Optimizing Multispecific Antibody Design for Therapeutic Application

Paul Moore, PhD
Chief Scientific Officer

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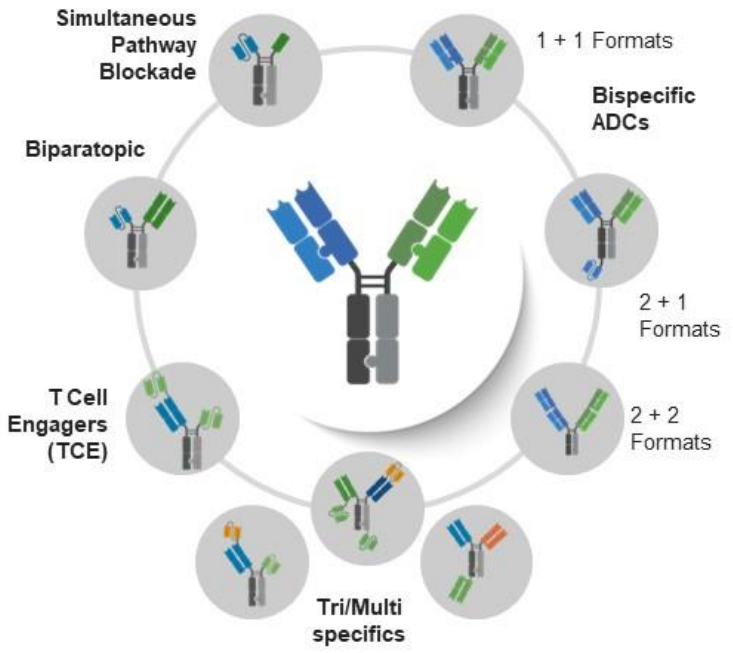
Pushing the boundaries of antibody-based therapeutics through multispecifics and optimized drug conjugates

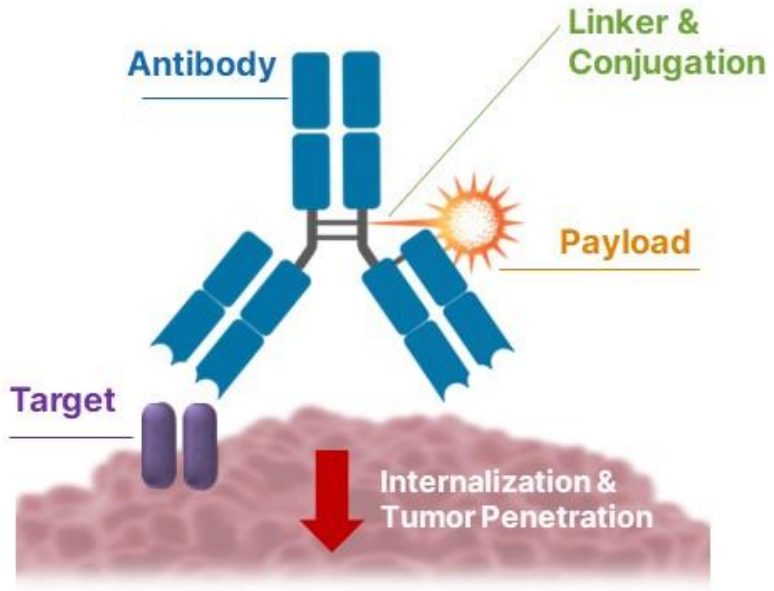
MULTISPECIFIC ANTIBODIES

Unlocking new biology and therapeutic possibilities through optimal design and format



ANTIBODY-DRUG CONJUGATES

Utilizing antibodies to more effectively deliver small molecules through optimal linker-payload design and antibody format



