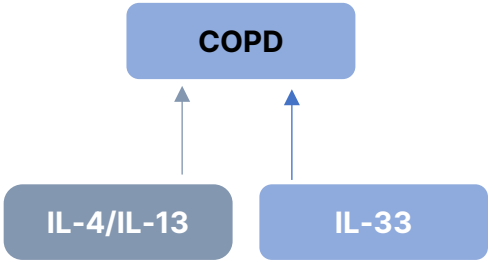
Technology

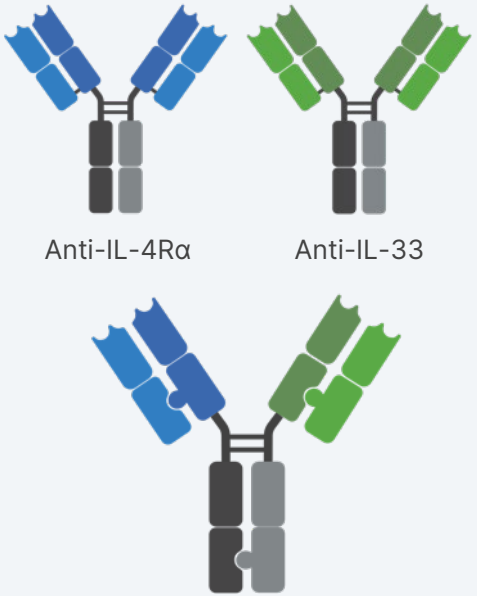
+ Clinically validated platform
+ Compatibility with Fc modifications (HLE)
+ High efficacy, convenient, cost-effective solution

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-4Rα as an Anchor Arm

- Dupixent®/dupilumab is a highly successful mAb targeting IL-4Rα
  - Approved for multiple atopic and inflammatory diseases
  - Generated revenues >$11Bn in 2023
- Blocking IL-4Rα 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**

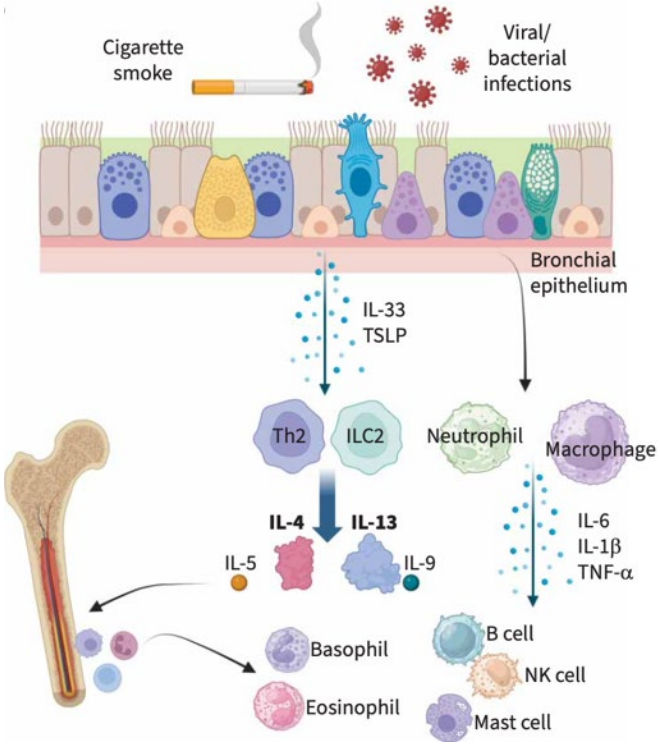




- Aim at complete, prolonged blockade of IL-4Rα
- Utilize potential advantages of local retention
- Take advantage of IgG-like geometry (PK, CMC)

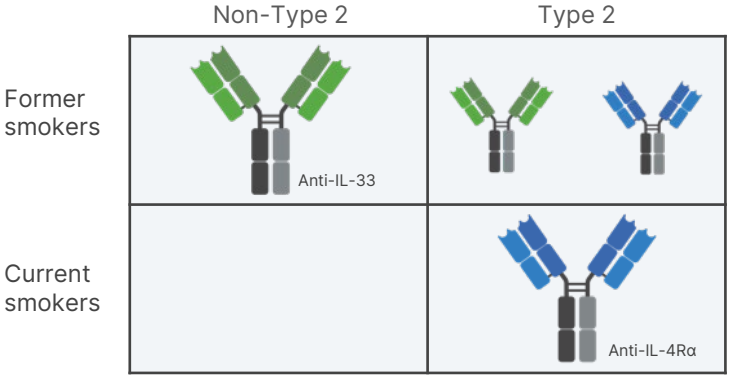
IL-33 as a Bispecific Arm for COPD and Other Respiratory Diseases

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

Anti-IL4Rα (Dupixent®) and anti-IL-33 (itepekimab) are being developed to treat different COPD populations

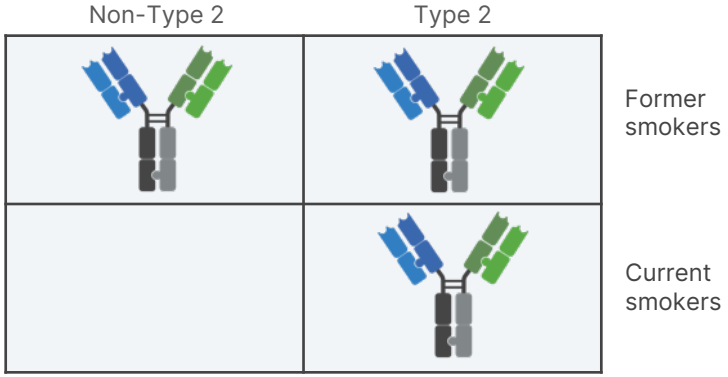


Anti-IL4Rα effective in Type 2 COPD (those with eosinophilia)

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

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

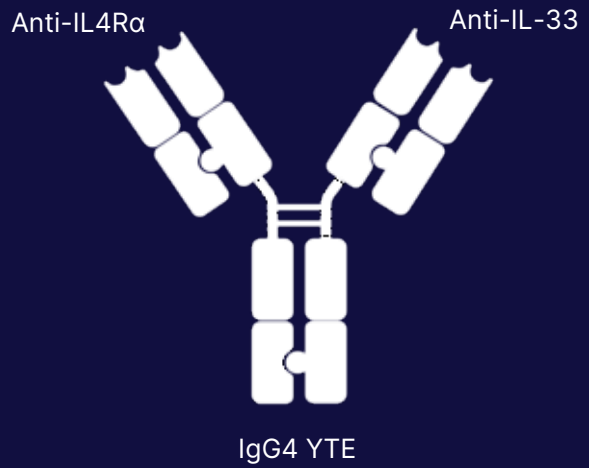
IL-4Rα x IL-33 bispecific provides opportunity to treat broader set of COPD patients with single molecule



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

Potential for increased efficacy in monotherapy-responsive patients

Diagrams taken from Sanofi R&D day presentation 2023



ZW1528
IL-4Rα x IL-33 Bispecific

Inhibits multiple pathways within complex pathophysiology of inflammation

Design

- In-house antibody discovery of novel anti-IL4Rα 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-4Rα blockade. Second arm adds inhibition of IL-33 - an upstream cytokine involved in perpetuating chronic inflammation.

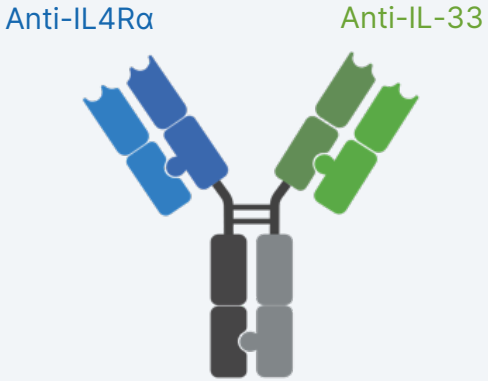
Mechanism

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

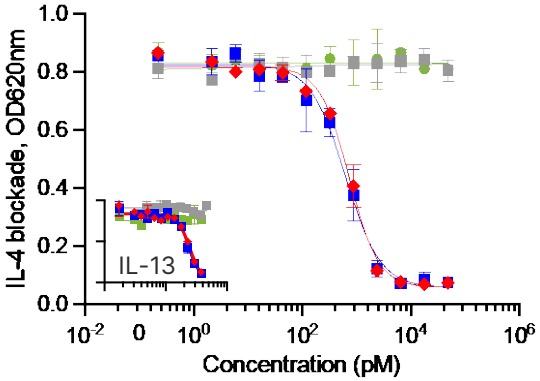
Profile

ZW1528 potently blocks of two complementary pathways of respiratory inflammation

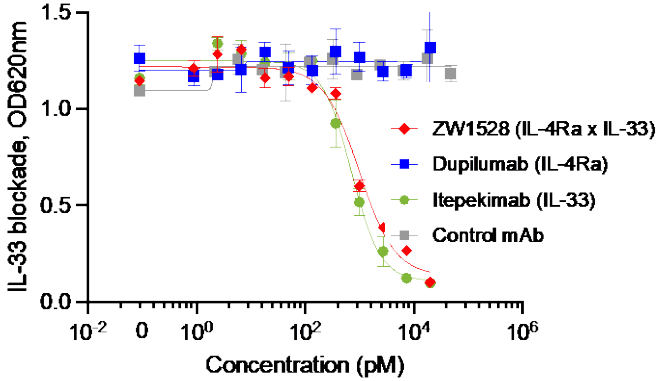
ZW1528 Effectively Blocks of IL-4/13 and IL-33 Signaling



