



Making a Meaningful Difference

On a mission to improve the standard of care for difficult-to-treat diseases

Investor and Analyst Presentation

APRIL 2024

Nasdaq: ZYME | zymeworks.com

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Zymeworks: A Differentiated Product Pipeline Built on Unique Capabilities in Antibody Engineering and Medicinal Chemistry



Seeking to address unmet patient needs in HER2+ GI Cancers

zanidatamab

(HER2 bispecific antibody)

- Licensed to Jazz and BeiGene
- **BTC 2L**: completed rolling USA regulatory submission seeking accelerated approval
- **GEA 1L**: targeting pivotal Phase 3 top-line data readout in late 2024
- Additional ongoing and planned clinical studies beyond BTC and GEA

5 new INDs planned Focus on Gyn CA, Lung CA, & GI CA

- **ZW171 (IND 2024)**
MSLN x CD3 bispecific antibody
- **ZW191 (IND 2024)**
FR α TOPO1i ADC
- **ZW220 (IND 2025)**
NaPi2b TOPO1i ADC
- **ZW251 (IND 2025)**
GPC3 TOPO1i ADC
- **Candidate 5 TBD (IND 2026)**
Pre-clinical TriTCE candidate nomination expected in 2H 2024

Continuing to innovate and move beyond oncology

- Unique/differentiated platform to build nextgen **ADC's** and **TriTCE's**
- Therapeutic focus to be expanded into **autoimmune and inflammatory disease (AIID)**
- Research scope to potentially expand into multifunctional engineered cytokines and dual checkpoint inhibitors

**Expanding product pipeline with potential near-term approval and launch of zanidatamab.
Cash runway forecast into 2H 2027, with receipt of certain anticipated regulatory milestones.**

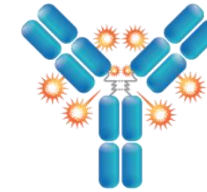
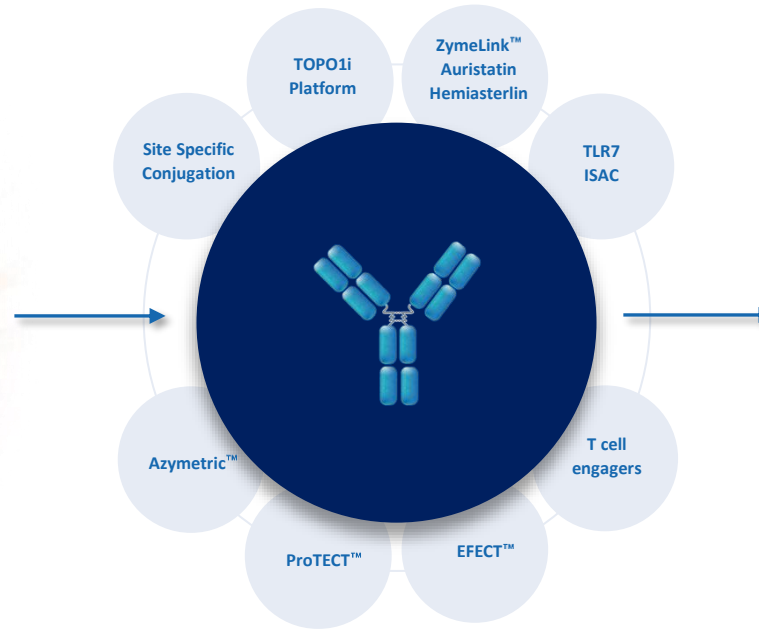
1L: first-line (treatment); 2L: second-line (treatment); ADC: antibody-drug conjugate; BTC: biliary tract cancers; CD3: cluster of differentiation 3 protein complex and T cell co-receptor; FR α : folate receptor alpha; GEA: gastroesophageal adenocarcinoma; GI CA: gastrointestinal cancer; GPC3: glypican-3; Gyn CA: gynecological cancer; HER2: human epidermal growth factor receptor 2; IND: investigational new drug (application); Lung CA: lung cancer; MSLN: mesothelin; NaPi2b: sodium-dependent phosphate transporter 2b; NSCLC: non-small cell lung cancer; TOPO1i: topoisomerase-1 inhibitor.

Unique Capabilities in Protein Engineering Provide Opportunity for Differentiated Pipeline of ADCs and Multispecific Antibodies

Select Difficult-to-Treat Cancers and Target

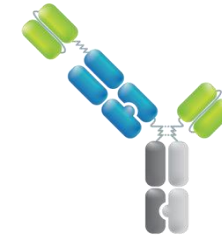
Design with Complementary Technology

Optionality with Two Foundational Fit-for-Purpose Modalities



Antibody Drug Conjugates
Customization:

- Antibody properties
- Antibody format
- Payload
- DAR



Multispecifics
Customization:

- Multiple MOA in a single molecule
- Synergistic biology
- Precision targeting through multivalency

5 New INDs expected by 2026

DAR: drug to antibody ratio; ISAC: immune stimulating antibody conjugate; MOA: mechanism of action; TLR7: toll-like receptor 7.

5x5 R&D Strategy: Diversified Portfolio Beyond Zanidatamab with Multiple Opportunities for Success

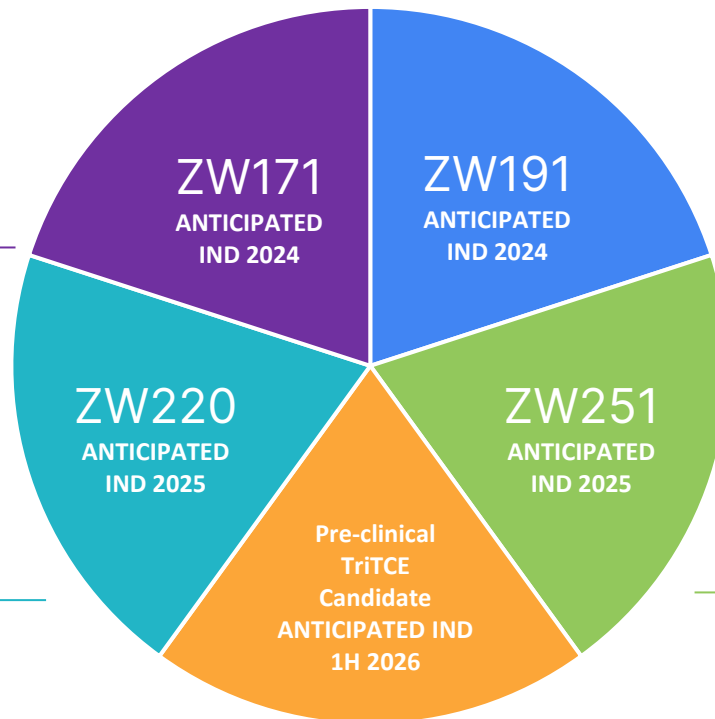


ZW171 (MSLN)

Bispecific T Cell Engager (2+1) targeting ovarian, NSCLC, and other mesothelin-expressing cancers

ZW220 (NaPi2b)

Antibody-Drug Conjugate targeting NaPi2b-expressing non-small cell lung cancer and ovarian cancer



ZW191 (FR α)

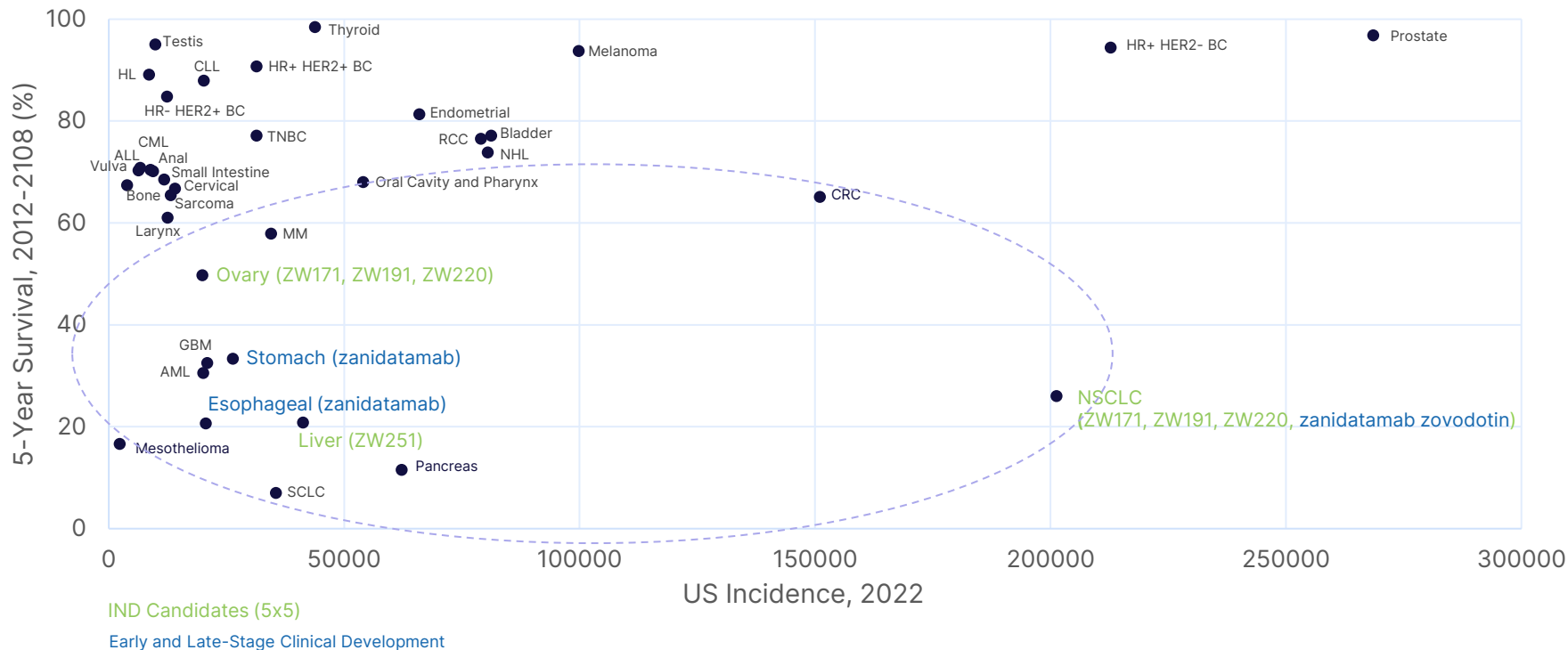
Antibody-Drug Conjugate targeting folate receptor alpha expressing tumors including ovarian, other gynecological, and non-small cell lung cancer

ZW251 (GPC3)

Antibody-Drug Conjugate targeting GPC3-expressing hepatocellular carcinoma

TriTCE: trispecific t cell engager.

R&D Focus on Cancers With Highest Unmet Medical Need



BC: breast cancer; CRC: colorectal cancer; SEER*Explorer, accessed 10 Oct 2022.

Extensive Expected News Flow over 2024 and 2025

1H 2024

2H 2024

2025

PIPELINE EVENTS

- Completion of rolling USA regulatory submission for zanidatamab seeking accelerated approval in 2L BTC
- Initiation of Phase 3 confirmatory trial for zanidatamab in 1L BTC
- Expected IND submission for first 5x5 candidate

- Pivotal Phase 3 top-line data readout in GEA 1L targeted in late 2024
- Expected BLA submission in China for zanidatamab in 2L BTC
- Expected initiation of Phase 3 trial for zanidatamab in Enhertu-experienced patients with HER2+ advanced BC
- Expected IND submission for second 5x5
- Nomination of 5th product candidate in 5x5

- Potential USA and China launch for zanidatamab in 2L BTC and initial royalty revenue from partners Jazz and BeiGene
- Expected IND submission for ZW220 (NaPi2b)
- Expected IND submission for ZW251 (GPC3)

PUBLICATIONS & CONFERENCES

- ASCO GI (January 18-20)
- JSMO (February 22-24)
- World ADC London (March 12-15)
- AACR (April 5-10)
- PEGS (May 13-17)

- ASCO (May 31-June 4)
- WCGQ (July 3-6)
- ESMO (September 13-17)
- EORTC-NCI-AACR (October 23-25)
- SITC (November 6-10)
- SABCS (December 10-14)

Manuscripts: Overview of ZD06519 (TOPO1i payload)

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; ESMO: European Society for Medical Oncology; JSMO: Japanese Society of Medical Oncology; PEGS: Protein Engineering Summit; SABCS: San Antonio Breast Cancer Symposium; SITC: Society for Immunotherapy of Cancer; World ADC: World Antibody Drug Conjugates Summit; WCGI: World Congress on Gastrointestinal Cancer.



