Early Research & Development Day

October 20, 2022

NYSE: ZYME
www.zymeworks.com

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Questions? Email ir@zymeworks.com

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Strategic Importance of Accelerating Early Research & Development (eRnD) Pipeline Efforts

- Zanidatamab partnership with Jazz Pharmaceuticals announced yesterday provides opportunity to reset near-term priorities and spending in early R&D pipeline, including ZW49
- Building a differentiated, early-stage clinical portfolio of ADCs, including ZW49, and multi-specific antibodies in difficult-to-treat cancers would provide strategic optionality for the growth of the business
- Over the next five years, our eRnD operations have capacity and capabilities to bring 5 new novel compounds into clinical studies, including ZW171 and ZW191 by 2024
- Accelerating development broadly provides opportunities for future partnerships and collaborations, and/or retaining unencumbered rights to a broad clinical product portfolio, especially in the US
- Initiatives underway to build early R&D capacity and to accelerate timelines in preclinical and early clinical development
- Processes to select and prioritize best opportunities over time with focus on potential to improve patient outcomes in commercially attractive markets

A Growing Product Candidate Pipeline of Potential Best-in-Class Therapeutics

PROGRAMS | COMMERCIAL RIGHTS	TARGET	LATE-DISCOVERY	IND-ENABLING	PHASE 1	PHASE 2	MILESTONE
LEAD PRODUCT CANDIDATES						
Zanidatamab *HER2 X HER2 Bispecific* * Jazz Pharmaceuticals ** BeiGene	HER2			Biliary Tract Cancer | *FDA Breakthrough Therapy designation* | HERIZON-BTC-01		HERIZON
	HER2			Gastroesophageal Adenocarcinomas | HERIZON-GEA-01		HERIZON
	HER2			Breast Cancer		
	HER2			HER2-Expressing Solid Tumors		
Zanidatamab Zovodotin (ZW49) *HER2 X HER2 Bispecific ADC* zymeworks ** BeiGene	HER2			HER2-Expressing Solid Tumors		
PRECLINICAL PROGRAMS						
ZW191 *TOPO1i ADC Program*	FRα			OVCA, Gynecological, NSCLC		IND: 2024
ZW171 *2+1 CD3-Engager Program*	MSLN			Pancreatic, OVCA, CRC		IND: 2024
ZW220 *TOPO1i ADC Program*	NaPi2b			OVCA, NSCLC		
ZW251 *TOPO1i ADC Program*	GPC3			Hepatocellular Carcinoma		

*Jazz to develop and commercialize across all indications in the United States, Europe, Japan.
**BeiGene to develop and commercialize in Asia Pacific countries including China, South Korea, Australia, and New Zealand (excluding Japan).

Paul Moore, PhD, Chief Scientific Officer

- Leads Zymeworks' Early Research & Development program
- Over 25 years of US-based experience in biologics drug discovery and development in biotechnology research
- Career efforts have led to the discovery and development of a range of FDA-approved and clinical-stage biologics for patients with difficult-to-treat cancers and autoimmune conditions
- Previously served as Vice President, Cell Biology, and Immunology at MacroGenics with additional experience at HGS and Celera
- He has an extensive research record co-authoring over 75 peer-reviewed manuscripts and is a named co-inventor on over 50 issued US patents
- Dr. Moore received a Ph.D. in molecular biology from the University of Glasgow. Post-Doctoral work at Roche Institute of Molecular Biology

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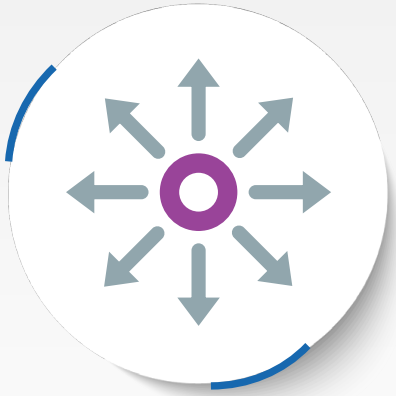
Generating Multifunctional Antibody Therapeutics for Oncology



Paradigm Shift Towards Next-Generation ADCs and Multifunctional Therapeutics

The future of drug development lies in therapeutics that target diseases with multiple mechanisms of action

Zymeworks Leading the Next Wave of Multifunctional Therapeutics

Zymeworks is at the forefront of this paradigm shift by developing multifunctional therapeutics through its proprietary platforms

Fully-Integrated R&D Pipeline from Target Selection through Pivotal Studies

Employee base with experience to discover, develop and commercialize our novel agents globally with partners and collaborators

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Novel Platforms Enable Unique and Differentiated Multifunctional Therapeutics

Platforms Driving the Next Generation of Antibody Based Therapeutics

Azymetric™

Multispecific Antibody Generation

- Biparatopic/Bispecifics
- Trivalent/Trispecifics
- Fc-Fusions
- IgG1-like biophysical, manufacturing, and purification protocols

Drug Conjugate Platforms

Fit-For Purpose ADC Candidate Creation

- ZymeLink™ Auristatin
- ZymeLink™ Hemiasterlin
- TOPO1i Platform
- Cysteine-Insertion Conjugation Platform
- Immune Stimulating (TLR7)

EFECT™

Tailored Immune Function Modulation

- Tailored sets of Fc modifications that can modulate immune cell recruitment and function
- Enhance or eliminate immune effector function to optimize therapeutics

ProTECT™

Tumor-Specific Immune Co-stimulation

- Tumor-specific activity via conditional blocking to reduce off-tumor toxicities
- Functional block adds co-stimulation or checkpoint modulation to enhance efficacy

Enable New Biology | **Modular** | **Scalable**

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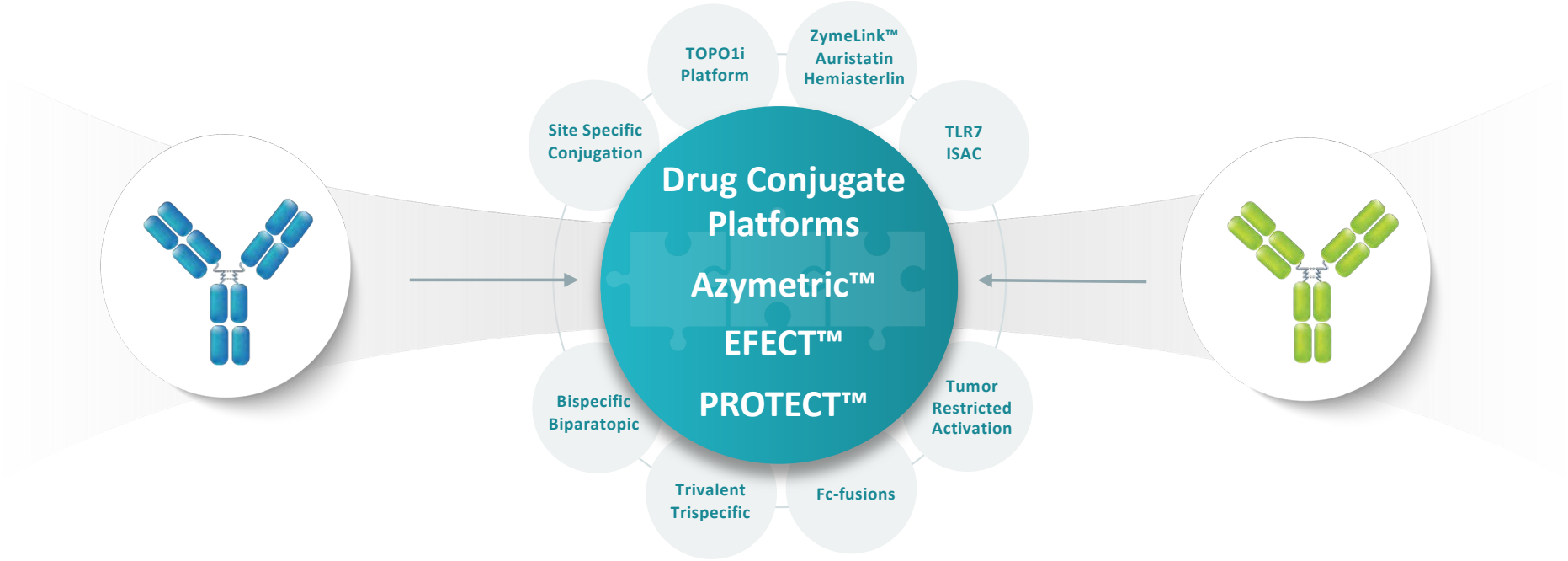
Interplay of Antibody-Based Technologies Enables Differentiation

Complementary Technology Platforms



Customize as Biology/Target Dictates

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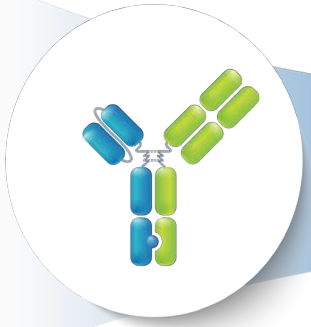
Clinically Proven: Zymeworks Technology Platforms Yield Therapeutics

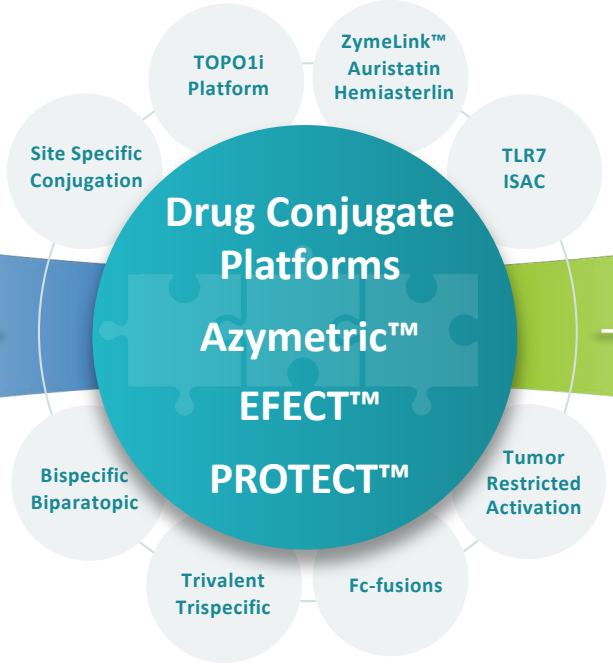
Zanidatamab (ZW25)

Biparatopic anti-HER2



Unique biology lends additional benefit achieved by mAb combinations

Pivotal clinical studies



Zanidatamab Zovodotin (ZW49)

Biparatopic anti-HER2 with proprietary auristatin payload

Efficient internalizer and payload delivery

Clinical POC study

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And is Further Validated via External Partnerships and Internal Programs

Azymetric™ → Multispecifics

T-cell Engagers

Johnson & Johnson INNOVATION e.g. JNJ-88306358 CD3 x HLA-G

Undisclosed Programs

Bristol Myers Squibb™ MERCK Daiichi-Sankyo gsk LEO

Oncology, Infectious Disease, Dermatology

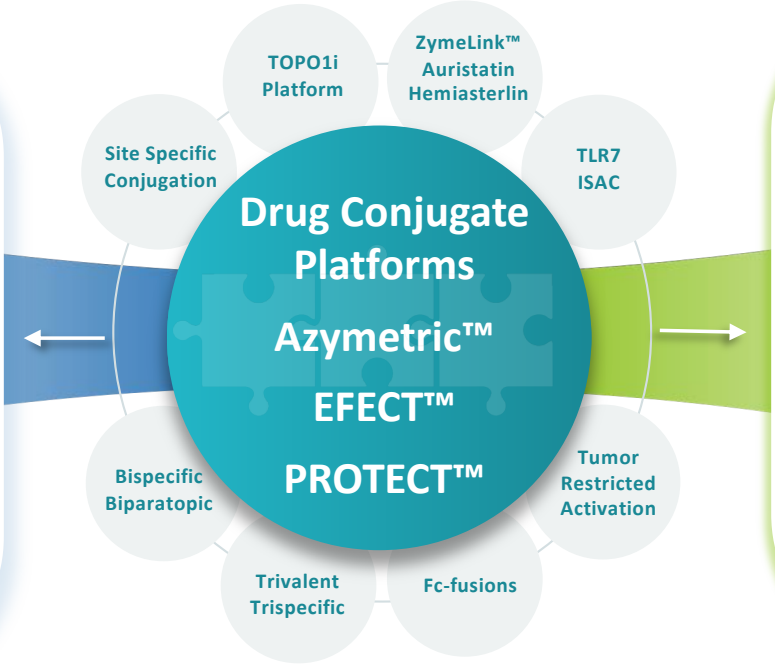
Conditional Co-stimulation

e.g. tumor dependent 4-1BB activation

Tumor Restricted Cytokine

e.g. tumor–protease released IL-12

AACR 2021



Antibody-Drug Conjugates

EXELIXIS® **Tissue Factor ADC**

XB002 (ICON-2)

AACR-EORTC-NCI 2022

ATRECA **EphA2 ADC**

ATRC-301

Immune-stimulating Antibody Conjugates (ISACs)

e.g. TLR7a- ISAC

SITC 2022

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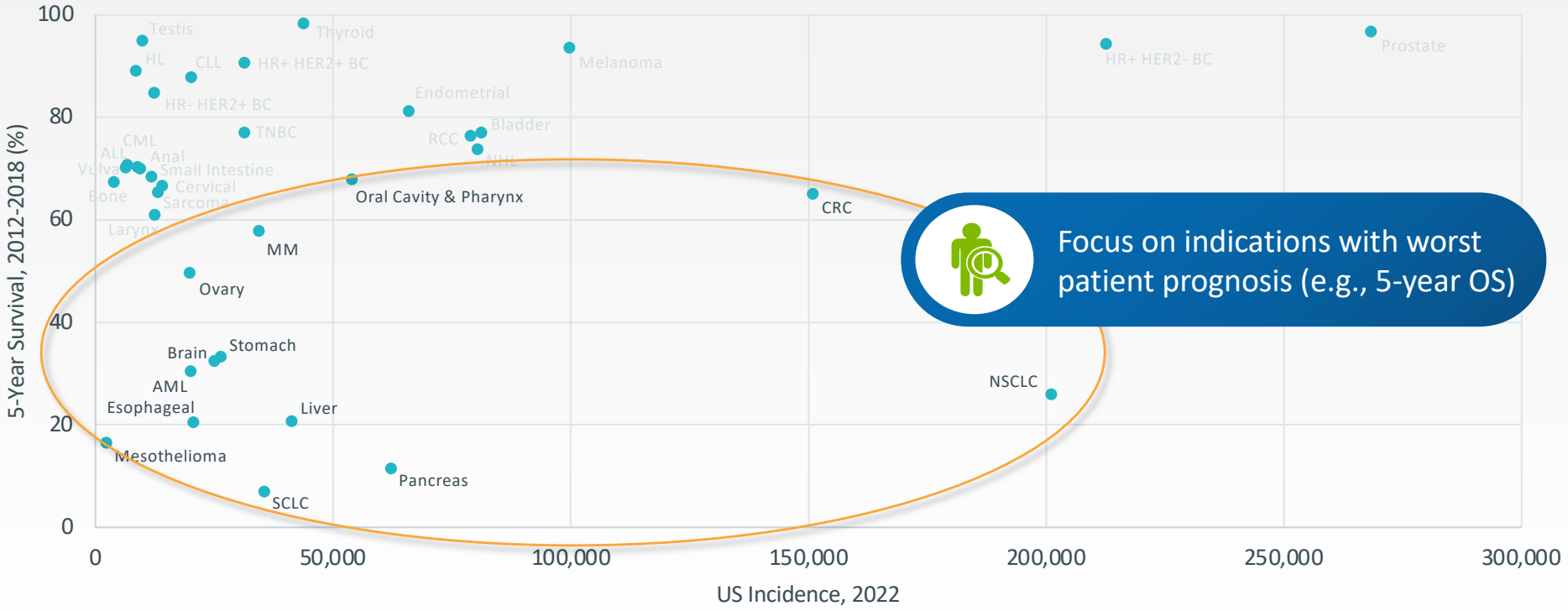
Goal: Focus on Cancer Indications with Greatest Unmet Patient Need



SEER*Explorer, accessed 10 Oct 2022

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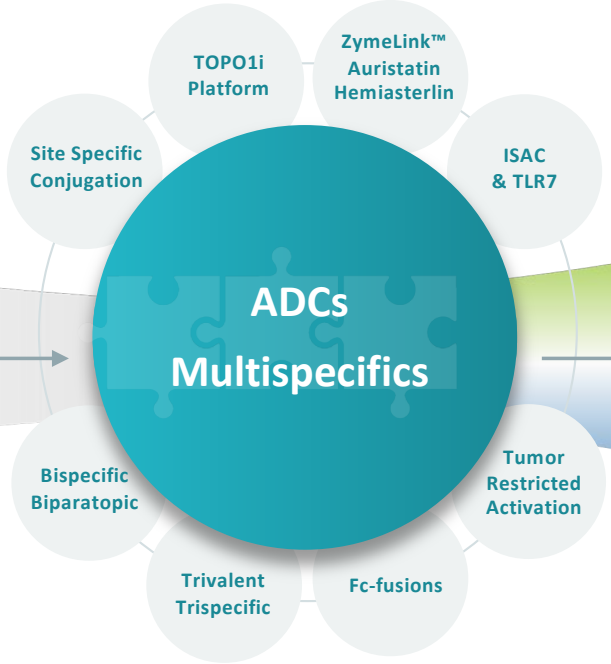
ADC and Multispecific Modalities Driving Pipeline

Select Difficult-to-Treat Cancers & Target

Design with Complementary Technology Platforms



Optionality with Two Foundational Fit-for-Purpose Modalities

Antibody-Drug Conjugates

Customization:

- Antibody properties & format
- Payload
- Linker/conjugation
- DAR

Multispecifics

Achieve:

- Multiple MoA in single molecule
- Synergistic biology
- Precision targeting through multivalency

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Zymeworks: Leading the Next Wave of BioTherapeutics

2017-2022

- Select Product Pipeline
- Platform Technologies & Tools
- Broad Platform Partnerships

2022-2027

- Increase In-House Pipeline
- Balance of ADCs and Multispecifics
- Maintain Technology Edge
- Select Product Partnerships

Our Early R&D Leadership Team

Nina Weisser, PhD
Director
Multispecific Antibody Research

Thomas Spreter Von Kreudenstein, PhD
Director
Protein Engineering

Stuart Barnscher
Director
Preclinical Programs
ADC Therapeutic Development

Jamie Rich, PhD
Director
Technology
ADC Therapeutic Development

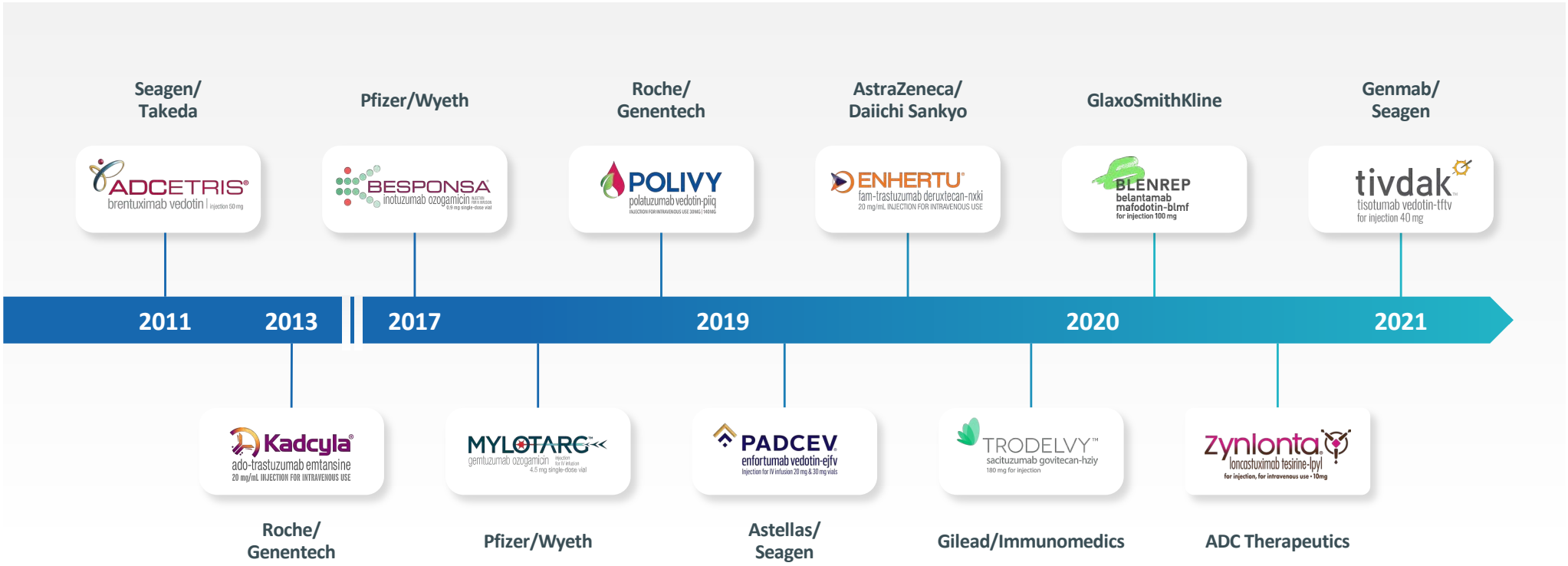
Agenda

	TOPIC	PRESENTER
Antibody-Drug Conjugates (ADC)	• Introduction to Zymeworks' Integrated Drug Conjugate Platform & Core Strategy	Stuart Barnscher
	• Topoisomerase 1 inhibitor (TOPO1i) ADC Platform	Jamie Rich
	• ZW191 – IND candidate	Stuart Barnscher
	• Additional TOPO1i ADC Assets - ZW251 and ZW220	Jamie R. & Stuart B.
	• Future directions for antibody-drug conjugates	Stuart Barnscher
Multispecifics	• Bispecific Landscape and Zymeworks' differential approach	Paul Moore
	• ZW171 - IND candidate	Nina Weisser
	• Trispecific T-cell Engager incorporating co-stimulation (TriTCE-costim)	Thomas Spreter Von Kreudenstein
	• Trispecific T-cell Engager incorporating checkpoint inhibition (TriTCE-CPI)	Thomas Spreter Von Kreudenstein

Antibody-Drug Conjugate Therapeutics

Stuart Barnscher
Director, Preclinical Programs, ADC Therapeutic Development

The Golden Age of ADCs: 64% of ADC Approvals have Occurred Over the Last 3 Years



Modified from Hanson Wade brochure, 12th World ADC, London 2022

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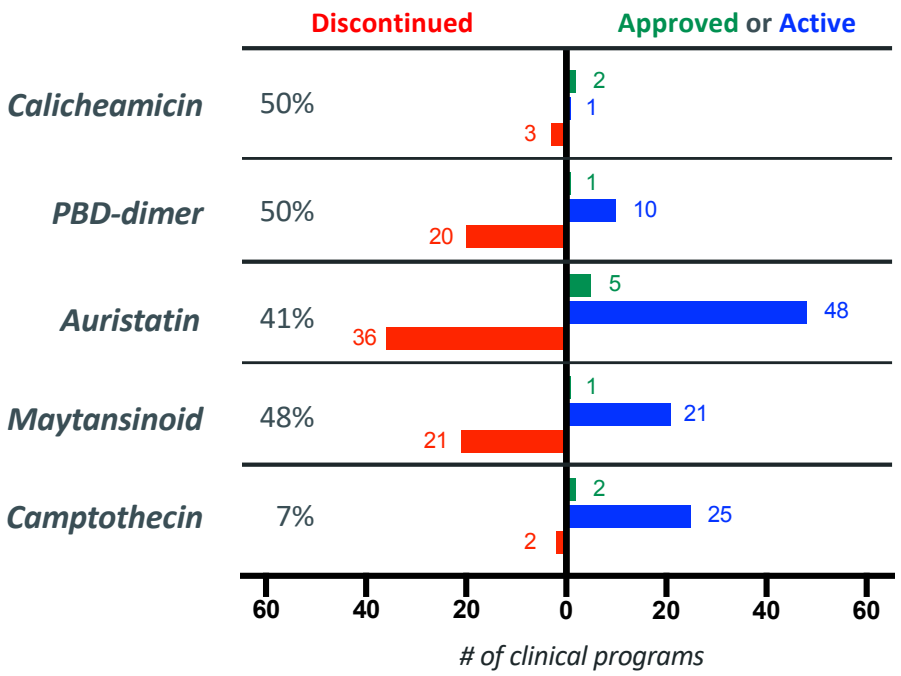
Harnessing the Power of ADCs is Not Trivial

Approved ADCs in liquid and solid tumors use a variety of payload mechanisms with a range of potency

Potency

	Liquid tumor	Solid Tumor
DNA Damaging Agents Calicheamicin PBD-dimer	BESPONSA inotuzumab ozogamicin MYLOTARG gemtuzumab ozogamicin Zynlonta loncastuximab tesirine-lpyl	
Microtubule Inhibitors Auristatin Maytansinoid	ADCETRIS brentuximab vedotin BLENREP belantamab mafodotin-blmf POLIVY polatuzumab vedotin-piiq	Kadcyla ado-trastuzumab emtansine tivdak tisotumab vedotin-tftv PADCEV enfortumab vedotin-ejfv
Topoisomerase 1 Inhibitors Camptothecin (DXd, SN38)		TRODELVY sacituzumab govitecan-hziy ENHERTU fam-trastuzumab deruxtecan-nxki

Despite recent success, the discontinuation rates are high across multiple payload mechanisms



Beacon Targeted Therapies - ADC Module (cut-off date: September 2022)

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A Successful ADC Requires the Right Tools, the Right Design, and the Right Team to Execute

The Right **Design**

Careful selection of target, antibody, linker/conjugation, and payload is required

The Right **Tools**

There is no one size fits all solution - A toolbox of ADC technologies is required

The Right **Team**

A fully integrated, multidisciplinary team dedicated to ADC development

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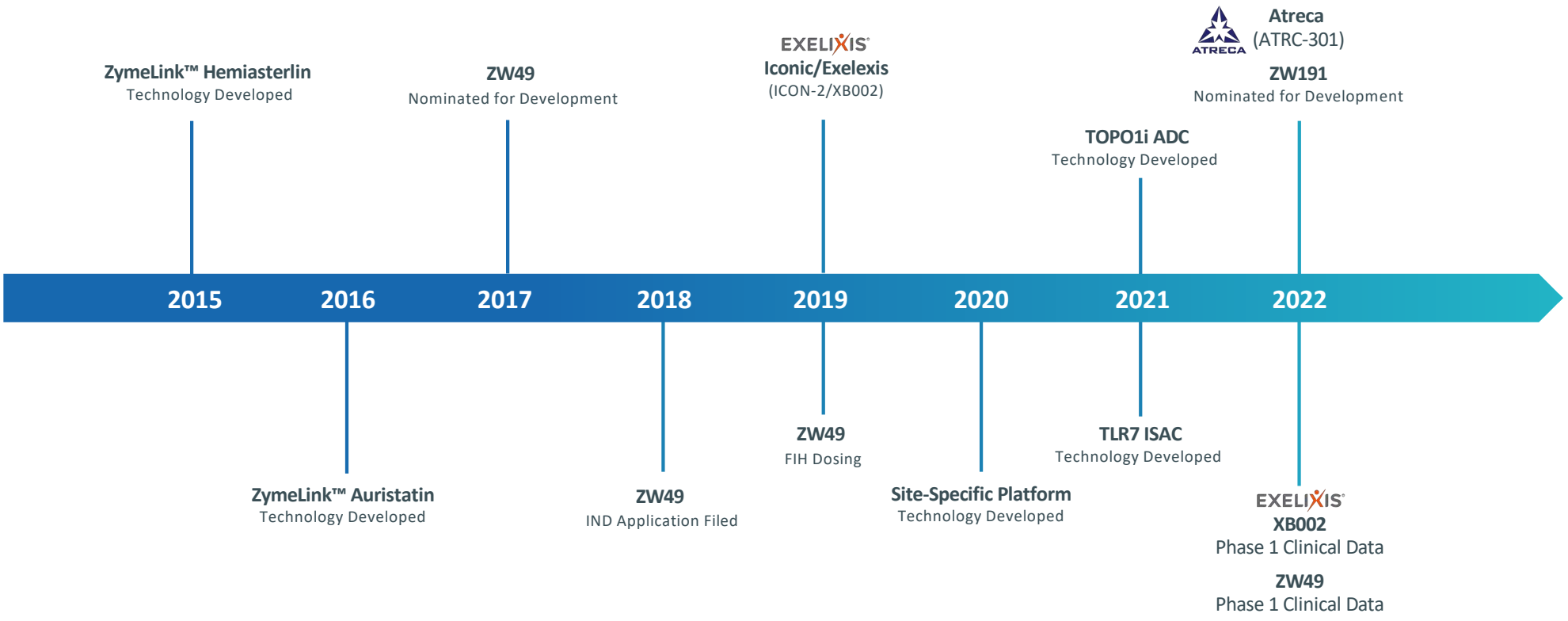
Zymeworks' Technologies Enable Fit-For-Purpose Design of ADCs