Blockade of IL-4/13



Blockade of IL-33



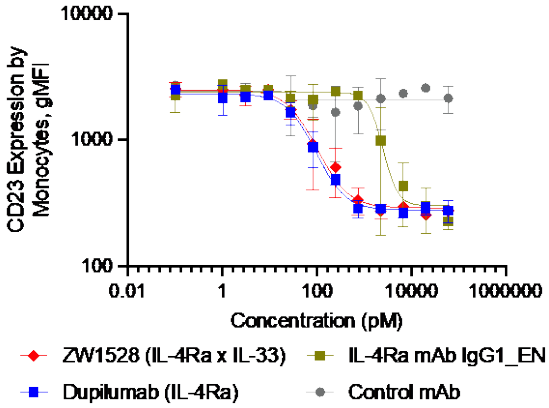
- Potency of ZW1528 similar to (bivalent) benchmark mAbs
- ZW1528 blocks both targets

Molecules generated by Zymeworks from published sequences

ZW1528 Exhibits Favorable *In Vitro* Potency in Primary Cells

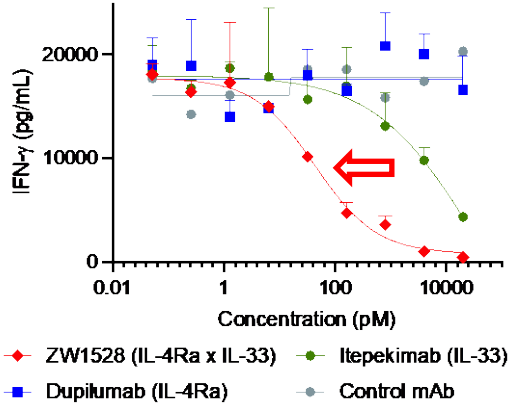
Anti-IL4Rα Anti-IL-33

Blockade of IL-4-driven Monocyte activation



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

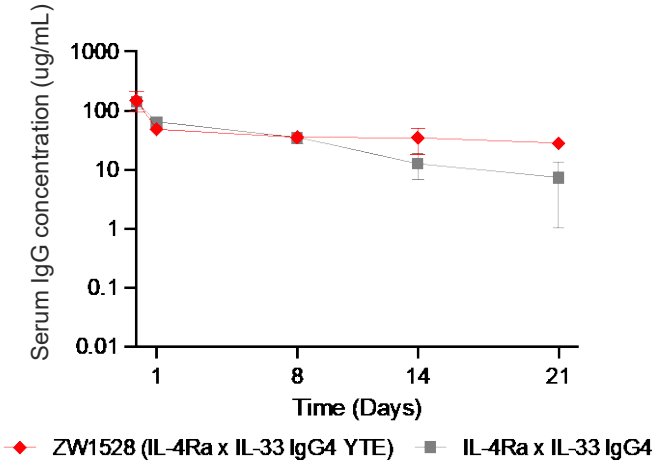
Blockade of IL-33 induced IFN-γ secretion in PBMCs



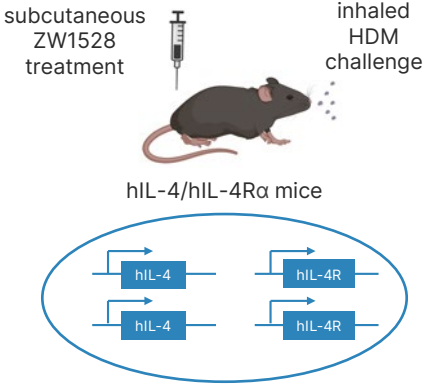
Superior potency vs Itepekimab in PBMC (blocking IFN-γ)

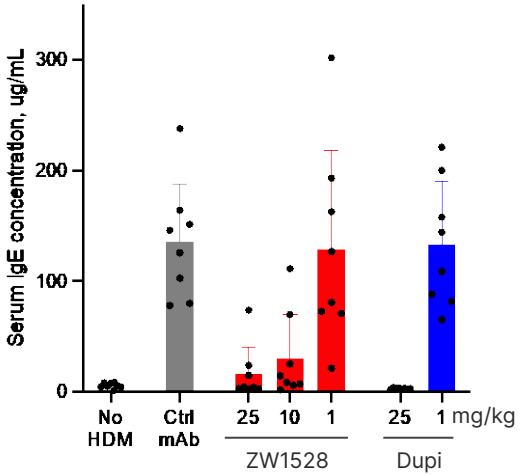
ZW1528 Demonstrate IgG-like PK and Block IL-4Rα *In Vivo*

IgG-like PK (Tg32 mice)



Suppression of IgE after inhaled allergen challenge



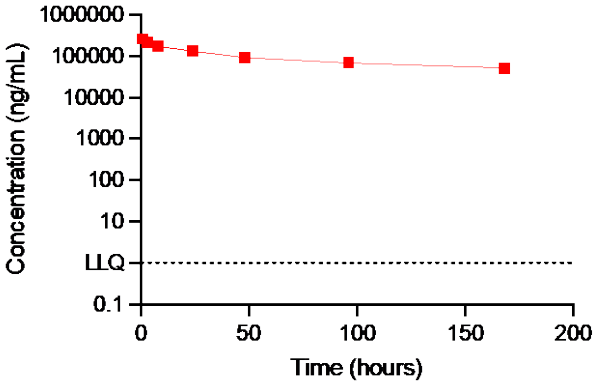


- IgG-like pharmacokinetics
- Suppression of IgE after inhaled allergen challenge

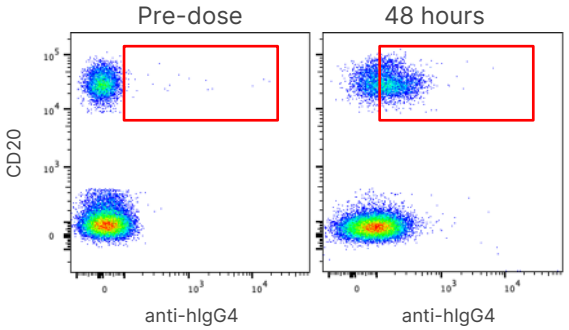
Left: PK in Tg32 mice after 5 mg/kg i.v. administration
Right: Challenge with house dust mite (HDM) inhalation

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

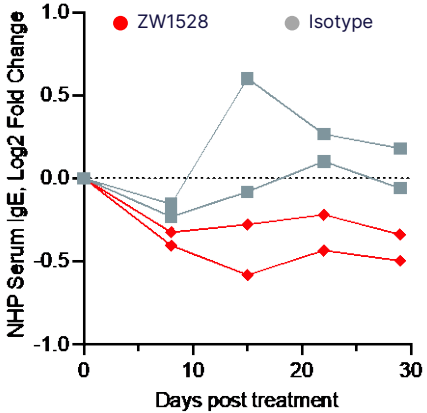
Pharmacokinetics



IL-4Rα Receptor Occupancy



Reduction of Serum IgE

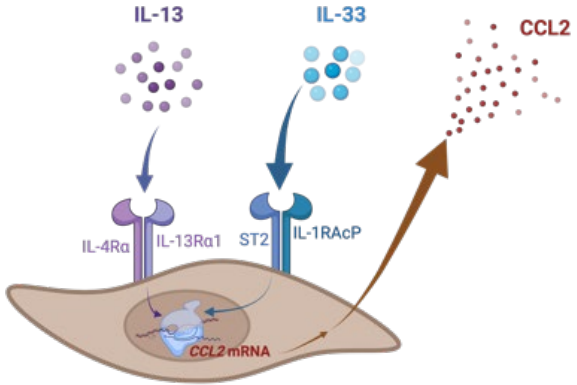


- IgG-like pharmacokinetics in non-human primates (NHP)
- Biomarkers of IL-4Rα/IL-33 blockade up to **6 weeks** after single administration

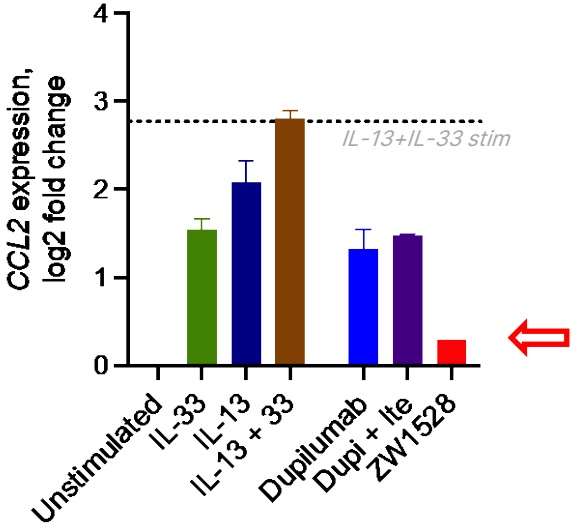
Cynomolgus monkey (N=2) were dosed with ZW1528 i.v. at 10 mg/kg