Projected Cash Runway Supports R&D Priorities into 2H 2027

Current Financial Status:

- Cash resources¹ of approx. \$456.3M (as of December 31, 2023)
- Includes December 2023 private placement of \$50M to EcoR1 Capital
- Anticipated cash runway into 2H 2027, which includes certain anticipated regulatory milestones

Potential sources to extend cash runway into 2H 2027:

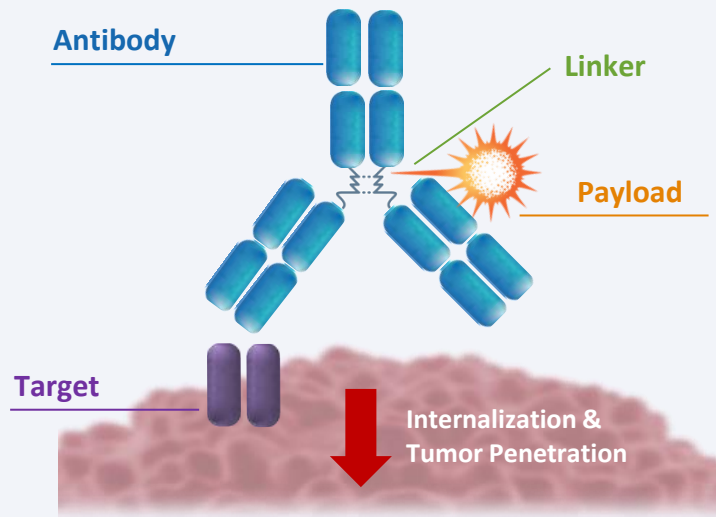
- Additional regulatory approval and commercial milestones for zanidatamab from Jazz and BeiGene
- Tiered royalties between 10-20% from Jazz and 10-19.5% from BeiGene sales (up to 20% when royalty reduction of 0.5% reaches cap in the low double-digit millions of dollars)
- Additional payments from legacy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

1. Cash resources consist of cash, cash equivalents, and marketable securities.

Antibody-Drug Conjugate (ADC) Program

Building Next-Generation ADCs

Core Competencies Utilized in Next-Generation ADC Design



- Focusing on **validated targets** provides opportunity for benchmarking in preclinical development and expected clinical differentiation; novelty of targets anticipated to increase over time
- Exploiting our **proprietary TOP01i payload (ZD06519)** while exploring alternate mechanisms of action for longer-term development
- Leveraging validated **peptide-cleavable linkers** and **stochastic conjugation**. New chemistries under development to complement novel payloads
- Optimizing **antibody properties** for the ADC mechanism, such as target-mediated binding and **enhanced internalization**. Biparatopic and bispecific ADC formats may also provide future differentiated therapeutics
- Utilize 3D cancer cell line spheroid models to select optimal ADC antibodies based on **tumor spheroid penetration and cytotoxicity**

Multiple proprietary topoisomerase I inhibitor ADCs^{1,2} **advancing towards the clinic**
with **broad investment in ADC technologies to support future programs**

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.



Commentary

The therapeutic window of antibody drug conjugates: A dogma in need of revision

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<https://doi.org/10.1016/j.ccell.2022.09.016>

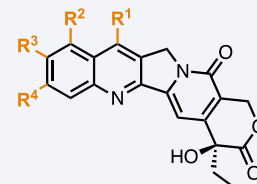
Despite a prevailing dogma wherein antibody drug conjugates (ADCs) increase the maximum tolerated dose of potent cytotoxin payloads while lowering the minimum effective dose, mounting clinical evidence argues that the tolerated doses of ADCs are not significantly different from those of related small molecules. Nonetheless, when dosed at or near the maximum tolerated dose, certain ADCs demonstrate improved efficacy. Understanding the challenges and opportunities for this class of biotherapeutics will help improve the design of next-generation ADCs.



Payload

Novel camptothecin with moderate potency and strong bystander activity

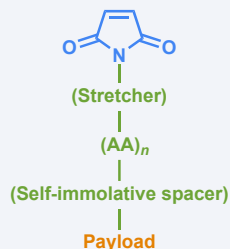
- Acknowledges complex mechanisms driving TOP01i ADC action
- Sufficient tolerability to achieve ADC dose > 5 mg/kg



Linker

Traceless, plasma-stable, cleavable peptide

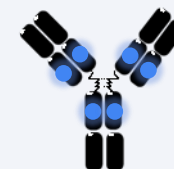
- Common to majority of approved ADCs
- Compatible with desired bystander activity
- Avoids highly stabilized linker-antibody conjugation to limit off target toxicities



Conjugation

Thiol-maleimide chemistry

- Stochastic conjugation utilized in all approved ADCs
- Facilitates DAR optimization
- Good balance of stability, safety, and anti-tumor activity



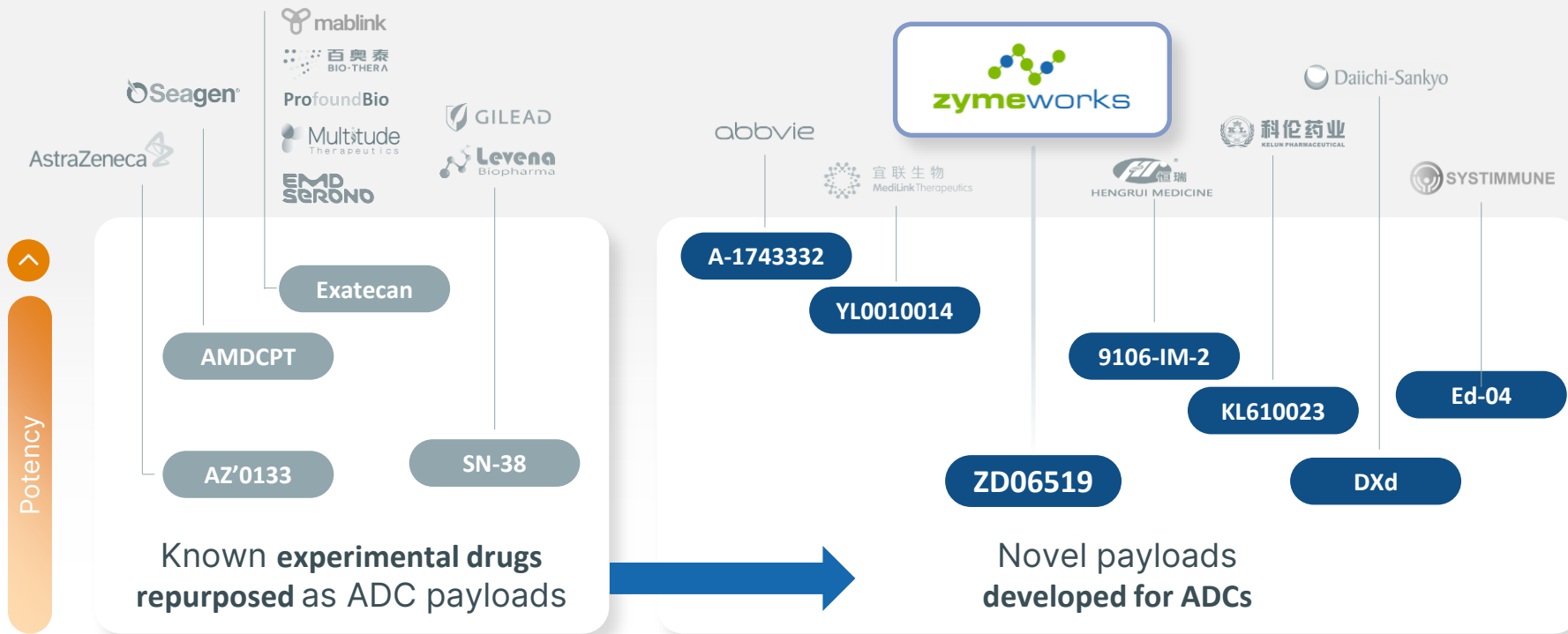
Differentiated Development of Antibody-Drug Conjugates

Designing next-generation antibody-drug conjugates on targets with evidence of clinical activity and addressing areas of unmet therapeutic potential

Program	Potential Indication	Target(s)	Payload	DAR (Range)	Preclinical	Phase 1	Phase 2	Pivotal	Collaboration Partners
ZW191	OVCA, other gynecological cancers, NSCLC	FRα	Topoisomerase I Inhibitor (ZD06519)	8		On track for IND filing in 2024			
ZW220	OVCA, NSCLC	NaPi2b	Topoisomerase I Inhibitor (ZD06519)	4		On track for IND filing in 2025			
ZW251	Hepatocellular carcinoma	GPC3	Topoisomerase I Inhibitor (ZD06519)	4		On track for IND filing in 2025			
Zanidatamab zovodotin	NSCLC	HER2	Auristatin (ZD02044)	2	NCT03821233				
XB002 (ICON-2)	Solid tumors	Tissue Factor	Auristatin (ZD02044)	4	NCT04925284				EXELIXIS ¹ mid-single digit royalty

1. Agreement with Iconic; XB002 in-licensed by Exelixis.
OVCA: ovarian cancer; TNBC: triple-negative breast cancer.

Zymeworks Novel Camptothecin Payload Was Selected With ADCs In Mind



Design of novel payloads enables incorporation of properties tailored for ADC mechanism



ZW191

FR α -targeting ADC

FR α is found in ~75% of high-grade serous ovarian carcinomas¹ and ~70% of lung adenocarcinomas²



Optimized Design³

- IgG1 antibody selected for its enhanced internalization and tumor penetration
- Novel moderate potency topoisomerase I inhibitor payload with bystander activity (ZD06519)
- Drug-to-antibody ratio ~ 8
- Validated peptide cleavable linker sequence



Differentiated Profile

- Differentiated anti-tumor activity in preclinical tumor models with a breadth of FR α expression¹
- Favorable safety profile in non-human primate toxicology studies³
- Opportunity to treat broader range of FR α -expressing cancers



Next Milestone

- Expected IND filing in 2024

1. Köbel, M., Madore, J., Ramus, S. et al. Br J Cancer 111, 2297–2307 (2014).

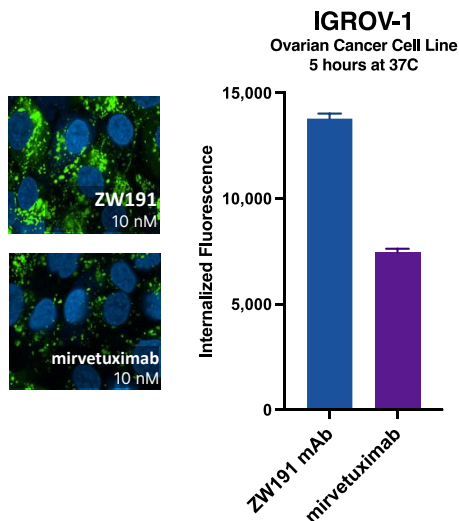
2. O'Shannessy DJ, et al., Oncotarget. 2012 Apr; 3(4):414-25.

3. Lawn S et al. Abstract # 2641 Presented at AACR 2023.

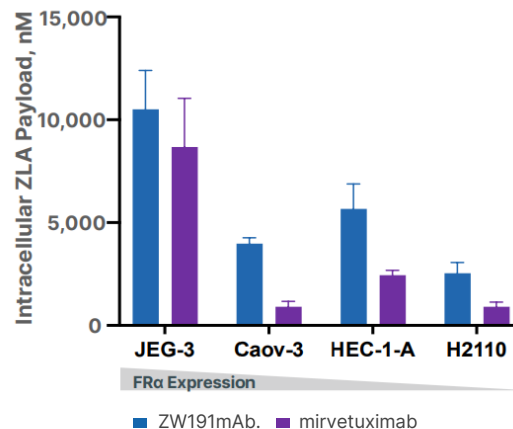
ZW191: Key Design Considerations; On Track for Clinical Studies in 2024

Customized format for enhanced function

Selected for Enhanced Internalization

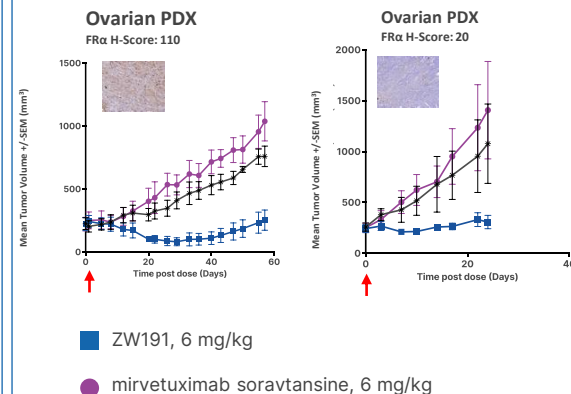


Designed for Superior Payload Delivery



Differentiated by Greater Anti-Tumor Activity

Anti-tumor activity of ZW191 and mirvetuximab soravtansine against ovarian patient derived xenografts (PDXs) expressing moderate and low FRα



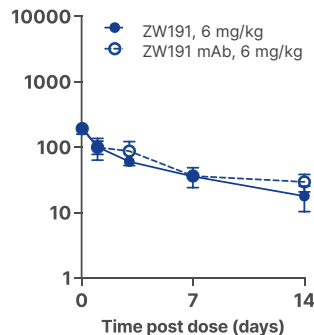
ZW191: Novel and Proprietary TOPO1i Payload Well-Tolerated

ZW191 shows a compelling tolerability profile of 60 mg/kg in NHP¹

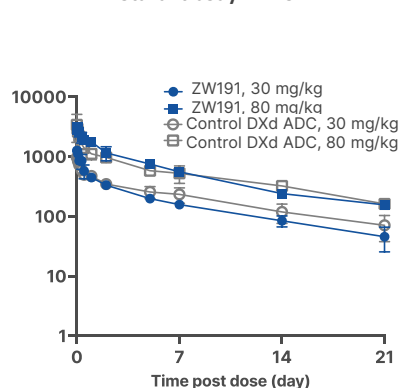
Dose mg/kg	Clinical observations	Histopathology	Clinical Chemistry	Hematology & coagulation	Adverse effects	HNSTD
10	None	None	↑ AST, ALT (n=1)	No effects	None	60 mg/kg
30	Emesis/vomitus	↓ Thymic lymphocytes, ↓ PACS	↑ AST, ALT			
60	Liquid/discolored feces Emesis/vomitus ↓ activity level (n=1)	↓ Thymic lymphocytes, ↓ PACS	↑ AST, ALT ↑ CK			

ZW191 has a favorable pharmacokinetic (PK) profile²

Total Antibody PK from a Mouse
Xenograft study



Total antibody PK from NHP



- No mortality or body weight effects
- No ophthalmic effects
- All effects were non-adverse and reversible
- HNSTD in NHP of 60 mg/kg presents a compelling profile, enabling expectation of achieving efficacious dose level

- **ZW191 displays favorable PK and is well tolerated in NHP at exposure levels above those projected to be efficacious**
- GMP process development is underway to support an expected 2024 IND filing

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; GMP: good manufacturing practices; HNSTD: highest non-severely toxic dose; MTD: maximum tolerated dose; NHP: non-human primates; PACS: pancreatic acinar cell secretion.
 1. Lawn S. et al. ZW191 – a FRA-targeting antibody-drug conjugate with strong preclinical activity across multiple FRA-expressing indications. Abstract # 1862 presented at American Association for Cancer Research annual meeting 2024.
 2. Lawn S et al. ZW191, a novel FRA-targeting antibody drug conjugate bearing a topoisomerase-I inhibitor payload. Abstract # 2641 presented at American Association for Cancer Research annual meeting 2023.