TECHNOLOGY	FEATURES	HIGHLIGHTS
ZymeLink™ Auristatin Auristatin Drug-linker	• N-acylsulfonamide spacer links auristatin core to cleavable linker • Bystander inactive • Induce markers of immunogenic cell death (ICD)	Used in: • Zanidatamab Zovodotin (ZW49) • XB002 (formerly ICON-2) • ATRC-301
ZymeLink™ Hemiasterlin Hemiasterlin Drug-linker	• N-acylsulfonamide spacer links hemiasterlin core to linker • Bystander active	• MTD ≥ 15 mg/kg in non-human primates
TOPO1i Platform Camptothecin Drug-Linker	• Novel camptothecin payload • Bystander active • ADC MTD ≥ 30 mg/kg in non-human primates	Used in pipeline programs: • ZW191 • ZW220 • ZW251
Site-Specific Conjugation Platform Cysteine-Insertion Technology	• Homogeneous conjugation at multiple sites • Combines with Azymetric™ allowing precise control of DAR	Used in non-core asset: • cMet-ZLA ADC
TLR7 ISAC Platform Immunostimulatory Drug Conjugate	• Purine-based scaffold using a peptide cleavable linker	• The Society for Immunotherapy of Cancer (SITC) 2022 abstract accepted

MTD = maximum tolerated dose

Eight Years of ADC Research and Development at Zymeworks



Our ADC Discovery Engine is Focused on Developing Pipeline Assets

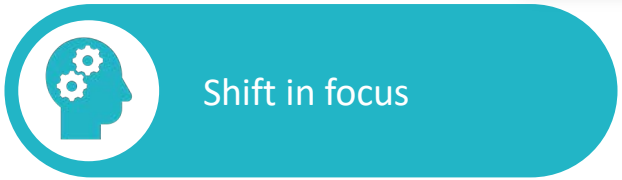
YESTERDAY

Platform Technologies & Tools

TODAY

Pipeline Assets:

- Zanidatamab zovodotin (ZW49)
- ZW191
- ZW220
- ZW251



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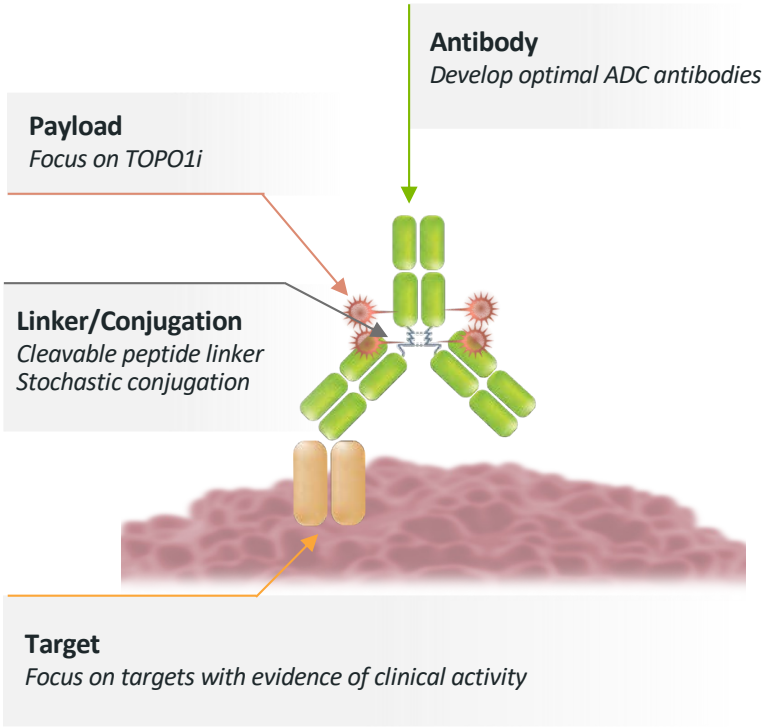
Building Clinically and Commercially Relevant ADCs Requires Careful Selection of Target, Antibody, Linker/Conjugation, and Payload

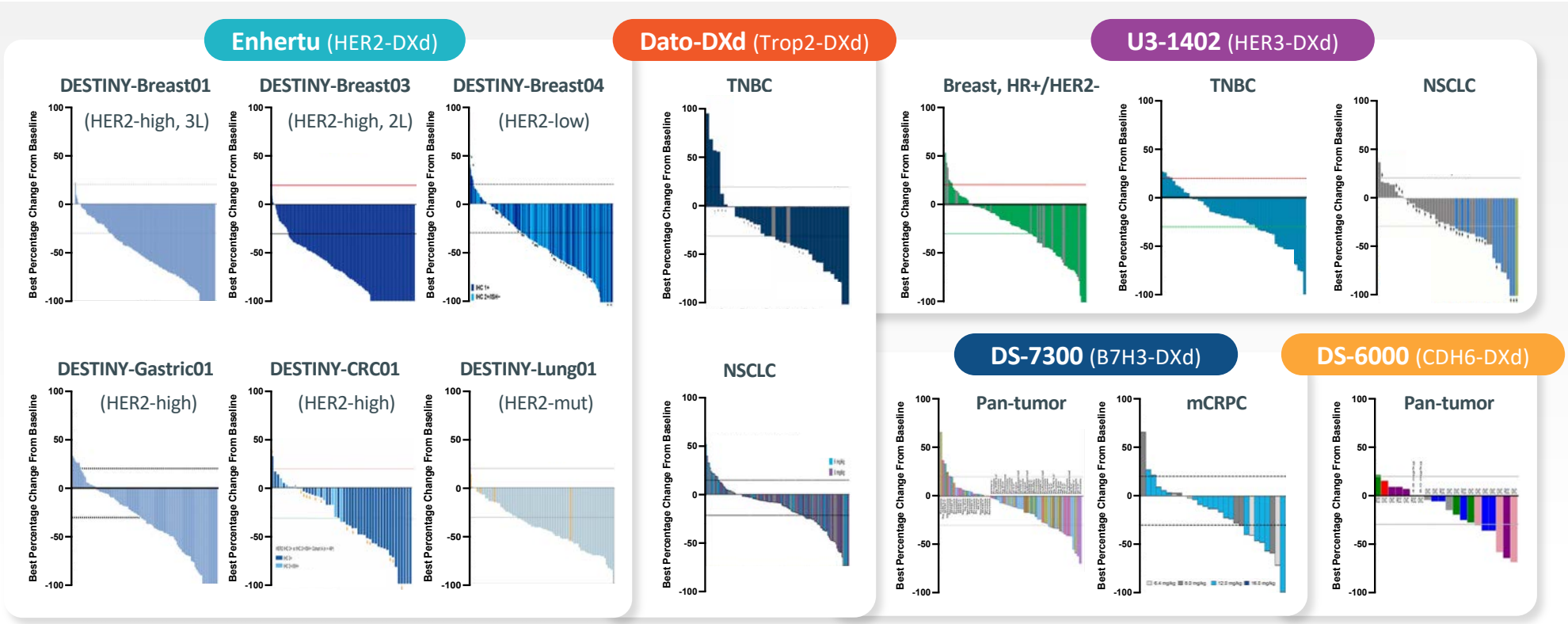
	Zymeworks Strategy Today	Rationale
Target	Focus on targets with evidence of clinical activity in indications of unmet need	Known targets are still actionable with the right technology and the right design
Antibody	Develop optimal ADC antibodies	Antibodies specifically selected for ADC use can increase the likelihood of success
Linker/ Conjugation	Leverage validated peptide-cleavable linkers & stochastic conjugation	Peptide-cleavable linkers are used in 55% of approved ADCs Stochastic conjugation is used in 100% of approved ADCs
Payload	Focus on novel TOPO1i ADC Platform	TOPO1i ADCs are providing meaningful benefits to patients



Topoisomerase 1 Inhibitor (TOPO1i) ADC Platform

Dr. Jamie Rich
Director, Technology, ADC Therapeutic Development

Topoisomerase 1 Inhibitor ADCs are Providing Meaningful Benefit to Patients



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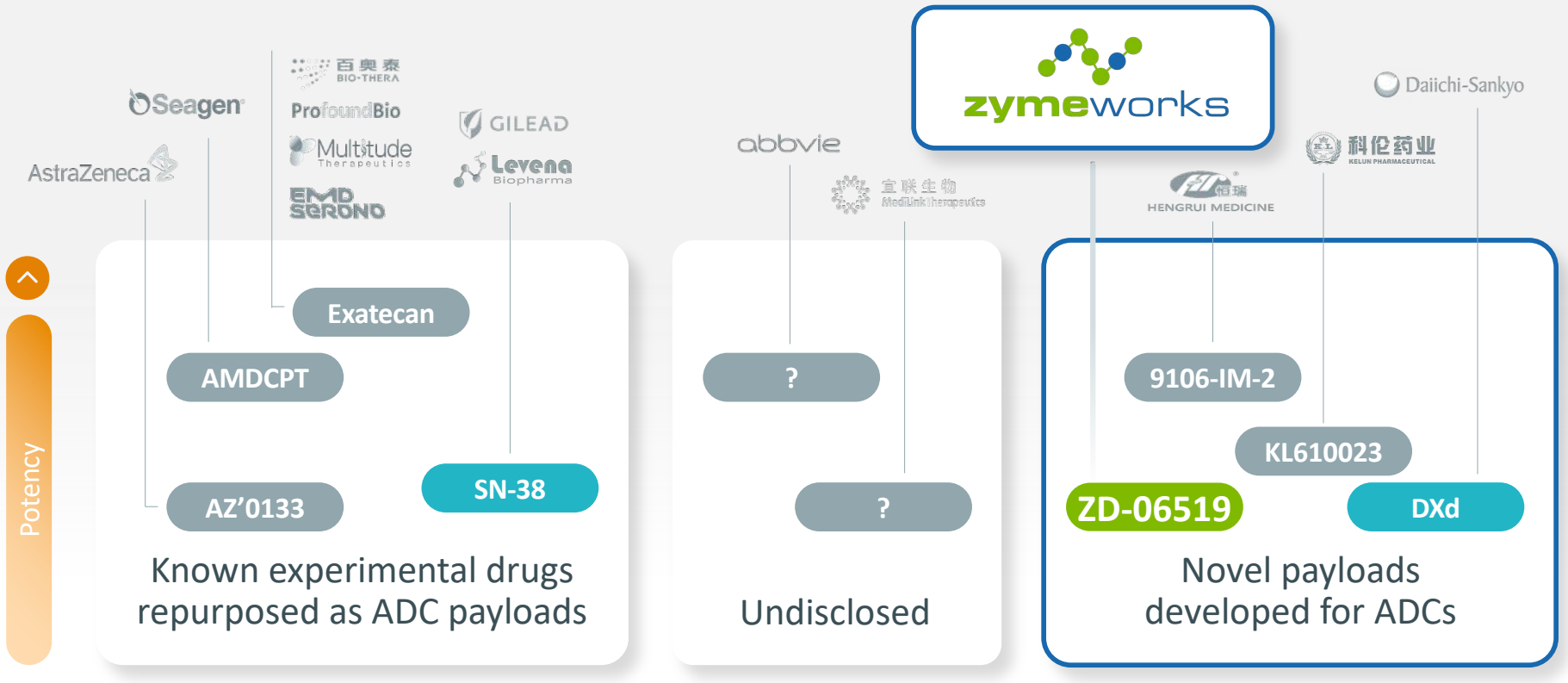
Clinical Stage TOPO1i ADC Competition Highlights Two Distinct Strategies



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

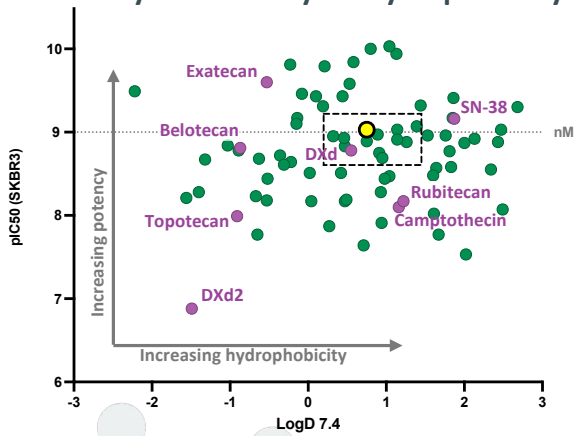
The Payload is Only One Critical Component of ADC Development

PAYLOAD

Novel camptothecin with moderate potency and strong bystander activity

- Acknowledges complex mechanisms driving TOPO1i ADC action
- Sufficient tolerability to achieve ADC dose > 5 mg/kg

Payload Potency vs. Hydrophobicity



LINKER

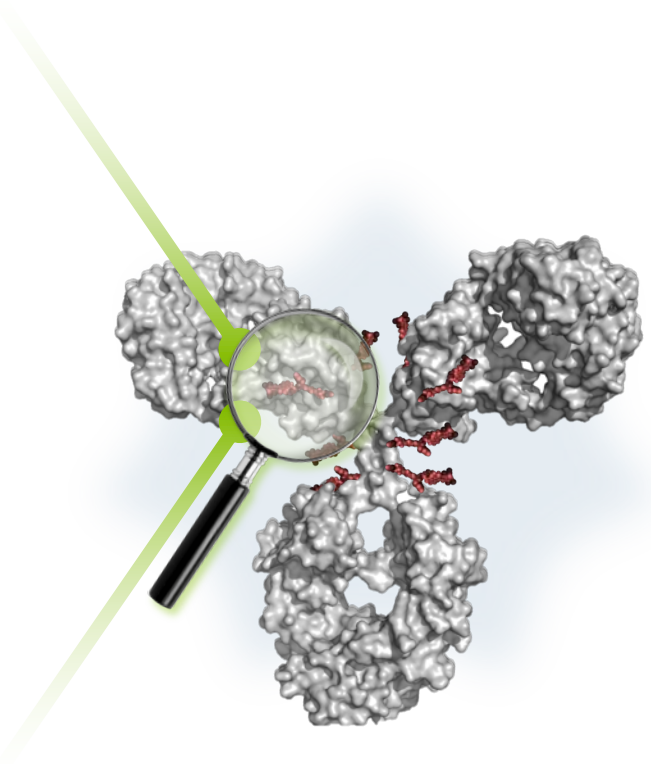
Traceless, plasma-stable, cleavable peptide

- Common to majority of approved ADCs
- Compatible with desired bystander activity

CONJUGATION

Thiol-maleimide chemistry

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



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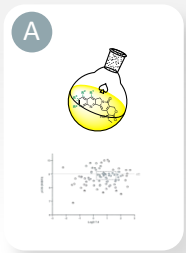
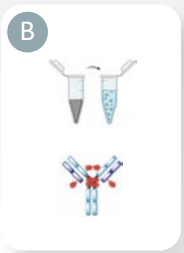
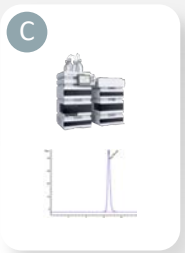
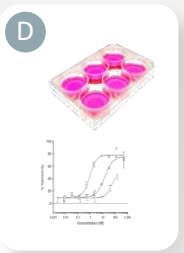
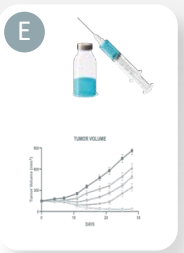
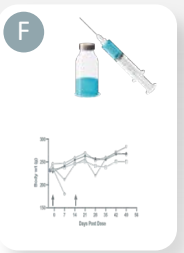
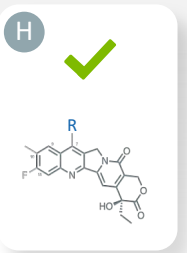
Robust Interrogation Yields Pipeline Ready Topoisomerase ADC Platform

From concept to pipeline:

Payload synthesis & screening	Conjugation of select payloads	ADC biophysical characterization	In vitro potency & stability	In vivo anti-tumor activity & PK	Rodent tolerability	Non-human primate toxicology & TK	Lead selection
A	B	C	D	E	F	G	H
							

From platform to pipeline

100	8	80	17	21	3	3
Payloads	Tumor targets	Cell lines	CDX models	PDX models	PK studies	Tox & TK studies

3 Pipeline programs
ZW191, ZW220, ZW251

Additional early-stage assets

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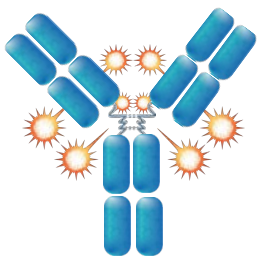
ZW191

A Potential Best-in-Class ADC Targeting Folate Receptor Alpha

Stuart Barnscher
Director, Preclinical Programs, ADC Therapeutic Development

ZW191- Folate Receptor Alpha Topoisomerase-1 Inhibitor ADC



ZW191

Target

Folate receptor alpha (FRα, FOLR1) is a clinically validated ADC target

FRα is over-expressed on the cell surface of ovarian cancer, other gynecological cancers, and additional high incidence solid tumors with unmet medical need (NSCLC, TNBC, etc.)

Antibody

Internally discovered, novel IgG1 monospecific antibody

Optimal internalization, payload delivery and tumor penetration

Drug Linker

Cysteine conjugated, DAR8, protease cleavable, traceless drug-linker

Novel bystander-active topoisomerase-1 inhibitor

Status

MTD ≥ 30 mg/kg in two dose non-human primate (NHP) toxicology study, with favorable PK

Strong anti-tumor activity in models with a range of expression

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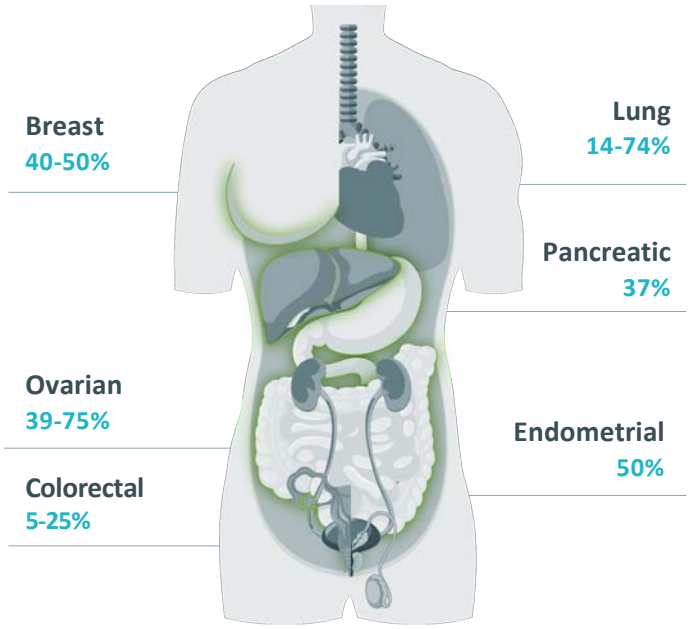
Folate Receptor Alpha is a Relevant and Exploitable Target in Cancer

Structure	Glycosylphosphatidylinositol (GPI)-anchored membrane protein
Normal Tissue Expression	Apical surfaces of tissues including, intestine, lung, Fallopian tube, placenta, choroid plexus. Luminal surface of kidney.
Cancer Tissue Expression	Elevated expression in numerous gynecological cancers including ovarian, and in NSCLC, TNBC.
Ligands	Folate
Function	Internalization of folate via endocytosis.

FOLATE RECEPTOR ALPHA EXPRESSING CANCERS



Expression levels cited from multiple sources including: Senol S et al 2015; Ayada et al. Med Mol Morphol 2018; Oza AM SGO 2021; O'Shannessy DJ et al Oncotarget 2012; Nunez MI et al 2012; D'Angelica et al. Mod Path 2011; Nature Review: Clinical Oncology; Vol. 17 June 2020.

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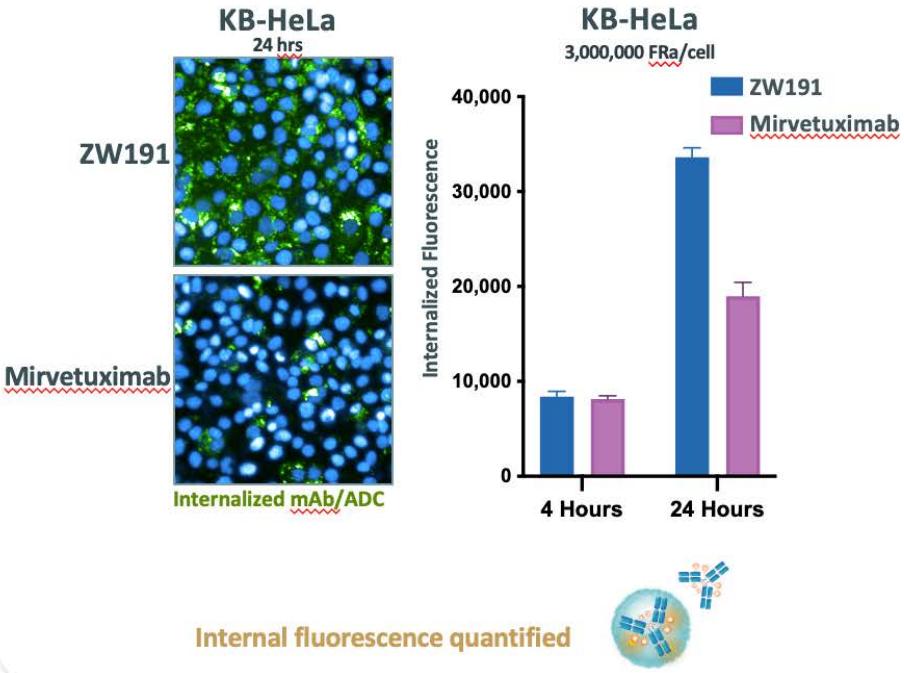
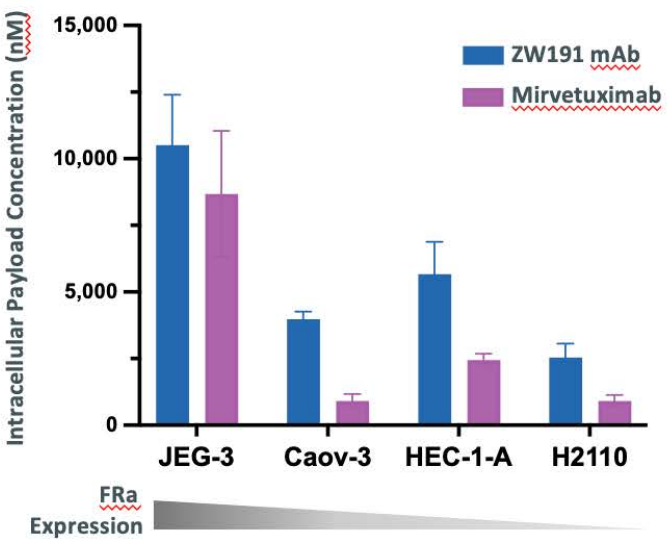
ZW191 Demonstrates Optimal Internalization and Payload Delivery

Superior Internalization Compared to Mirvetuximab



Superior Payload Delivery Compared to Mirvetuximab



The ZW191 mAb shows greater intracellular payload delivery compared to Mirvetuximab in FRα-expressing cell lines

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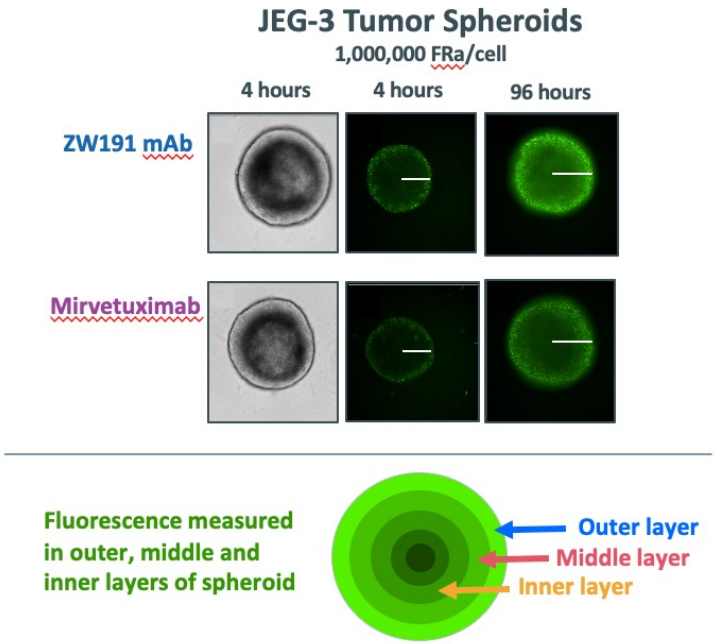
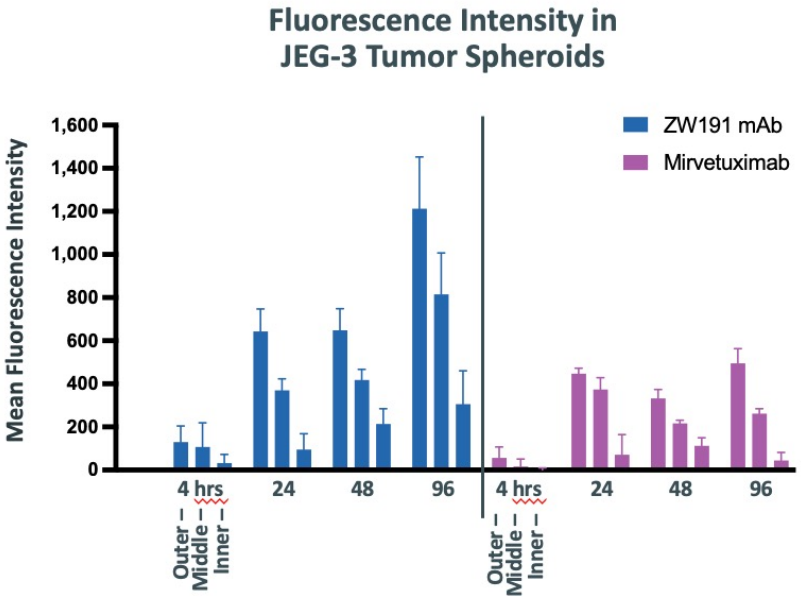
ZW191 Demonstrates Optimal Tumor Spheroid Penetration

Superior Tumor Spheroid Penetration Compared to Mirvetuximab





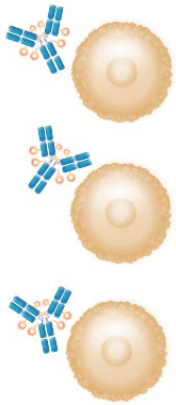
ZW191 Exhibits Strong Bystander Activity In Vitro

Bystander Activity in Tumor Cell Co-culture Assay

In Vitro Bystander Assay:

Monoculture

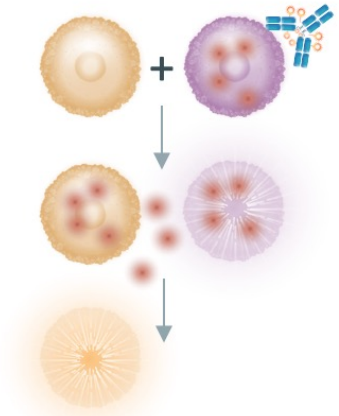
FRα⁻ cells
MDA-MB-468



No cytotoxicity in FRa-negative cells

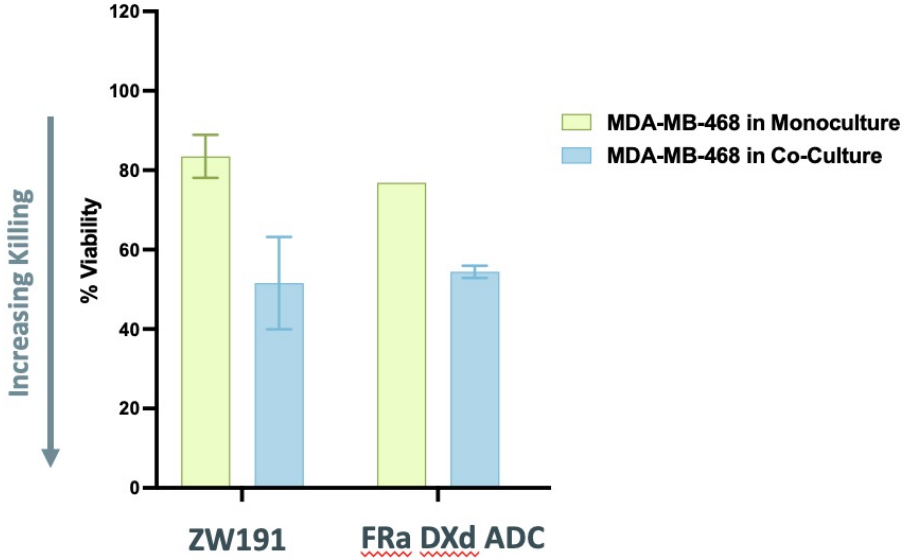
Co-culture

FRα⁻ cells MDA-MB-468 + FRα⁺ cells JEG-3



Cytotoxicity in FRα-negative cells when in co-culture with FRa-positive cells

Viability of Antigen Negative Cells



DXd Control ADC contains same mAb as ZW191, conjugated to DXd

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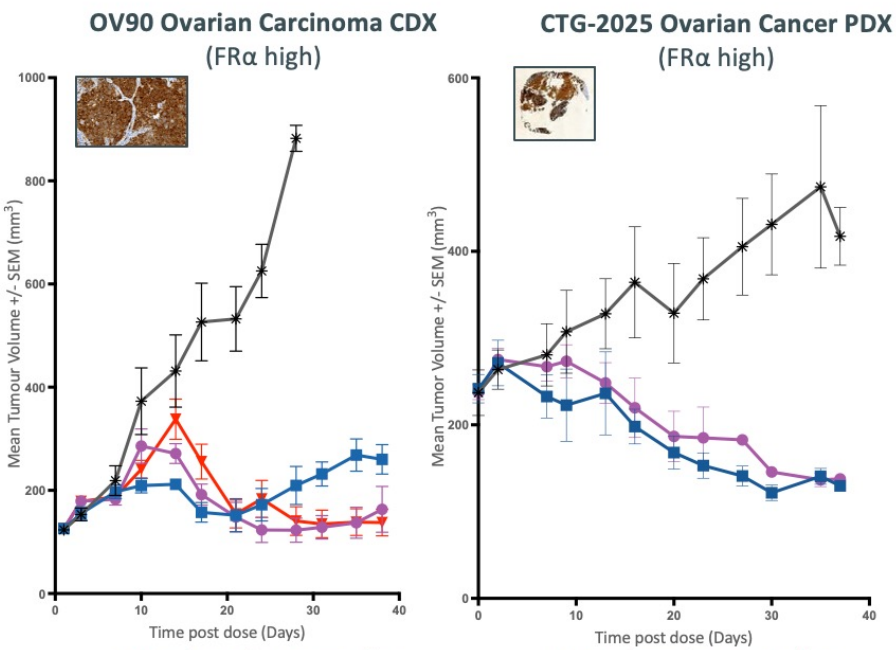
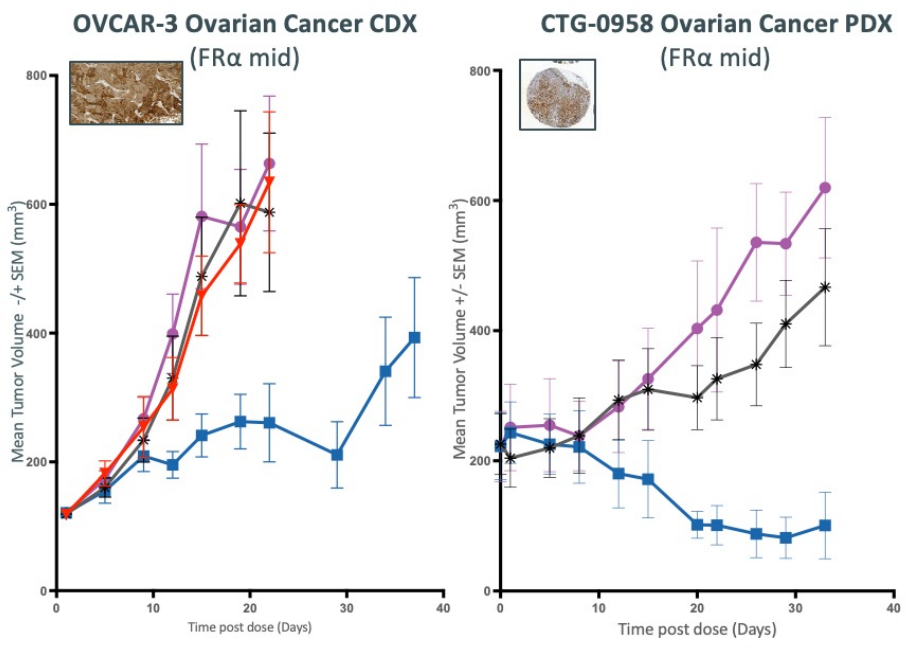
ZW191 Demonstrates Strong Anti-Tumor Activity in FRα-Expressing Models

Equivalent Anti-Tumor Activity Compared to Competitors in FRα-High Expressing Xenograft Models



Superior Anti-Tumor Activity Compared to Competitors in FRα-Mid Expressing Xenograft Models

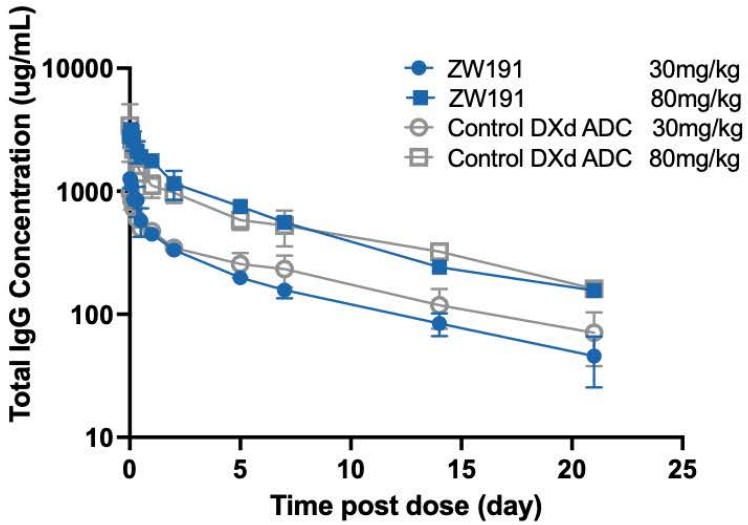


ZW191 is Well-Tolerated in Rodent & Non-Human Primates

- Tolerated at 30 mg/kg Following Two IV Doses every 3 Weeks in Non-Human Primates (antigen-binding species)
- ZW191 Demonstrates tolerability up to 200 mg/kg Following Dosing in Mice and Rats (non-antigen binding species)

Two-dose (Q3W) Non-Human Primate Toxicology Study		
Test Article	**Dose (mg/kg)**	**Tolerated?**
Vehicle	N/A	Yes
ZW191	30	Yes
	80	No
Control DXd ADC	30	Yes
	80	No

Note: Control DXd ADC contains the same mAb as ZW191 conjugated to DXd



Strong anti-tumor activity and NHP tolerability predict a favorable therapeutic index

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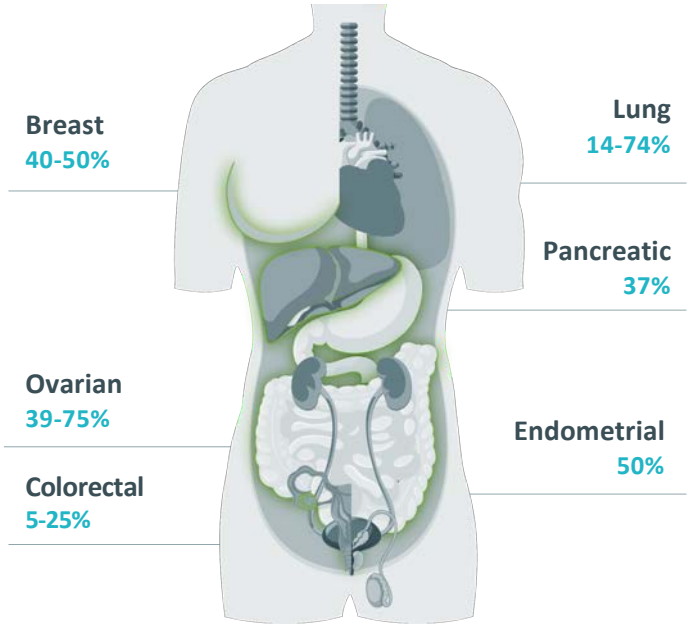
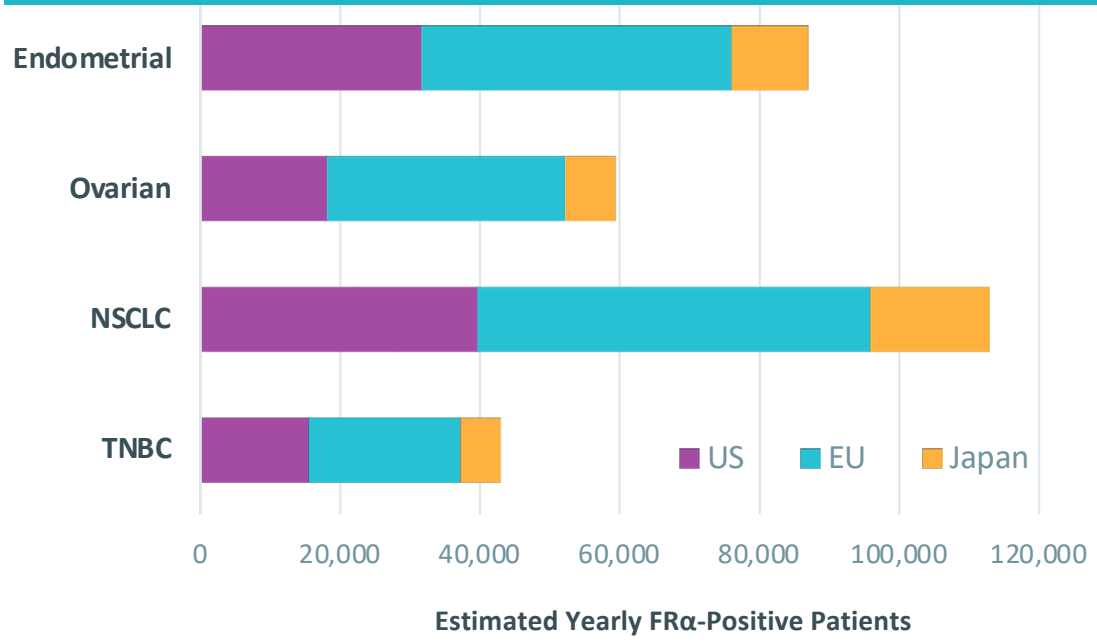
FRα-Expressing Cancers Represent a Significant Commercial Opportunity

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

FOLATE RECEPTOR ALPHA EXPRESSING CANCERS



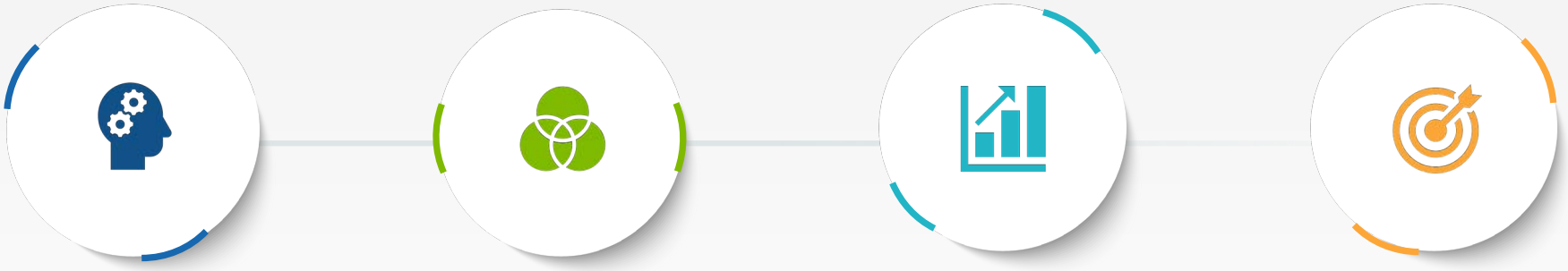
ESTIMATE OF NEWLY-DIAGNOSED FRα+ PATIENTS IN KEY INDICATIONS



Expression levels cited from multiple sources including: Senol S et al 2015; Ayada et al. Med Mol Morphol 2018; Oza AM SGO 2021; O'Shannessy DJ et al Oncotarget 2012; Nunez MI et al 2012; D'Angelica et al. Mod Path 2011; Nature Review: Clinical Oncology; Vol. 17 June 2020.

ZW191: A Differentiated FRα Targeting ADC

Development underway and on track for 2024 IND



Therapeutic Rationale

FRα is a clinically validated ADC target in ovarian cancer with good potential in other gynecological and solid tumors.

Topoisomerase-1 inhibition is a clinically validated MOA in ovarian cancer and other solid tumors

Product Differentiation

Compelling internalization, payload delivery, tumor penetration and anti-tumor activity

Novel topoisomerase-1 inhibitor likely to provide a **differentiated safety profile** compared to MIRV and STRO-002

Opportunity

Potential best-in-class opportunity to improve over MIRV in FRα-high ovarian cancer

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

Next Milestones

GMP process development underway

GLP toxicology study scheduled

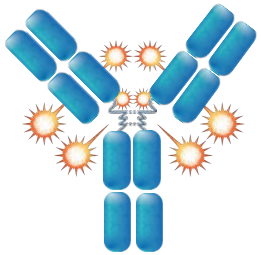
IND 2024

ZW251

A Potential First-in-Class ADC Targeting Glypican-3

Dr. Jamie Rich
Director, Technology, ADC Therapeutic Development

ZW251 – A Glypican-3 Topoisomerase-1 Inhibitor ADC



ZW251

Target

Glypican-3 (GPC3) is a clinically validated target

GPC3 is over-expressed on the cell surface of hepatocellular carcinomas (HCC)

Antibody

Novel IgG1 monospecific antibody

Strong binding and internalization in GPC3-expressing cells

Drug Linker

Cysteine conjugated, protease cleavable, traceless drug-linker

Novel bystander-active topoisomerase-1 inhibitor

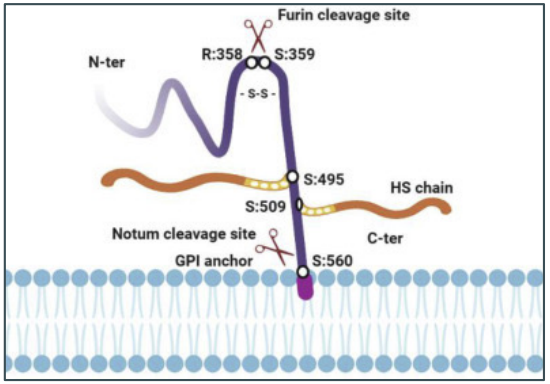
Highlights

Strong anti-tumor activity observed in preclinical models with a range of GPC3 expression

Favorable PK profile in Tg32 mice

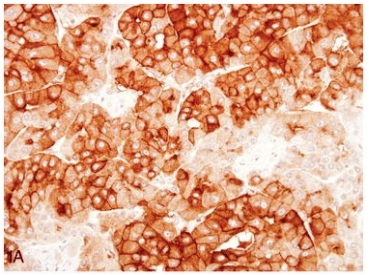
Localization and Expression Profile of GPC3 is Ideal for ADC Targeting

Structure	Glycosylphosphatidylinositol (GPI)-anchored oncofetal membrane protein
Normal Tissue Expression	Expressed in placenta and fetal tissue, such as liver, lung and kidney, but down regulated in adult tissues
Cancer Tissue Expression	High and homogenous expression in >70% of HCC Limited expression in normal adult tissues and non-neoplastic liver lesions
Function	Regulates morphogenesis and growth, possibly via Wnt, hedgehog, fibroblast growth factor, bone morphogenic factor and/or insulin-like growth factor signaling.

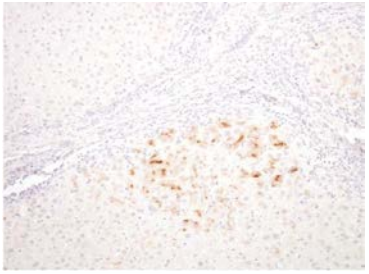


Shih T et al. Liver Research, 2020, https://doi.org/10.1016/j.livres.2020.11.003

Hepatocellular Carcinoma



Cirrhotic Liver



As determined by immunohistochemistry using 1G12 antibody.
Adapted from Wang et al. 2008. *Arch. Pathol. Lab. Med.*

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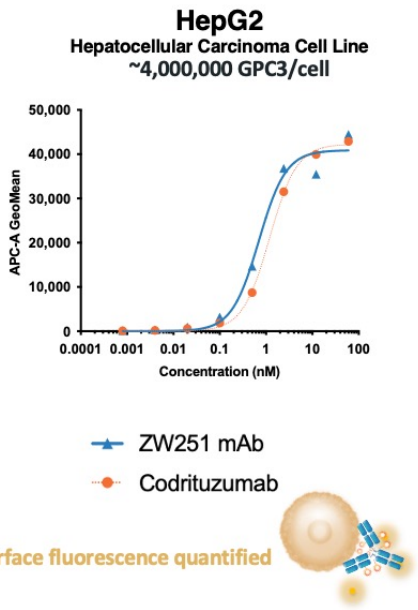
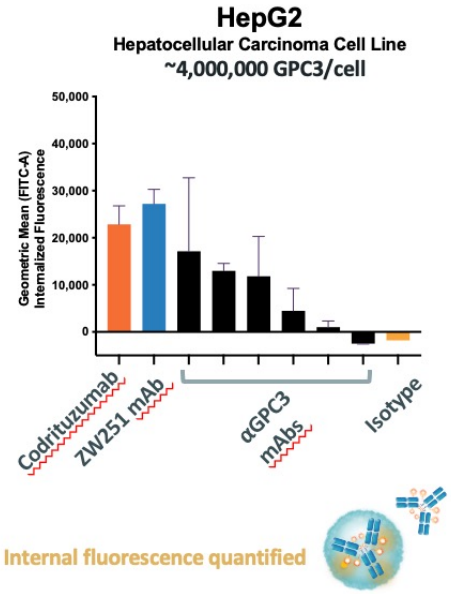
ZW251 Exhibits Desired In Vitro Functional Characteristics

Strong Cellular Binding



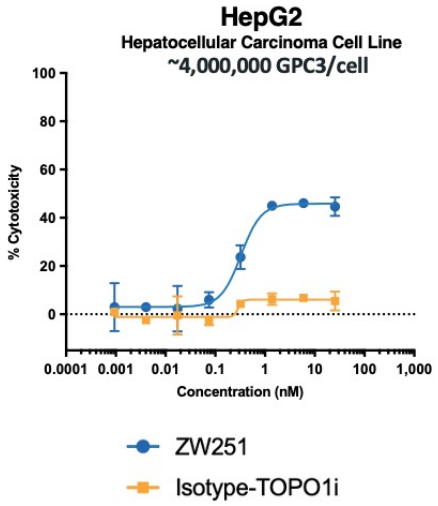
Strong tumor binding comparable to clinical-stage antibody Codrituzumab

Optimized Cellular Internalization



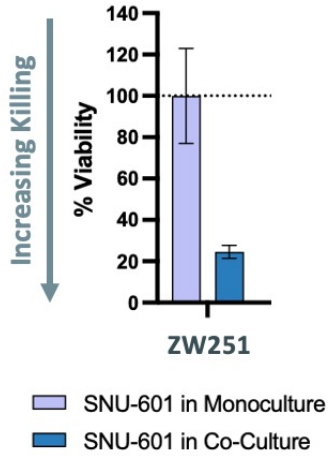
ZW251 antibody selected based on distinguished internalization in HCC tumor cells

Potent Tumor Spheroid Killing



Potent and selective dose-dependent killing of GPC3-expressing tumor spheroids

Bystander Activity in Co-culture Assay



Strong bystander killing of GPC3-negative SNU-601 cells when co-cultured with GPC3-positive tumor cells

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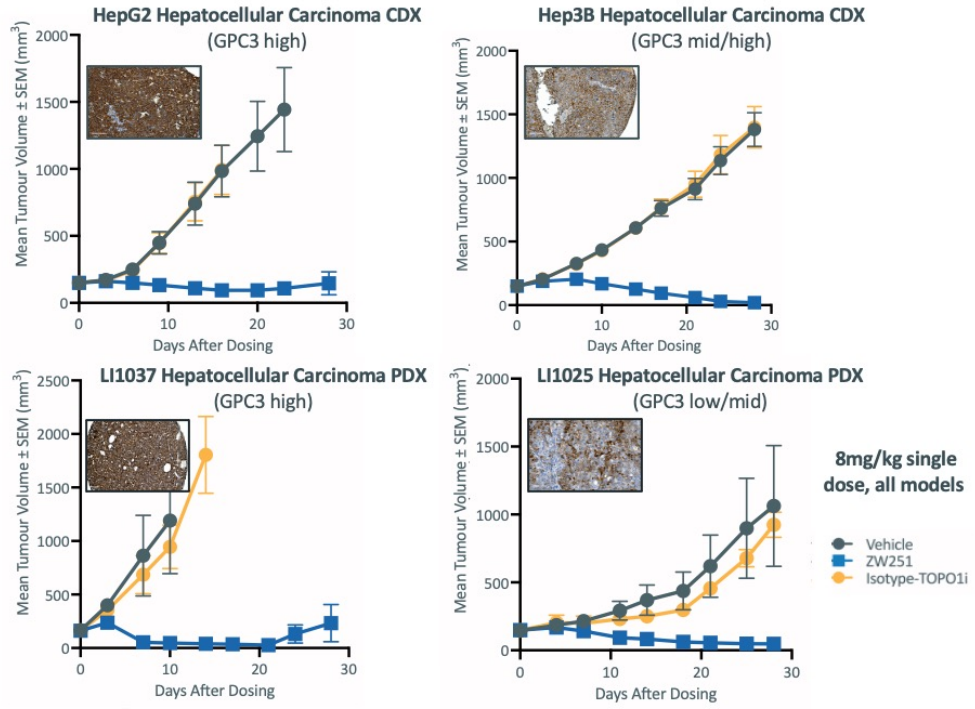
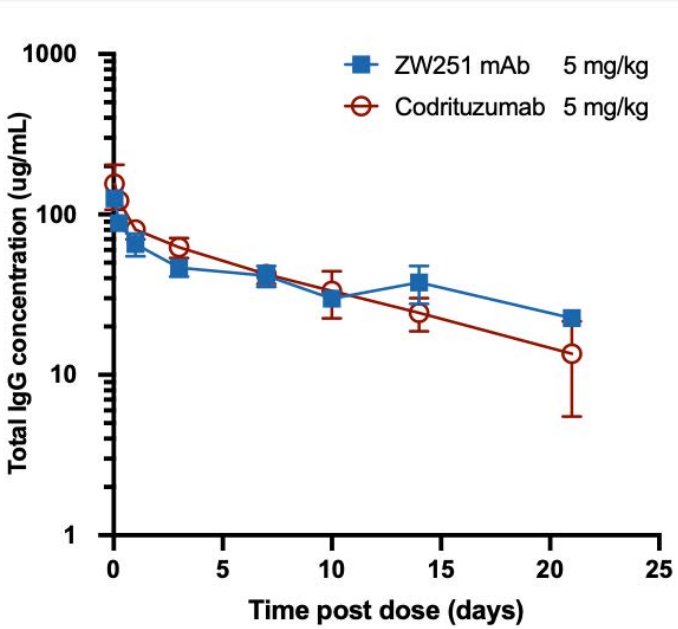
ZW251 Exhibits Strong Anti-Tumor Activity in Multiple Models of Liver Cancer

Selective Anti-Tumor Activity Across Models with Diverse GPC3 Expression



ZW251 Antibody has Favorable Pharmacokinetics



Tg32 mouse model is considered predictive of human PK

ZW251 Takeaways

A first-in-class Glypican-3 targeting topoisomerase-1 inhibitor ADC

Therapeutic Rationale

Hepatocellular carcinoma is a disease with limited treatment options and increasing mortality

Glypican-3 is a prevalent and selective marker for hepatocellular carcinoma

Product Differentiation

Novel antibody with strong target binding and internalization

Novel bystander-active topoisomerase-1 inhibitor ADC presents an alternative MOA in hepatocellular carcinoma

Promising anti-tumor activity in preclinical models

Opportunity

Potential first-in-class opportunity for an ADC against hepatocellular carcinoma

Next Milestone

Pilot NHP toxicology study initiated

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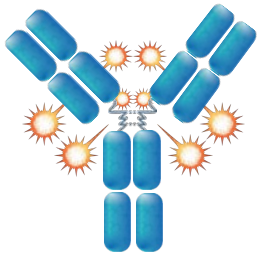
ZW220

A Potential Best-in-Class ADC Targeting NaPi2b

Stuart Barnscher
Director, Preclinical Programs, ADC Therapeutic Development

ZW220 – A NaPi2b Topoisomerase-1 Inhibitor ADC



ZW220

Target

NaPi2b (SLC34A2) is a clinically validated target

NaPi2b is over-expressed in ovarian cancer, NSCLC, and other solid tumors

Antibody

Internally discovered, novel IgG1 monospecific antibody

Strong target binding and optimal internalization

Drug Linker

Stochastic, cysteine conjugated, protease cleavable, traceless drug-linker

Novel bystander-active topoisomerase-1 inhibitor

Highlights

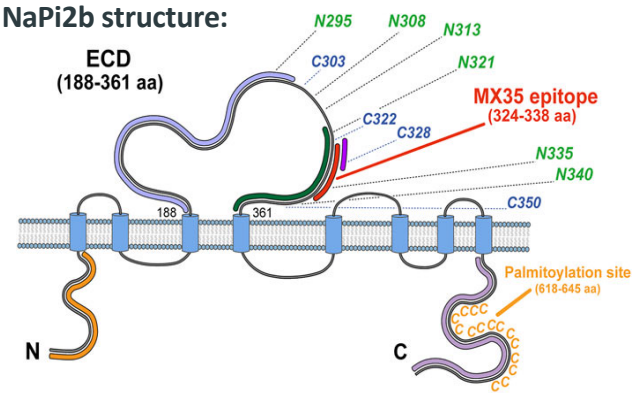
Promising anti-tumor activity in preclinical models

Favorable PK profile in Tg32 mice

NaPi2b is a Promising and Clinically Validated ADC Target for the Treatment of Solid Tumors

Structure	NaPi2b (SLC34A2) is a multi-transmembrane protein, consisting of 4 extracellular loops
Normal Tissue Expression	Normal NaPi2b expression in epithelial cells of the lung, small intestine, and in mammary gland
Cancer Tissue Expression	Highly expressed in 90% of ovarian cancer, 60-80% of non-small cell lung cancer, and 95% endometrial cancers
Function	NaPi2b functions as a sodium phosphate transporter and contributes to phosphate homeostasis

NaPi2b structure:



NaPi2b mAb Epitopes:

- 188-300 aa (Megale et al., 2016)
- 320-361 aa (Lin et al., 2015)
- 323-330 aa (Bobeck et al., 2015)
- 1-100 aa (N-NaPi2b (15/1) Gryshkova et al.
- N-terminal domain (Cell Signaling, Abcam, and others)
- C-terminal domain (Cell Signaling, Abcam, and others)
- 324-338 aa epitope MX35 region (Yin, Kiyamova et al., 2008)

Front. Mol. Biosci. 2022 Jul; DOI: doi.org/10.3389/fmolb.2022.895911

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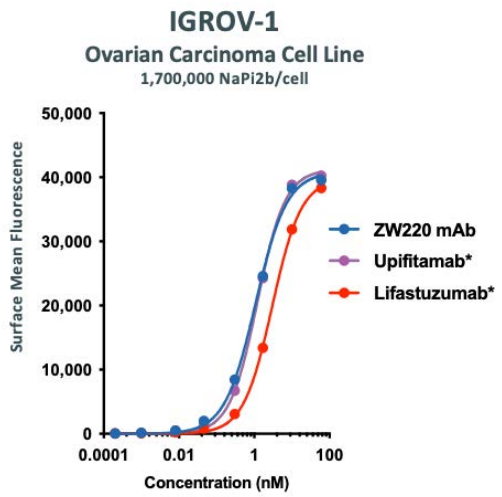
ZW220 Demonstrates Strong Target Binding and Optimal Internalization