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

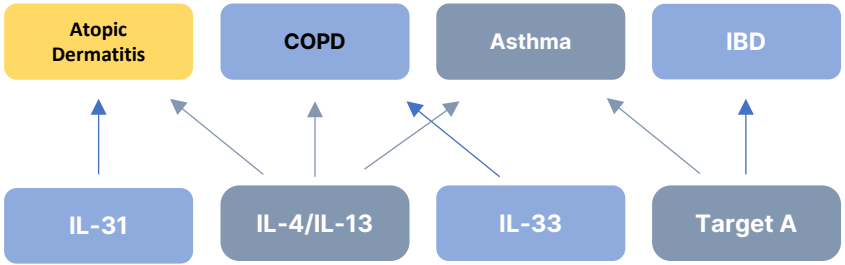


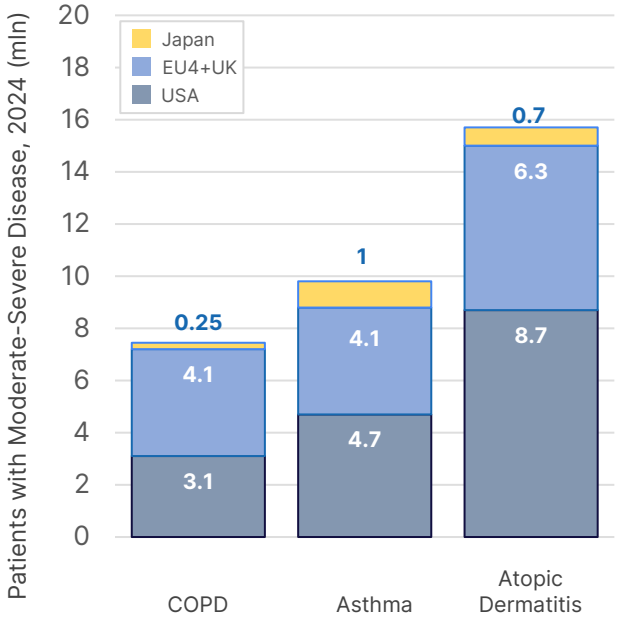
- IL-13 and IL-33 treatment induces disease-relevant genes in keratinocytes
- ZW1528-mediated blockade is superior to dupilumab, itepekimab and the combination of two antibodies

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.

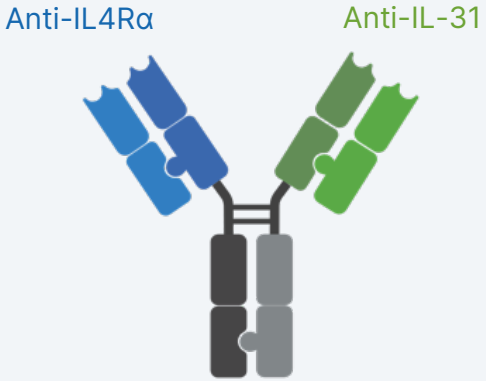
Expansion to AIID: Broadens Portfolio using Validated IL-4Rα Blocker

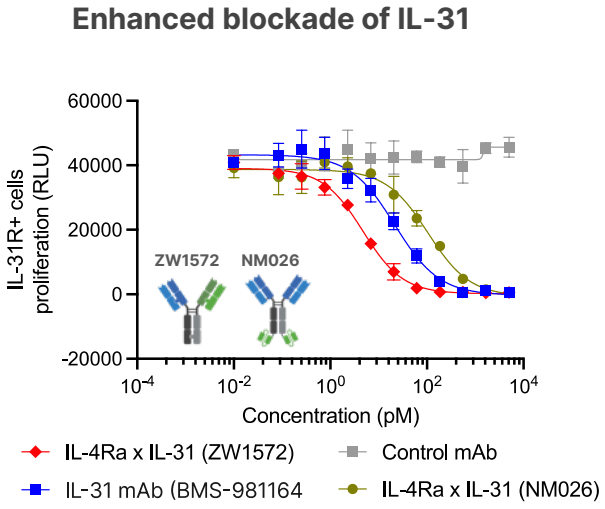
Program	Target Pair	Target Validation
ZW1528 (IND-enab)	IL4Rα x IL-33	Anti-IL4Rα approved in COPD Anti-IL-33 in pivotal COPD phase 3 studies
ZW1572 (Candidate nomination)	IL4Rα x IL-31	Anti-IL4Rα approved in Atopic Dermatitis Anti IL-31 validated clinically for itch control
Next gen (ADVANCE)	IL4Rα x Target A	Anti-IL4Rα approved in Asthma Target A efficacious in multiple AIIDs



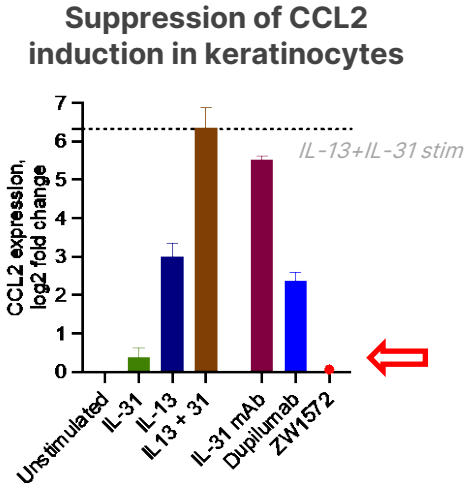


ZW1572: Bispecific Inhibitor of IL-4Rα and IL-31 for Atopic Dermatitis





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



Superior potency vs. individual mAbs in primary cells

Summary: ZW1528, an IL-4Rα 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-4Rα and inhibition of (non-Th2) IL-33-driven inflammation
- Favourable PK profile and biomarkers of IL-4Rα/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-4Rα and/or IL-33 role
- Spearhead development of other Zyme AIID therapeutics

ADVANCE PROGRAM

Next Generation Technologies

ADVANCE PROGRAM

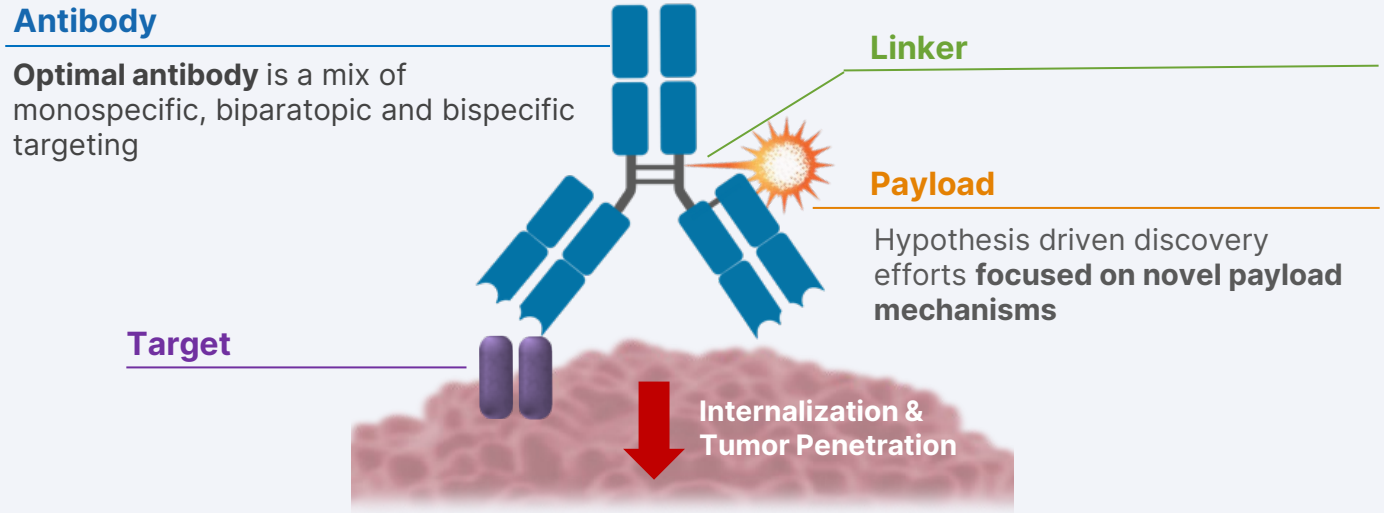
Antibody-Drug Conjugate Technologies

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



ADVANCE ADCs will support our 2027+ IND pipeline

Therapeutic Applications

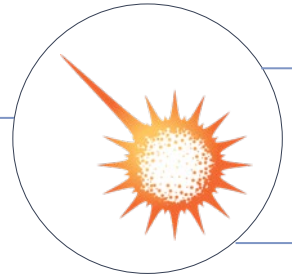
- Solid Tumors: current focus GI tumors including CRC, PDAC, esophageal, HNSCC
- Heme Onc: current focus AML

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

Novel Payloads to Help Drive Innovation in the ADVANCE ADC Portfolio

40 years of ADC payloads:[1]