Azymetric™: adaptable to different formats & applications

Engineering

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

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

Flexibility

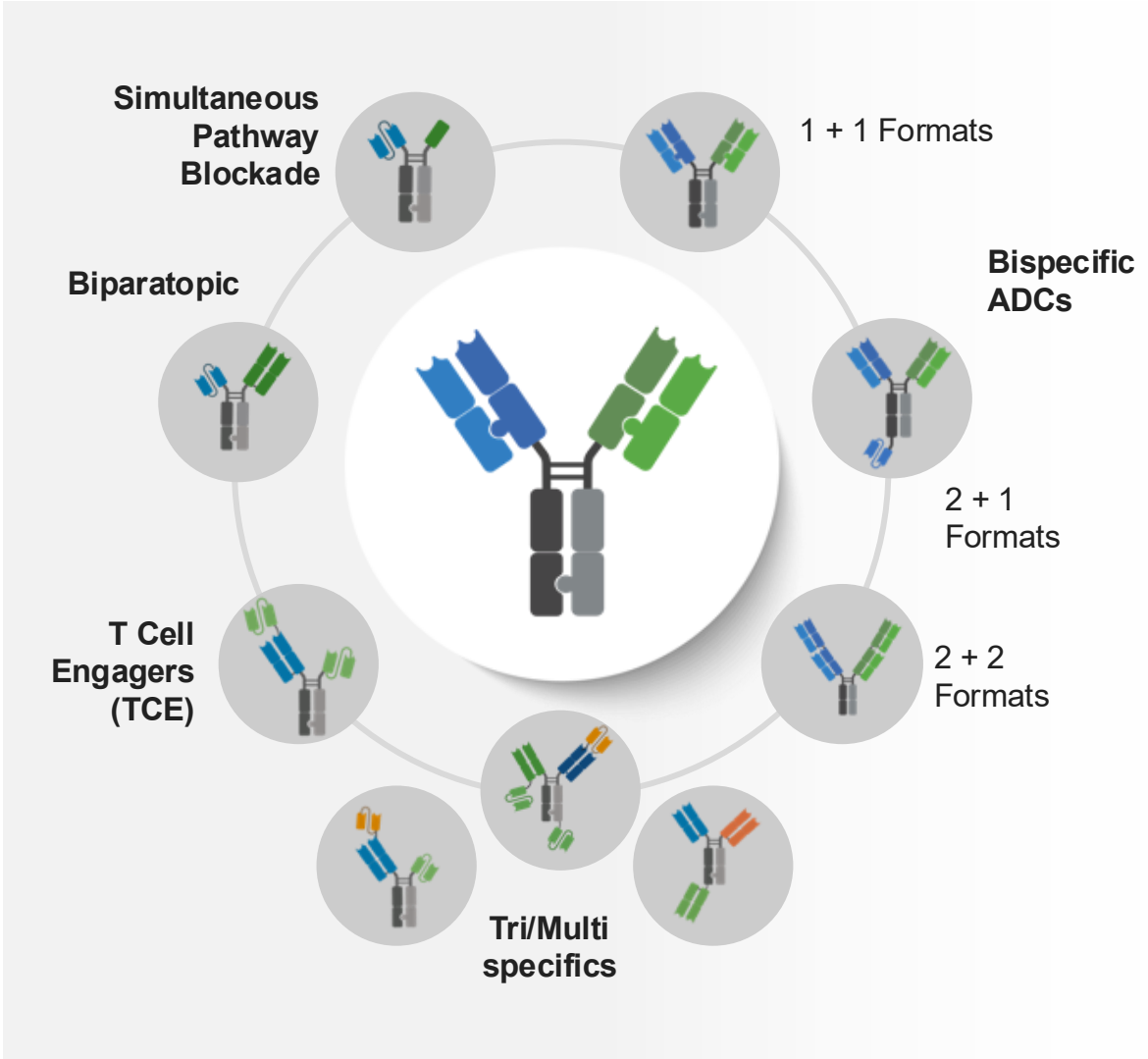
Can employ novel or existing antibody paratopes; human (IgG1, IgG2A, IgG4) and mouse frameworks; other CH2 and glyco-engineering approaches (eg YTE). Compatible with linker/payload conjugation

High-throughput Screening

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

Highly Manufacturable

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



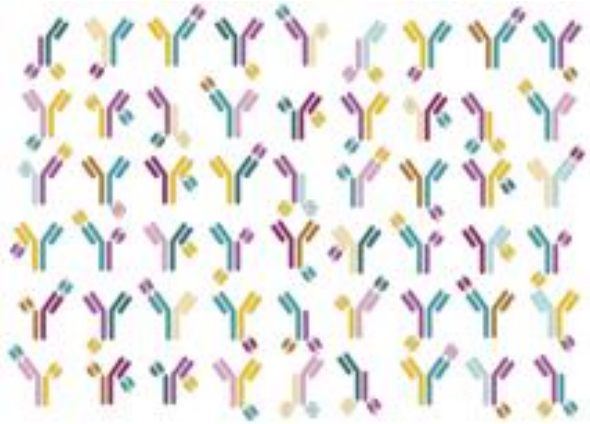
MERCK Daiichi-Sankyo Johnson&Johnson GSK

Azymetric: unique formats drive novel biology

Interrogating a broad geometric and format space is critical to identifying candidates with desired and potentially novel biology