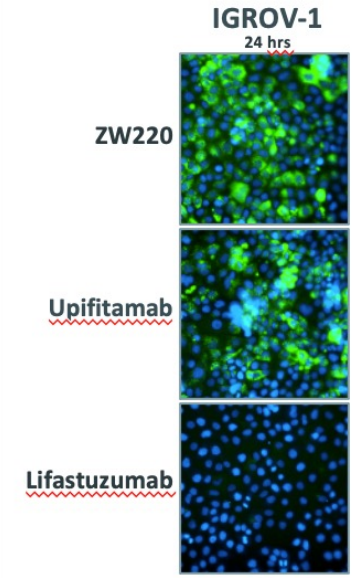
Strong Cellular Binding

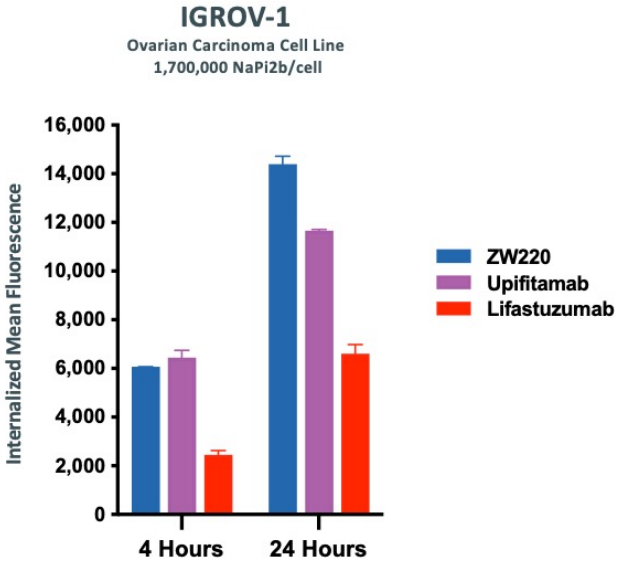


*Conjugated version; conjugation does not affect binding affinity

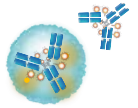
Surface fluorescence quantified

Superior Internalization to Lifastuzumab





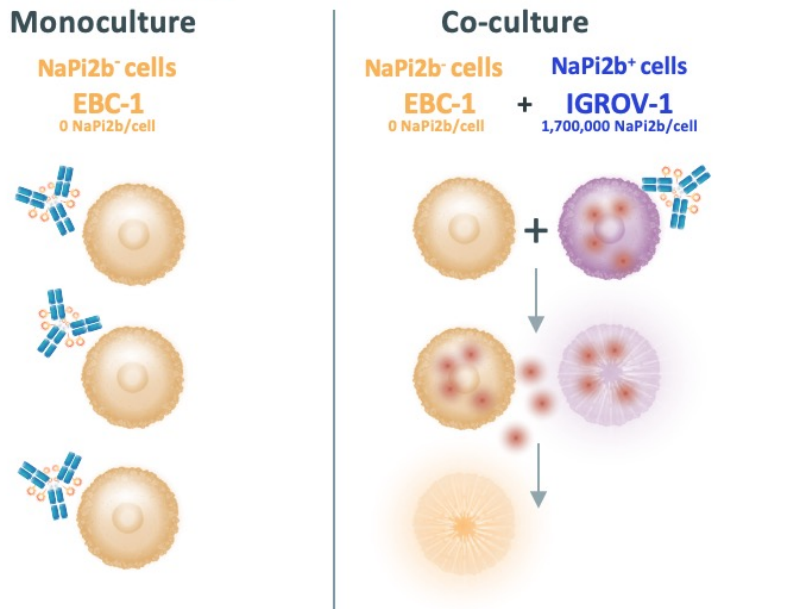
Internal fluorescence quantified



ZW220 Exhibits Strong Bystander Activity

Bystander Activity in Tumor Cell Co-culture Assay

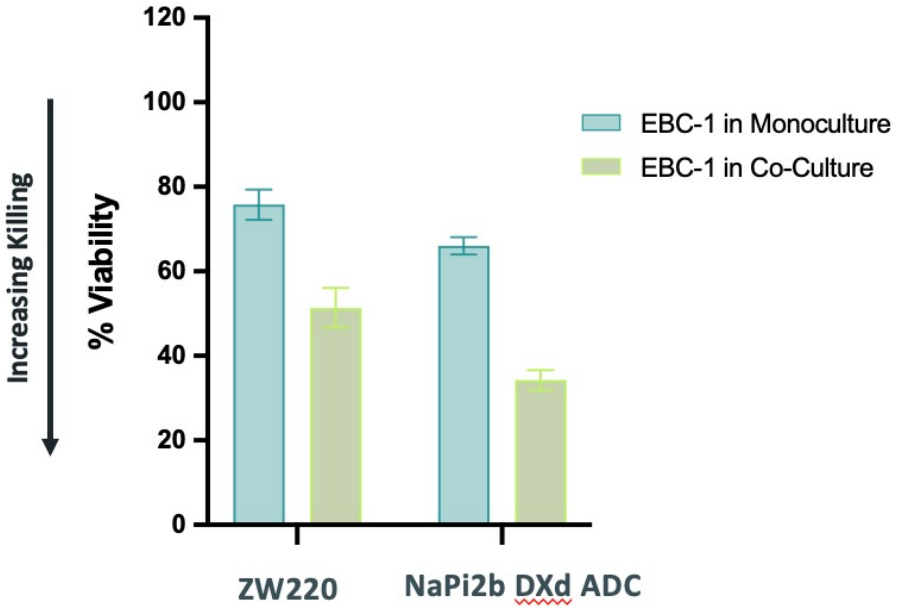
In Vitro Bystander Assay:



No cytotoxicity in NaPi2b-negative cells

Cytotoxicity in NaPi2b-negative cells when in co-culture with NaPi2b-positive cells

Viability of Antigen Negative Cells



DXd Control ADC contains same mAb as ZW220, conjugated to DXd

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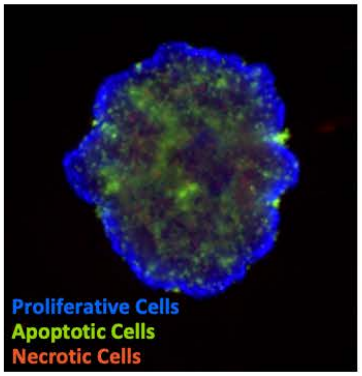
ZW220 Exhibits Potent Killing in NaPi2b-Expressing Tumor Spheroids

Potent Tumor Spheroid Killing

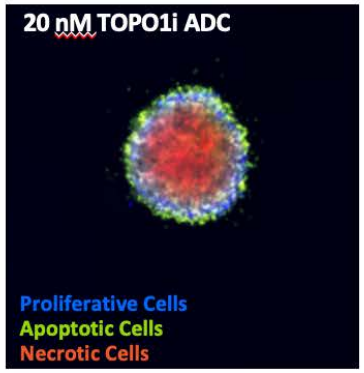
Tumor Spheroids

No Treatment

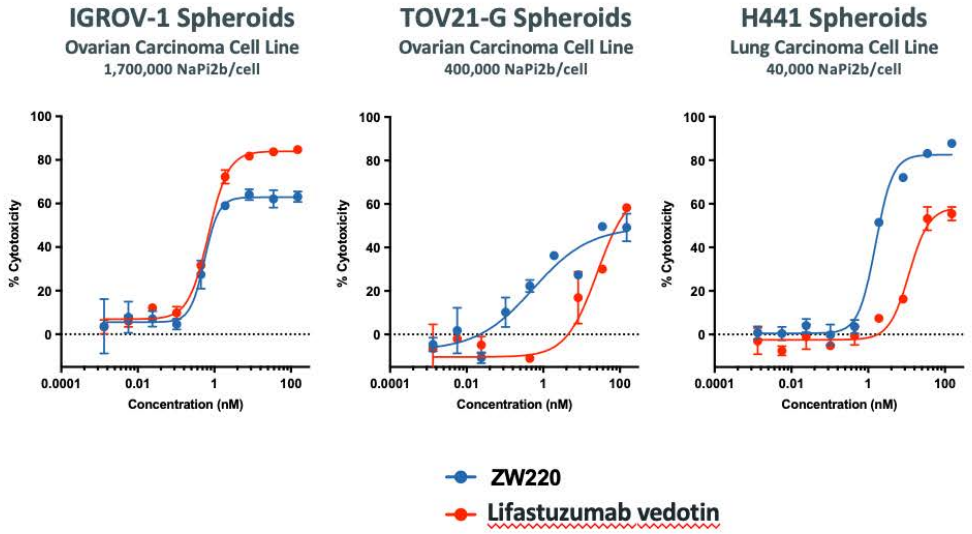


Untreated Tumor Spheroid
- Large volume
- Visible proliferation

6-Day Treatment with ADC



ADC Treated Tumor Spheroid
- Reduced volume
- Evidence of apoptosis and necrosis



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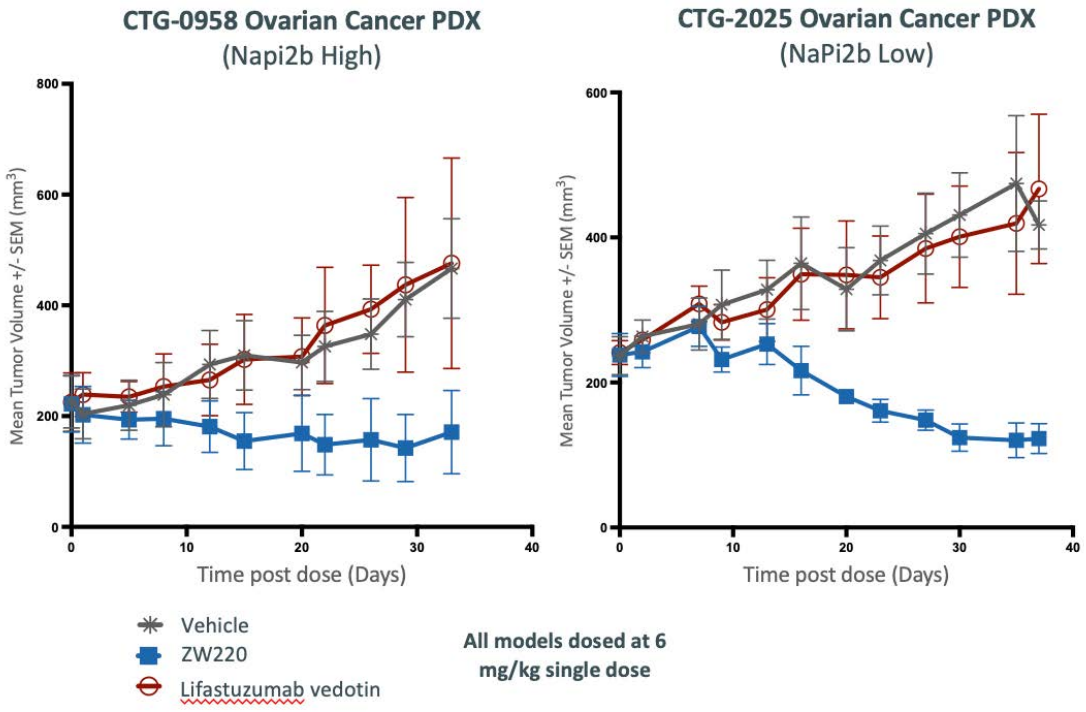
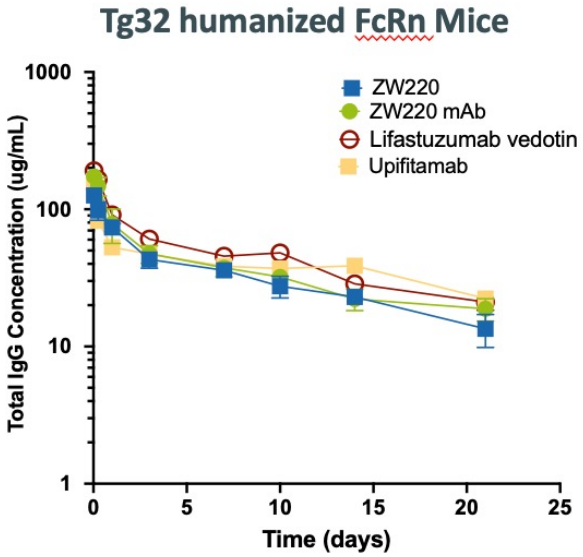
ZW220 Demonstrates Strong Anti-Tumor Activity in NaPi2b-Expressing PDX Models and Favorable PK

Superior Anti-Tumor Activity Compared to Lifastuzumab Vedotin



Stable and Linear Pharmacokinetics



- Tg32 mouse model is considered predictive of human PK
- The PK of ZW220 is comparable to that of the ZW220 mAb
- ZW220 PK compares favorably with that of Lifastuzumab vedotin and Upifitamab

ZW220 Takeaways

A potential best-in-class NaPi2b targeting topoisomerase-1 inhibitor ADC

Therapeutic Rationale

NaPi2b is a clinically validated ADC target in ovarian cancer with good potential in NSCLC and solid tumors.

Topoisomerase-1 inhibition is a clinically validated MOA in ovarian cancer and other solid tumors

Product Differentiation

Novel antibody with strong target binding and internalization

Novel bystander-active topoisomerase-1 inhibitor is a unique approach to targeting NaPi2b

Promising anti-tumor activity in preclinical models

Opportunity

Potential best-in-class opportunity for NaPi2b-expressing ovarian cancers

Potential first-in-class opportunity for NaPi2b-expressing lung carcinomas and other solid tumors

Next Milestone

Pilot NHP toxicology study initiated

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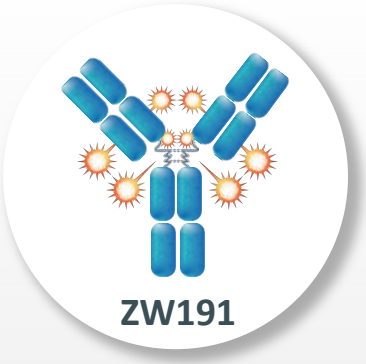
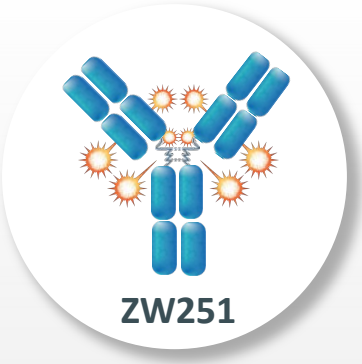
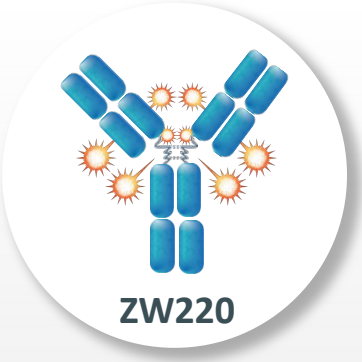
Zymeworks Preclinical ADC Assets Show Significant Near-Term Potential

	 ZW191	 ZW251	 ZW220
Target	**FRα**	**GPC3**	**NaPi2b**
Format/Technology	Monospecific/TOPO1i ADC	Monospecific/TOPO1i ADC	Monospecific/TOPO1i ADC
Potential Indications	Ovarian cancer, other gynecological cancers, and other solid tumors	Liver cancer	Ovarian cancer, NSCLC
Stage	IND-Enabling	Late Discovery	Late Discovery
Next Milestone	IND 2024	Pilot NHP toxicology study initiated	Pilot NHP toxicology study initiated

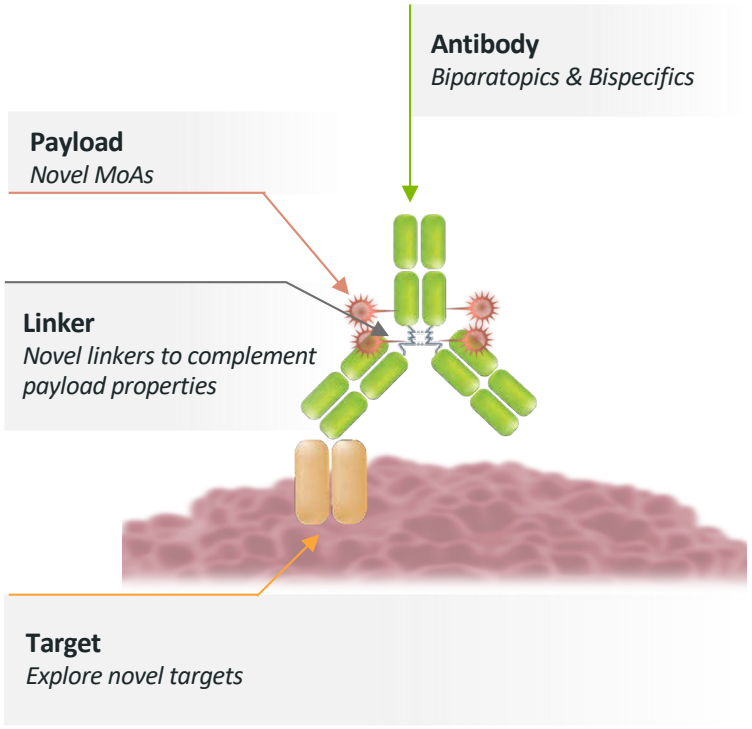
Additional early-stage assets in development

What's Next For Zymeworks ADC Pipeline

Stuart Barnscher
Director, Preclinical Programs, ADC Therapeutic Development

Zymeworks has the Potential to Develop Additional Innovative Technologies to Advance Novel Fit-for-Purpose ADC Assets

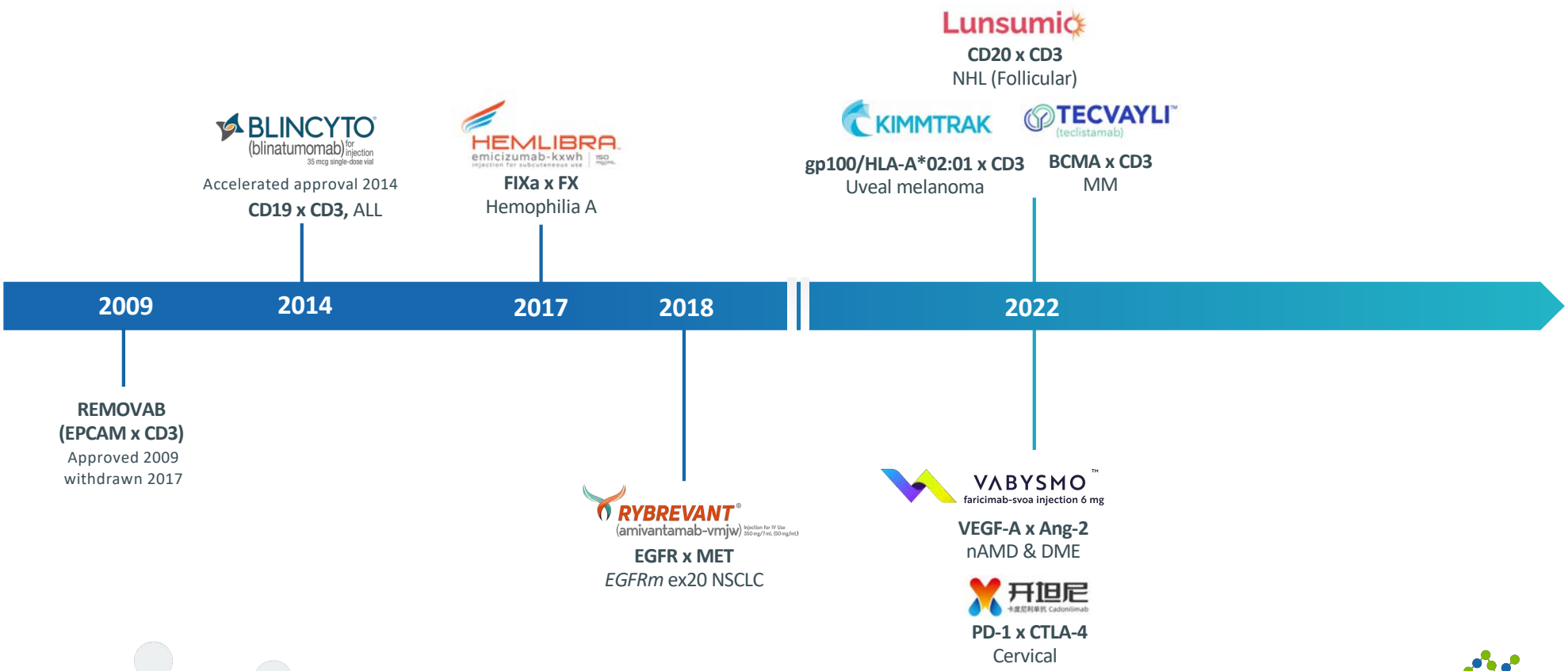
	Zymeworks Strategy Tomorrow	Rationale
Target	Explore novel targets	Addressing difficult to treat cancers may require exploring targets with less validation
Antibody	Leverage bispecific and biparatopic know-how to develop optimal ADC antibodies	Opportunity to improve internalization, specificity, and lower the target expression threshold
Linker/ Conjugation	Devise novel linkers to complement payload properties	Linker design should be dictated by payload potency, solubility, metabolism, and mechanism
Payload	Develop novel payloads by adapting MoAs with clinical validation to novel ADC application	More opportunity to match disease and target biology with payload mechanism



Multispecific Antibody Therapeutics (MSAT)

Dr. Paul Moore
Dr. Nina Weisser
Dr. Thomas Spreter Von Kreudenstein

Broad Use of Bispecifics Across Therapeutic Areas, with an Accelerating Pace of Approvals



Zymeworks' Technologies Enable Fit-For-Purpose Design of Multi-specifics

TECHNOLOGY	FEATURES	HIGHLIGHTS
Azymetric™ HetFc and HetFab heterodimeric IgG	• **Industry-leading heterodimeric IgG solution** • **Enabling technology for bispecific and multispecific therapeutics** • ***Superior stability, purity and modularity of Azymetric™ allows HTP screening and development of multispecifics***	• **Clinically validated technology** • **Multiple pharma partners employing**
Biparatopic mAbs	• Enhanced receptor cross-linking via binding of independent epitopes	• Zanidatamab, ZW49
T cell Engagers (TCE)	• 1+1 T cell engager applications • 2+1 T cell engager engineered to maximize therapeutic window	• JNJ-78306358; JNJ-78278343 (Phase 1) • ZW171 (2024 IND)

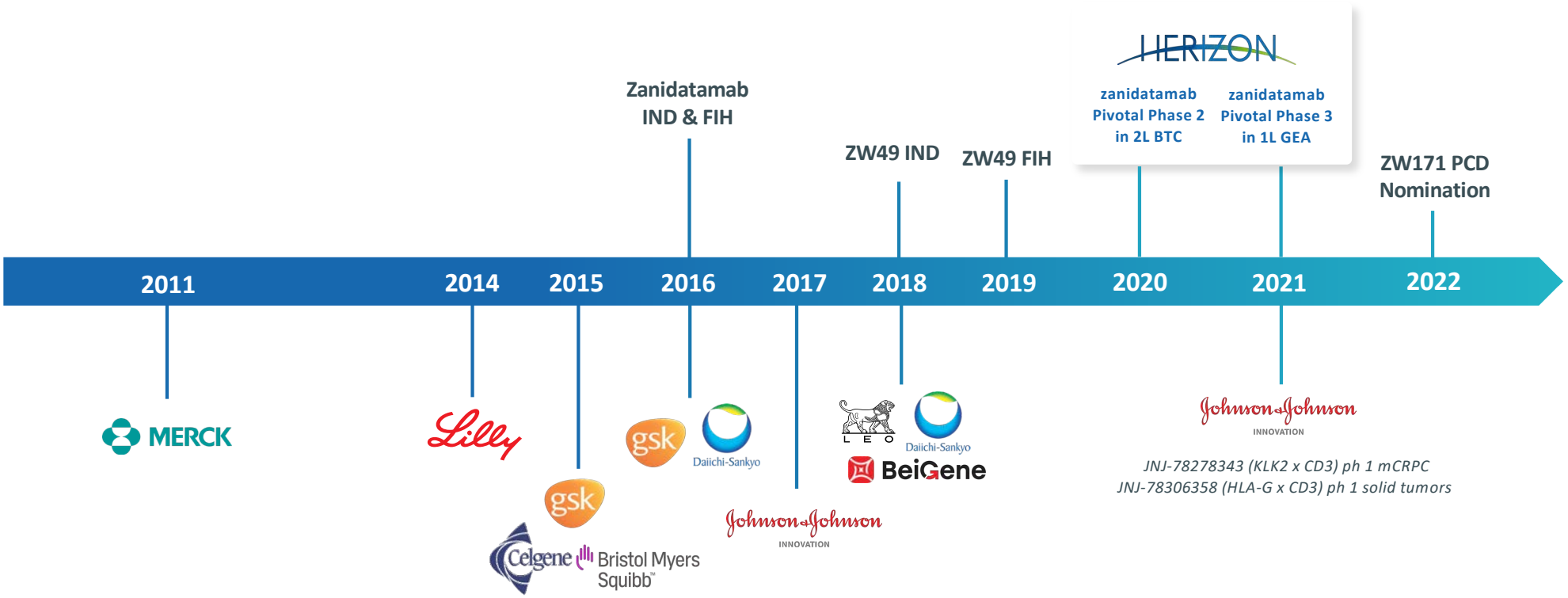
TriTCEs
Next Gen trispecific T cell engagers
	• Novel next gen trispecific designed to overcome TCE limitations
	  • TriTCE-costim with potential to re-invigorate 'cold' tumors
	  • TriTCE-CPI (checkpoint inhibition) to overcome suppressive TME
		• Candidate selection ongoing

ProTECT™ Tumor-specific immune stimulation	• Tumor-specific activity via conditional blocking to reduce off-tumor toxicities • Functional block adds checkpoint modulation to enhance efficacy	• Widens scope of possible tumor targets • Interfaces with TriTCE, Antibody or ADC
Cytokine Fc-fusions Tumor-specific cytokine activation	• Novel cytokine engineering approach combining reduced potency and tumor specificity • Can be combined or integrated with other ZW molecules	• Non-core asset: Tumor restricted IL-12 (AACR 2021)

MTD = maximum tolerated dose

10+ Years of Protein Engineering and Bispecific Development at Zymeworks

Partnerships and Zymeworks' Milestones using Azymetric™ or EFECT™ Platforms



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Zymeworks 2022 and Beyond: Building Multispecific Assets to Address Biological Challenges in Indications with High Unmet Medical Need

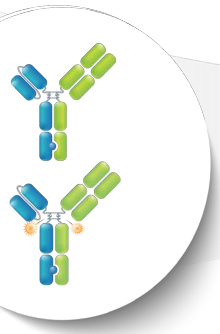
Platform Focused

Build industry leading platforms and first bispecific antibodies and ADCs

Azymetric™

EFECT™

ProTECT™



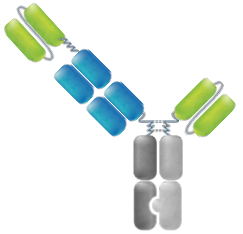
Achievements

- **3** Zymeworks platforms out licensed to **10** Pharma partners
- **2** investigational drugs in clinical study, including **2** pivotal trials

Azymetric™ Platform

Pipeline Focused

Harness flexibility of Azymetric™ as a foundation to solve biological challenges with T cell engagers in oncology



2 + 1 TCE
TriTCE

Build **multispecific** clinical assets to address clinical challenges in indications with high unmet medical need

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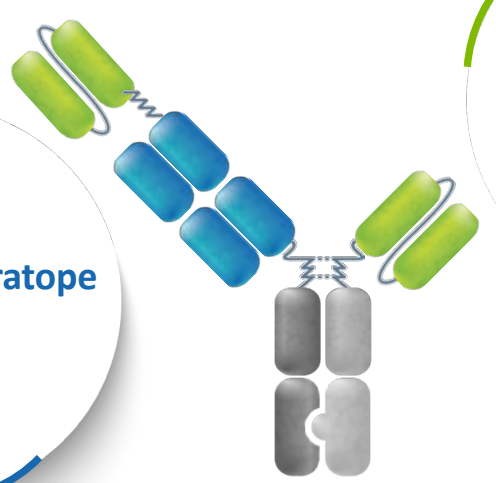
Engineering and Optimizing the Design of T Cell Engagers is Not Trivial

1

Anti-CD3 paratope

- Affinity
- Epitope
- Stability
- Format



e.g. ZW171

2

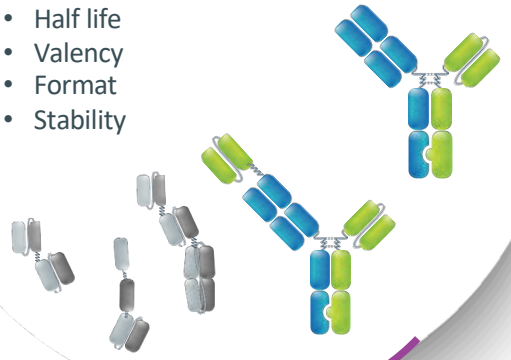
Anti-TAA paratope

- Affinity
- Epitope
- Valency
- Stability
- Format

3

Antibody Format and Geometry

- Half life
- Valency
- Format
- Stability



TCE antibody design is critical for a widened therapeutic index and optimal T cell synapse formation

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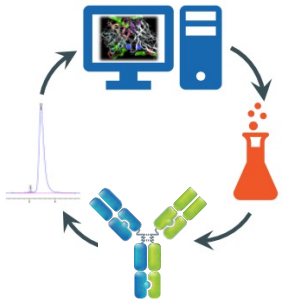
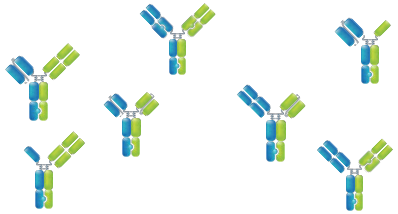
Core Competency of Protein Engineering & Flexibility of Azymetric™ Platform Enables Screening of Multiple Parameters in Parallel

- Core competency of Protein Engineering harnessed to engineer and optimize multiple parameters *in silico*
- Flexibility of Azymetric™ Platform enabled extensive screening of antibodies based on valency, geometry, and affinity

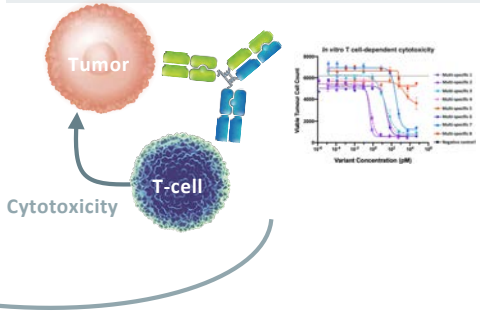
Paratope screening & optimization, *in silico* affinity engineering



Generate panel of extensively engineered antibodies: valency, geometry & affinity



In vitro & *in vivo* biophysical and functional characterization of multispecific antibodies