Imperative: novel payload discovery for next-gen ADCs



Payload mechanisms tailored to Zymeworks' **priority indications**

Emphasis on **drug-like properties** of payloads

Challenging nature of ADC Platform development necessitates multiple approaches

Cytotoxic ADCs

\+ Validated approach
\+ Broad utility
– Normal tissue toxicity

Conditionally Cytotoxic ADCs

\+ Reduced normal tissue tox
\+ Built in patient biomarker
– Restricted patient group

Protein Degradation

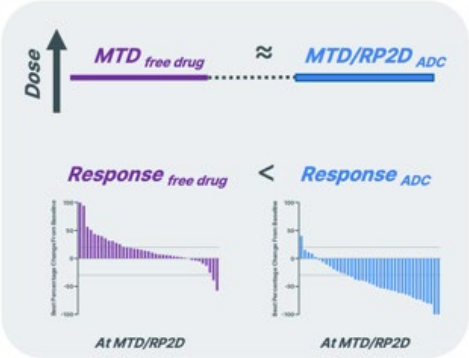
\+ New and existing targets
\+ Potential tissue selectivity
– Limited validation
– Restricted patient group

1. R. Colombo et al, Cancer Discov 2024, 14(11):2089–2108.

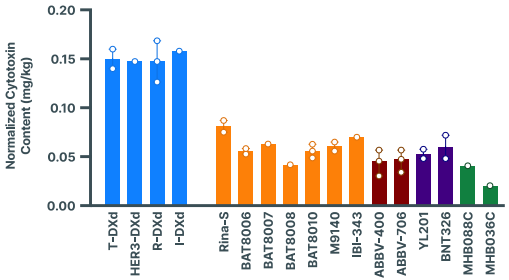
Our Hypothesis on ADC Mechanism Guides our Approach to Novel Payload Discovery

zymeworks

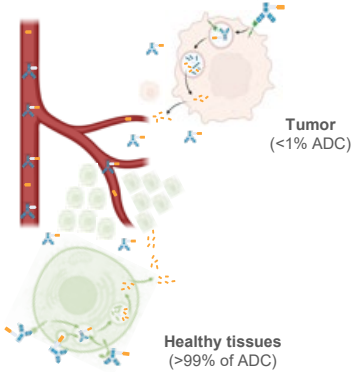
1 Conjugation does not improve payload MTD[1]



2 More potent payloads limit protein dose[2]



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 TOPO1i 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 Degrader Conjugates**

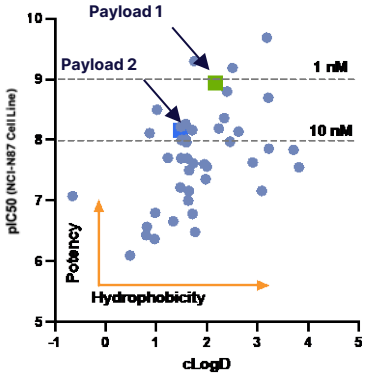
Degrader antibody conjugate modality holds significant promise across diverse diseases

Interest in AML, PDAC, and CRC targets

Protein Synthesis Inhibitor ADCs Demonstrate Preclinical Promise

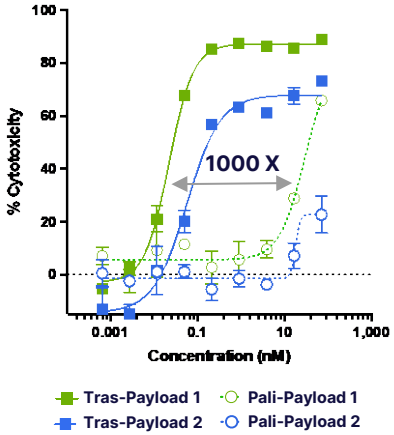
- Targeting a pathway critical to cancer cell growth enables potential first in class ADC opportunity
- Optimized ADCs demonstrate potency, selectivity, strong anti-tumor activity, and promising rodent tolerability
- Evaluation in target indications is ongoing (H&N, PDAC, CRC); planned non-human primate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

Payload Optimization



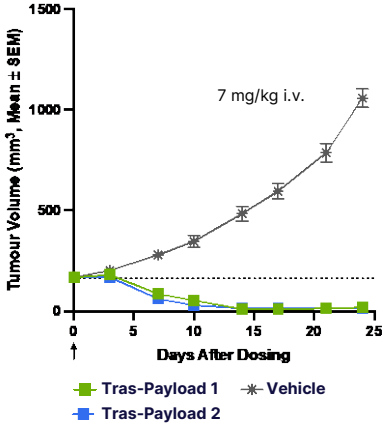
In Vitro Potency & Selectivity

SK-BR-3 Breast Adenocarcinoma Cell Line



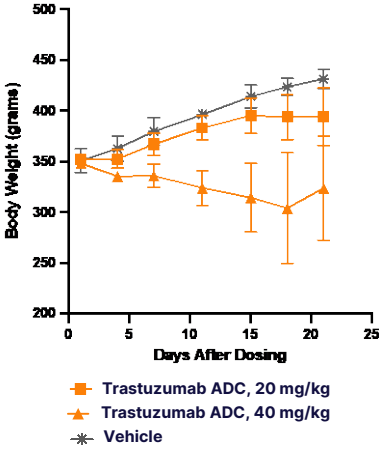
In Vivo Anti-tumor Activity

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

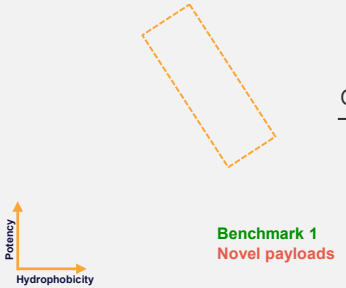
- First in class ADC opportunity with cytotoxic mechanism that is well validated in our priority indications
- ADC approach may improve on small molecule drugs via increased exposure, efficacy, and tolerability
- Currently evaluating in vivo efficacy

ADCs are potent and selective in vitro

H358 Lung Adenocarcinoma Cell Line

Payload analogues retain potency

H358 Lung Adenocarcinoma Cell Line

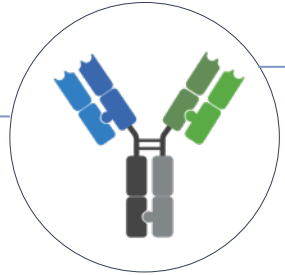


Novel payload ADCs retain potency

H358 Lung Adenocarcinoma Cell Line

Multi-Pronged Approach to Antibody Discovery:
Seeking Optimal Antibodies for Development of Differentiated ADCs

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



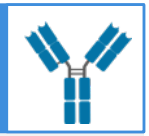
Modular discovery platform for maximum flexibility

Animal	Discovery Technology	Characterization	Developability	Engineering
Use of **wildtype** and **transgenic animal** platforms for maximum diversity	Use of **internal** B-cell culture & **external** antibody discovery technologies	Robust, high throughput screening to evaluate optimal **ADC properties**	Comprehensive **evaluation of developability risks** early in discovery process	**Optimized format**

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

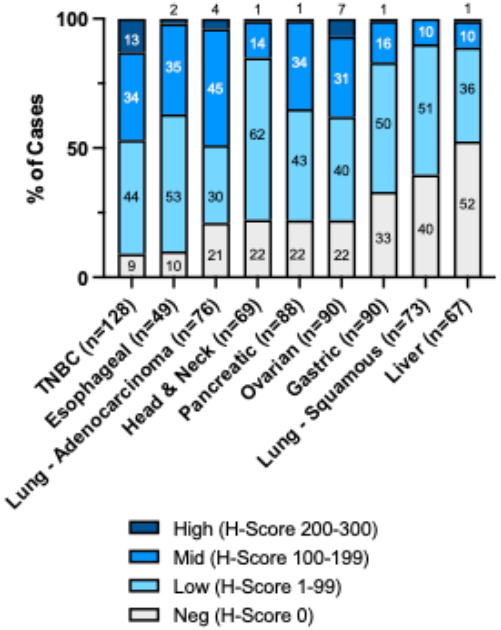
Binds to two distinct targets

- 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

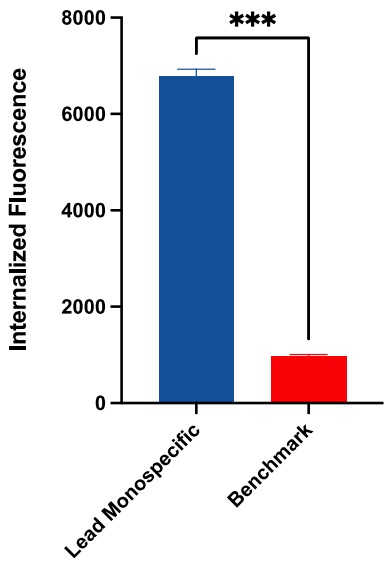
Monospecific Targeting: ADVANCE Solid Tumor ADC#1