Differentiation is Critical for ZW191 in the Competitive FR α ADC Space for TOPO1i

A novel design to target FR α

1. Potential best-in-class antibody

The ZW191 antibody was selected for enhanced internalization, payload delivery, and tumor penetration.¹

2. Topoisomerase I inhibitor (TOPO1i) payload mechanism

TOPO1i containing ADCs have proven to be an effective mechanism to treat ovarian cancers.^{2,3}

3. Moderate payload potency

A moderate potency TOPO1i payload (ZD06519) was selected for ZW191 to enable a higher protein dose, which may be advantageous for target engagement, tumor penetration, and drug exposure.⁵ Exatecan is 3-10X more potent than the ZW191 payload.

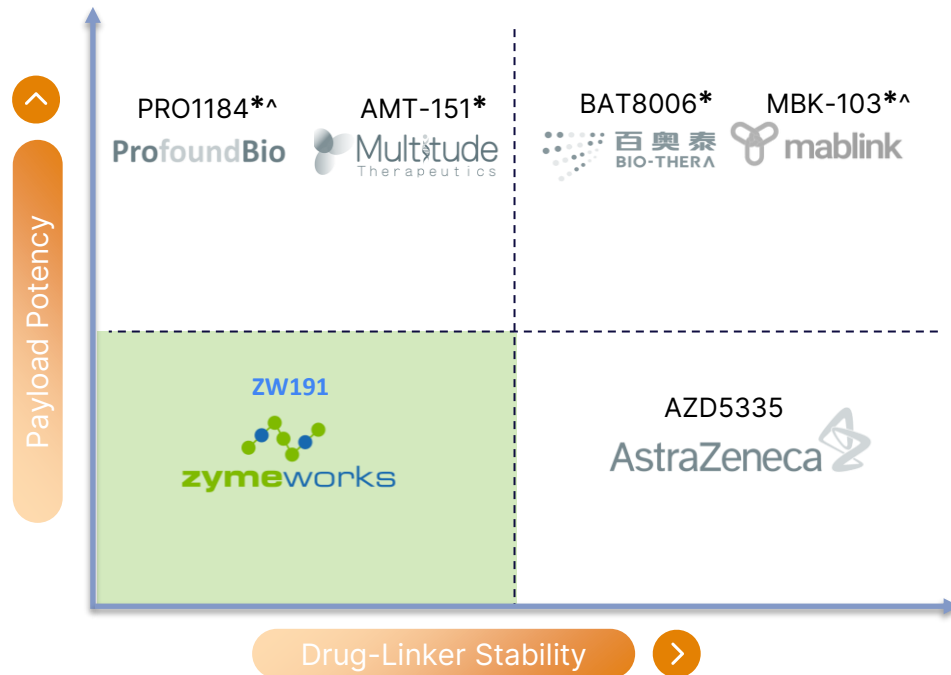
4. Moderate antibody-linker stability

A 'designed instability' approach was taken with ZW191; all approved ADCs feature an element of linker instability.⁴

5. Strong bystander activity

Strong bystander activity is beneficial when treating tumors with low and heterogenous expression of FR α .¹

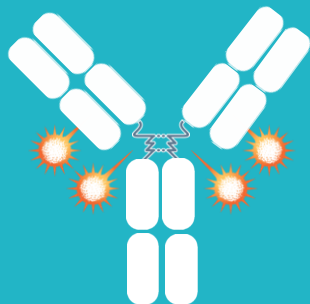
The balance between **drug-linker stability** and **payload potency** differentiates ZW191 from other FR α -TOPO1i ADCs



1. Lawn S et al. Abstract # 2641 Presented at AACR 2023; 2. Meric-Bernstam F, et al., Journal of Clinical Oncology 2023 41:17; 3. Moore K, et al., Jannonc.2023.09.1924; 4. Colombo R, Barnscher SD, Rich JR. Cancer Res 2023, 83 (7). Abstract #1538 presented at AACR 2023 5. Lawn S. ZW191: A Potential Best-in-Class TOPO1i ADC for Treatment of FR α -Expressing Solid Tumors, Presented at World ADC London 2023.

* Denotes use of exatecan payload

[^] Denotes use of Fc-silenced antibody



ZW220

NaPi2b-targeting ADC

NaPi2b is found in ~96% of ovarian serous adenocarcinomas¹ and ~87% of non-small cell lung adenocarcinomas¹



Design²

- IgG1 antibody selected for its strong binding and internalization
- Moderate potency topoisomerase I inhibitor payload with bystander activity (ZD06519)
- Intermediate drug-to-antibody ratio ~ 4
- Validated peptide cleavable linker sequence



Profile

- Strong preclinical activity in models with a breadth of NaPi2b expression¹
- Encouraging tolerability in repeat dose non-human primate toxicology studies²
- First-in-class ADC potential for NaPi2b-expressing solid tumors



Next Milestone

- Expected IND filing in 2025

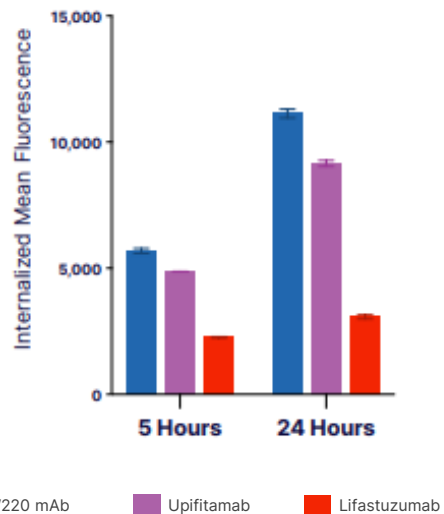
1. Lin K, et al. Clin Cancer Res. 2015;21(22):5139-5150 (prevalence % based on 26 cases of ovarian serous adenocarcinomas and 31 cases of non-small cell lung adenocarcinomas).

2. Hernandez Rojas A et al., Abstract #1533 presented at AACR 2023.

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

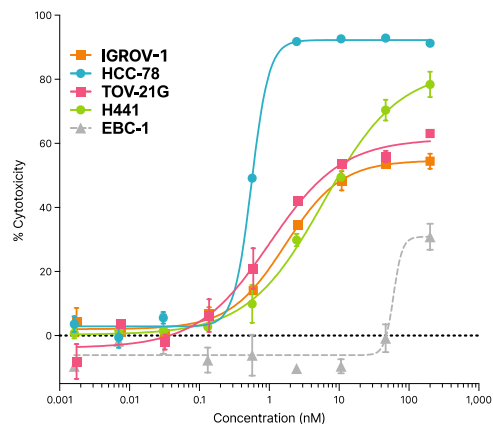
Customized format for function with best-in-class and first-in-class potential

Efficient and Rapid Internalization



Growth Inhibition in Ovarian Cancer and NSCLC Models

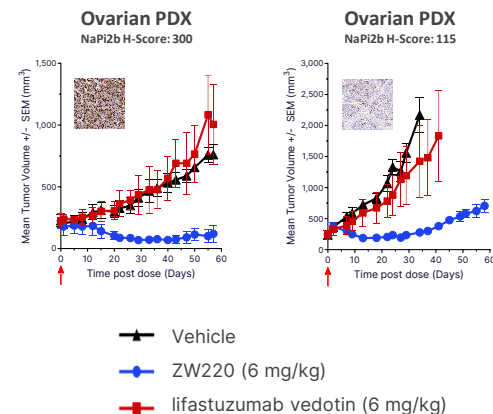
ZW220 DAR 4 cytotoxicity in 3D spheroids



Representative dose-response cytotoxicity curves for ZW220 DAR 4, relative to untreated, in a panel of NaPi2b^{+/+} tumor cell line spheroids.

Anti-Tumor Activity in Ovarian Cancer Models

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



Cell line spheroids with NaPi2b/Cell expressed: IGROV-1 (Ovarian) 1,770,00 expressed; HCC-78 (NSCLC) 820,000 expressed; TOV21G (Ovarian) 350,000 expressed; H441 (NSCLC) 41,000 expressed; EBC-1 (NSCLC) 0 expressed.

Data generated with ZW220 wildtype (wt) fragment crystallizable region of antibody (Fc).

1. Hernandez Rojas A et al., Abstract #1533 presented at AACR 2023; 2. Hernandez Rojas A et al. Presentation at World ADC 2023.

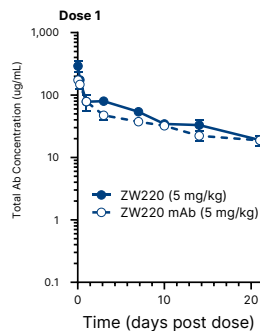
ZW220: Novel and Proprietary TOPO1i Payload Well-Tolerated

ZW220 3-dose non-GLP NHP toxicology study, Q3Wx3				
Test article	Dose	Tolerated?	Histopathology; Clinical Chemistry; Hematology	MTD
ZW220	30 mg/kg	Yes	None	90 mg/kg
	60 mg/kg	Yes	None	
	90 mg/kg	Yes	None	

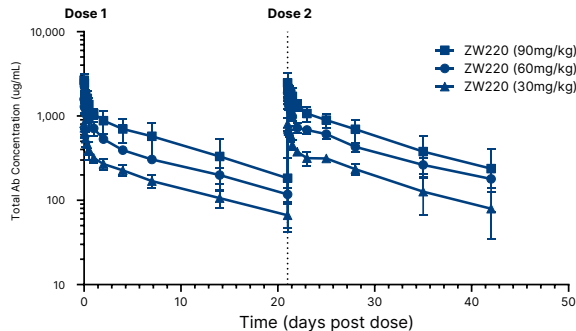
- The MTD of ZW220 in NHPs is 90 mg/kg
- No mortality or adverse pathology findings were observed at high doses

ZW220 has a favorable pharmacokinetic (PK) profile

Total Antibody PK from a Tg32 Humanized FcRn Mice



Total antibody PK from NHP

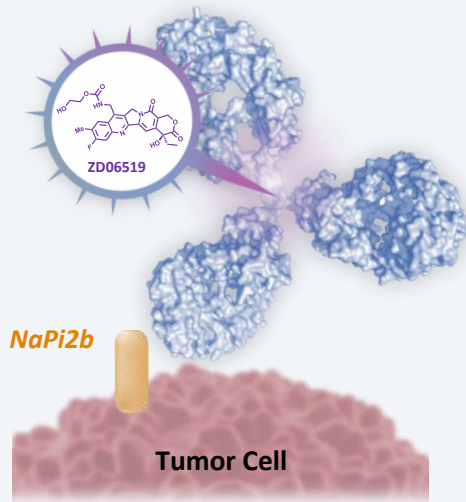


Data generated with ZW220 wildtype (wt) fragment crystallizable region of antibody (Fc).
Hernandez Rojas A et al., Abstract #1533 presented at AACR 2023.