Azymetric™ facilitates efficient heterodimeric antibody assembly

- Allows for HTP production and screening of multiple formats, antibody binding domains, and affinity range
- Enables empirical identification of lead molecules with optimal biological profile



Example case studies to present:

Bi-paratopic Antibodies

HER2 Biparatopic

Multispecific T Cell Engager

ZW209 *

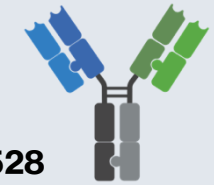
DLL3 x CD3 x CD28

Biparatopic ADCs

ZW418

PTK7 Biparatopic RAS ADC

Simultaneous Cytokine Blockade



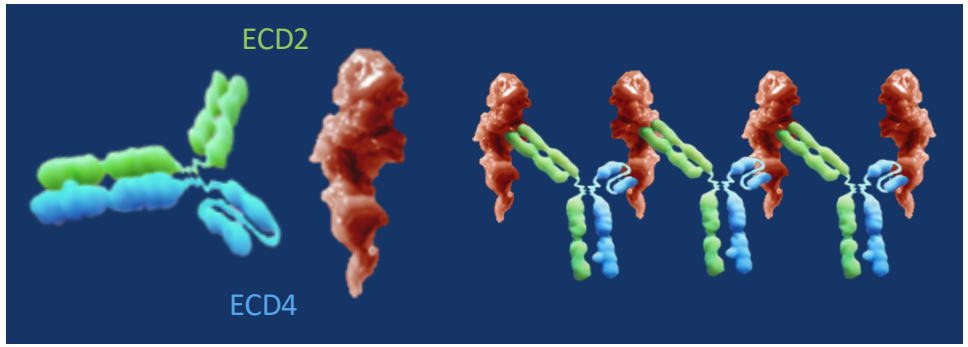
ZW1528

IL4R x IL33

* Representative structure

Zanidatamab: a bispecific antibody for HER2-expressing cancers

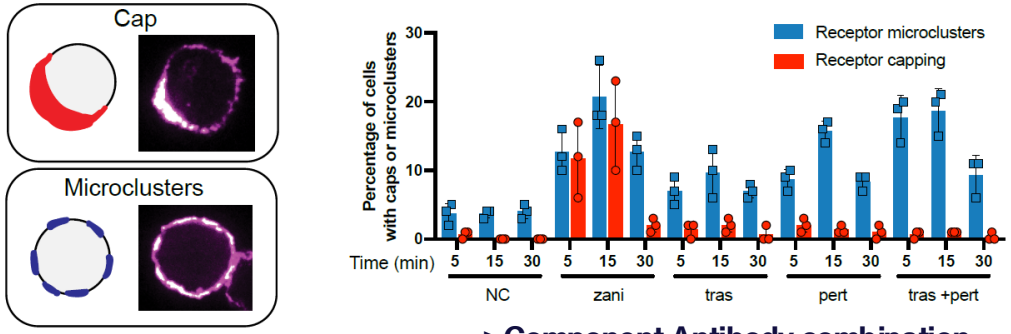
Binds Two Distinct Epitopes of HER2



Azymetric Bispecific comprising Trastuzumab and Pertuzumab Binding Domains

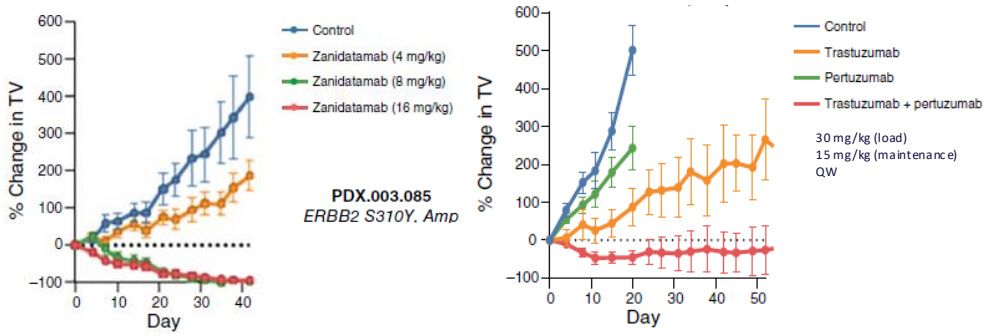
Induces Rapid HER2 Clustering on Cell Surface