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

Prevalent Target Expression

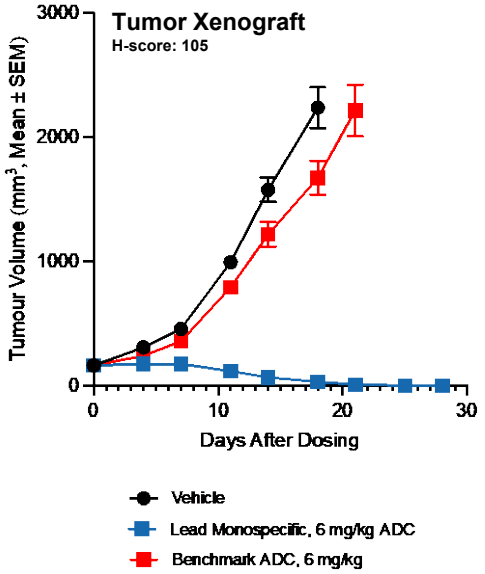


~7x Better Internalization



* p-value<0.001 – Unpaired t-test

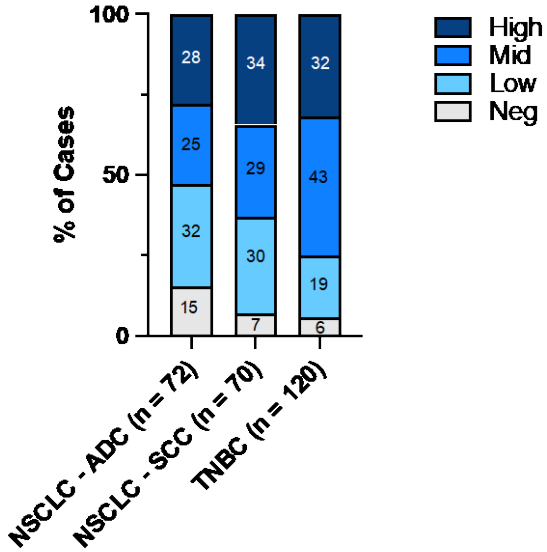
Superior Anti-tumor Activity



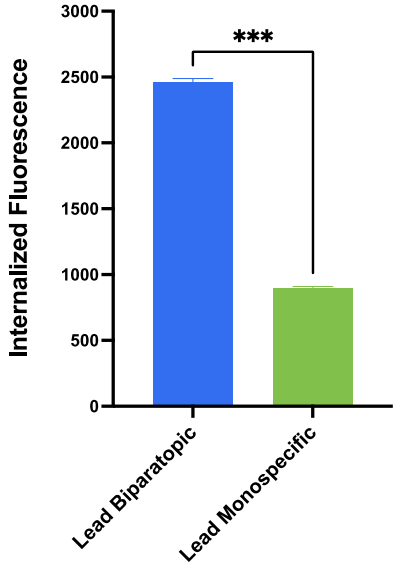
Biparatopic Targeting: ADVANCE Solid Tumor ADC#2

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

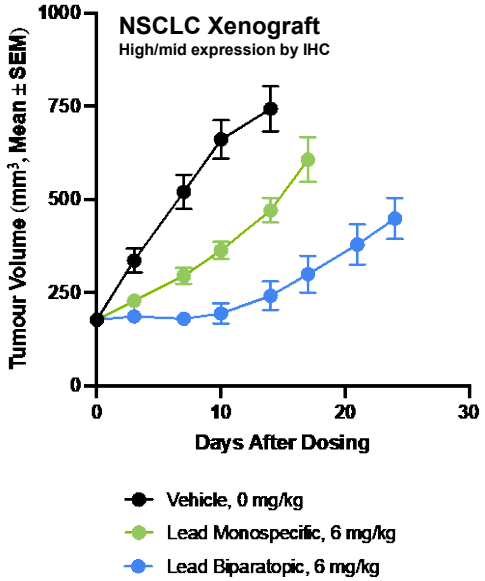


~3x Better Internalization



*** p-value<0.001 – Unpaired t-test

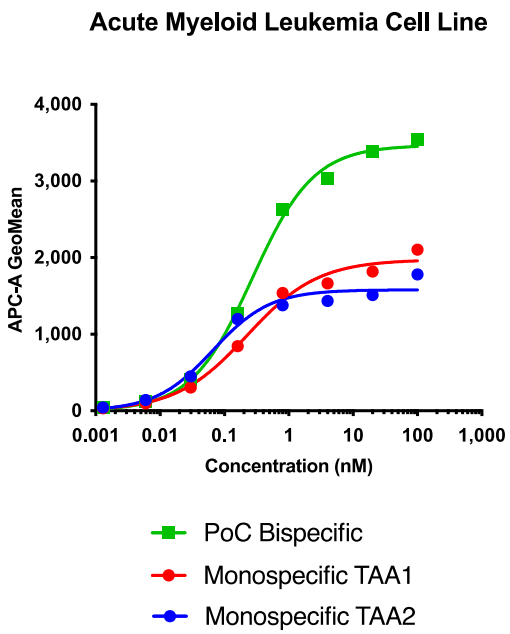
Superior Anti-Tumor Activity



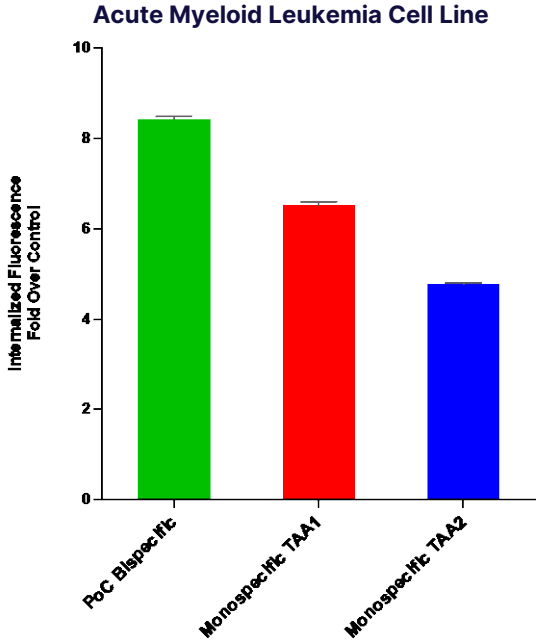
Bispecific Targeting: ADVANCE AML ADC

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

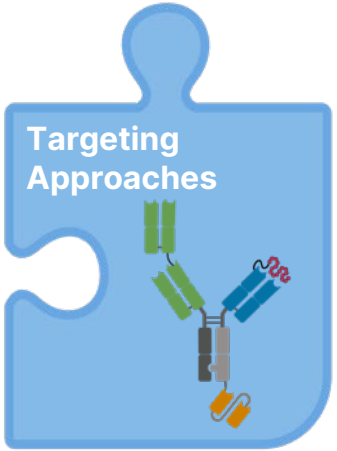
Tailored Designs

Applying flexibility of Azymetric™ to screen multiple antibody formats

Enhanced Functionality

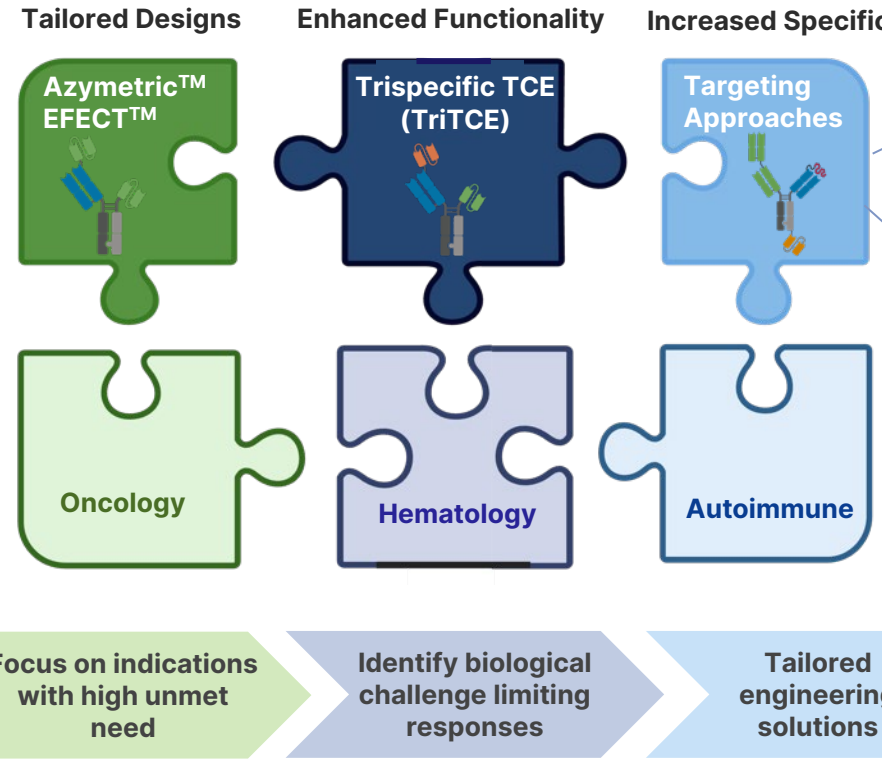
Enhance anti-tumor activity and T cell responses (e.g. TriTCE Co-stim)

Increased Specificity



Increase tumor targeting and activity within the TME

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



Targeting Selectivity
- 2+1 formats
- Novel targets (proteomics)
- Multi-antigen targeting
- Intracellular targets