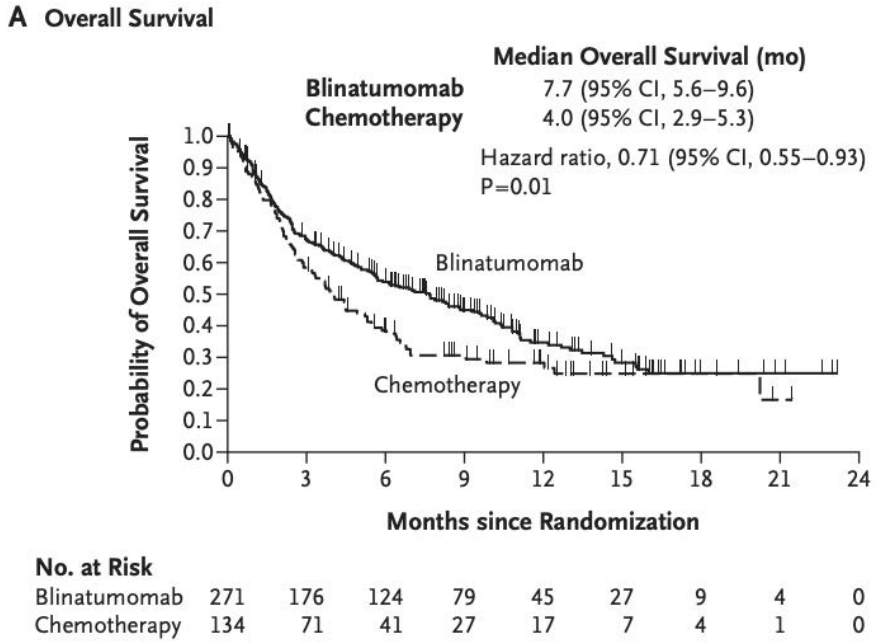


Single lead optimized to:

- Target TAA over-expressing cells
- Improve T cell responses
- Maximize therapeutic index
- Modulate cytokine release

Blinatumomab Provided Initial POC for TCE's Clinical Utility

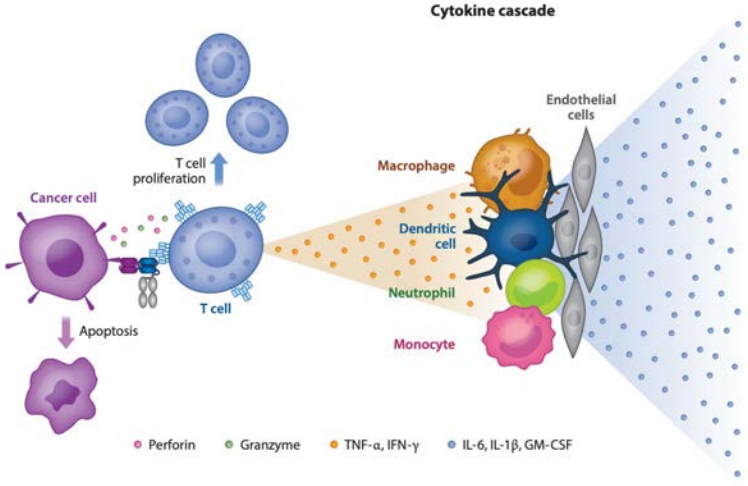
Clinical Benefit Shown vs. Chemo - But Limited Improvement in Durable Survival



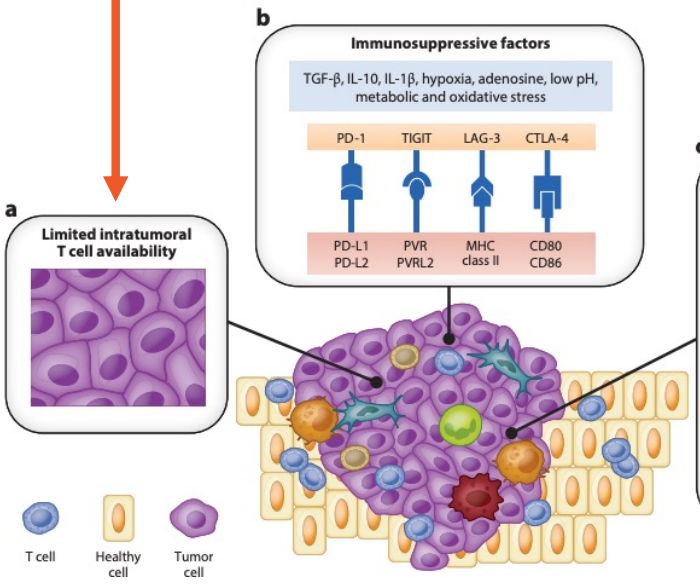
Kantarjian H et al NEJM 2017

Challenges Remain: Gen 1 TCE Limited by Narrow Therapeutic Window & Solid Tumors Present Obstacles not Found in Blood Cancers

Key Problem 1:
Narrow therapeutic window and limitations due to concomitant cytokine release



Key Problem 2:
Low T cell infiltration
T cell anergy



Key Problem 3:
Immunosuppressive tumor microenvironment

Arvedson T et al Ann Rev Cancer Biol 2022

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Zymeworks Multispecific T Cell Engager Strategy: Utilizing Azymetric™ Advantage to Build Differentiated & Next Generation T Cell Engagers

Biological Problem	Zymeworks Solution
1 Narrow therapeutic window and toxicity due to CRS associated with Gen 1 TCE in solid tumors	**2+1 T Cell Engager (ZW171)** Mitigate CRS with low affinity T cell binding and enhanced efficacy and selectivity with avidity-driven tumor antigen binding
2 Limited T cell intratumoral availability and T cell anergy in solid tumors	**TriTCE Co-stim** Increase T cell fitness, activation and proliferation via tumor-dependent T cell co-stimulation
3 Immunosuppressive tumor microenvironment limiting T cell responses in solid tumors	**TriTCE CPI** Increase T cell responses through simultaneous checkpoint blockade and avidity-driven binding

ZW171

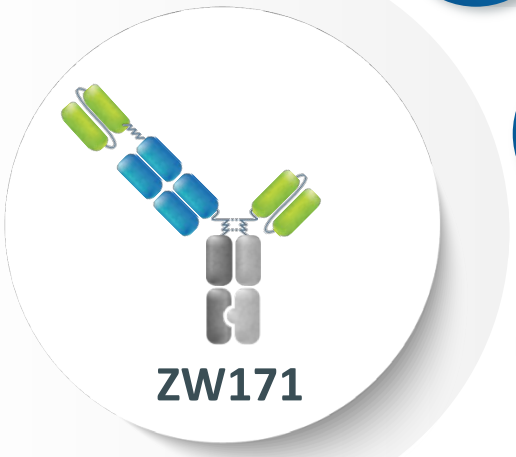
2+1 anti-MSLNxCD3

Potential Best-in-Class Antibody for MSLN

Dr. Nina Weisser
Director, Multispecific Antibody Research

ZW171 Takeaways

Industry-leading Platform for Generating Bispecific and Multispecific Antibodies:



CD3
MSLN

MSLN Targeted

Antibody targets mesothelin (MSLN), a glycoprotein that is elevated in many cancers including pancreatic, mesothelioma and ovarian cancer

Target is clinically validated, indications have high unmet clinical need

CD3 Targeted

Targeting CD3 receptor to redirect T cell cytotoxicity towards cancerous cells

Anti-CD3 antibody targeting novel epitope that mediates low T cell binding and cytokine release and potent tumor cell lysis

Format Engineering

Extensive assessment of different formats with different valences & geometries

2+1 dual scFv identified as avidity-driven format with optimal activity and safety profile

Validation

In preclinical development

IND 2024

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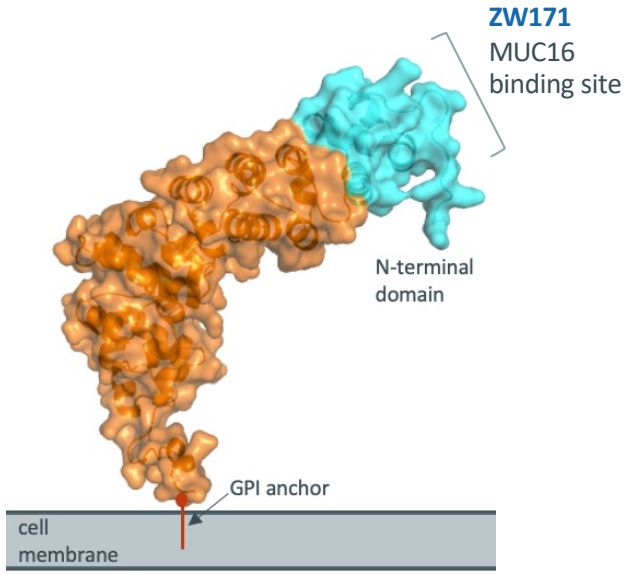
Mesothelin is Expressed in Many Tumor Types and has an Ideal Profile for Bispecific Immune Cell Targeting

Structure	Glycosylphosphatidylinositol (GPI)-anchored membrane glycoprotein
Normal Tissue Expression	Restricted to the mesothelial cells of pleura, pericardium, and peritoneum
Cancer Tissue Expression	Elevated surface expression in many solid tumors, including mesothelioma, pancreatic, ovarian, lung adenocarcinoma, cholangiocarcinoma, and triple negative breast cancer
Function	Binds MUC16 and may play a role in cell adhesion, tumor progression, metastasis, chemo-resistance and formation of cancer-associated fibroblasts that induce immunosuppressive regulatory T cell (Treg) formation
Clinical	Clinically validated target with recent data showing response (20% ORR) in cholangiocarcinoma , mesothelioma and ovarian cancers with autologous T cell therapy (gavo-cel)



ZW171 Identified via Extensive Engineering and Screening

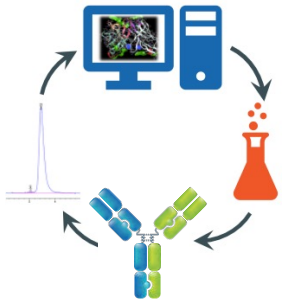
- Core competency of Protein Engineering harnessed to engineer and optimize multiple parameters *in silico*
- Flexibility of Azymetric™ Platform enabled extensive screening of antibodies based on valency, geometry, and affinity

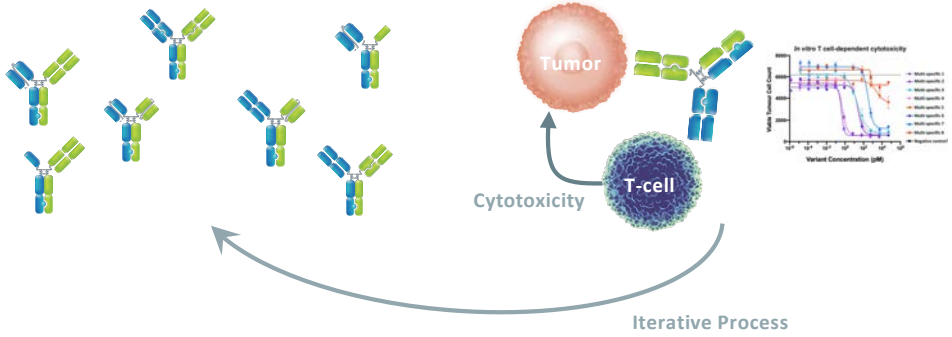
Paratope screening & optimization, *in silico* affinity engineering

Generate extensive panel of engineered antibodies: valency, geometry & affinity

In vitro & *in vivo* biophysical and functional characterization of multispecific antibodies under stringent conditions

Single lead optimized to:

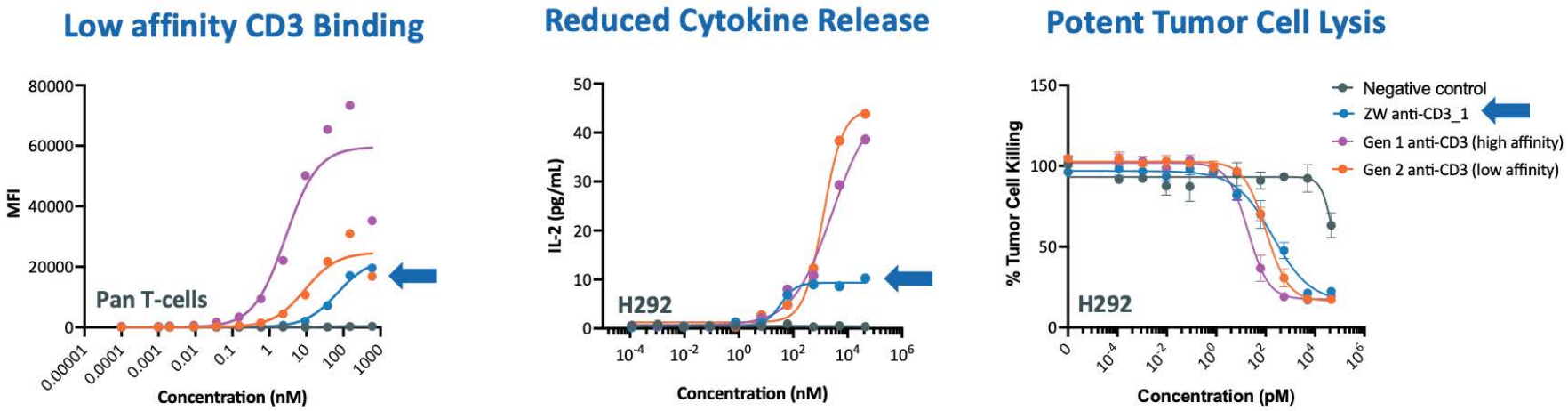




- Target TAA over-expressing cells
- Improve T cell responses
- Modulate cytokine release
- **Maximize therapeutic window**

Anti-CD3 Paratope Engineered to Widen the Therapeutic Window

First-gen TCEs based on SP34 and OKT3 paratopes have high-affinity CD3 binding, and dose-limiting toxicity related to cytokine release syndrome (CRS)



Data generated with MSLNxCD3 bispecifics; αRSV or HAxCD3 used as negative controls

ZW anti-CD3_1 paratope has **low affinity** and **reduced** CD3 binding, **low** cytokine release and **potent** tumor cell lysis to maintain anti-tumor activity and avoid dose-limiting toxicity related to CRS

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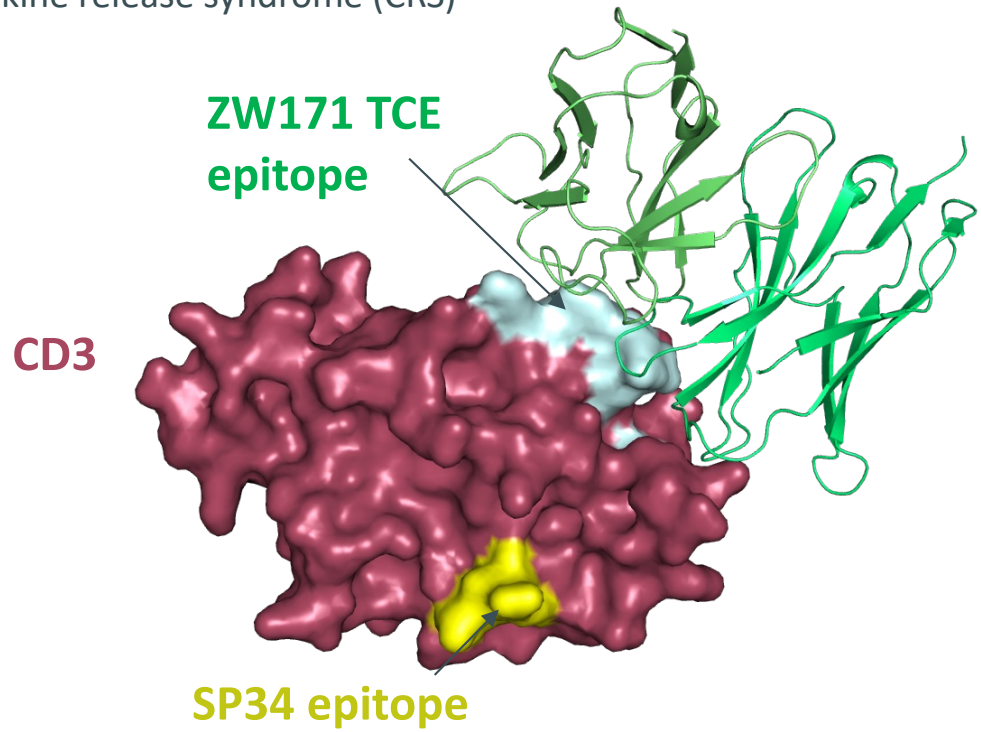
Zymeworks Anti-CD3 Paratope Engages CD3 at a Different Epitope than Gen 1 Anti-CD3 Antibodies

First-gen TCEs based on SP34 paratopes have high-affinity CD3 binding, and dose-limiting toxicity related to cytokine release syndrome (CRS)

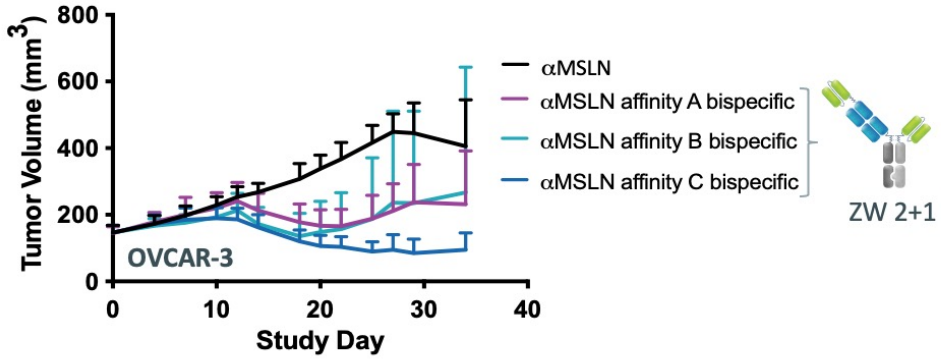


Distinct binding geometry to CD3 may provide more optimized engagement and biology for MSLN and other tumor targets

Cross-reactive to cynomolgus CD3

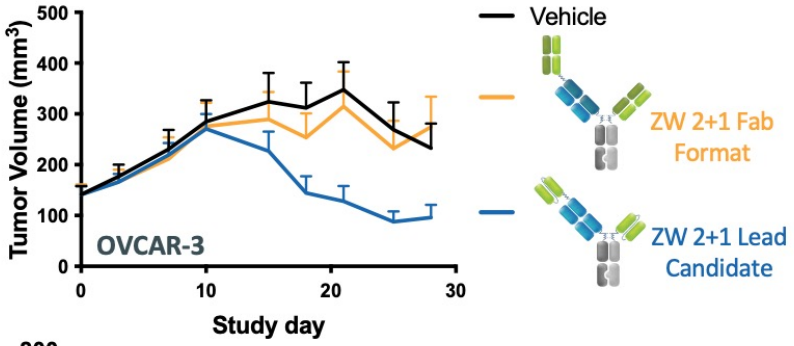
Lead Candidate Confirmed Through Format and Affinity Screening In vivo

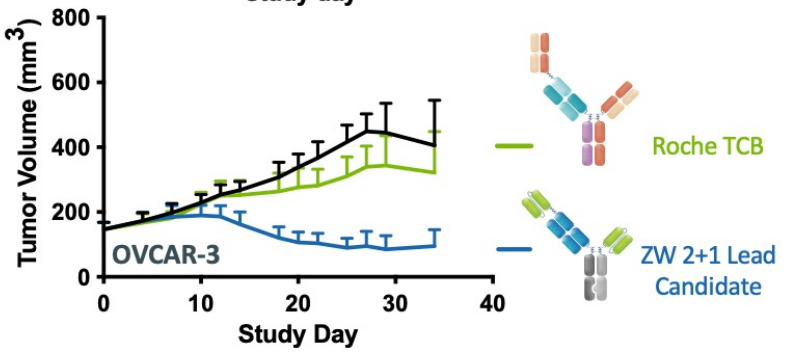
Anti-MSLN Paratope Affinity is Critical



In vivo anti-tumor activity evaluated with established tumor models that have reduced sensitivity compared to co-implantation (tumor + PBMC) models

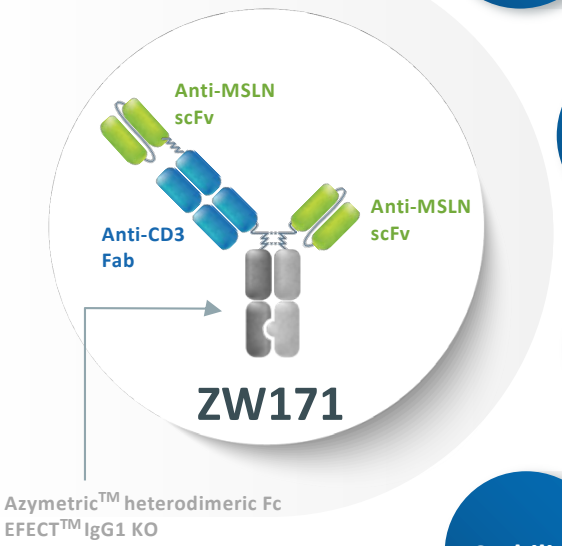
2 + 1 Geometry is Critical





OVCAR-3 tumor fragments were engrafted subcutaneously in NOG mice. After tumors reached 100-200 mm3, mice were humanized with donor PBMC (3 donors) then treated 2QW x4 with test article. HuPBMC = human peripheral blood mononuclear cells

ZW171: Engineered for Enhanced Anti-tumor Activity & Safety



MSLN Targeted

Anti-MSLN paratope affinity optimized to increase anti-tumor activity

CD3 Targeted

Low affinity anti-CD3 paratope to reduce the risk of CRS in the clinic

Format Engineering

Antibody format and geometry optimized for enhanced anti-tumor activity and safety

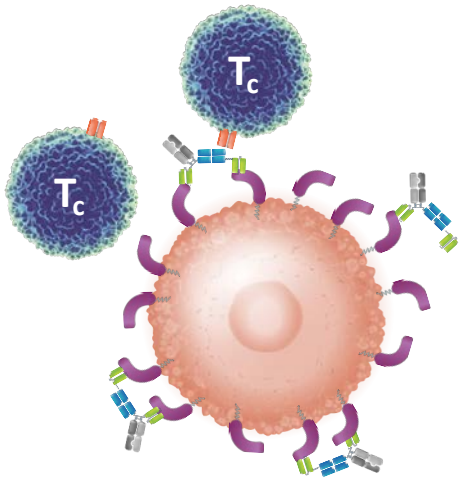
2 + 1 format facilitates avidity driven tumor-specific binding and cytotoxicity, mitigating risk of on-target off-tumor toxicity

Stability

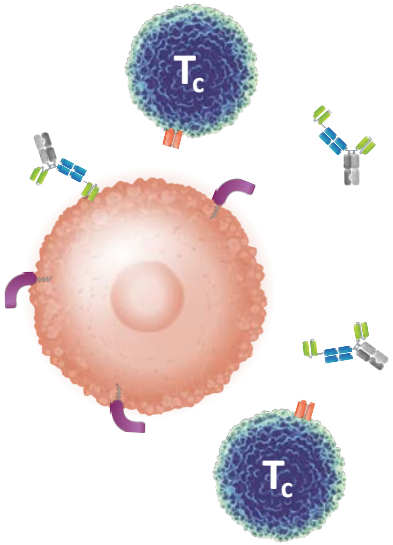
Format and paratopes engineered for improved stability

ZW171 Engages High MLSN-Expressing Cells But Not Low MSLN-Expressing Cells, Mitigating the Risk of On-Target Off-Tumor Toxicities

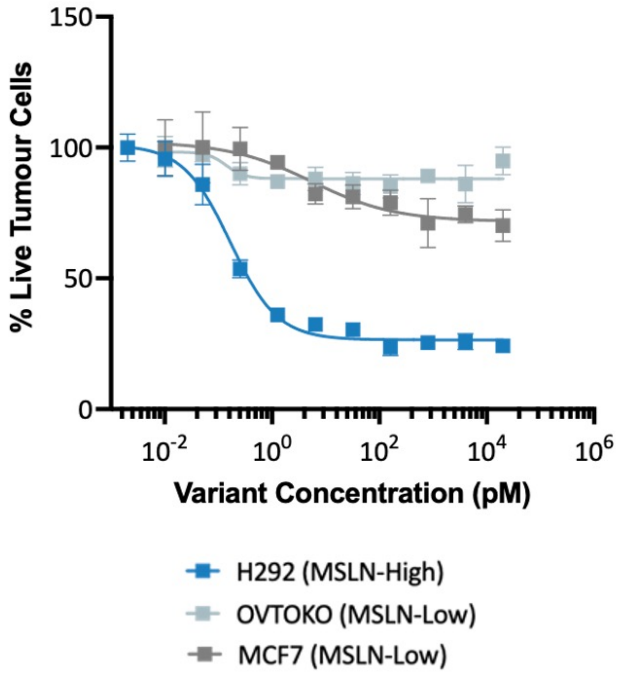
Cancer Cell
(High MSLN-Expression)



Healthy Cell
(Low MSLN-Expression)



ZW171 Tumor Cell Cytotoxicity



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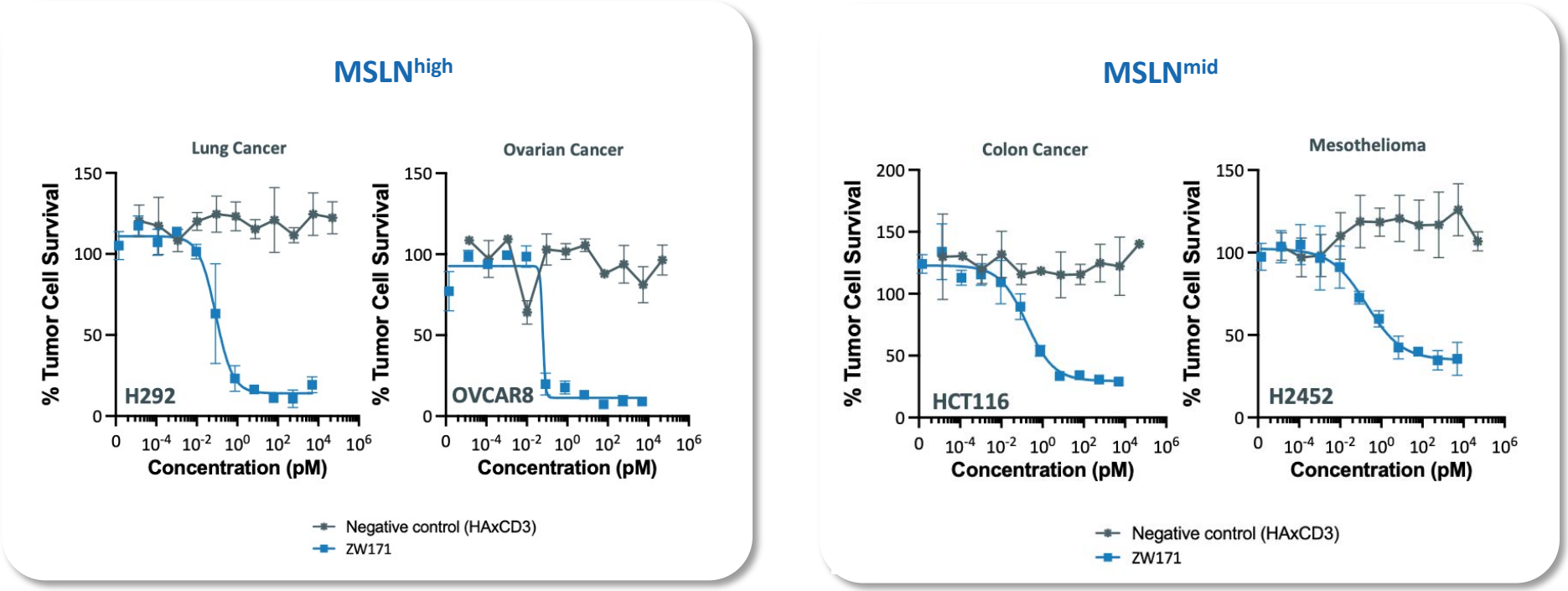
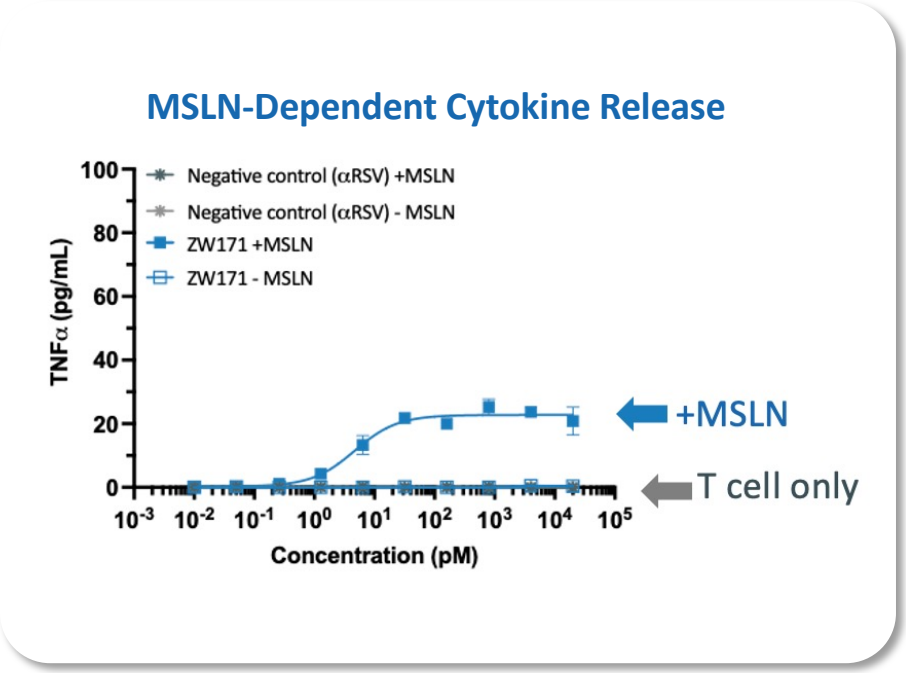
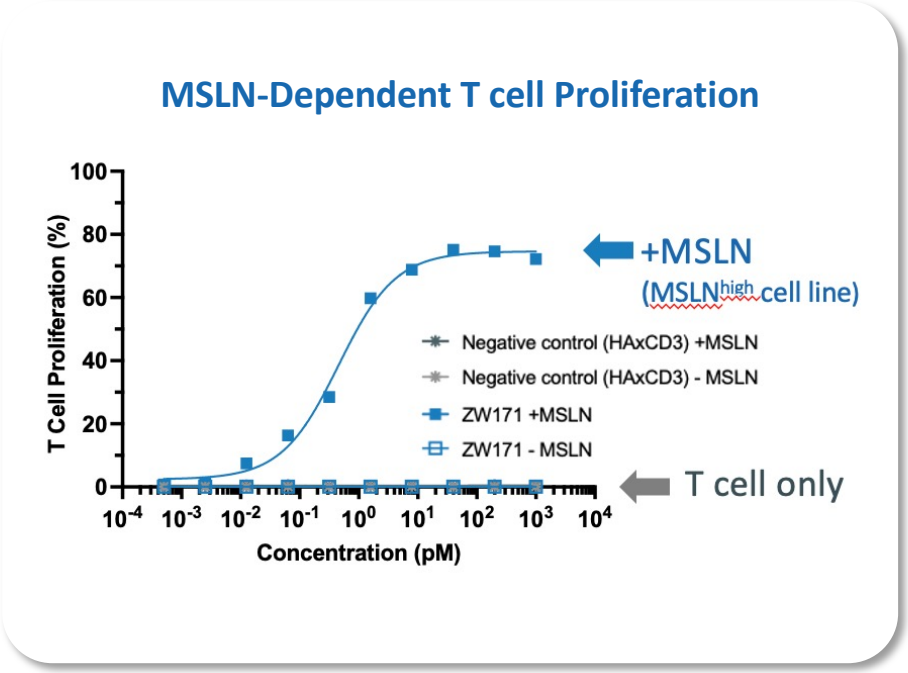
ZW171 Exhibits TAA-Dependent Cytotoxicity in MSLN-Expressing Lung, Ovarian, Colon and Mesothelioma Cancer Cell Lines



Human pan T cells and tumor cells were co-cultured at an effector-to-target ratio of 5:1 in the presence of ZW171 or negative control for 72 hours.