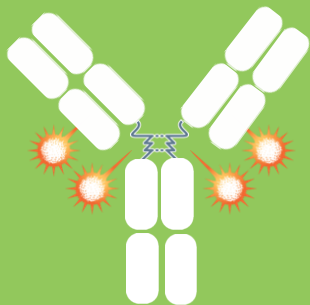
- **ZW220** displays desirable PK characteristics and is well tolerated at high doses
- IND enabling activities are underway

ZW220: A NaPi2b-Targeting Antibody-Drug Conjugate (ADC)

Design



	Design Feature	Benefit
1	Strong internalizing antibody	Strong internalization and payload delivery may result in the potential for improved antitumor activity and the ability to target lower levels of NaPi2b
2	Topoisomerase I inhibitor (TOPO1i) payload mechanism	Proven ADC mechanism in solid tumors across multiple tumor-associated antigens
3	Moderate payload potency	NHP MTD ≥ 90 mg/kg; potential for high doses in humans
4	Moderate antibody-linker stability	Limits antibody-driven toxicities
5	Strong bystander activity	Beneficial when treating tumors with low and heterogenous expression of NaPi2b
6	DAR4	Balance desired antitumor activity with potential for on-target toxicities
7	FcγR silenced	Potential to minimize toxicities driven by cellular uptake via FcγR



ZW251

Glypican 3-targeting ADC

GPC3 is expressed in 76% of hepatocellular carcinomas (HCC)¹



Design²

- An IgG1 antibody with enhanced ADC characteristics
- Topoisomerase I inhibitor mechanism of action
- Novel moderate potency payload with bystander activity (ZD06519)
- Intermediate drug-to-antibody ratio ~ 4
- Validated peptide cleavable linker sequence



Profile

- Strong preclinical activity in models with a breadth of GPC3 expression²
- Noteworthy tolerability in repeat dose non-human primate toxicology studies²
- First-in-class ADC potential for HCC
- Glypican 3 is expressed in 76% of hepatocellular carcinomas (HCC), with high expression observed in ~55% of HCC¹



Next Milestone

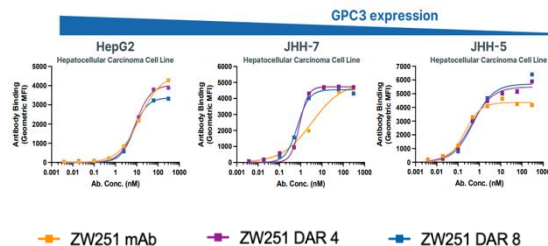
- Expected IND in 2025

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

ZW251 demonstrates target-mediated uptake and anti-tumor activity

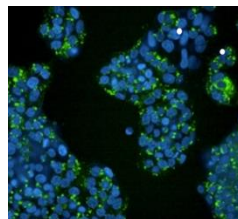
Selected For Strong Binding Over Various Levels Of Expression

Binding of ZW251 mAb and ADC to cancer cell lines across a range of GPC3 expression



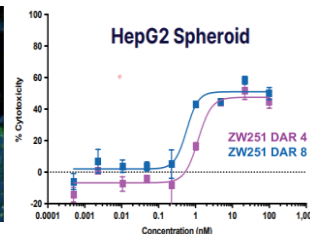
Enhanced ADC Internalization and Cytotoxicity

ZW251 internalized in HepG2 cell line



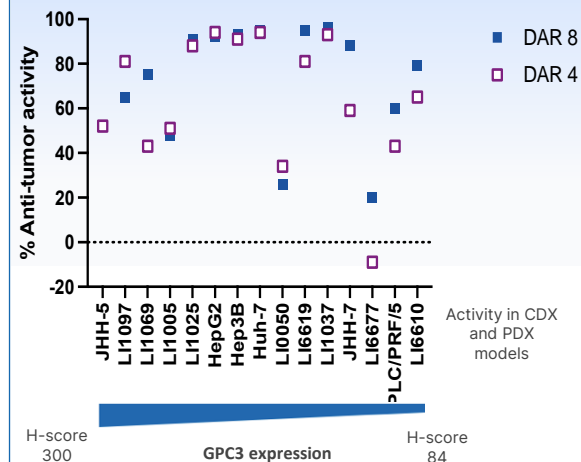
Internalization visualized after 24-hour treatment

Tumor spheroid cytotoxicity in HCC cell line



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

Differentiated Modality Demonstrates Anti-tumor Activity Across A Range of HCC Models



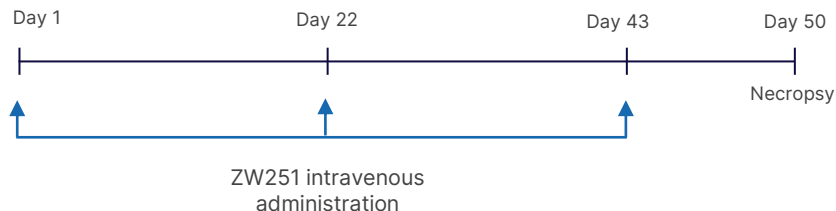
% anti-tumor activity was determined by % tumor growth inhibition (%TGI) calculated as $[(1 - TV_{treatment}/TV_{vehicle}) \times 100]$ at Day 21, or at the closest evaluable time point.

CDX: cell derived xenograft.

1. Madera L et al., Abstract #2658 presented at AACR 2023; 2. Madera L et al, presentation at World ADC 2023.

ZW251: Novel and Proprietary TOPO1i Payload Well-Tolerated

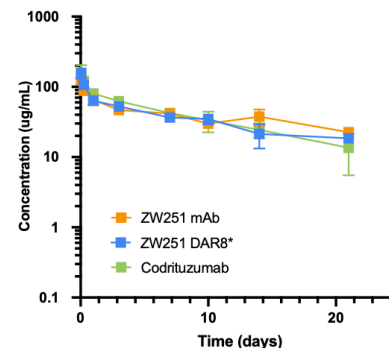
Three Dose Non-Human Primate (NHP) Toxicology Study



Test Article	Doses		
ZW251 DAR 8	10 mg/kg	30 mg/kg	60 mg/kg
ZW251 DAR 4	20 mg/kg	60 mg/kg	120 mg/kg

- Minimal changes in body weight, hematology parameters, and clinical chemistry parameters in all treatment groups
- No mortality observed in any treatment group prior to necropsy**

Total IgG in Tg32 Mouse Serum



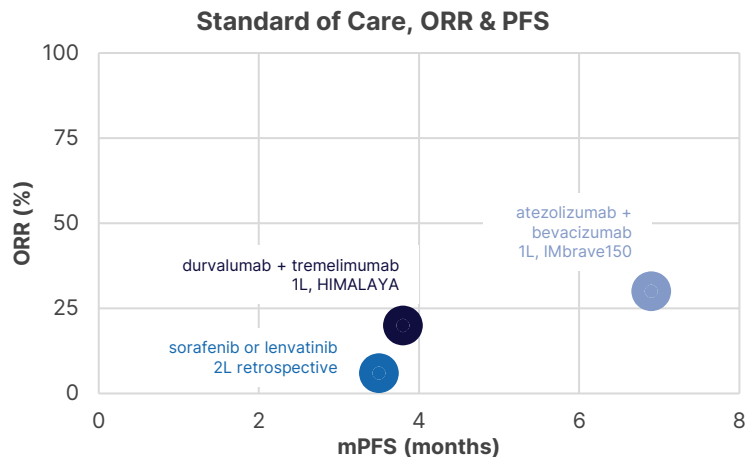
*Analog utilizes ZW251 mAb conjugated to a closely related linker-payload.

- ZW251 mAb exhibits comparable PK to a clinical-stage antibody comparator
- PK of ZW251 mAb unaffected by conjugation
- No mortality was observed** in a repeat dose NHP toxicology study with doses up to 60 mg/kg (DAR 8) or 120 mg/kg (DAR 4)

Potential Therapeutic Agent with Alternative Mechanism for HCC Patients

HCC: Limited Treatment Options

- Globally, liver cancer is the sixth most common cancer and third most common cause of death from cancer¹
- In USA, 1L and 2L SOC provide < 9 months PFS



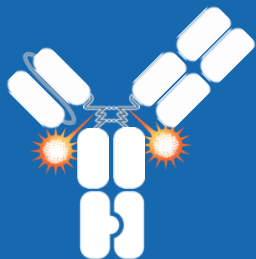
As a potential first-in-class TOP01i-based ADC for HCC, ZW251 offers the potential of a **new MOA** for patients and an **opportunity to improve upon the current standard of care**

- GPC3 highly expressed in HCC and being targeted by other modalities including TCEs and engineered T cells.
- ADC approach provides alternate to counter limitations associated with immune-related suppressive HCC microenvironment and a potential therapeutic strategy amenable to combination with SOC.
- ZW251 drug design with potential first-in-class potential
 - Bystander active TOP01i payload with tailored potency
 - Optimized drug-linker stability and intermediate DAR
 - Strong tumor growth inhibition across tumors displaying range of GPC3 expression

TCE: T cell engager.

Finn RS et al NEJM 2020; Abou-Alfa GK et al NEJM Evid 2022; Yoo C et al Liver Cancer 2021.

1. WHO. International Agency of Cancer Research. Cancer Today. 2020. Available at: <https://gco.iarc.fr/today/home>. Accessed October 2023 SEER. Cancer Stat Facts. National Cancer Institute. Available at <https://seer.cancer.gov/statfacts/>.



Zanidatamab zovodotin

A Bispecific HER2-targeting ADC



Design¹

- Novel cross-linking binding designed to enhance internalization of payload and initializes immunogenic cell death (ICD)
- Delivery of novel auristatin payload (ZD02044) covalently linked via a protease cleavable linker in a DAR 2 configuration



Profile

- Differentiated format offers options to overcome potential points of resistance via geometry and cytotoxin; manageable low-grade adverse events; inducer of ICD markers and potential adaptive immune responses, which warrants investigation of its combination with checkpoint inhibitors^{2,3}



Next Milestone

- Zanidatamab zovodotin remains ready for a Phase 2 study; however, the initiation of the planned Phase 2 study has been deprioritized, pending more clarity from the evolving clinical landscape

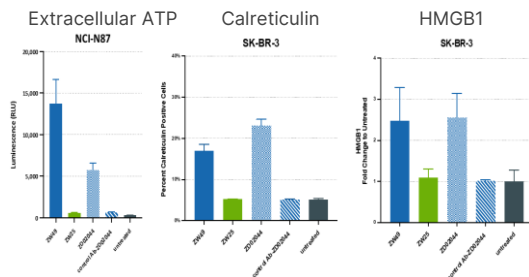
Zanidatamab zovodotin: Summary of Key Potential Differentiators

Pre-clinical data demonstrates potential synergism to combine with immunotherapy. Safety profile from Phase 1 data supports focus in NSCLC population with a recommended dose of 2.5mg/kg Q3W.

Enhanced Internalization of Payload, with ICD

Biparatomic binding elicits internalization, auristatin-mediated cytotoxicity and strong hallmarks of immunogenic cell death^{1,2}

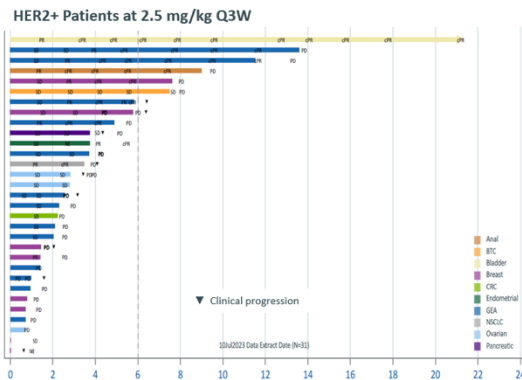
Hallmarks of ICD in HER2 expressing tumor cells



Stronger inducer across hallmarks when compared to trastuzumab based ADCs with DXd or MMAE payloads

Antitumor Activity Across Solid Tumors Including NSCLC

Confirmed ORR of 30%
In 2.5mg/kg Q3W cohort (N=30), median duration of response was 6.8 months with a range of 1.4 – 19.8 months⁴



Differentiated Safety Profile

In 67 patients, low grade, manageable adverse events with no ILD or pneumonitis reported³

- MTD not reached
- The PK of ADC and total antibody was comparable and appeared to be linear among the three dose regimens examined

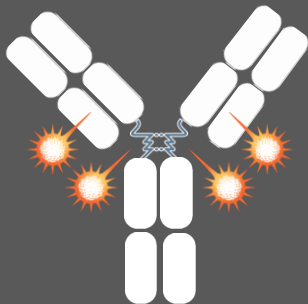
Safety: 2.5mg/kg Q3W cohort, N=31⁴

- Gr≥3 TRAEs 16%
- Any grade keratitis of 45%; all cases ↓ to grade 1 or resolved
- Alopecia & IRR: any grade = 16%
- Diarrhea any grade = 29% (No Gr≥3)

Zanidatamab zovodotin is an investigational product that has not received FDA (or any regulatory authority) approval and has not been demonstrated safe or effective for any use.

IHMGB1: high mobility group box 1 protein; ICD: immunogenic cell death; ILD: Interstitial lung disease; IRR: immune related reaction; MMAE: Monomethyl auristatin E; Q3W: every three weeks; TRAE: treatment-related adverse event.

1. Hamblett, KJ et al., Cancer Res 2018;78(13 Suppl); 2. Barnscher S et al., Abstract #2633 presented at AACR 2023; 3. Jhaveri K et al., presented at ESMO 2022; 460MO Annals of Oncology 33(7) 4. Oh Y et al., Abstract# 33234 presented at AACR-NCI-EORTC 2023.