Conditional Activation
- Conditional masking with proprietary cleavage sequence

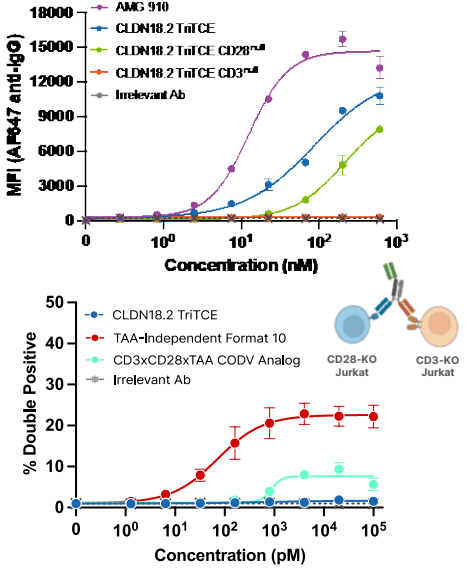
ZW239: CLDN18.2 Targeted TriTCE Co-stim to Help Improve Depth and Durability of Responses in CLDN18.2 Expressing Tumors

Focus indication of high unmet need
Gastric and Pancreatic

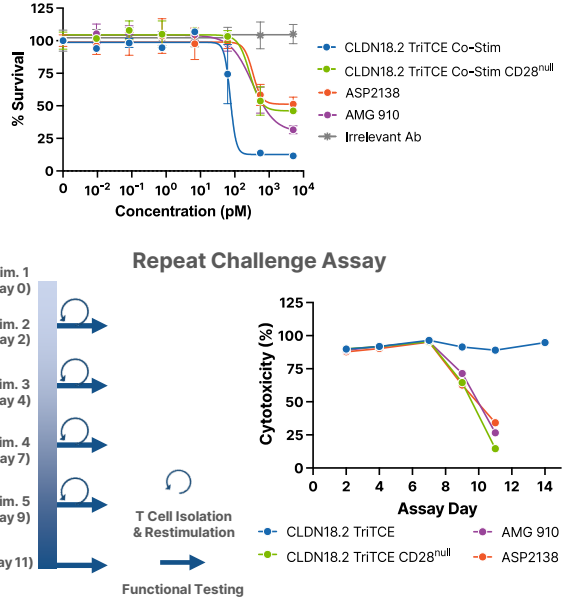
Biological challenge limiting responses
Low T cell Infiltration and T cell Dysfunction

Tailored engineering solutions
CLDN18.2 TriTCE Co-stim

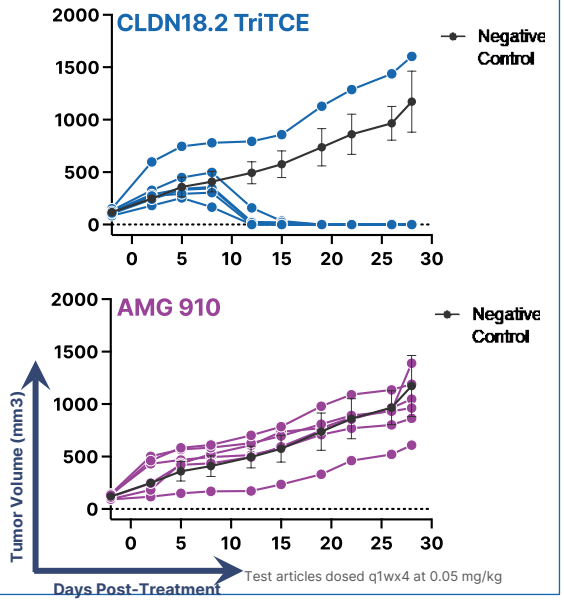
Conditional Binding of CD28, Requiring Co-engagement of CD3; Obligate cis Binding



Improved and Sustained Cytotoxicity over Bispecific TCE



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

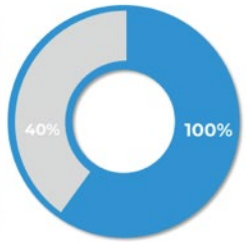
Tailored engineering solutions
Novel Target TriTCE Co-Stim

Multi-indication TriTCE Co-stim to novel target

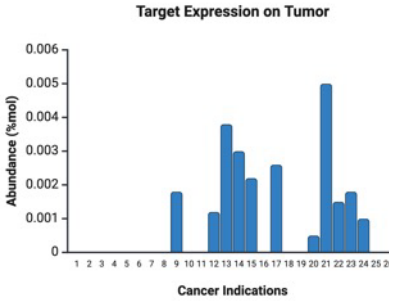
Novel proteomic approach[1] used to identify **unique membranous tumor-specific targets** with ideal TCE target profile

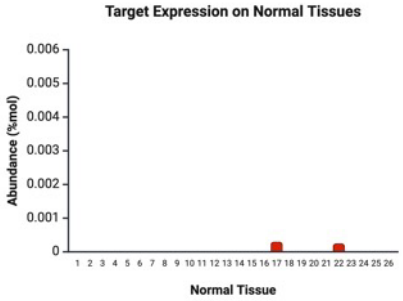
- No/minimal normal tissue expression
- Supportive biology and expression profile
- **Novel target** with **multi-indication potential**

- × **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**





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

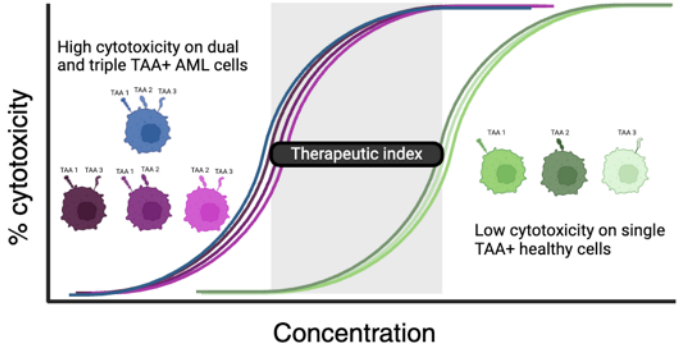
Focus indication of high unmet need
AML

Biological challenge limiting responses
Healthy Tissue Expression, Antigen Escape & T cell Dysfunction

Tailored engineering solutions
Multi-targeted Co-Stim

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^+)