ZW171 Mediates MSLN-Dependent Cytokine Release and T cell Proliferation, Mitigating the Risk of Peripheral T cell Activation and CRS



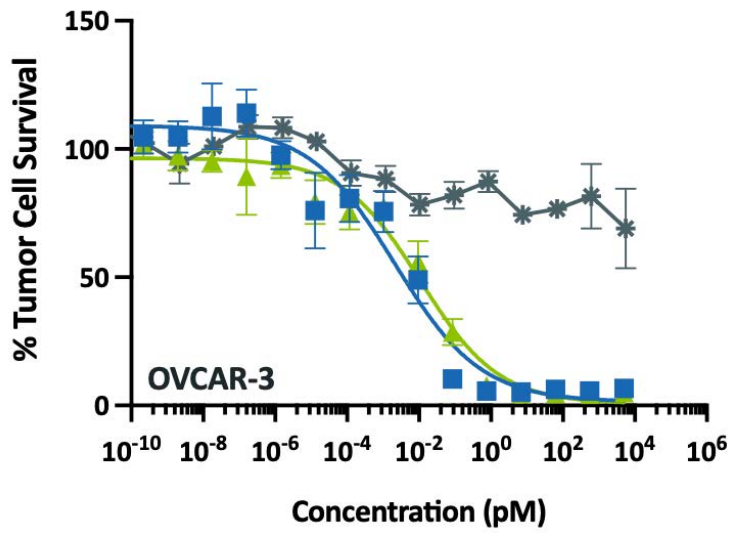


No cytokine production or T cell proliferation in the absence of MSLN-expressing tumor cells

MLSN, mesothelin; CRS, cytokine release syndrome

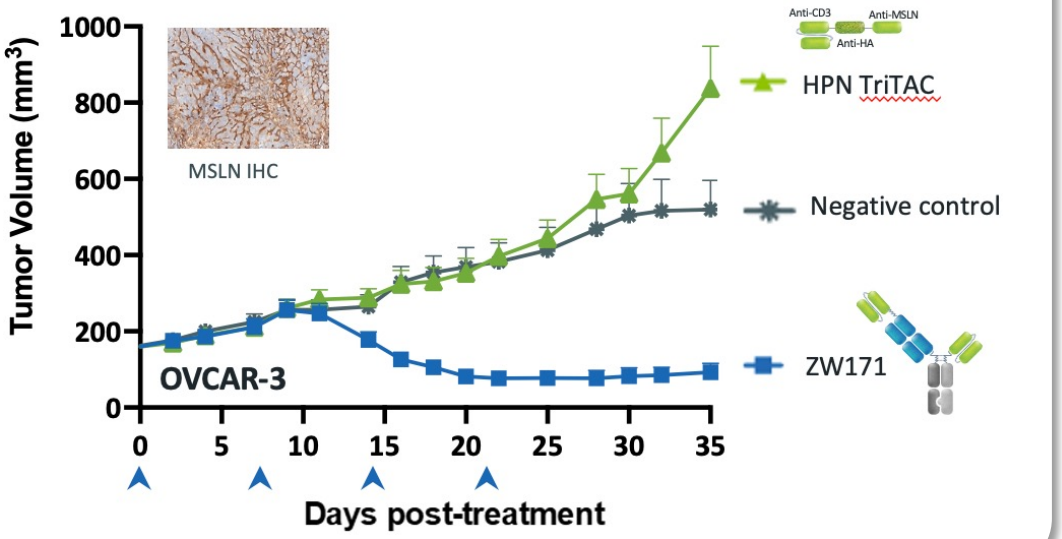
ZW171 Mediates Greater In Vivo Anti-Tumor Activity Compared to Benchmark in an Established MSLN^{High}-Expressing Ovarian Cancer Model

In Vitro Cytotoxicity



Human pan T cells and OVCAR3 cells were co-cultured at an effector-to-target ratio of 5:1 in the presence of ZW171 or HPN triTAC for 72 hours.

In Vivo Anti-Tumor Activity



OVCAR-3 tumor fragments were engrafted subcutaneously in NOG mice.
After tumors reached 100-200 mm^3, 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. Negative control is anti-hemagglutinin x CD3 bispecific.

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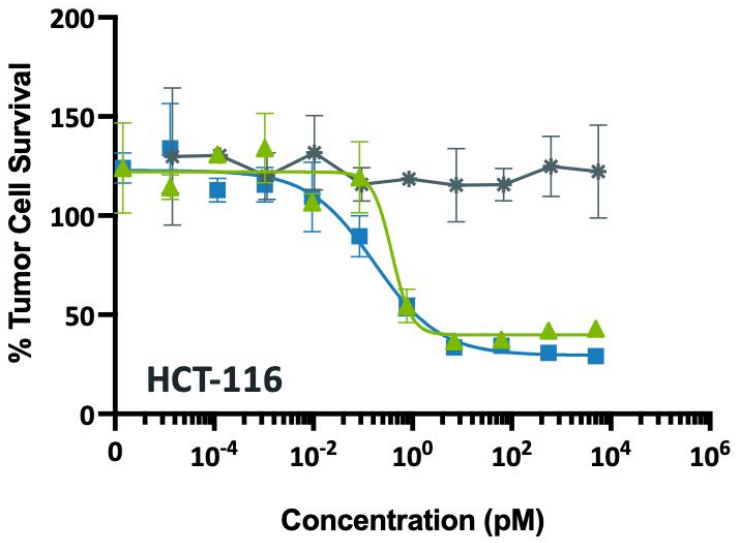
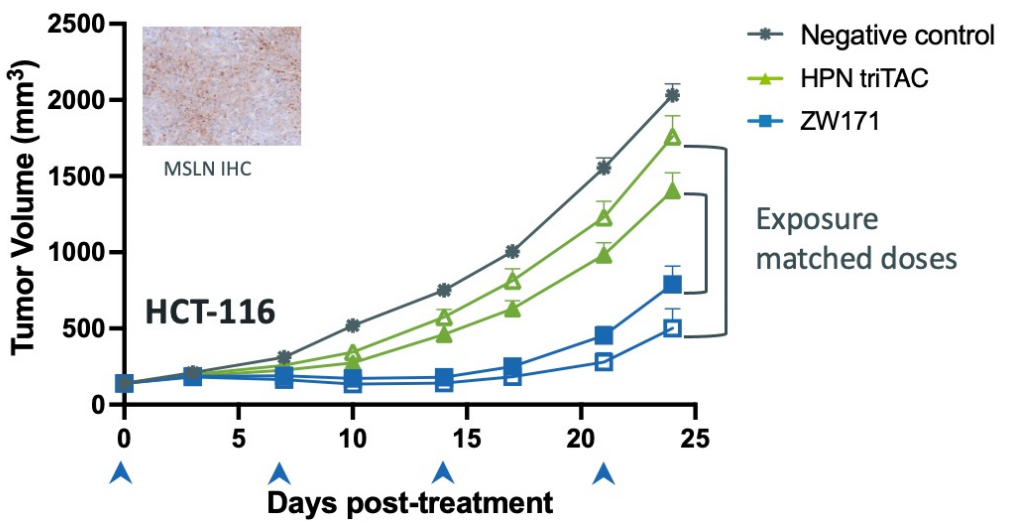
ZW171 Mediates Greater In Vivo Anti-Tumor Activity Compared to Benchmark in an Established MSLN^{mid}-Expressing Colon Cancer Model

In Vitro Cytotoxicity



Human pan T cells and HCT116 cells were co-cultured at an effector-to-target ratio of 5:1 in the presence of ZW171 or HPN triTAC for 72 hours.

In Vivo Anti-Tumor Activity



NPG mice were engrafted with HCT116 cells and human PBMC (2 donors) intraperitoneally. When tumors reached 100-200 mm^3, dosed i.v. QW x4 with ZW171 or i.p. daily x 18 with HPN triTAC. Serum exposure concentrations and matched exposure doses confirmed by PK analysis. Negative control is anti-hemagglutinin x CD3 bispecific.

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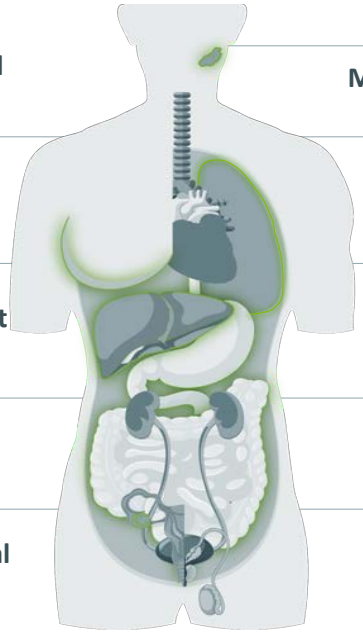
ZW171 Commercial Opportunity

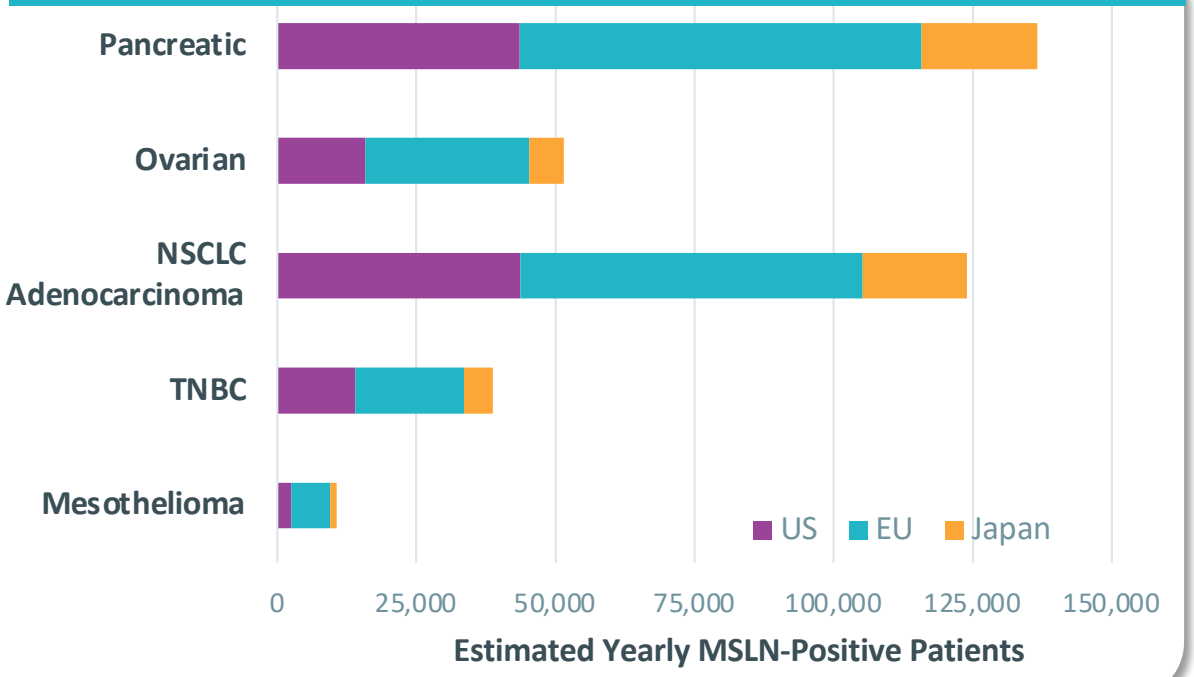
- Potential first and best-in-class treatment for MSLN+ pancreatic, ovarian, NSCLC, TNBC, mesothelioma and other MSLN-expressing cancers

MSLN EXPRESSING CANCERS



- Thymic 40-45%
- Esophageal 35-40%
- Mesothelioma 75-80%
- Breast 25-30%
- Lung 60-65%
- Biliary Tract 60-65%
- Gastric 50-55%
- Ovarian 60-65%
- Pancreatic 80-85%
- Endometrial 20-25%
- Colorectal 40-45%

ESTIMATE OF NEWLY-DIAGNOSED MSLN+ PATIENTS IN KEY INDICATIONS



Modified from Morello et al Cancer Discovery; Vol. 6 Feb 2016 and Inaguma et al Oncotarget; Vol 8 Apr 2017

ZW171 Summary

Widening the therapeutic window of bispecific T cell engagers

Therapeutic Rationale

MSLN is a **clinically validated target** with high **expression in many solid tumor types** that represent a **high unmet medical need**

Investigational MSLN-targeted biologics have demonstrated clinical activity in MSLN-expressing cancers

Product Differentiation

Engineered for optimal format, paratope affinity and stability

Reduced anti-CD3 affinity and 2+1 avidity-driven format expected to translate to **improved safety profile and widened therapeutic index**

Opportunity

First and best-in-class treatment for MSLN-expressing cancers

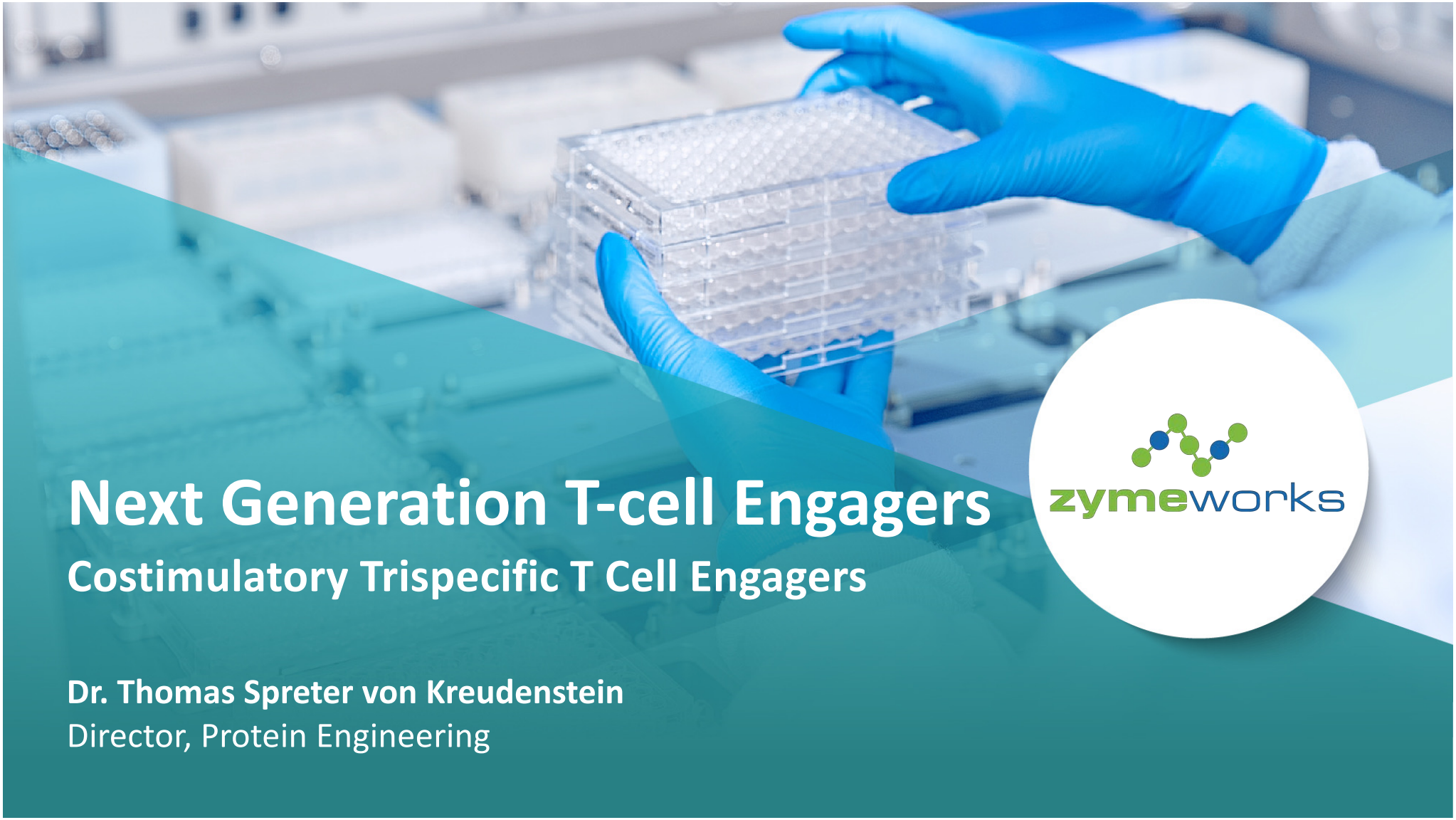
Improved anti-tumor activity in MSLN expressing in vivo tumor models **compared to clinical benchmark**

Next Milestones

GLP NHP toxicology

GMP process manufacturing underway

IND (2024)



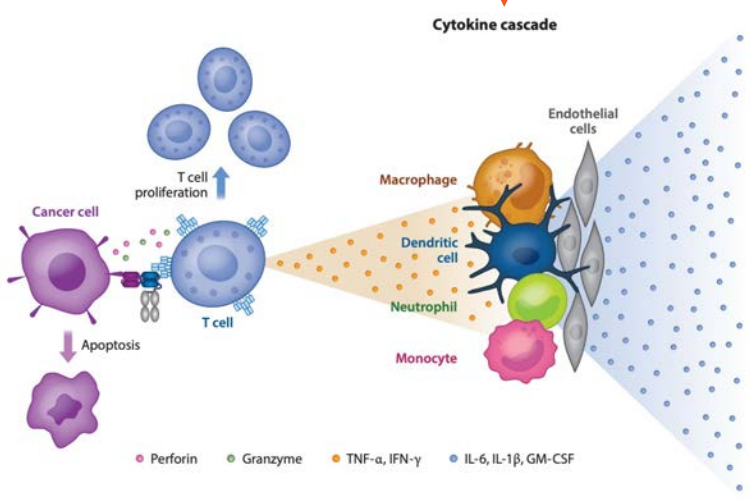
Next Generation T-cell Engagers

Costimulatory Trispecific T Cell Engagers

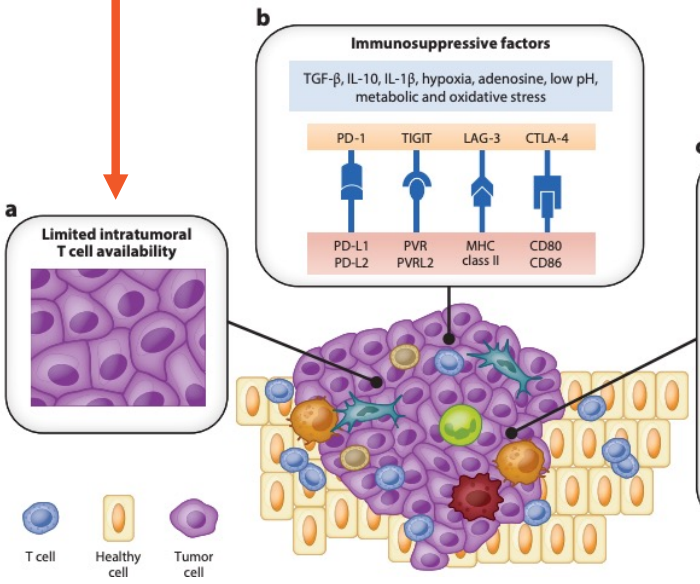
Dr. Thomas Spreter von Kreudenstein
Director, Protein Engineering

Challenges Remain: Gen 1 TCE Limited by Narrow Therapeutic Window & Solid Tumors Present Obstacles Not Found in Blood Cancers

Key Problem 1:
Narrow therapeutic window and limitations due to concomitant cytokine release



Key Problem 2:
Low T cell infiltration
T cell anergy



Key Problem 3:
Immunosuppressive tumor microenvironment

Arvedson T et al Ann Rev Cancer Biol 2022

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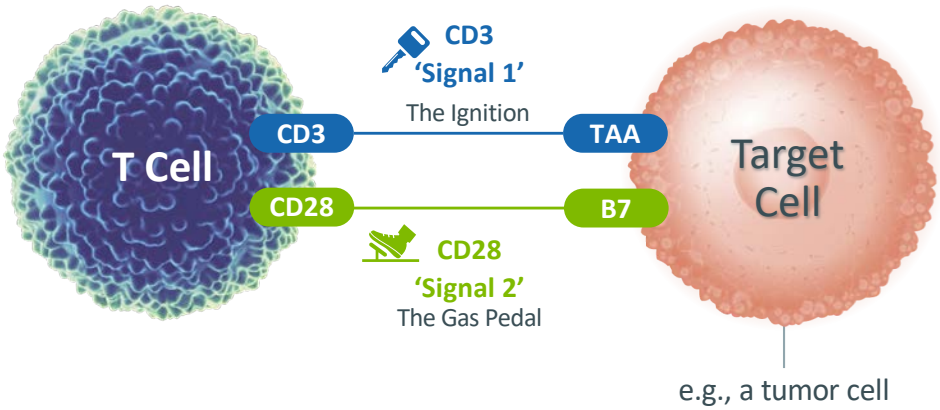
Emerging Limitations of Bispecific T Cell Engagers: Lack of Co-stimulation Limits *Efficacy* and *Durability* of Responses in Solid Tumors

T cell activation and sustained proliferation is regulated by 'Signal 1' and 'Signal 2'

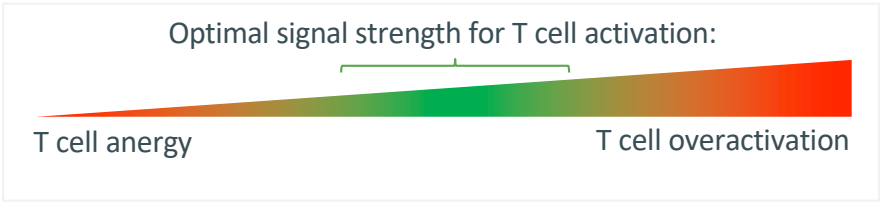


- **Activation by 'Signal 1' and co-stimulation by 'Signal 2' are required** for optimal activation and sustained proliferation of T cells
- **Lack of expression of co-stimulatory ligands (B7)** on solid tumors limits activity and durability of bispecific T cell engager anti-tumor responses
- **Co-stimulatory trispecific T cell engagers have the potential** to provide more durable responses and to re-invigorate 'cold' tumors with lower T cell infiltration

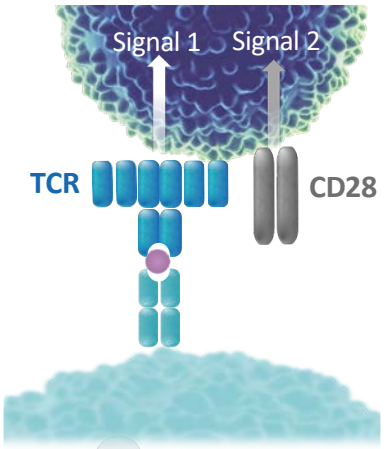
Acuto & Michel, Nature Immunol Rev (2003)
Feucht et al., Oncotarget (2016)

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

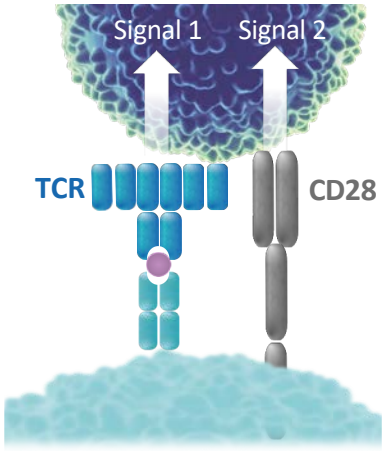
T cell Activation Requires Balance of Signal 1 and Signal 2



Lack of Signal 2 co-stimulation leads to **T cell anergy, no** sustained **T cell proliferation**

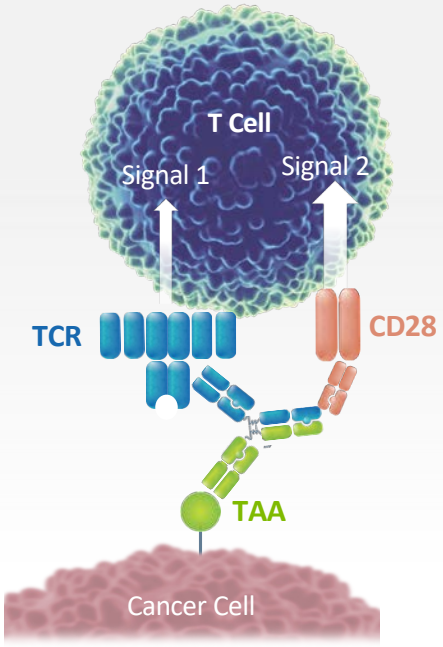


Very strong activation leads **to T cell dysfunction, excessive cytokine release**



Zymeworks Approach of Differentiated Trispecific Engineering

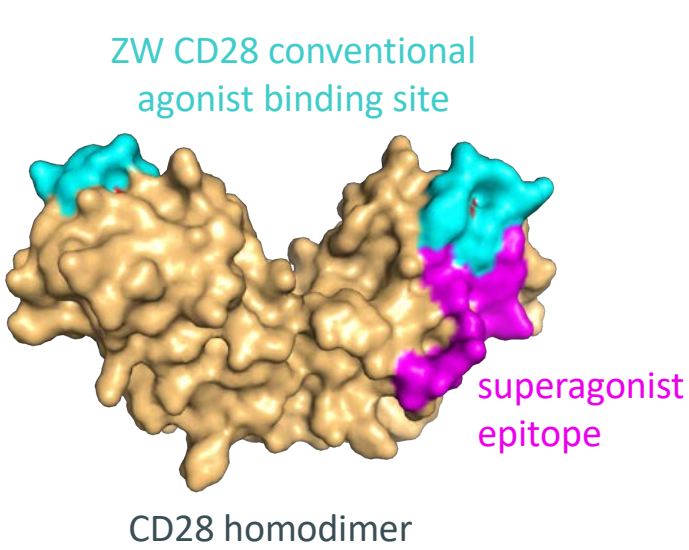
Azymetric allows screening of multiple trispecific formats and affinities for optimization of T cell activation

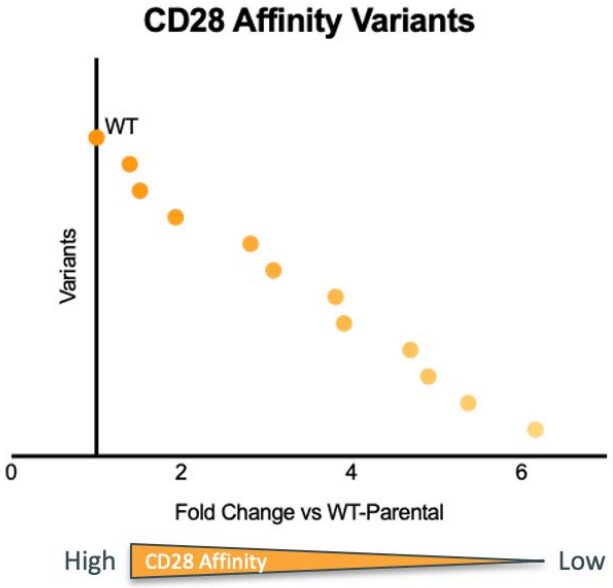


- Novel approach of screening multiple trispecific geometries
- Different CD3 and CD28 geometries and affinities interrogated in screening process
- Opportunity to optimize Signal 1 and 2 in trispecific for optimal tumor specific T cell activation and tumor cell killing