XB002 (ICON-2) A Novel Tissue Factor Targeting ADC



Design

- Novel antibody that recognizes a Tissue Factor epitope that does not interfere with Factor VII binding
- Delivery of Zymeworks novel auristatin payload (ZD02044) covalently linked via a protease cleavable linker in a DAR 3.8 configuration



Profile

- Differentiated ADC versus Tisotumab Vedotin on tolerability, exposure and combinability



Status










- Phase 1 studies in advanced solid tumors (JEWEL-101)

Multispecific Antibody Therapeutic (MSAT) Program

Driving The Evolution of MSATs

Differentiated Development of Multispecific Antibody Therapeutics

Versatile multispecific antibody therapeutics enhancing potency and precision with proven track record and robust clinical pipeline

Program	Potential Indication	Target(s)	Preclinical	Phase 1	Phase 2	Pivotal	Collaboration Partners
Zanidatamab Bispecific	BTC	HER2 x HER2	HERIZON-BTC-302				 Jazz Pharmaceuticals  BeiGene  Jazz Pharmaceuticals  BeiGene  Jazz Pharmaceuticals  BeiGene  Jazz Pharmaceuticals  BeiGene
	GEA	HER2 x HER2	HERIZON-GEA-01				
	BC	HER2 x HER2	EMPOWHER-BC-303 ¹				
	BC and other solid tumors	HER2 x HER2	8+ ongoing Phase 1 and Phase 2 trials (view)				
ZW171 Bispecific T cell Engager	OVCA, NSCLC and other MSLN-expressing cancers	MSLN x CD3 (2+1)		Expected IND filing in 2024			
TriTCE Co-Stimulatory Trispecific T cell engager	Under active evaluation	CLDN18.2 x CD3 x CD28 DLL3 x CD3 x CD28		IND candidate nomination studies			
TriTCE Checkpoint Inhibition Trispecific T cell engager	Under active evaluation	TAA x PD-L1 x CD3		Pilot toxicology studies			
Selected Partnered Programs							
JNJ-78278343 Bispecific	Castration-Resistant Prostate Cancer	CD3 x KLK2	Azymetric™ EFECT™				

CD28: cluster of differentiation 28; CLDN: claudin; DLL3: delta-like ligand 3; KLK2: kallikrein-related peptidase 2; PD-L1: programmed cell death ligand 1; TAA: tumor associated antigen.

1. Trial initiation expected in the second half of 2024.

Zanidatamab: \$2B+ Peak Sales Potential*

1

Expect to enter market first in BTC (pending regulatory approval)¹

- Completed rolling BLA submission seeking accelerated approval in 2L BTC
- Confirmatory Phase 3 trial initiated in 1L metastatic BTC



Represents ~12,000 HER2+ cases annually² In USA, Europe³, and Japan

2

Path to approval in 1L GEA with sBLA

- HER2+/PD-L1 negative: opportunity to address unmet need and replace trastuzumab
- HER2+/PD-L1 positive: opportunity to replace trastuzumab as HER2-targeted therapy of choice¹
- Opportunity to explore potential in neoadjuvant populations¹



Represents larger patient opportunity with ~63,000 HER2+ cases annually² in USA, Europe³, and Japan

3

Expanded opportunity across lines of Breast Cancer (BC)¹

- Early lines of therapy (neoadjuvant)
 - Post T-DXd
 - Novel combinations¹
- Ongoing trials in early breast cancer:
- I-SPY2 Trial⁴
 - MD Anderson collaboration



Considerable market opportunity with more than 150,000 cases annually⁵ in USA, Europe³, and Japan

4

Broad potential beyond BTC, GEA, and BC in multiple HER2-expressing indications⁶

- | | | |
|--------------|---------------|--|
| • Colorectal | • Endometrial | • Salivary Gland |
| • NSCLC | • Pancreatic | • Ampullary |
| • Ovarian | • Bladder | • And other HER2-expressing solid tumors |

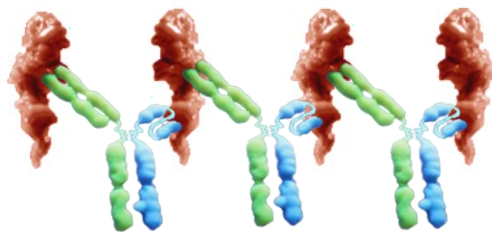
*Adapted from Jazz Pharmaceuticals' Guidance

sBLA: supplemental biologics license application; T-DXd: trastuzumab deruxtecan. 1. Pending regulatory approvals. 2. Incidence sources: Kantar reports, ToGA surveillance report; SEER, cancer.gov; ClearView Analysis; GLOBOCAN, Data on file. 3. Major markets, U.K, France, Germany, Spain, Italy. 4. NCT01042379; 5. Incidence source estimates derived from multiple sources: Decision Resources Group, Kantar Health, Jazz Market Research, data on file; 6. Funda Meric-Bernstam et al, Zanidatamab, a novel bispecific antibody, for the treatment of locally advanced or metastatic HER2-expressing or HER2-amplified cancers: a phase 1, dose-escalation and expansion study, The Lancet Oncology, Volume 23, Issue 12, 2022, Pages 1558-1570, ISSN 1470-2045, [https://doi.org/10.1016/S1470-2045\(22\)00621-0](https://doi.org/10.1016/S1470-2045(22)00621-0).

Zanidatamab's Unique Format

- Ability to target two distinct HER2 epitopes which results in HER2 binding across a range of expression levels (low to high)¹
- HER2-receptor cross-linking, enhanced receptor clustering, internalization, and receptor downregulation¹
- Inhibition of cellular proliferation
- Fc-mediated cytotoxicity: ADCC, ADCP, CDC¹
- FDA Breakthrough Designation

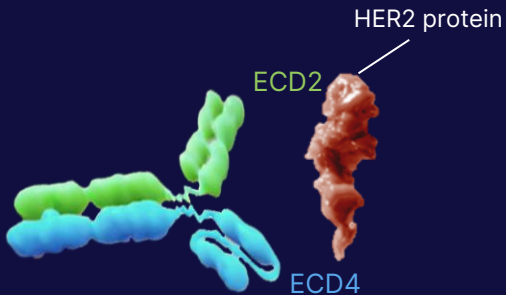
Biparatopic HER2-Binding of Zanidatamab Drives Multiple Mechanisms of Action



The geometry of zanidatamab prevents it from binding to the same HER2 molecule¹

Zanidatamab

A Bispecific Antibody for
HER2-Expressing Cancers



ADCC: antibody-dependent cellular cytotoxicity; ADCP: antibody-dependent cellular phagocytosis; CDC: complement-dependent cytotoxicity; ECD: extracellular domain; Fc: fragment crystallizable region of antibody; FDA: U.S. Food and Drug Administration.

1. Weisser N et al., Nature Communications 2023.

Clinical Data

Differentiated tolerability profile amongst HER2-targeted therapies; majority of adverse events low grade

Single Agent Activity in Second-Line BTC Pivotal Study

- 41.3% ORR (51.6% in the IHC3+ patients), 12.9 months mDoR¹

Combination Activity in First-Line GEA studies

- 79% ORR with a mDOR of 20.4 months and 84% 18-month OS rate²
- 75.8% ORR with mDOR 22.8 months and mPFS 16.7 months³

Pivotal Trials

HERIZON-BTC-01

A Global Pivotal Study in Second-Line HER2-Amplified BTC

- Results presented at ASCO 2023 with concurrent publication in The Lancet Oncology¹

HERIZON-GEA-01

A Global Pivotal Study in First-Line HER2-Positive GEA⁴

- Supported by promising Phase 2 clinical data presented at ASCO GI 2023² and Phase 1b/2 data at ESMO 2023³



Upcoming Milestones

- Completed rolling USA regulatory submission seeking accelerated approval in 2L BTC
- Confirmatory Phase 3 trial initiated in 1L metastatic BTC
- Topline data for the Phase 3 HERIZON-GEA-01 trial expected in late 2024

Collaboration Partners:




mDOR: median duration of response; ORR: overall response rate; OS: overall survival; mPFS: median progression-free survival.

1. Harding et al., Lancet Onco 2023; 2. Elimova E et al., Abstract #347 presented at ASCO GI 2023, JCO 41(45); 3. Lee KW et al., Abstract #3088 presented at ESMO 2023; 4. NCT05152147.

Zanidatamab: Licensing Agreement with Jazz

Licensing Agreement Terms¹

Counterparty	 Jazz Pharmaceuticals
Upfront Payments	\$375M received in 4Q22
Regulatory Milestones	Up to \$525M
Commercial Milestones	Up to \$862.5M
Royalties	Tiered royalties of 10 to 20% of net sales
Territories	USA, EU, Japan and all other territories except those in APAC covered by BeiGene agreement
Future R&D Spend	Jazz to fund 100% of costs of future zanidatamab studies

Key Benefits to Zanidatamab Licensing Agreement

- **Meaningful improvement to financial position and reduction in future expenditures** allows focus on growth of exciting early-stage pipeline while zanidatamab advances to commercialization
- **Accelerate and expand R&D programs (5x5 and ADVANCE)** while maintaining anticipated cash runway into 2H 2027 with a goal of advancing **5 new programs into clinical studies by 2026**
- **Continued development** of zanidatamab program managed by Jazz
- **Substantial potential milestone payments** based on global regulatory milestones for zanidatamab in BTC and GEA with further upside from royalties and commercial milestones
- **Leverage** Jazz's global commercial infrastructure together with BeiGene's complementary strengths in APAC regions to **optimize commercialization of zanidatamab without requirement for investment in commercial infrastructure** within Zymeworks

APAC: Asia Pacific.
1. All dollar values in US Dollars.

Zanidatamab: Licensing Agreement with BeiGene for Asia Pacific

Licensing Agreement Terms¹

Counterparty	 The BeiGene logo, consisting of a square icon with a stylized 'B' and the word "BeiGene" in a bold, sans-serif font.
Upfront Payments	\$40M
Development and Commercial Milestones	Up to \$195M
Royalties	Tiered royalties of up to 19.5% of net sales in BeiGene territories (up to 20% when royalty reduction of 0.5% reaches cap in the low double-digit millions of dollars)
Territories	Asia-Pacific region (excluding Japan and India)*
Co-development Funding	Currently for BTC and GEA global development

Additional Details

- Received approx. \$40M upfront payment in 2018 and approx. \$20M in milestones to date
- BeiGene has development and commercial rights to zanidatamab
- Collaborate on certain global studies including HERIZON-BTC-01 and HERIZON-GEA-01 with BeiGene responsible for clinical and regulatory activities in their territory
- Co-development funding agreed for any global studies

1. All dollar values in US Dollars.

* Zymeworks BC granted BeiGene a royalty-bearing exclusive license for the research, development and commercialization of zanidatamab zovodotin in Asia (excluding Japan but including the People's Republic of China, South Korea and other countries), Australia and New Zealand (collectively, the "Territory").

Zanidatamab: Details on Pivotal Studies in BTC and GEA

HERIZON-BTC-01

A Global Pivotal Study in Second-Line
HER2-Amplified BTC

Population: PATIENTS WITH HER2-AMPLIFIED BTC WHO RECEIVED PRIOR
GEMCITABINE

N = 100

Cohort 1: 75 with IHC 2+ or 3+

Cohort 2: 25 with IHC 0 or 1+

Regimen: 28 Day Cycles

Day 1: Zanidatamab, 20 mg/kg IV

Day 15: Zanidatamab, 20 mg/kg IV

Imaging every 8 Weeks

Locations: Canada, USA, Chile, France, Italy, Spain, United Kingdom, China,
South Korea

Primary End Points: ORR (RECIST 1.1 by ICR¹)

Secondary End Points: Proportion of patients with DOR \geq 16 weeks, DOR, DCR,
PFS, OS, safety

Additional Details: Meaningful clinical benefit demonstrated including ORR of
41.3%, median DOR of 12.9 months with a mPFS of 5.5 months presented at
ASCO 2023, concurrent publication in The Lancet Oncology².

HERIZON-GEA-01

A Global Pivotal Study in First-Line
HER2-Positive GEA

Population: PATIENTS WITH HER2-POSITIVE ADVANCED OR METASTATIC GEA
N = 918

Regimen: 21 Day Cycles

ARM 1: Trastuzumab + SOC chemotherapy³, N=238

ARM 2: Zanidatamab + SOC chemotherapy, N=238

ARM 3: Zanidatamab + tislelizumab + SOC chemotherapy, N=238

Imaging every 6 weeks for first 54 weeks, every 9 weeks thereafter

Locations: Australia, China, India, Malaysia, South Korea, Singapore, Taiwan,
Thailand, Belgium, Czech Republic, Estonia, France, Italy, Georgia, Germany,
Greece, Ireland, Netherlands, Poland, Portugal, Romania, Serbia, South Africa,
Spain, Turkey, Ukraine and United Kingdom, Canada, Mexico, Guatemala,
Argentina, Brazil, Chile, Peru

Primary End Points: PFS, OS (RECIST 1.1 by BICR¹)

Secondary End Points: ORR, DOR, Safety, HRQoL

Additional Details: Anticipate topline readout in 2H 2024

BICR: blinded independent central review; DCR: disease control rate; HRQoL: health-related quality of life; ICR: independent central review; IHC: immunohistochemistry; mPFS: median progression-free survival; ORR: overall response rate;

RECIST: response evaluation criteria in solid tumors; SOC: standard of care.

1. Response assessments until progression (per ICR or BICR) or withdrawal of consent; 2. Harding et al., Lancet Onco. 2023 24(7) 772-782; 3. CAPOX (capecitabine and oxaliplatin) or FP (5-fluorouracil and cisplatin).