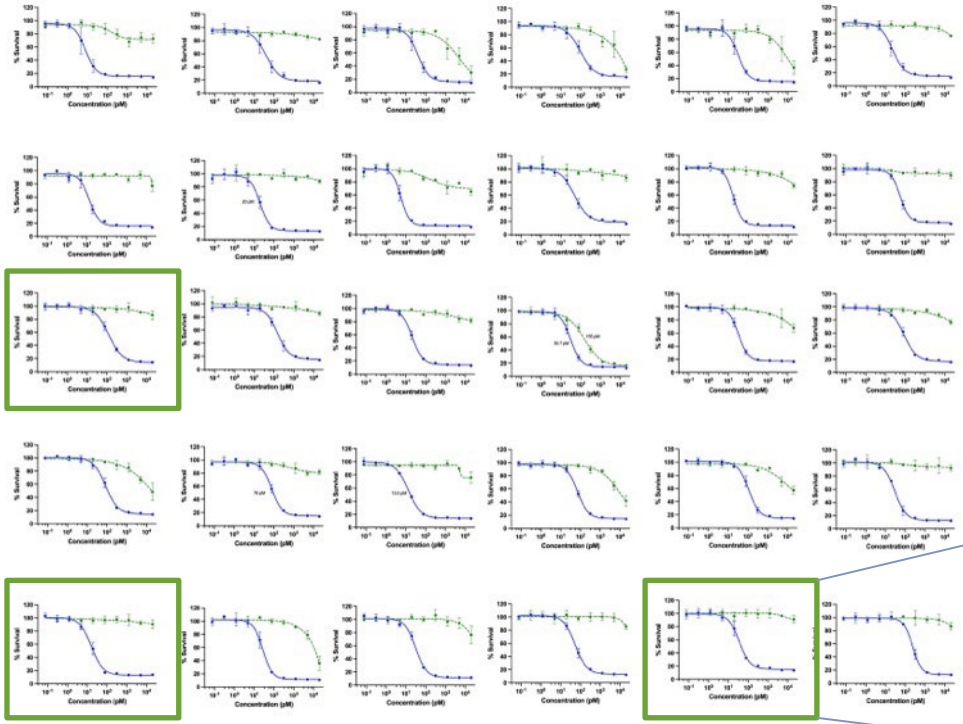
TAA 2^+

Triple positive cell

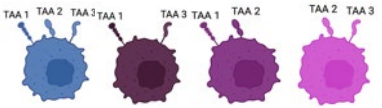
TAA 1 TAA 2 TAA 3

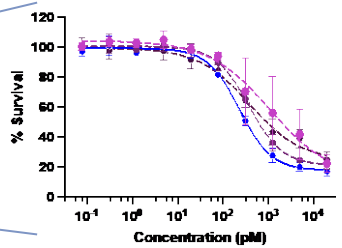
Single positive cell

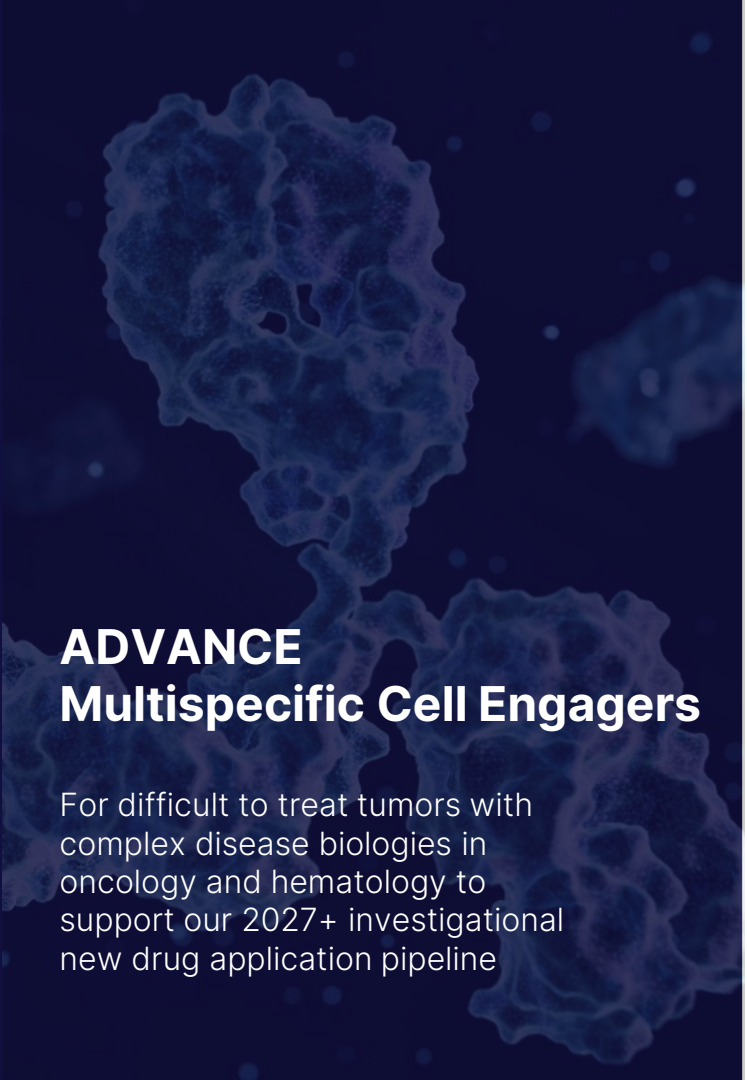
TAA 2



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

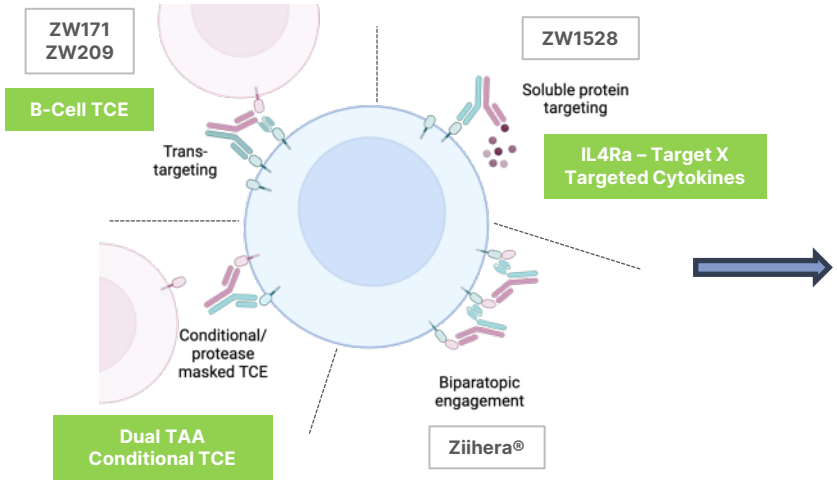
Driving the Forefront of Next Generation T cell Engagers

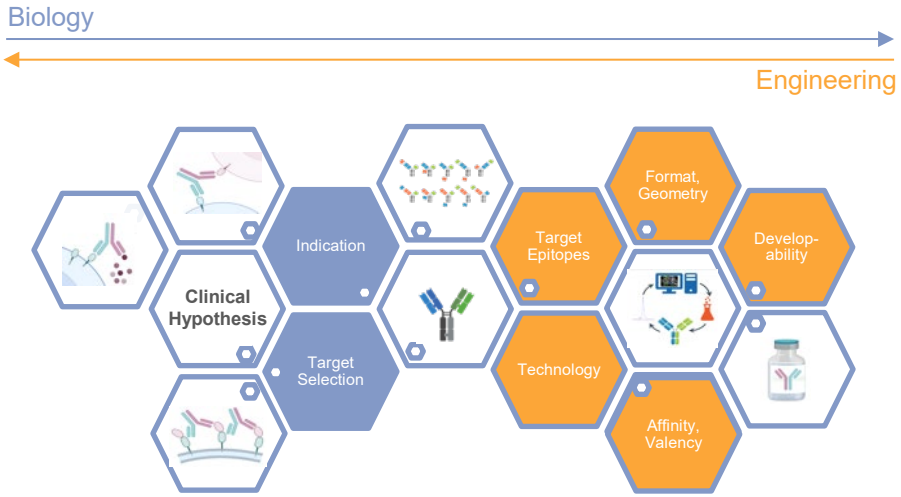
- Enhancing functionality and specificity to drive deep and durable responses in difficult to treat tumors
- Plug and play platforms enable fast development to rapidly address patient need

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





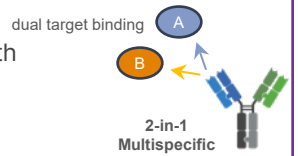
Integration of AI/ML with Azymetric™ Engineering Expertise Enables Novel Technology Driven Drug Development

Accelerating Multispecific Discovery

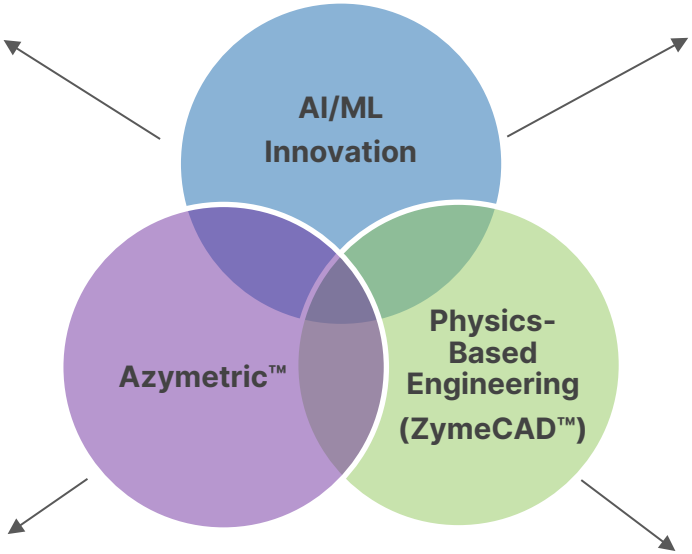
Accelerating multispecific discovery through "Lab in loop" Azymetric™ HTP workflow

2-in-1 Antibody Engineering

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



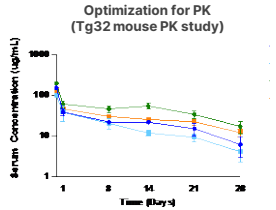
Opportunities for Combining AI/ML with Multispecific Engineering Expertise



Multi-parameter Antibody Optimization

Enhanced Multispecific Engineering

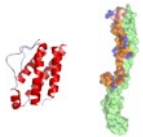
- Multifactorial optimization for affinity, stability, developability
- Engineering for improved PK and s.c. formulation



Cytokine and Receptor Engineering

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

Difficult targets
(low stability, manufacturability)

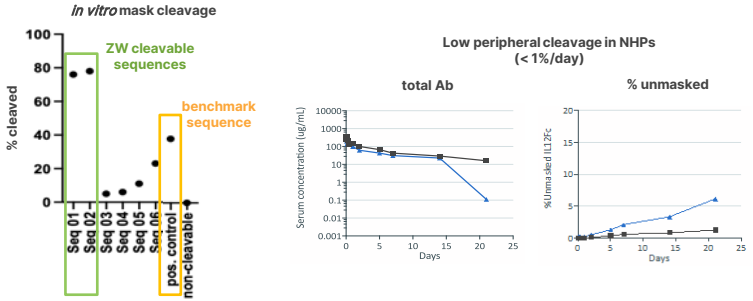


Next Gen Technologies: Conditional Masking Technologies

- 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

Proprietary Protease Cleavable Sequences

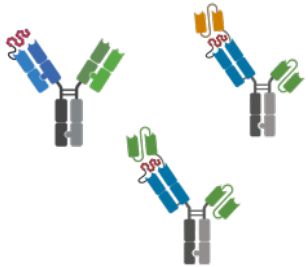
- Highly efficient cleavage compared to benchmark
- Low peripheral cleavage in non-human primates
- Tested in different preclinical programs