Acuto & Michel, Nature Immunol Rev (2003)

Zymeworks' Conventional CD28 Agonist is Engineered with a Broad Range of Affinities to Avoid Potential Toxicity Issues of Traditional CD28 Super-agonists

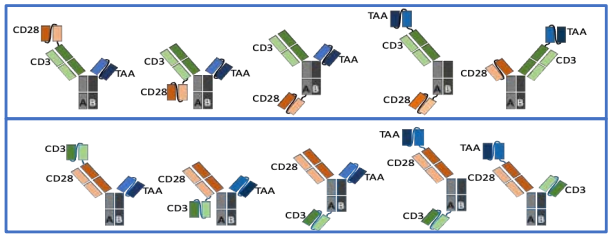


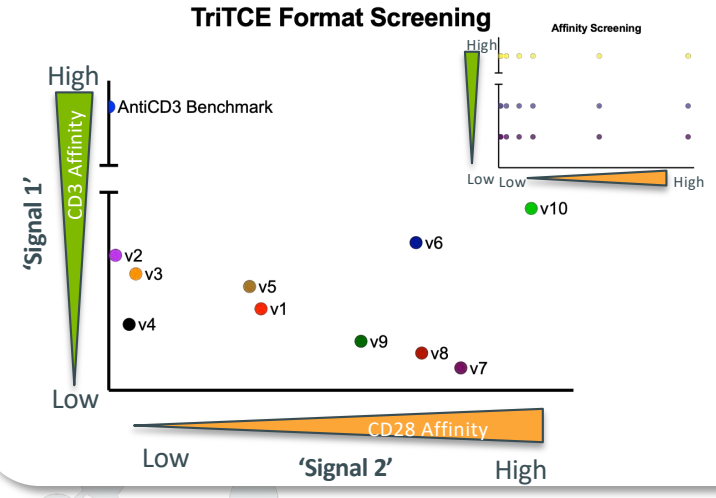


- Conventional anti-CD28 agonist with no super-agonist activity
- Potentially less risk of CD28 mediated toxicities
- Library of anti-CD28 affinities from medium to low
- Flexibility of stable Fab and scFv format to test different trispecific T cell engager geometries

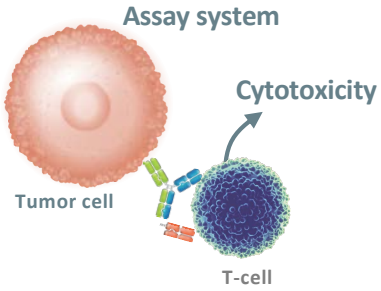
Integrated Screening of Multivalent Geometries and Affinities to Select Best-in-Class Trispecific T cell Engagers with Optimized CD3 and CD28 Activity

Screening of multiple CD3-CD28-TAA geometries and affinities

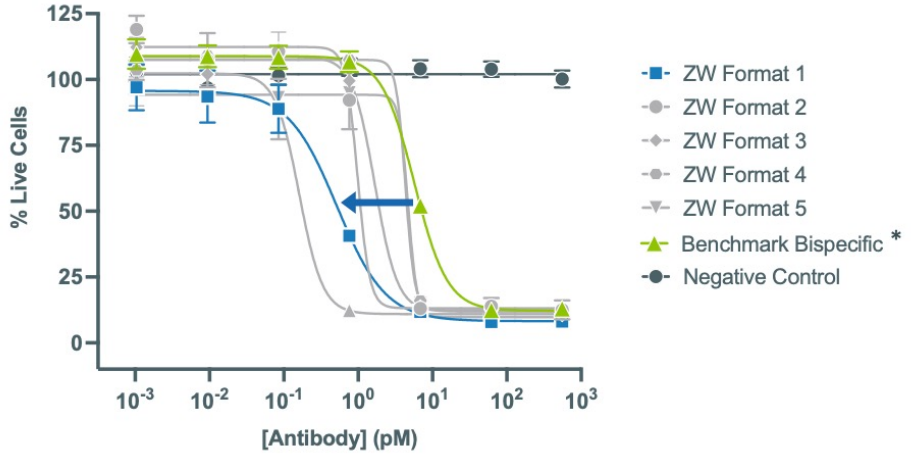




Novel screening approach enables identification of optimal format for robust Signal 1 + Signal 2 T cell activation and synapse formation



T Cell-Dependent Cytotoxicity



* Benchmark Bispecific targets same TAA as TriCE; TAA arm identical for all TriTCEs

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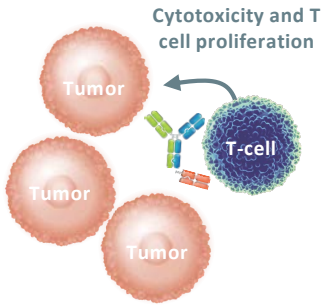
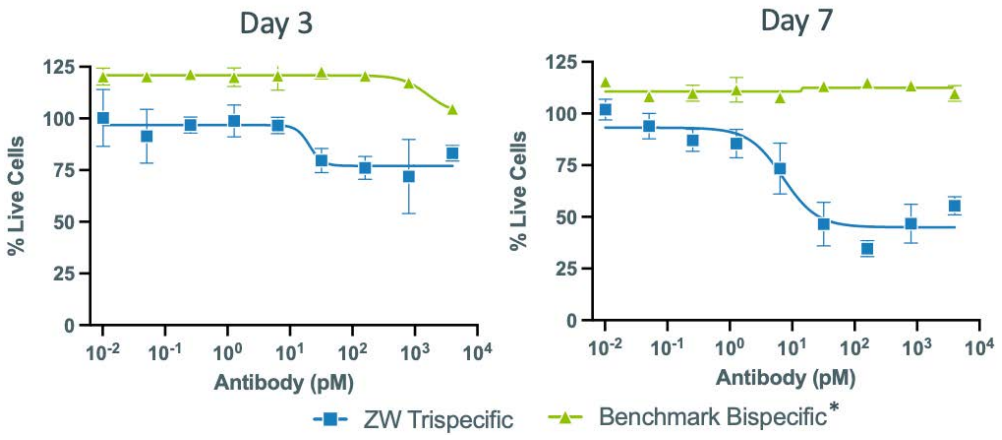
Trispecifics Exhibit Improved Potency & Maximum Cytotoxicity Over Bispecifics with Long term Co-culture at Low T cell to Tumor Cell Ratios

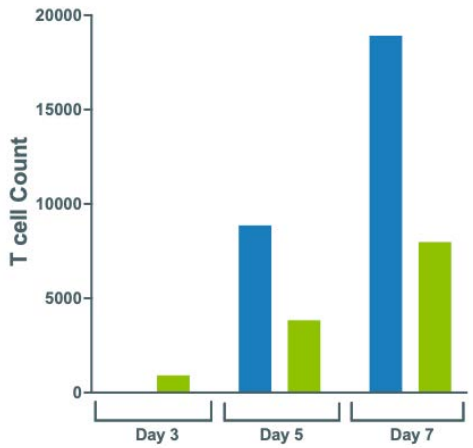
Low E:T Assay System



T Cell-Dependent Cytotoxicity at Low Effector to Tumor Cell Ratio



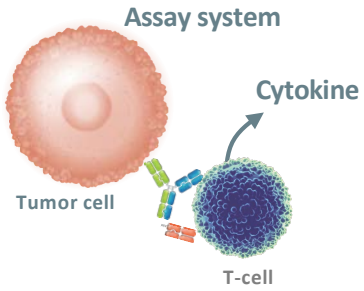
T Cell Proliferation at Low Effector to Tumor Cell Ratio



- Developed **long term co-cultures** at **low T cell to tumor cell (E:T) ratios** to better represent conditions in solid tumors
- Activity in long term low E:T cultures differentiates trispecifics vs bispecific benchmarks

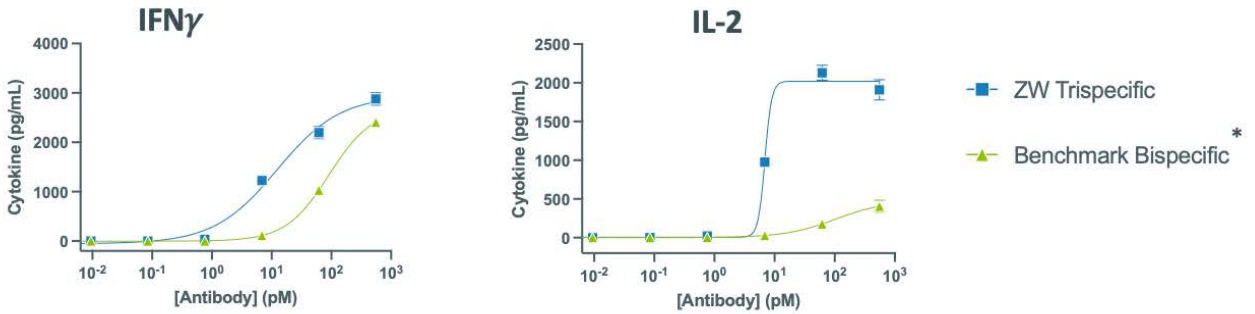
* Benchmark Bispecific targets same TAA as trispecific

Costimulatory Trispecifics Exhibit Strict Target-Dependent Activation of T Cells Suggesting No Activation of T Cells in the Periphery



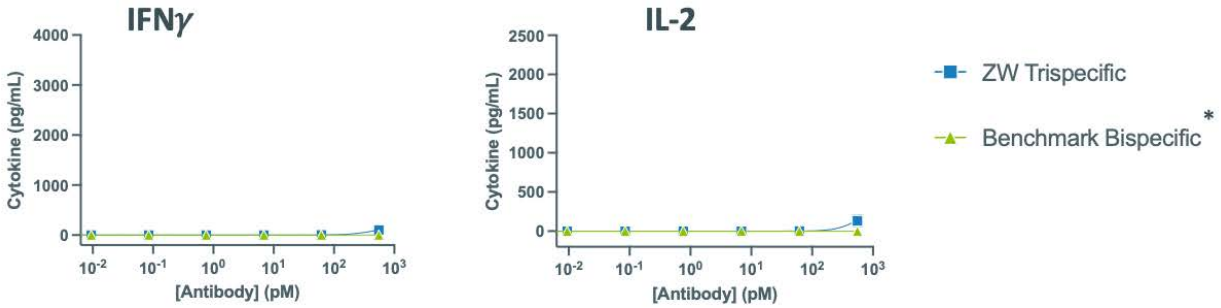
Trispecifics Show Enhanced Cytokine Release in the Presence of Tumor Cells

T Cells + Tumor Cells



Trispecifics Show Strict Target Cell Dependent Cytokine Release and No Activation of Isolated T Cells

T Cells Only



* Benchmark Bispecific targets same TAA as trispecific

Next Gen Costimulatory Trispecific T cell Engager (TriTCE-costim)

Addressing lack of activity of bispecific TCEs in solid tumors with low T cell infiltration

Therapeutic Rationale

Activity of bispecific T cell engagers in solid tumors is limited by **low numbers of intratumoral T cells and T cell anergy**

Next Gen TriTCE-costim 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-costim show **superior *in vitro* activity** to bispecific benchmarks at **low effector to target ratios**

TriTCE-costim show no activation of T cells without presence of tumor cells

Opportunity

TriTCE-costim may provide more durable responses in solid tumors and show superior activity in 'cold' tumors with low T cell counts

Next Milestone

Lead molecule selection

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Next Generation T-cell Engagers

Trispecific T Cell Engager With Checkpoint Inhibition

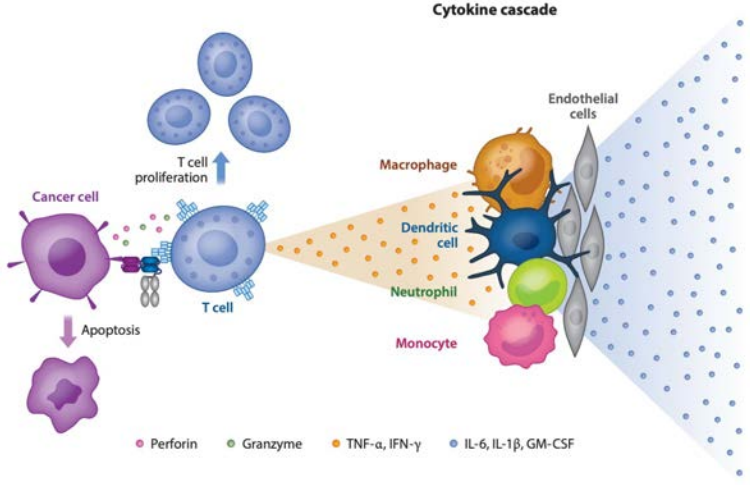
Dr. Thomas Spreter von Kreudenstein
Director, Protein Engineering

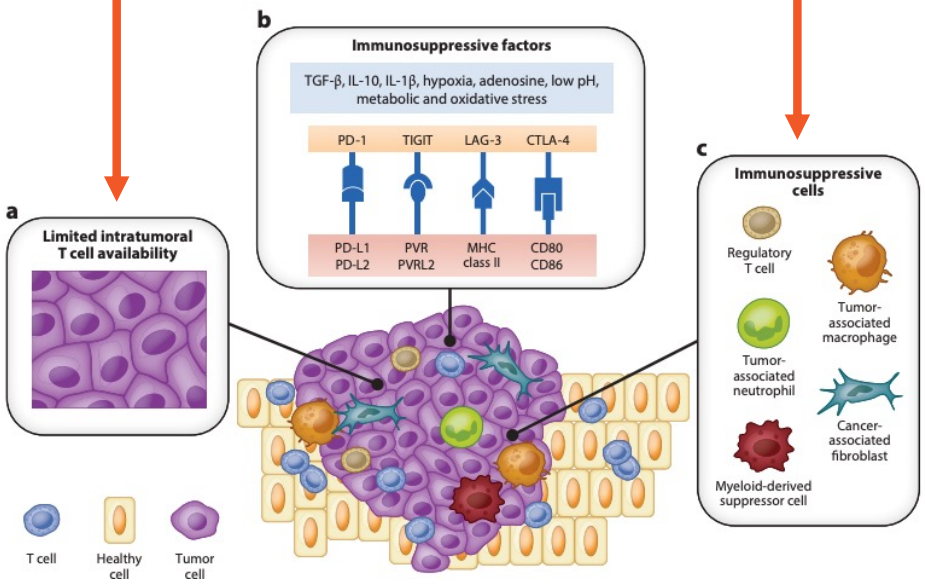
Challenges Remain: Gen 1 TCE Limited by Narrow Therapeutic Window & Solid Tumors Present Obstacles Not Found in Blood Cancers

Key Problem 1:
Narrow therapeutic window and limitations due to concomitant cytokine release

Key Problem 2:
Low T cell infiltration
T cell anergy

Key Problem 3:
Immunosuppressive tumor microenvironment





Arvedson T et al Ann Rev Cancer Biol 2022

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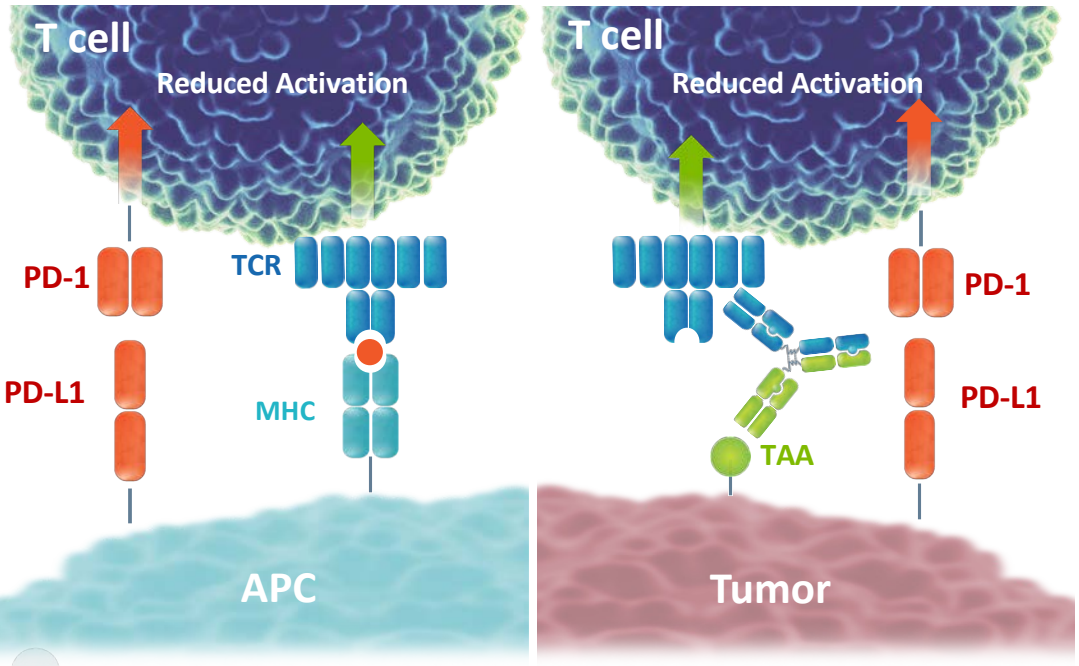
Natural T Cell Activation is Regulated by PD-1/PD-L1 Expression and Activity of TCEs is Limited by PD-1/PD-L1 Checkpoint Inhibition in Tumor Microenvironment

PD-1/PD-L1 engagement **negatively regulates T cell activation**

Activity of TCE is limited by PD-1/PD-L1 upregulation in the tumor microenvironment



- PD-1/PD-L1 upregulation is a natural mechanism to reduce T cell activation and prevent autoimmune reactions
- In tumors, PD-1/PD-L1 upregulation impairs T cells mediated killing of tumor cells
- TCE activity induces rapid upregulation of PD-1/PD-L1 and limits activity of TCE
- High levels of PD-1+ exhausted, dysfunctional T cells limit TCE activity

Krupka et al., Leukemia (2016)
Koehnke et al., J Hematol Oncol. (2015)

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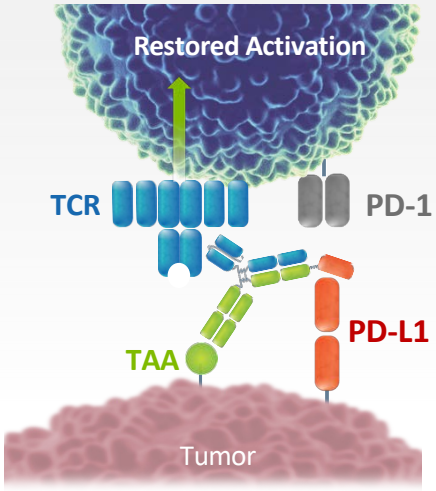
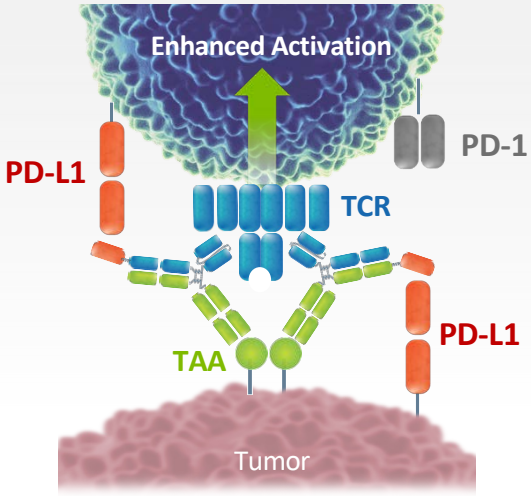
Trispecific T Cell Engager with Checkpoint Inhibition (TriTCE-CPI) to Address Limited Activity of T Cell Engagers due to PD-1/PD-L1 Upregulation in Tumor Microenvironment

Zymeworks approach of differentiated **TriTCE CPI (checkpoint inhibition)** utilizing PD-1/PD-L1 inhibition and enhanced efficacy of T cell redirection

MOA 1:
Blocking of CPI in the synapse restores TCR signal and T cell activation



MOA 2:
Enhanced synapse avidity increases activity and T cell activation in tumor microenvironment



- Enhanced activity of trispecific driven by dual MOA of PD-1/PD-L1 blockade in synapse and increased avidity
- Dual MOA has potential for enhanced activity of trispecific compared to combination therapy
- Building on learnings and engineering expertise from ProTECT™-TCE

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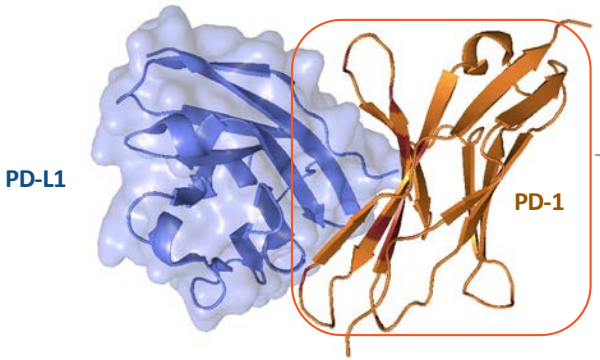
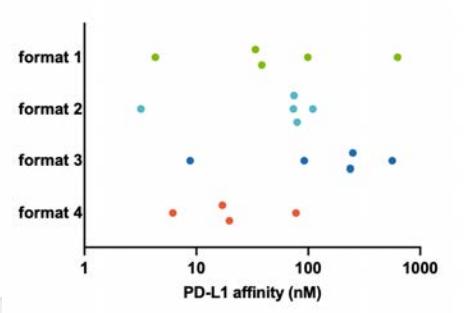
Natural PD-1 Domain Engineered for Enhanced PD-L1 Affinity is Used to Design Differentiated Trispecific T Cell Engagers with Varied Format

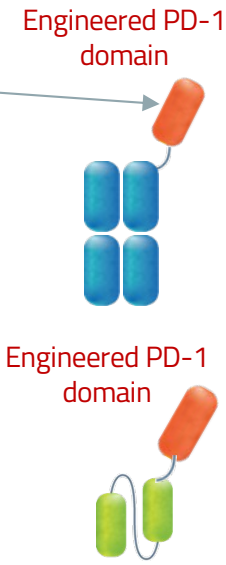
Engineered PD-1 domains bind wt PD-L1 and block PD-1/PD-L1 interaction



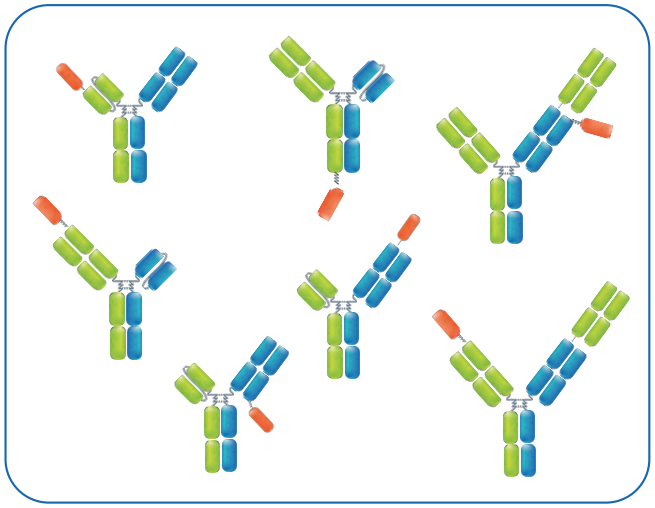
PD-L1 affinities



Azymetric advantage and **modular PD-1 domain** allows screening of multiple trispecific formats to **optimize dual MOA of CPI and avidity**



Panel of trispecific TCEs with PD-1 domain to inhibit PD-1/PD-L1 interaction



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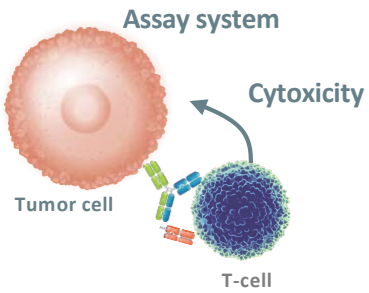
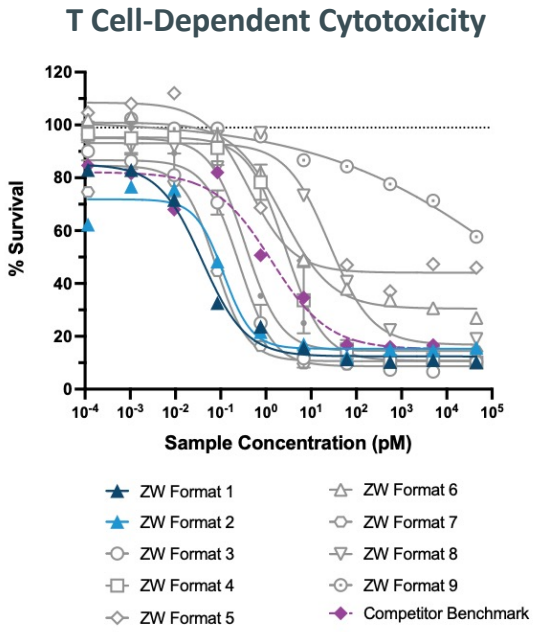
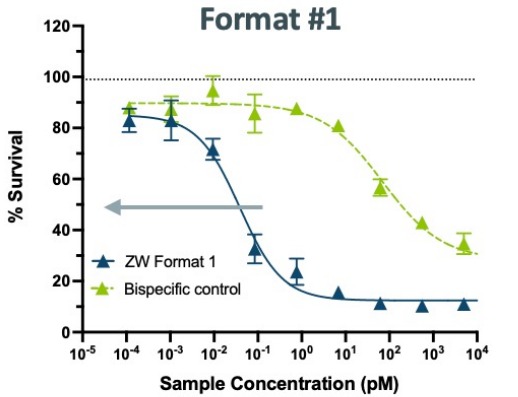
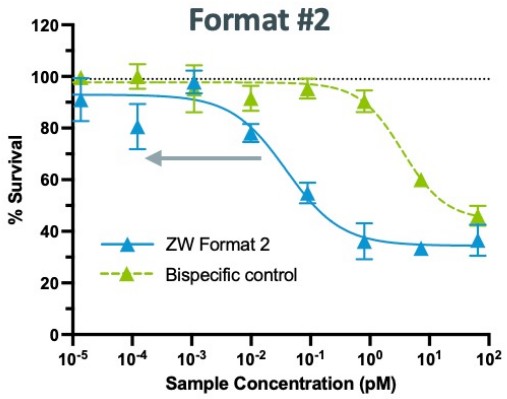
Screening of Trispecific Formats to Select Best-in-Class Multispecific Antibody

- Screening of panel of TriTCE-CPI formats with different geometries to optimize CPI and avidity
- Lead trispecific formats show >100x enhanced potency over format-matched bispecific control



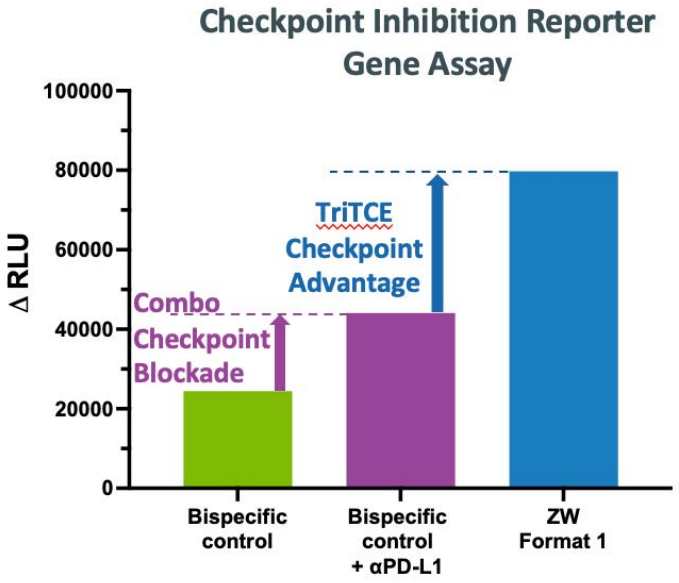




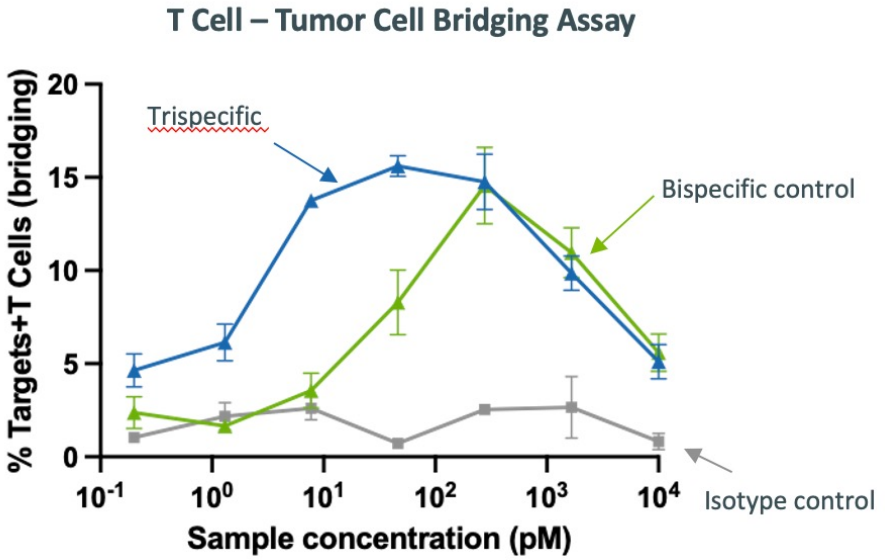


Trispecific T Cell Engagers Show Checkpoint Blockade Advantage Over αPD-L1 Combination Treatment Supporting Dual MOA of Trispecific