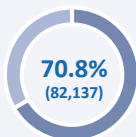
Zanidatamab: Epidemiology of Biliary Tract Cancers

Biliary Tract Cancers (BTC) are molecularly diverse tumors which include gallbladder cancer (GBC), intrahepatic cholangiocarcinoma (ICC), and extrahepatic cholangiocarcinoma (ECC).¹ Gall bladder cancer is the more prevalent diagnoses among BTC cases.²

Epidemiology (World)

Incidence varies globally:

- Globally, it was estimated ~210,878 new cases of BTC in 2017, increasing to 219,420 in 2018.³
- Occurs at rate between 1-4 cases per 100,000 people / year in most regions; yet some regions exceed this age-standardized annual incidence rate ^{4,5}
- Chile had the highest incidence, followed by Japan and South Korea (10.83, 8.88, and 8.55/100,000, respectively)⁶



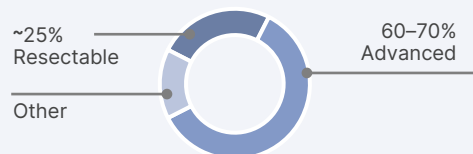
of all estimated new GBC cases occurred in Asia, with 10% (~12,570) in Europe in 2020⁷

Epidemiology (United States)

Most cases are diagnosed at an advanced stage:

- BTC is reported to occur at a rate of 1.2 (GBC), 1.7 (ICC), 1.8 (other) per 100,000 people per year in the United States⁸ which is estimated to be ~15,000 patients per year

Cases by stage at diagnosis ^{9, 10}



Progression

Second-line:

- Survival from first-line treatment is modest, ~35% of patients get second-line, but it ranges by geographical region^{11, 12, 13}
- 2L chemotherapy yields response rates of < 10%; mOS of patients is often < 6 months¹⁴ with a recent phase II trial reporting 8.6 months¹⁵
- ~40-60% of BTC patients have possible targetable alterations with differences between anatomical subgroups^{9,16}

19% of GBC
17% of ECC
5% of ICC



Overexpress
HER2¹⁷

1. Bogenberger JM et al., Precision Oncol. 2018; 2. Lazcano-Ponce EC et al., CA: Cancer J Clin. 2001; 3. Ouyang G et al., Cancer 2021; 4. Tam V et al., Curr. Oncol. 2022; 5. Miranda-Filho A et al., Int. J. Cancer 2020; 6. Zhang Y et al., Cancer Epidemiology. 2021; 7. GLOBOCAN. World fact sheets (GallBladder), 2020; 8. NCI. SEER. SEER*Explorer: Access Feb 2023. conditions included intrahep, Gallb, other; 9. Gómez-España MA, et al., Clin Transl Oncol. 2021; 10. Banales JM et al., Nat Rev Gastroenterol Hepatol. 2020; 11. Rizzo A et al., Anticancer Research, 2019; 12. Chiang N-J et al., Biomolecules. 2021; 13. Fornaro L et al., Br J Cancer. 2014; 14. Lamarca A et al., J Clin Oncol. 2019; 15. Yoo C et al., Final results (NIFTY) abstract 55P presented at ESMO Congress 2022; 16. Bridgewater JA et al., Am Soc Clin Oncol Educ Book. 2016; 17. Galdy S et al., Cancer Metastasis Rev. 2017.

Zanidatamab: Targeted Treatment Options are Rapidly Evolving in BTC

Actionable driver mutations have been identified and are generally mutually exclusive from one another (including FGFR pathway, IDH1, BRAF, NTRK, ERBB2 (HER2) MSI-high or MMR deficiency)¹

Advanced / Metastatic Biliary Tract Cancers

First-line treatment options²

Guideline option from the ABC-02 trial³
gemcitabine + cisplatin

ORR = 26%, mPFS = 8.4 months,
mOS = 11.7 months

Guideline option from the TOPAZ-1 trial^{4,5}

cisplatin + gemcitabine + durvalumab
ORR = 26.7%_{IA}, mPFS = 7.2 months,
mOS = 12.9 months

Recent option from the KN-966 trial⁶

cisplatin + gemcitabine + pembrolizumab
ORR = 29%_{BICR}, mPFS = 6.5 months,
mOS = 12.7 months

Progression in Metastatic Biliary Tract Cancers

Second-line treatment options²

Guideline option from the ABC-06 trial⁷

FOLFOX ORR= 5%, mPFS= 4.0 months,
mOS = 6.2 months

Is Targeted Treatment More Effective Than Chemotherapy?

FGFR2 fusions+: mPFS= 7.0 – 9.0, mOS= 17.5 – 21.7 months⁸
IDH1 mutation: mPFS = 2.7 months, mOS = 10.3 months⁹

Ongoing Results from HER2 Targeting Agents in 2L+ Trials*

trastuzumab + FOLFOX mPFS = 5.1 months, mOS = 10.7 months¹⁰
TDXd (HERB trial) mPFS = 5.1 months, mOS = 7.1 months¹¹
trastuzumab + pertuzumab (MyPathway) mPFS = 4.0, mOS = 10.9 months¹²

BRAF: activating serine/threonine-protein kinase B-raf kinase; ERBB2: receptor tyrosine-protein kinase erB-2; FGFR2 fusions+: fibroblast growth factor receptor 2 fusions and alterations; FOLFOX: folinic acid, fluorouracil, and oxaliplatin; IDH1: isocitrate dehydrogenase 1; MMR: mismatch repair; MSI: microsatellite instability; NTRK: neurotrophic receptor tyrosine kinase. * have not received FDA (or any regulatory authority) approval for BTC 2L indication.

1. Valle JW et al., Lancet 2021; 2. Vogel A et al., ESMO Open (BTC Guidelines) 2022; 3. Valle JW et al., NEJM 2010; 4. Oh D-Y et al., NEJM Evid 2022; 5. Oh D-Y et al., Annals of Oncol 2022 (33 suppl.7); 6. Kelley K et al., Lancet 2023; 7. Lamarca et al., J Clin Oncol 2019; 8. Vogel A et al., Annu Rev Med 2023; 9. TIBSOVO US PI Aug 2021; 10. Lee, C-K et al., Lancet Gastroenterol. Hepatol. 2023; 11. Ohba A et al., J Clin Oncol 2022 v40, no.16_suppl; 12. Javle M et al., Lancet Oncol 2021.

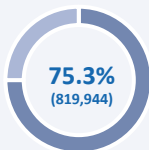
Zanidatamab: Epidemiology of Gastroesophageal Adenocarcinoma

- Gastroesophageal adenocarcinoma (GEA) encompasses gastric (stomach), gastroesophageal junction (GEJ) and esophagus adenocarcinomas
- As of 2020, global incidence rate of gastric cancer is estimated to be 5.6%, while esophageal cancer is 3.1%¹
- There is a wide geographic variation incidence: 15- to 20-fold difference between high- and low-incidence regions⁴
- Most patients present at a late stage of disease^{1,2,3}

Gastric Cancer^{1,2}

Globally, ~1.1 million patients diagnosed with an estimated increase of 62% to 1.77 million by 2040

- Majority of gastric cancers are adenocarcinomas (~95%)⁵



of all estimated new gastric cancer cases occurred in Asia in 2020

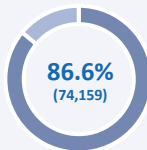
Incidence rates¹¹

USA	Europe	Japan
1.2%	3.1%	13.5%

Esophageal Cancer^{1,3}

Globally, 604,100 patients diagnosed annually, with an estimated increase by 58.4% to ~957,000 by 2040

- 85,672 esophageal cancer patients were diagnosed with esophageal adenocarcinoma (EAC)



of those patients were diagnosed with EAC in high developed countries in 2020

Incidence rates¹¹

USA	Europe	Japan
0.8%	1.2%	2.6%

HER2-Positivity

HER2+ in GEA ranges 7-34%^{6,7}

- Men > Women
- Moderate > Poor differentiated
- GEJ (32.2%) > Gastric (21.4%)
- Intestinal > Diffuse subtype

Prognostic significance of HER2 is unclear,⁸ and influenced by:

- Intra-tumoral heterogeneity
- Treatment line
- Clonal evolution^{8,9,10}

1. Sung H et al., (Globocan 2020) CA Cancer J Clin. 2021; with factsheet <https://gco.iarc.fr/today/fact-sheets-populations>; 2. Morgan E et al., Lancet 2022; 3. Morgan E et al., Gastroenterology 2022; 4. Sitarz R et al., Cancer Manag Res 2018; 5. Ajani JA, et al., Nat Rev Dis Primers 2017; 6. Gambardella V et al., Ann Oncol 2019; 7. Van Cutsem E et al., Gastric Cancer, 2015; 8. Ajani JA et al., J Natl Compr Canc Netw 2022; 9. Zhao D et al., J Hematol Oncol 2019; 10. Janjigian YY et al., Cancer discover 2018; 11. Incidence rates as a percent of global cancer cases.

Zanidatamab: Targeted Treatment Options For Patients with HER2+ GEA

Summary: First-line treatment guidelines for patients with HER2+ Gastric and GEJ adenocarcinoma^{1,2,3,4}

Advanced / Metastatic HER2+ Gastric or GEJ Adenocarcinoma

Guideline option based on the ToGA trial⁴

Doublet chemo (fluoropyrimidine + platinum)
± trastuzumab

ORR = 47 vs 35%
mDOR = 6.9 vs 4.8 months
mPFS = 6.7 vs 5.5 months
mOS = 13.8 vs 11.1 months

NCT01041404

Advanced / Metastatic HER2+ Gastric or GEJ Adenocarcinoma

Guideline option for patients based on Keynote 811 trial⁵
(CPS ≥1 and if no contraindications exist for immunotherapy)

Doublet chemo (fluoropyrimidine & platinum)+trastuzumab
±pembrolizumab

ORR = 73.2 vs 58.4%
mDOR = 11.3 vs 9.5 months
mPFS = 10.9 vs 7.3 months
mOS = 20.5 vs 15.6months

*ITT OS was not significant. Early ITT data led to accelerated approval by FDA (ORR: 74vs 52%)
May 2021. FDA and EMA approval for PD-L1 CPS ≥1 with dataset from second and third
interim analyses*

NCT03615326

Options for patients with esophageal adenocarcinoma: ToGA (and many other HER2-directed trials in the advanced setting) excluded esophageal adenocarcinoma: in clinic, these patients can be treated with chemotherapy (capecitabine + cisplatin or fluorouracil + cisplatin) + trastuzumab in the first-line setting^{1,2}

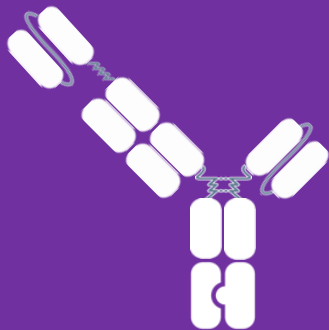
CPS: combined positive score; GEJ: gastroesophageal junction; HER2+: epidermal growth factor receptor 2 positive; ITT: intention-to-treat population; mOS: median overall survival.

1. Catenacci et al., ESMO Open 2022 7(1) 2. Ajani JA et al., J Natl Compr Canc Netw 2022; 3. Lordick F et al., Ann Oncol 2022; 4. Bang et YJ, Lancet 2010- TOGA updated OS (13.1 vs 11.7months) reported in FDA label, accessed https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s25201bl.pdf; 5. Janjigian Y et al., Lancet 2023.

Zanidatamab: Regulatory Designations and Exclusivity

Designation	Indications/ Patent description	Company	Territory	Status
Breakthrough therapy	BTC that has failed prior systemic therapies	BeiGene	China	Granted
Breakthrough therapy	Previously treated HER2 gene-amplified locally advanced /unresectable or metastatic BTC	Zymeworks	USA	Granted
Fast Track	HER2-overexpressing GEA (in combination with standard of care chemotherapy) and previously treated or recurrent gene-amplified BTC	Zymeworks	USA	Granted
Orphan drug	BTC	Zymeworks	USA EU	Granted
Orphan drug	Gastric Cancer HER2 expressing Gastric Cancer	Zymeworks	USA EU	Granted
Key patents	Bispecific antigen binding constructs targeting HER2	Zymeworks	USA	Granted

1. Patent end date includes certain regulatory extensions including term extensions and supplementary production certificates.



ZW171

MSLN x CD3 Multispecific

MSLN has strong expression in ovarian cancer (~84%)², with moderate to strong expression levels within NSCLC (~36%)²



Design¹

- Optimized 2+1 avidity driven geometry incorporating novel low affinity CD3 binder to direct T cell targeting of MSLN expressing tumors
- Engages immune system via MSLN-dependent T cell activation to direct efficient tumor killing with limited cytokine release



Profile¹

- Enhanced anti-tumor activity and safety profile in preclinical models supports opportunity to overcome clinical limitations of prior MSLN-directed therapies



Next Milestone

- Expected IND filing in 2024

scFV: single-chain variable fragment.