Conditionally Masked TCE and TriTCE

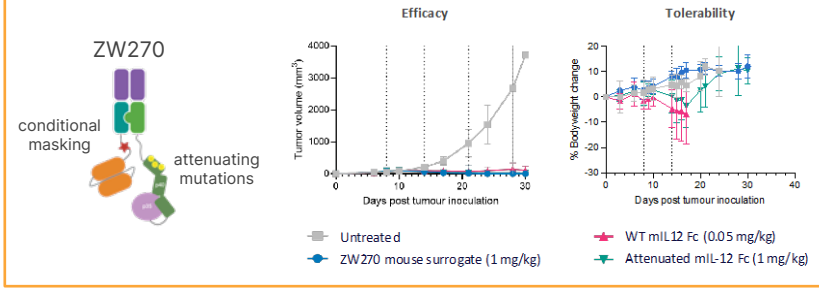
Expanding target space for TCE and TriTCE portfolio

Potential to combine with 2+1 and CD3 engineering



Conditionally Masked Cytokines

Novel approach of conditionally masked, attenuated IL-12



Next Gen Technologies: Novel Engineering for Autoimmune and Inflammatory Indications

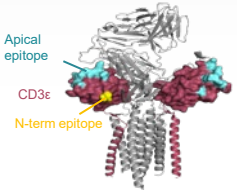
T Cell Engager Engineering for AIID

Significant opportunity for enhanced B cell depleting therapies for AIID

Critical engineering for high activity with reduced cytokine release syndrome potential

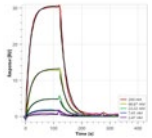
ZW has panel of anti-CD3 binders with fast Kon/off and different epitopes to fine tune activity

CD3ε structure with structural and non-structural epitopes

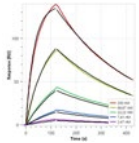


Name	Epitope	k_{on} (1/Ms)	k_{off} (1/s)	K_d (nM)
ZW1	Epitope 1	1.38E+05	3.12E-03	22.7
ZW2	Epitope 2	5.20E+05	4.08E-03	7.84
ZW3	Epitope 1	1.62E+05	1.10E-02	68.3
ZW4	Epitope 2	1.45E+05	1.26E-02	87.1
ZW6	Epitope 1	1.59E+05	2.54E-02	159.9

ZW fast Kon/off CD3



Benchmark CD3

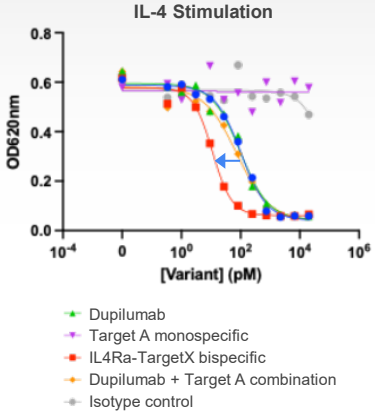


Novel Bispecific Cytokine Antagonists

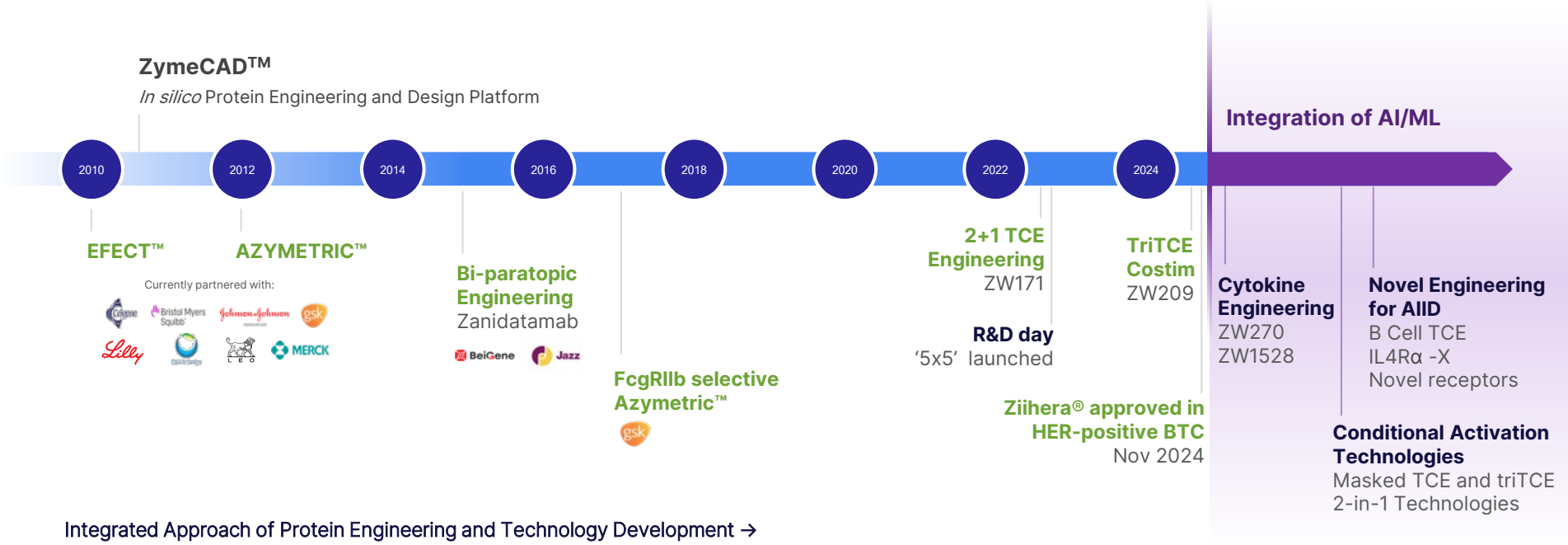
Additional IL4Rα-X bispecific cytokine antagonists

Engineering for optimized PK

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



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



Integrated Approach of Protein Engineering and Technology Development →

RESEARCH & DEVELOPMENT DAY

R&D Strategy Summary: 2025-2027

Kenneth Galbraith
Chair and CEO

R&D Strategy Summary for 2025-2027

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

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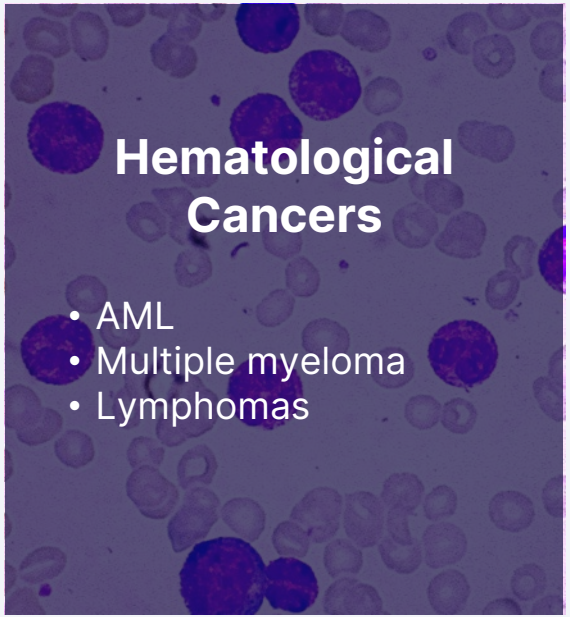

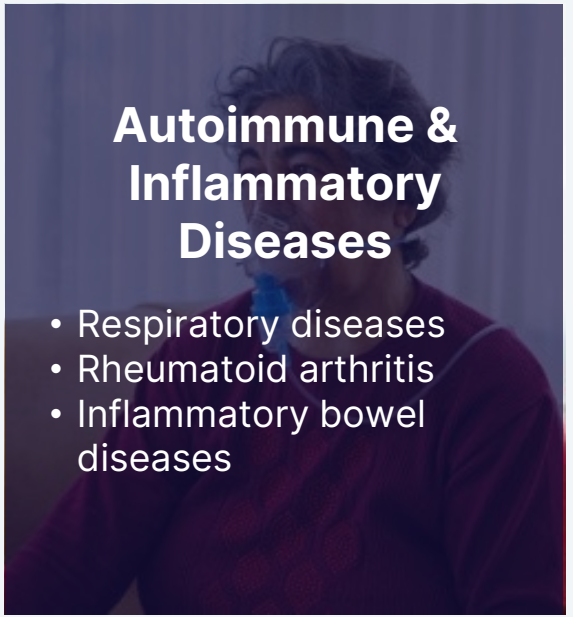

R&D Organization

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

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

Strong Balance Sheet to Support Meaningful Catalysts in R&D Portfolio

Current Financial Status:

- Cash resources[1] 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

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

[1]cash, cash equivalents, and marketable securities

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	FRα	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	IL4Rα x IL-33				IND 2H 2026		
ZW1572 Dual Cytokine Blocker	Azymetric™ Hetero-Fab | YTE	IL4Rα x IL-31						

Meaningful Catalysts Expected Throughout 2025 & 2026

PIPELINE EVENTS

1H 2025

- 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

2H 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

2026

- 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 RUNWAY[1] 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 additional 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


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