TriTCE-CPI Show Checkpoint Blockade Advantage Over Anti-PD-L1 Combination Treatment



TriTCE-CPI Can Simultaneously engage All 3 Targets and Show Enhanced T Cell-Tumor Cell Avidity



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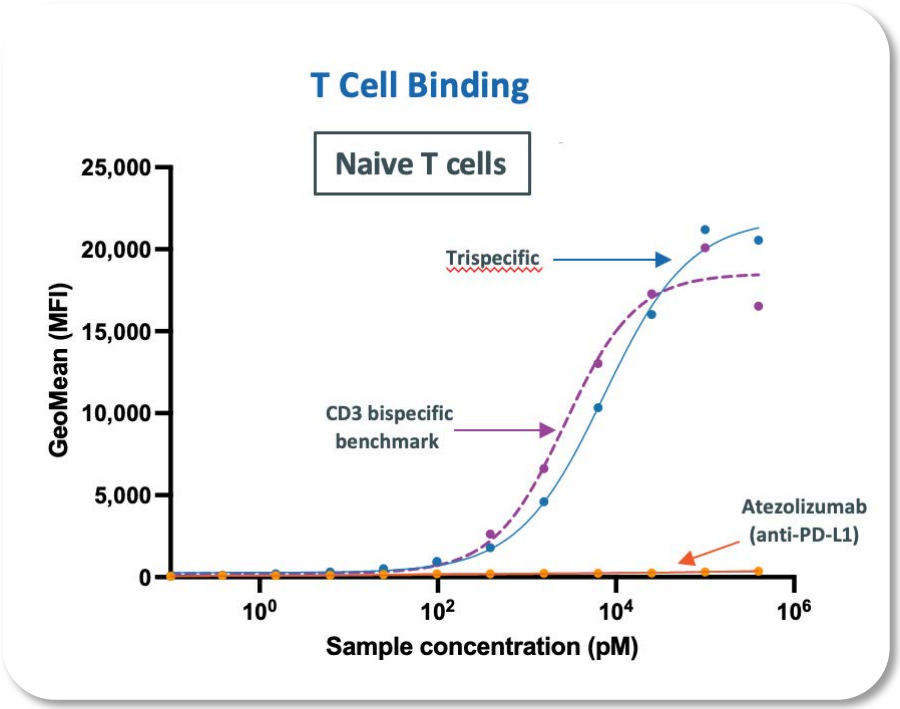
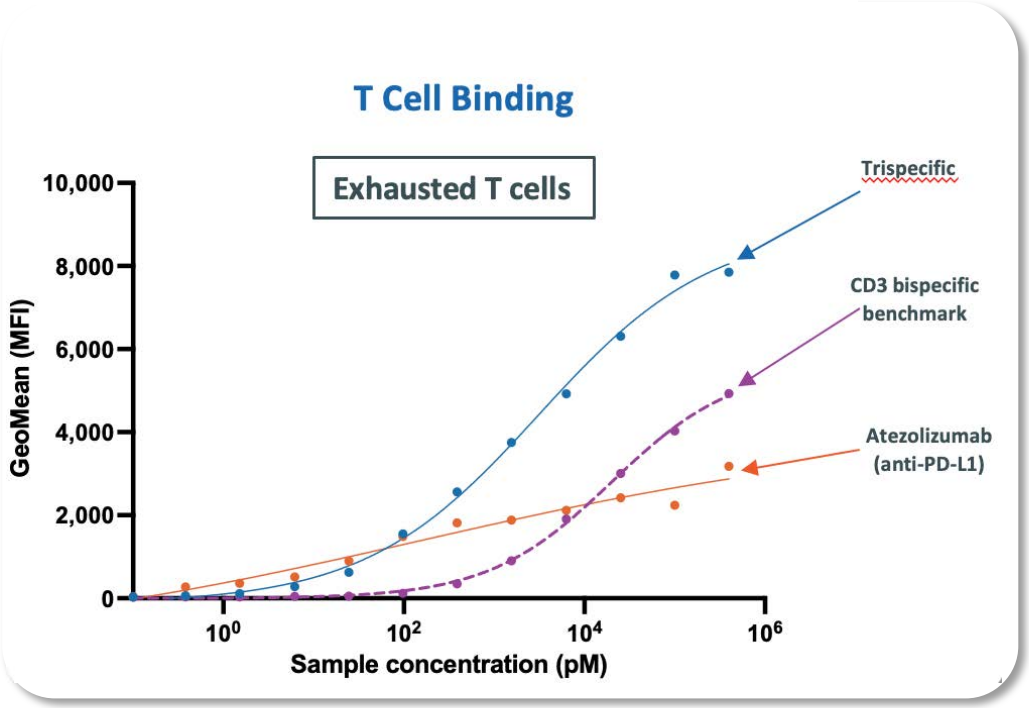
TriTCE-CPI Shows Superior Binding to Exhausted T Cells than Benchmark CD3 Bispecific

- As T cells become activated and exhausted, they express PD-L1 and downregulate CD3
- Trispecifics can bind to PD-L1 on exhausted T cells resulting in an avidity advantage

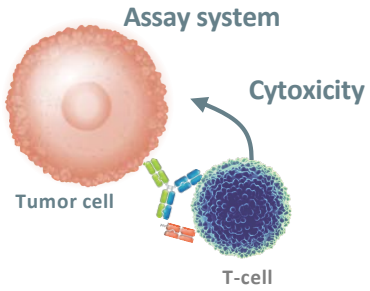


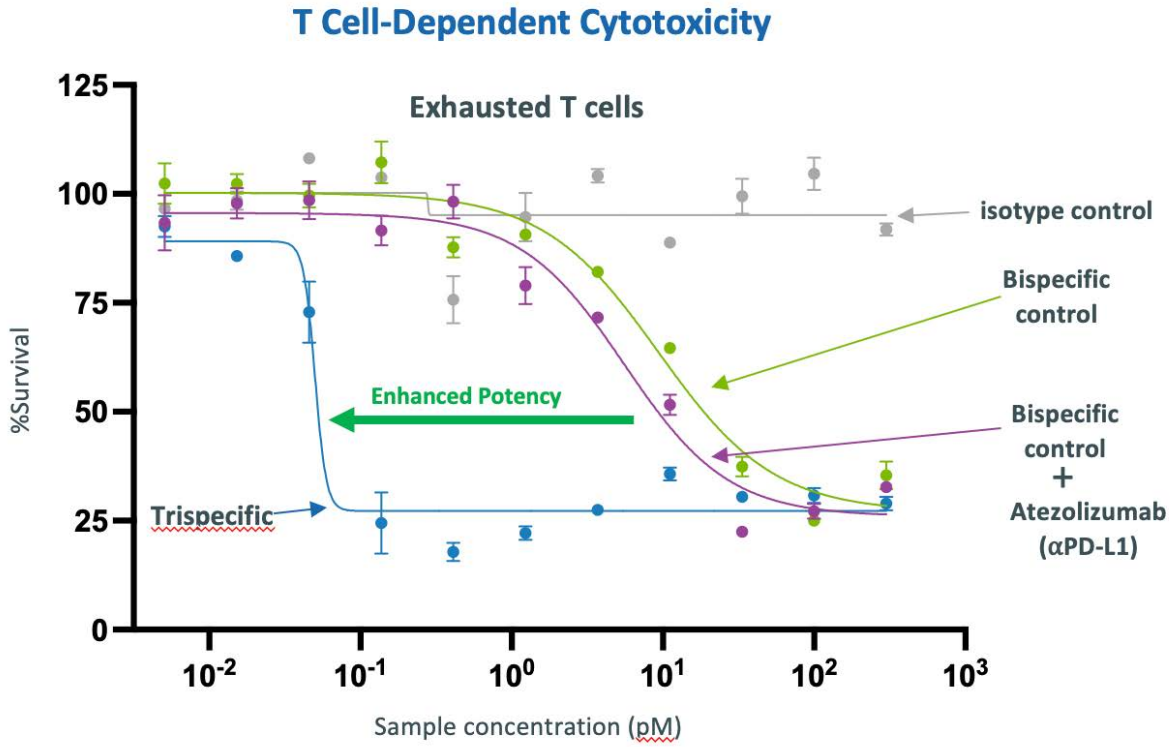


Lanzavecchia et al., J Exp Med (1997)

TriTCE-CPI Shows Superior Activity to Benchmark with Exhausted T Cells

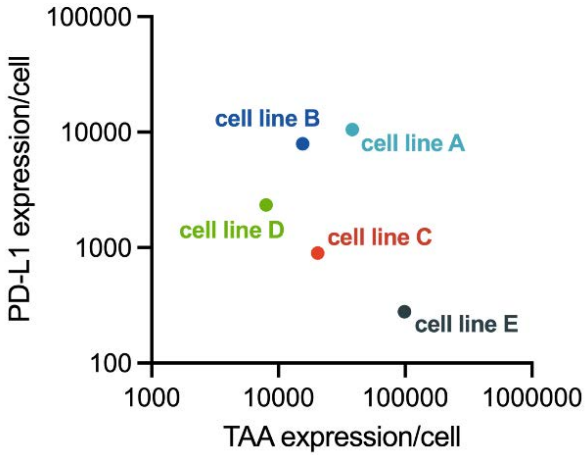
- Trispecific shows increased potency compared to bispecific and bispecific + atezolizumab combination when exhausted T cells are used as effector cells

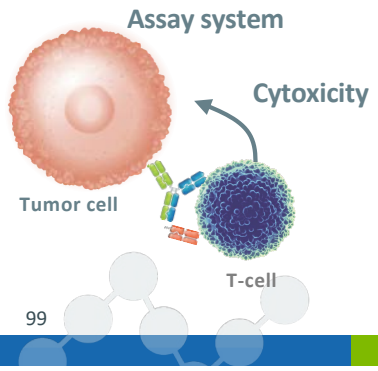




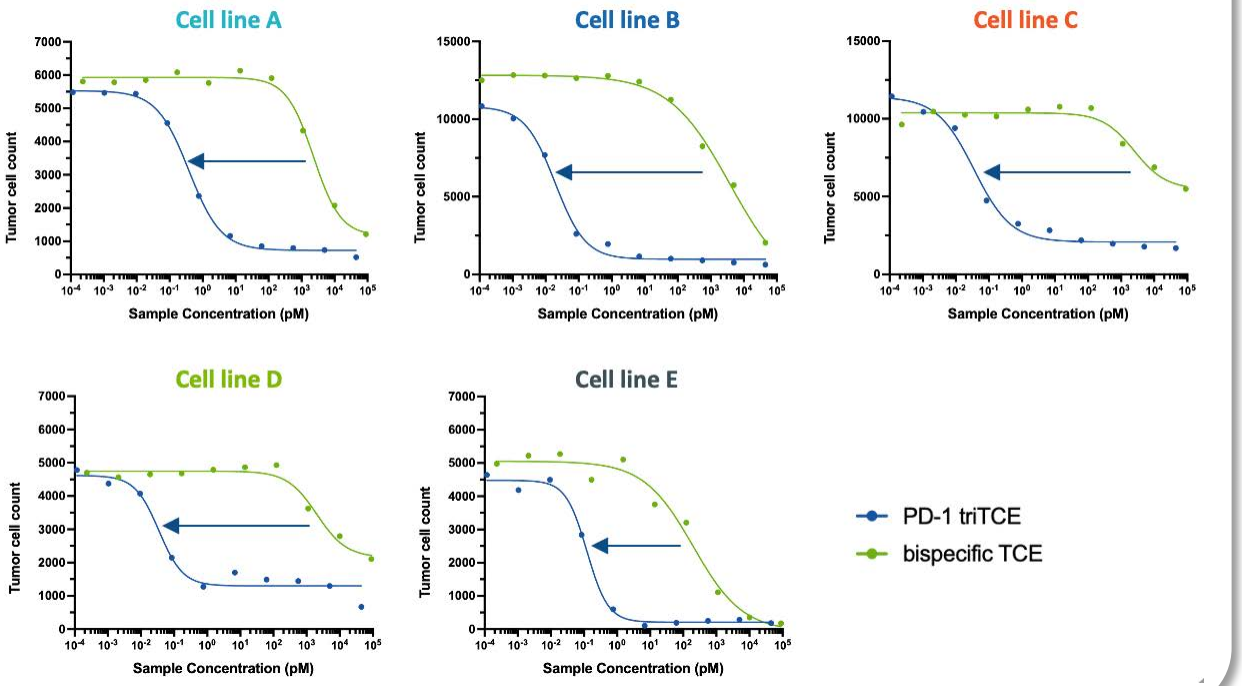
Improved Potency of TriTCE-CPI Over Bispecific Control Across Multiple Tumor Cell Lines that have Varying Level of TAA and PD-L1 Expression

TAA and PD-L1 Expression Level





T Cell-Dependent Cytotoxicity



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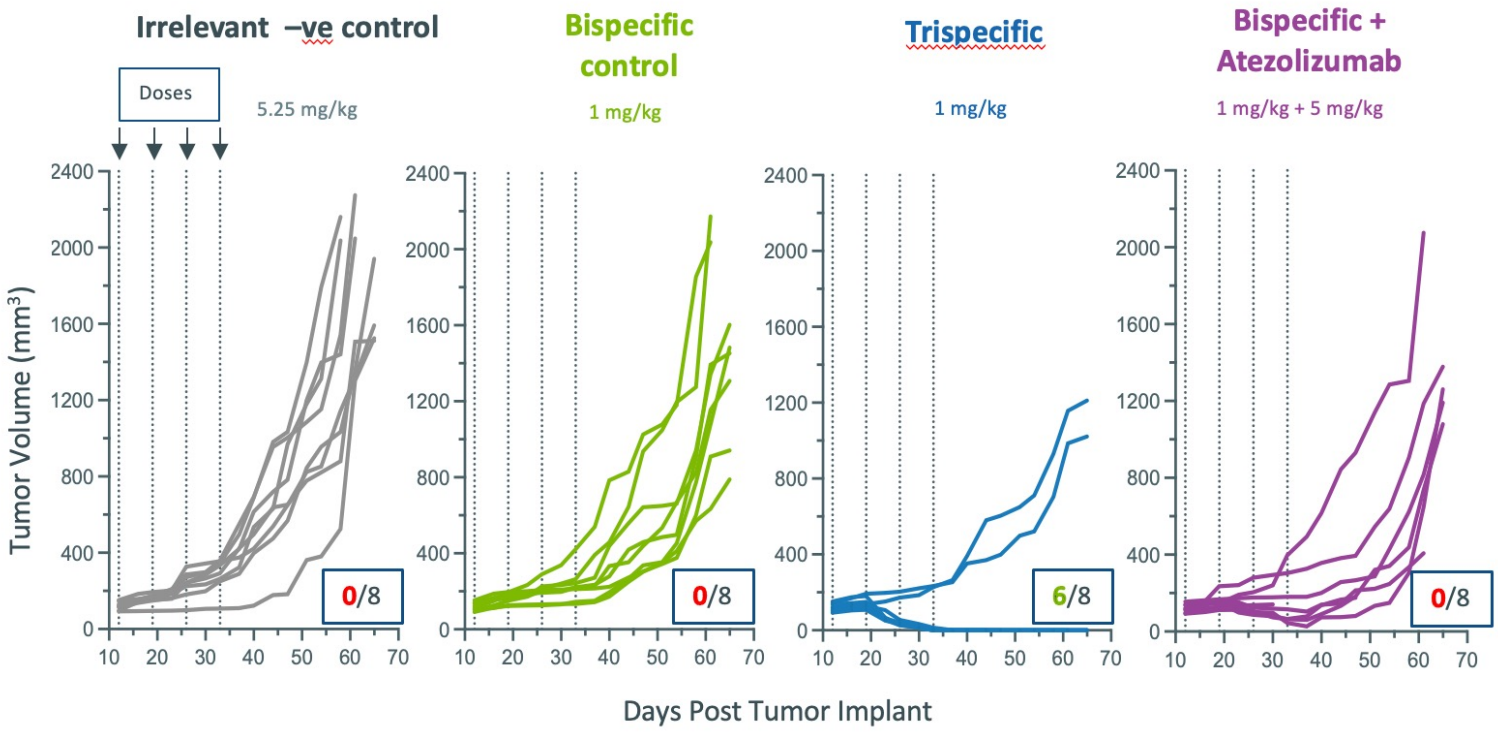
TriTCE-CPI is Efficacious In Vivo and Shows Advantage Over αPD-L1 Combination Treatment



Complete and durable tumor responses seen for trispecific

No complete tumor responses seen for bispecific controls including bispecific control + Atezo (αPD-L1)

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Next Gen Trispecific T cell Engagers with Checkpoint Inhibition (TriTCE-CPI)

Addressing lack of activity of bispecific TCEs in suppressive tumor microenvironment

Therapeutic Rationale

PD-1/PD-L1 upregulation in solid tumors and **suppressive tumor microenvironment** are resistance mechanism to bispecific T cell engagers

Next Gen trispecific T Cell engager (TriTCE-CPI) combining redirected T cell killing with immune checkpoint modulation to enhance activity and therapeutic applications for T cell engagers in solid tumors

Product Differentiation

Novel trispecific T cell engager with **dual MOA** of both checkpoint inhibition (CPI) and avidity driven T cell activation

Demonstrated potent and **differentiated activity** *in vitro* and *in vivo* and **high activity in exhausted T cells**

Superior activity of trispecifics **to combination therapy** of bispecific with checkpoint inhibitor *in vivo*

Opportunity

Potential for **TriTCE-CPI** to be **active** in **suppressive tumor** microenvironments

TriTCE-CPI potentially less susceptible to PD-1/PD-L1 mediated secondary resistance and provide **more durable responses**

TriTCE-CPI can be used as ProTECT™ to mitigate potential on-target toxicities of more 'difficult' targets

Next Milestone

Lead molecule selection

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Early Research and Development: Integrated Pipeline of ADCs and Multispecifics

Dr. Paul Moore

Chief Scientific Officer

Focused R&D Strategy to Drive Next Wave of Development in Difficult-to-Treat Cancers

Integrated R&D Engine

- Multispecifics
- ADCs

Product Profile

- First and second-line
  market opportunities
- Accelerated approval
  regulatory pathway allows potential of early market entry

Focus on indications with worst patient prognosis (e.g., 5-year OS)

Lead indications with global peak sales potential **>$500MM**

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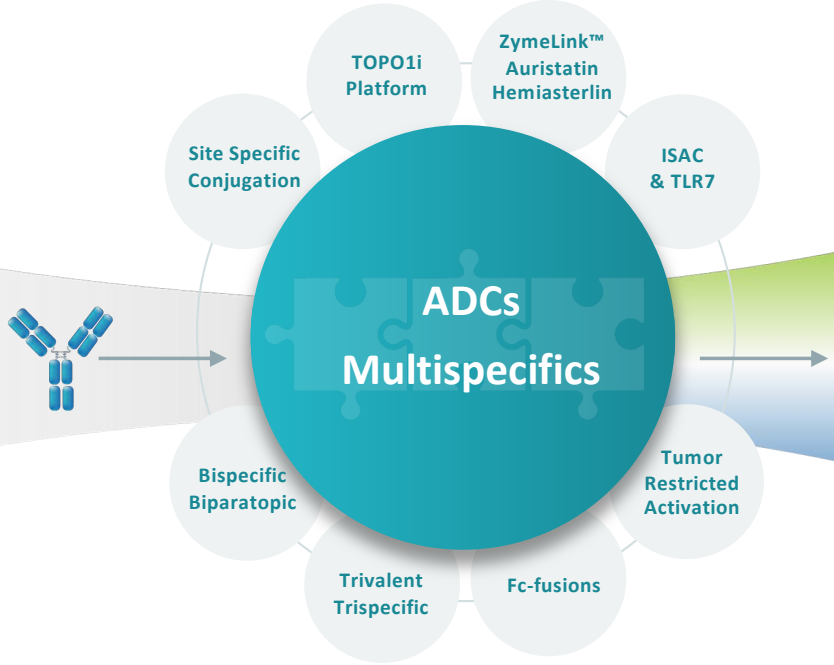
ADC and Multispecific Modalities Driving Future Product Candidates

Select Tumor Indications with High Unmet Need:

Examples :

Pancreatic
Ovarian
NSCLC
Liver
Mesothelioma
CRC

Design with Complementary Technology Platforms



Optionality with Two Foundational Fit-for-Purpose Modalities

Antibody-Drug Conjugates

Customization:

- Antibody properties & format
- Payload
- Linker/conjugation
- DAR

Multispecifics

Achieve:

- Precision targeting through multivalency
- Multiple MoA in single molecule
- Synergistic biology

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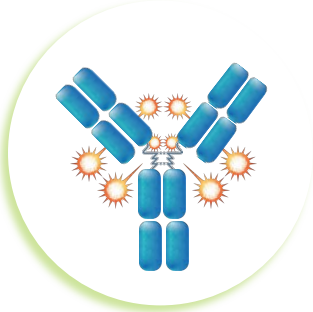
Zymeworks' Integrated Early Research Oncology Pipeline

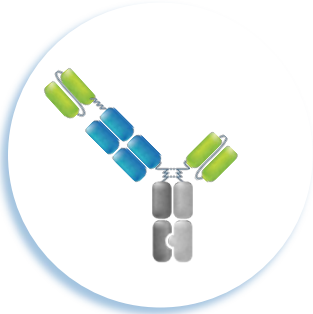
IND Candidates



ADC

ZW-191: FRa-TOPOi

- High internalizing mAb
- Proprietary Topo-based payload
- Ovarian Cancer, NSCLC, TNBC
  - FRa high and mid expression



Multispecifics

ZW-171: 2 x 1 MSLN x CD3

- Avidity driven MSLN engagement
- Affinity modulated CD3
- Pancreatic Cancer, Mesothelioma

Research Engine

TOPOi Conjugates

- **ZW251: GPC3**
- **ZW220: NaPi2b**
- TAA* (Biparatopic)

Trispecific T-cell Engagers

- Incorporate co-stim (aCD28)*
- Incorporate CPI (PD-1)*
- ProTECT T-cell Engager*

Alternative Payload Strategies

Novel target selection based on disease indication (hard to treat cancers)

Dual targets/pathways to enable gated activation and increase

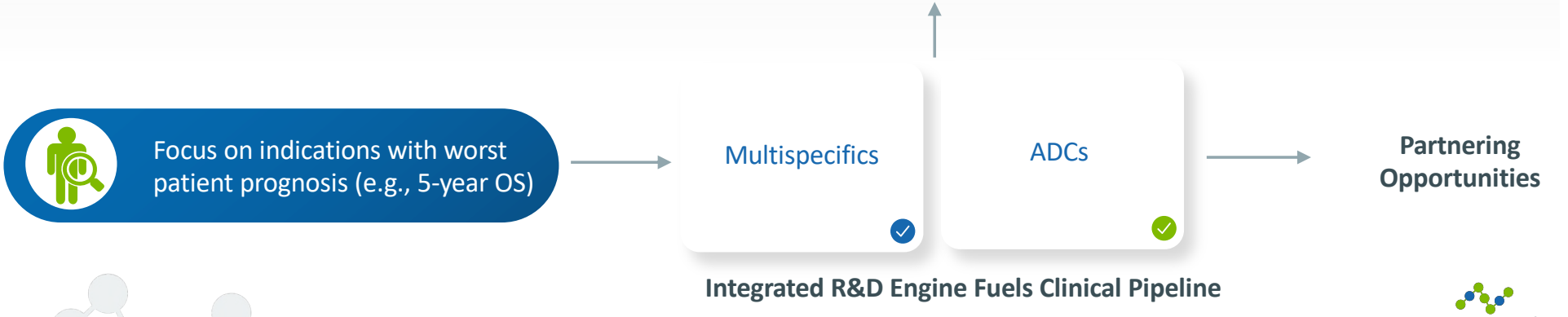
Simultaneous tumor cell lysis and reversal of immune suppression

Optimal Effector Cell recruitment

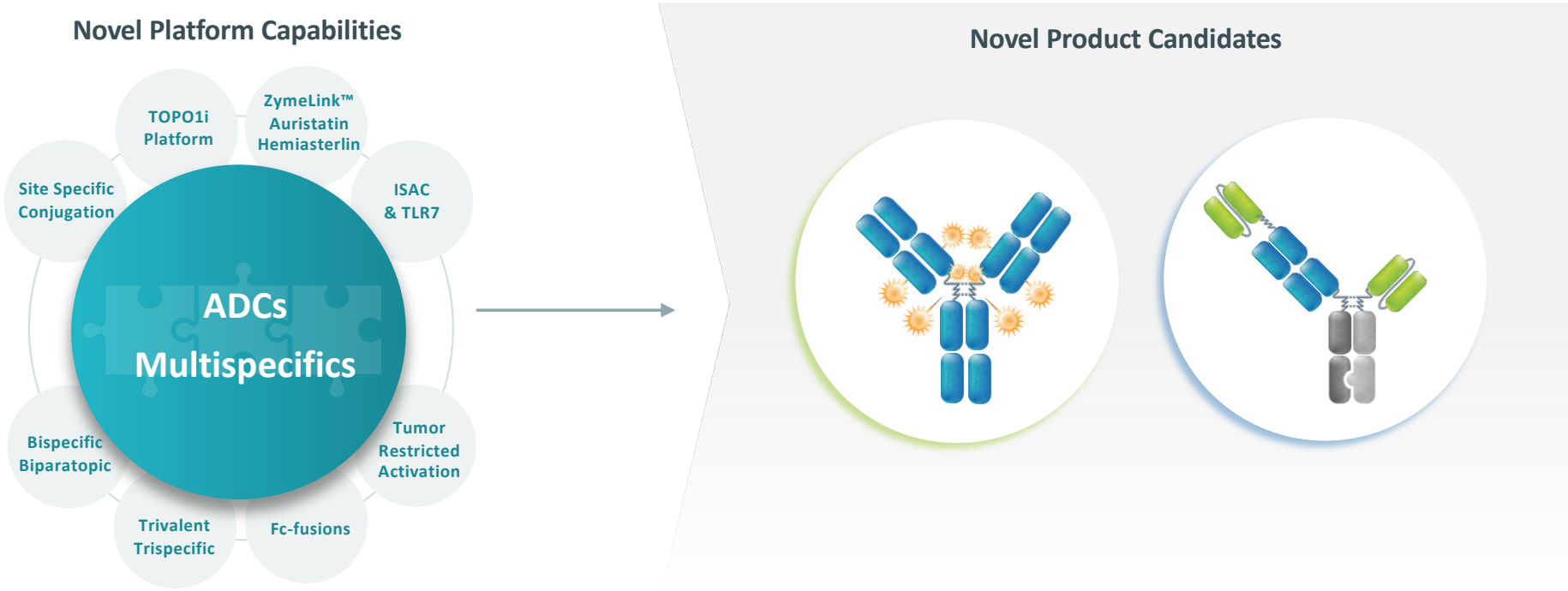
*Tumor Associated Antigens Selected

Integrated Platforms Drive Growing Product Candidate Pipeline

PROGRAMS | COMMERCIAL RIGHTS	TARGET	LATE-DISCOVERY	IND-ENABLING	PHASE 1	PHASE 2	MILESTONE
PRECLINICAL PROGRAMS						
ZW191 *TOPO1i ADC Program*	FRα	OVCA, Gynecological, NSCLC				IND: 2024
ZW171 *2+1 CD3-Engager Program*	MSLN	Pancreatic, OVCA, CRC				IND: 2024
ZW220 *TOPO1i ADC Program*	NaPi2b	OVCA, NSCLC				
ZW251 *TOPO1i ADC Program*	GPC3	Hepatocellular Carcinoma				



Future Partnering Strategy Focused on Deriving Value From Product Candidates and Novel Platform Capabilities



- Strategy to partner future product candidates in ex-US markets prior to registrational studies (inc. ZW49)
- Additional partnerships to generate further product candidates in both ADC and MSAT platforms
- Early-stage collaborations to access technologies/programs that are complementary to in-house capabilities

Zymeworks Moving Forward “5 by 5”

2017-2022

- Select Product Pipeline ✓
- Platform Technologies & Tools ✓

2022-2027

- **Accelerate Product Pipeline**
- **5 New Molecules in Clinic in 5 Years**
- **Select Product Partnerships**

5 new Zymeworks developed programs in clinic in 5 years

5 Zymeworks developed programs in clinic by 2025

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Key Takeaways

Focused Development

Renewed focus on multi-specific and ADC therapeutic research areas to generate novel therapeutics

Pipeline Expansion

Goal of generating **five** Zymeworks developed programs in the clinic **by 2025**

Partnership Strategy

Strategy to prioritize partnerships for future product candidates in ex-US markets prior to registrational studies

Q&A

*Email **ir@zymeworks.com** with questions*