1. Afacan N et al., Abstract #2942 presented at AACR 2023.

2. Weidemann, S. et al. Biomedicine 2021, Apr 7;9(4):397.

ZW171: Designed to Widen the Therapeutic Window with Enhanced Safety and Anti-tumor Activity

Antibody Format

2 +1 format (two α MSLN paratopes, one α CD3 paratope) optimized for tumor-dependent antitumor activity

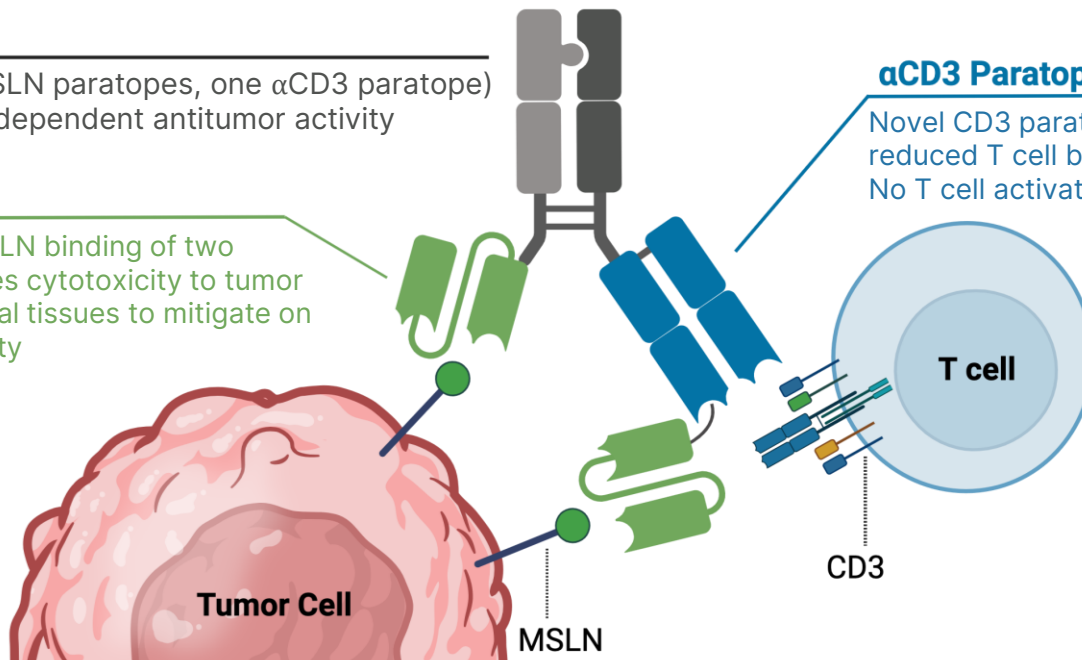
α MSLN Paratopes

Avidity dependent MSLN binding of two α MSLN paratope drives cytotoxicity to tumor cells and spares normal tissues to mitigate on target off tumor toxicity

Azymetric™ and EFECT™ KO Fc

α CD3 Paratope

Novel CD3 paratope with low affinity and reduced T cell binding to mitigate CRS
No T cell activation in absence of tumor



CRS: cytokine release syndrome.

Mesothelin (MSLN):

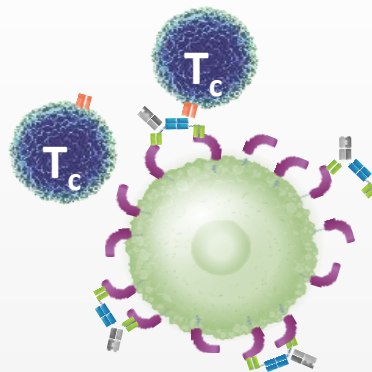
- Clinically amenable to T cell-mediated therapy (eg. Gavo-cel¹) but limited success with other systemic therapy (eg, ADCs,²⁻⁴ immune toxins,⁵ prior TCEs^{6,7})

Designed to overcome limitations of prior targeted therapies

- Avidity-dependent MSLN binding⁸
 - Enable selective binding
 - Cytotoxicity of high/moderate MSLN-expressing cancer cells
 - Spares normal tissue
- Novel CD3 paratope⁸
 - To limit cytokine release
 - Supporting effective tumor cell killing

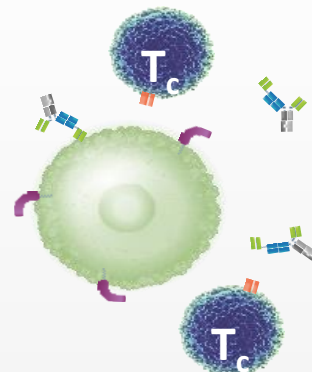
ZW171

Designed to engage cancer cell (MSLN^{high})



ZW171 drives anti-tumor activity through MSLN and T cell co-engagement

Designed to avoid healthy cell (MSLN^{low})



No T cell activity on normal tissue or periphery as no MSLN engagement

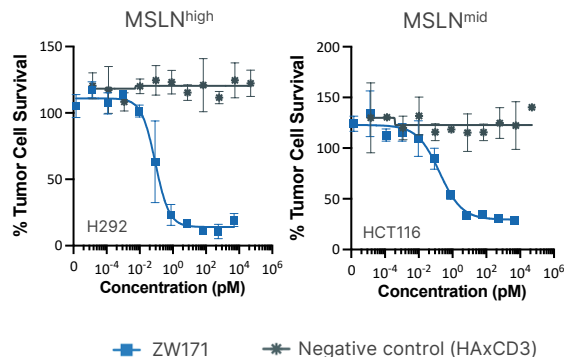
Gavo-cel: gavocabtagene autoleucel.

1. Hassan R, et al. Nat Med. 2023;29:2099-2109; 2. Kindler HL, et al. Lancet Oncol. 2022;23(4):540-552; 3. Rottey S, et al. Clin Cancer Res. 2022;28(1):95-105; 4. Weekes CD, et al. Mol Cancer Ther. 2016;15(3):439-447; 5. Hassan R, et al. Cancer. 2020;126(22):4936-4947; 6. Harpoon Therapeutics Investor Presentation, February 2022; 7. Molloy M, et al. Clin Cancer Res. 2021;27(5):1452-1462; 8. Piscitelli S. Engineering and Preclinical Development of ZW171: A 2+1 Format Anti-MSLN T Cell Engager. Presented at: PEGS Boston Summit; 2023.

ZW171: Key Design Considerations; On Track for Clinical Studies in 2024

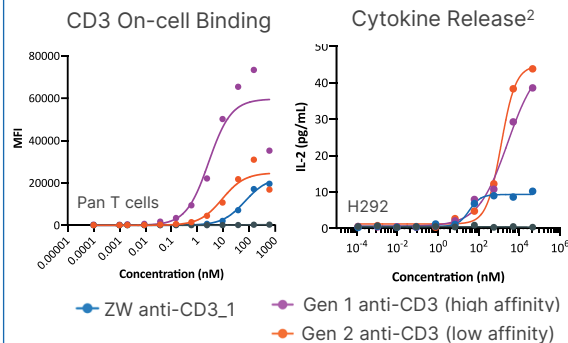
Engineered with 2+1 Format Facilitates Avidity-Driven Binding¹

Tumor Cell Cytotoxicity in Mid-to-High Expressing MSLN Models¹



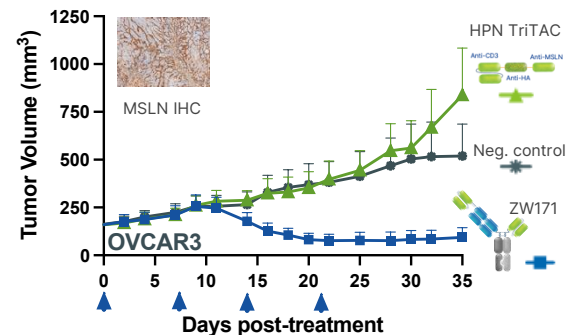
Novel CD3 Paratope with Enhanced Safety

Proprietary CD3 engager has low affinity CD3 binding and cytokine release¹



Pilot NHP toxicology data shows ZW171
is well-tolerated up to 30 mg/kg¹

Differentiated by Greater Anti-Tumor Activity in MSLN-Expressing Tumor Models¹



OVCAR-3 tumor engrafted mice were humanized with donor PBMC (3 donors) and dosed i.v. QW x4 with ZW171 or i.p. daily x 18 with HPN triTAC. Neg control (HAXCD3)

bsAb: bispecific antibody; gen: generation.

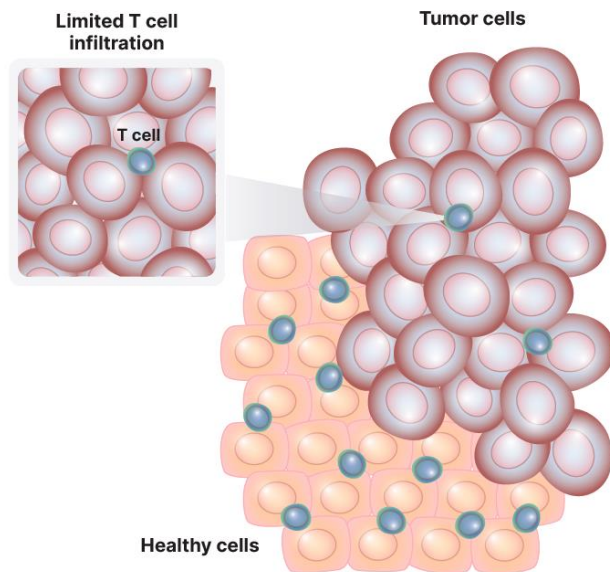
1. Afacan N et al., Abstract #2942 presented at AACR 2023; 2. Cytokine release from T cell dependent cytotoxicity assay with pan T cells and H292 tumor cells at 5:1 E:T.

Multispecific Antibody Therapeutic Development

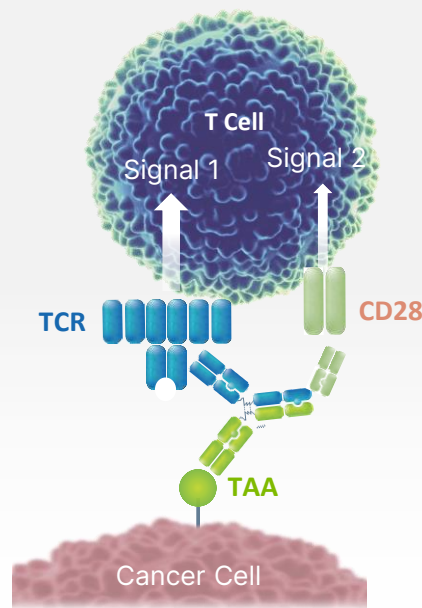
TriTCE Co-Stimulatory Therapeutic Program

Zymeworks Trispecific Co-Stimulatory TCE: Overcoming Lack of Efficacy and Durability of Responses in Solid Tumors by Optimization of Signal 1 and 2

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



Zymeworks Trispecific Co-stimulatory Program



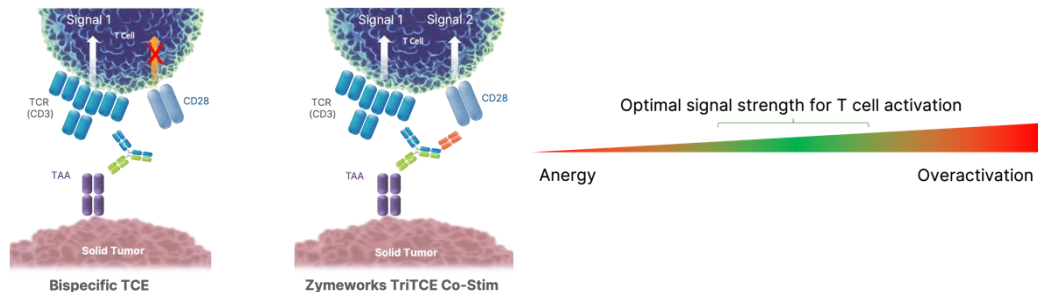
Provides Signal 1 (CD3) and Signal 2 (CD28) in one molecule to increase T cell activation and proliferation

Engineered to balance signal 1 and 2 for optimized TAA-dependent T cell activation and expansion

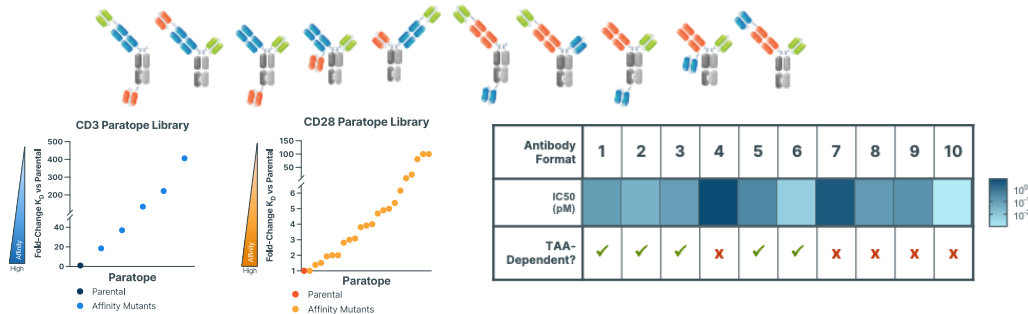
TriTCE Co-stim have the potential to provide more durable responses and reinvigorate T cell responses in 'cold' tumors with lower T cell infiltration

Novel Engineering and Screening Approach Identifies Co-stimulatory Trispecifics with Greater Anti-tumor Activity and Target-Dependent T Cell Activation

Co-stimulatory trispecific TCEs (TriTCE Co-stim) have the potential to provide more durable responses and re-invigorate 'cold' tumors with lower T cell infiltration



Novel screening approach enables identification of optimal TriTCE format and paratope affinities for robust 'Signal 1' + 'Signal 2' T cell activation and synapse formation

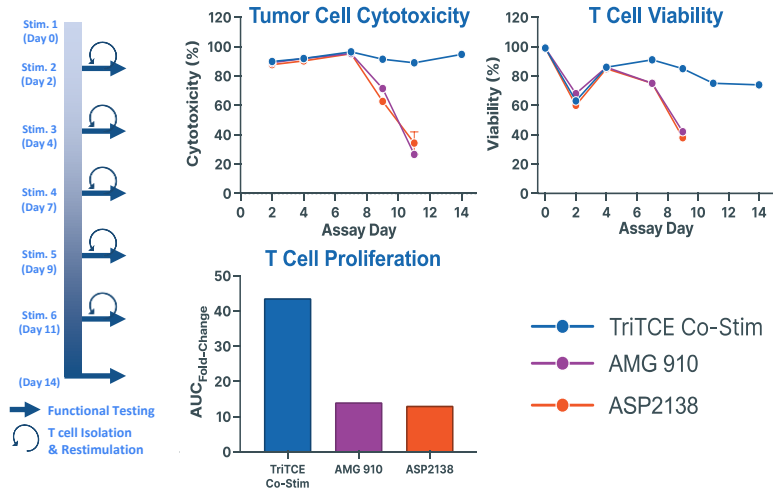


- Engineering solutions employed to optimize signal strength for T cell activation and anti-tumor activity, including modifications to paratope affinities and antibody format geometries
- In vitro screening identified TriTCE Co-stim molecules with **enhanced TAA-dependent anti-tumor activity compared to a bispecific TCE**, and transferability across TAA targets

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

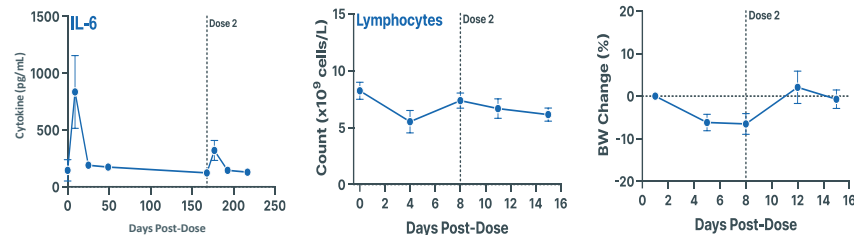
Designed to overcome prior barriers to T cell engagers through stimulating T cell proliferation and providing more durable anti-tumor control by enhancing T cell activation. Using CLDN 18.2 as a model tumor antigen:

TriTCE Co-Stim Mediates Enhanced T cell Responses and Anti-tumor Activity Relative to Comparator T cell Bispecifics



NHP Toxicology Findings Were Mild and Associated with the Known Mechanism of Action of TCEs

No histopathological changes observed in the stomach where CLDN18.2 is expressed

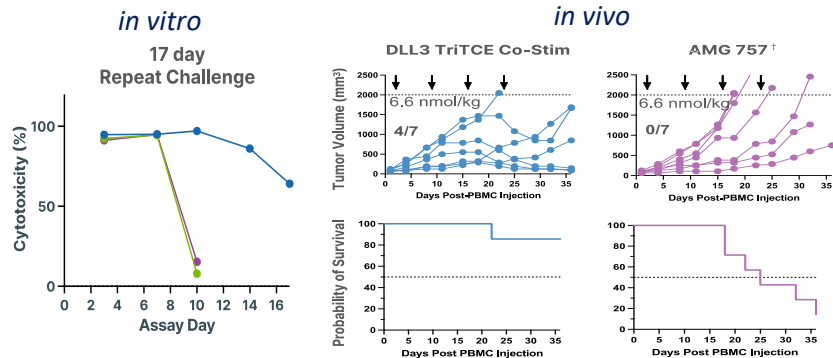


TriTCE Co-Stim has the potential to **provide more durable responses**, re-invigorate tumors with low T cell infiltration, and avoid potential toxicities such as systemic cytokine release

DLL3 TriTCE Co-Stim: A Next Generation Trispecific T Cell Engager

Designed to incorporate CD28 co-stimulatory to improve over conventional DLL3xCD3 bispecifics through durable responses by prolonging T cell survival and cytotoxicity and increasing response rates by stimulating T cell proliferation and activation in poorly infiltrated 'cold' tumors

Greater cytotoxicity compared to bispecific TCEs



Improved T Cell Survival compared to bispecific TCEs

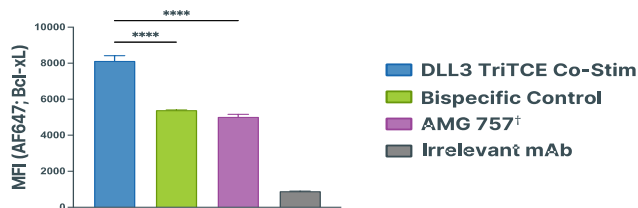
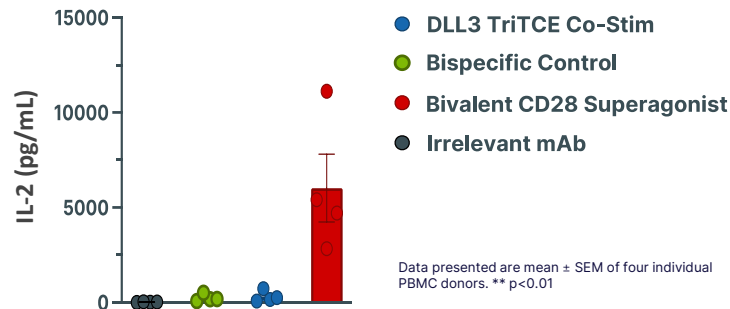


Plate-bound DLL3 TriTCE Co-Stim does not mediate IL-2 production by PBMCs

Predictive in vitro model for cytokine release syndrome (CRS)



Has the potential to **provide more durable responses by prolonging T cell-mediated cytotoxicity** as well as increasing response rates by stimulating T cell proliferation and survival

PBMC: peripheral blood mononuclear cells.

[†] AMG 757 (DLL3/CD3 BiTE) produced in-house.

Repenning P et al., Abstract #6716 Presented at AACR Annual Meeting 2024.

TriTCE Co-Stim: Differentiated Co-Stimulatory (CD28) Platform vs. Clinical Competitors

Co-stimulatory (CD28) TCE Strategies	Zymeworks' Advantage and Limitations of Alternative Strategies
Zymeworks TriTCE Co-stim ^{1,2}	<ul style="list-style-type: none"> ✓ Zymeworks TriTCE Co-Stim provides balanced CD3 and CD28 activation to prevent overactivation of T cells^{1,2} ✓ No CD28 binding in absence of CD3 engagement, potentially low risks of CD28-mediated immune related adverse events (irAEs) and demonstrated safety in in vitro and in vivo CRS models^{1,2} ✓ Platform optimized for TAA-dependent activity including low T cell binding and no T cell activation in periphery^{1,2}
CD28xTAA Bispecific (e.g. Regeneron, Xencor)	<ul style="list-style-type: none"> ❑ Optimized for strong CD28 agonism, potentially difficult to optimize by dose adjustment^{3,4} ❑ Dependent on presence of signal 1 primed T cells in TME^{3,4} ❑ Potential for severe irAEs in combination with anti-PD-1, similar to CPI toxicities^{5,6,7,8,9}
CD3xTAA + CD28xTAA Bispecific Combinations (e.g. Regeneron, Janssen, Roche)	<ul style="list-style-type: none"> ❑ Increased development and challenging dose optimization requirements for two molecules¹⁰ ❑ Potential for CD28 bispecific irAEs⁶ ❑ Challenging TAA pairs or non-overlapping epitope targets requirements³
CD28xCD3xTAA Trispecific (Sanofi)	<ul style="list-style-type: none"> ❑ High affinity CD3 and CD28 paratopes, activation of peripheral T cells^{11,12} ❑ T cell binding and TMDD observed in the periphery^{11,12} ❑ CD28 paratope based on CD28 super-agonist, potentially limiting application^{11,12}

1. Newhook et al., Cancer Res. (2023); 2. Newhook et al., JTC (2023); 3. Skokos et al., Sci. Transl. Med. (2020); 4. Dragovich et al., Cancer Research (2023); 5. Stein et al., Journal Clinical Oncology (2023); 6. Martins et al., Nature Reviews Clin Oncol (2019); 7. Eastwood et al., BJP (2010); 8. Roemer et al., Blood (2011); 9. Hui et al., Science (2017); 10. Humphrey et al. (2011) J Natl Cancer Inst. 11. Seung et al., Nature (2022); 12. Promsote et al., Nature Communications (2023).

Next Generation CD28 Co-stimulatory Trispecific T cell Engager

Designed to provide more durable responses in solid tumors and superior activity in 'cold' tumors



Therapeutic Rationale

- Next Gen TriTCE Co-stim can provide increased T cell fitness, activation, and proliferation via tumor-dependent T cell co-stimulation



Product Differentiation

- Novel approach of modular geometry and avidity screening of trispecifics to optimize T cell activation by Signal 1 and Signal 2
- TriTCE Co-stim show superior anti-tumor activity to bispecific benchmarks and exhibit no activation of T cells in absence of tumor cells



Next Milestones

- IND candidate nomination expected in 2H 2024
- Potential to expand utility to additional tumor targets

Expansion of R&D Strategy Beyond "5x5"



Long-Term R&D Strategy ("ADVANCE")

- Focus on developing new product candidates with the potential for two new IND's annually from 2027+
- Therapeutic focus to be expanded into autoimmune and inflammatory disease
- Expand research interests in multifunctional engineered cytokines and immune modulators



Therapeutic Optionality

- ADC development to focus on novel payloads and bispecific/biparatopic binding
- MSAT development to focus on novel trispecific platforms, including dual TAA's



Financial Structure

Combination of internally-funded and partnered development programs

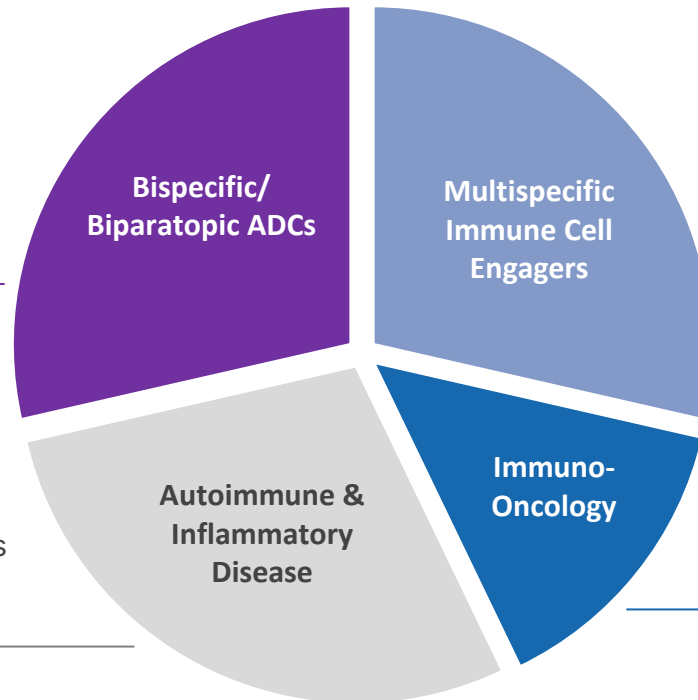
ADVANCE Portfolio Framework

Advancing design of ADCs and Multispecifics to address complex disease states

Continue to apply technology to hard-to-treat cancers and expand utility to additional therapeutic applications

ADCs

- Bispecific/Biparatopic(s)
- Novel Payload(s)
- Dual Payloads
- Solid tumors/Hem Onc



Multispecific Cell Engagers

- Next-Gen T Cell Engagers
- Alternative Immune Cell recruitment
- Dual Tumor Associated Antigens
- Solid Tumors/Hem Onc

AIID

- Bispecifics
- Dual cytokines or disease pathways
- Existing platform technology application

Additional IO

- Cytokine Engineering
- Multifunctional Immune Modulators

Potential for 2 IND-ready molecules per year from 2027+

Differentiated, Multifunctional Antibody Therapeutics for Oncology and Other Potential Diseases with the Greatest Unmet Patient Need



On A Mission to Improve the Standard of Care For Difficult to Treat Diseases

Committed to transform current standard of care for cancer patients with poor prognosis (e.g., lowest 5-year overall survival)

Potential to expand beyond oncology to AID patients



Integrated R&D Engine

5x5 portfolio provides diversity and multiple opportunities for success with 5 new IND's expected by 2026

ADVANCE provides opportunity for further innovation and broader R&D scope with 2 potential IND's annually from 2027+



Desired Product Profile

First and second-line market opportunities

Pursuing products with global peak sales potential >\$1 BN

Strategy to retain US commercial rights and collaborate in ex-US markets

1. Combinable proprietary technologies include: Azymetric™; EFECT™; ProTECT™; ADC Platform includes cysteine insertion technology and novel payloads.

Milestone Opportunities in 2024 & 2025



Cash resources as of December 31, 2023 **\$456.3M***



Current cash runway projected to support development goals into the second half of **2027 and potentially beyond**



Potential to nominate 2 candidates every year from in-house drug discovery platform



Several opportunities for business development with global rights for novel compounds



Multiple value generating opportunities expected in 2024 and 2025, with **5 IND submissions expected by 2026**



- **Top-line data from HERIZON-GEA-01** targeted for late 2024
- **Potential U.S. and China approval** for zanidatamab in 2L BTC during or before 2025

*includes cash, cash equivalents and marketable securities.

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