Weisser et al, Nature Communications 2023



> Component Antibody combination

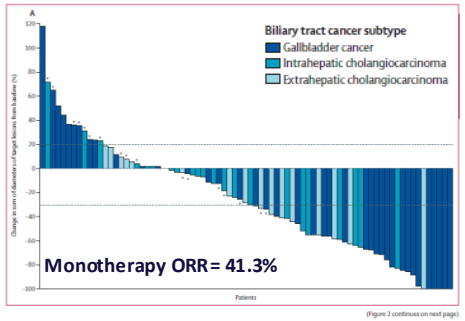
Anti-Tumor Activity in Preclinical Models



Di Peri et al, Clinical Cancer Research 2025 (BTC)

Clinically Efficacious in HER2+ Cancers

HER2+ Biliary Tract Cancer



Harding et al, Lancet Oncology 2023 (BTC)

Approved for treatment of HER2+ve BTC

Zanidatamab outperforms Trastuzumab in GEA phase 3 study

The NEW ENGLAND JOURNAL of MEDICINE

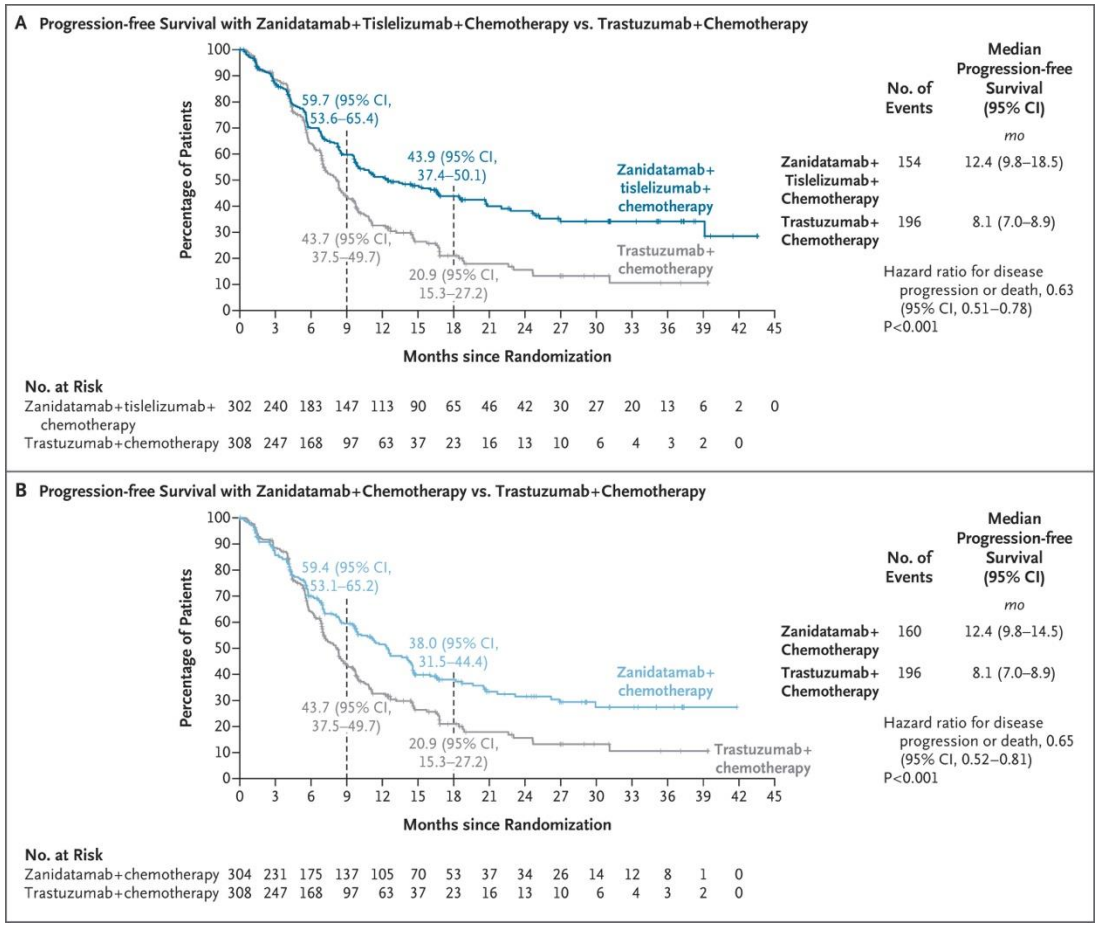
ORIGINAL ARTICLE

Zanidatamab with and without Tislelizumab in HER2-Positive Gastroesophageal Cancer

K. Shitara,[1] E. Elimova,[2] T. Liu,[3] J. Tabernero,[4-7] K.-W. Lee,[8] M. Schenker,[9,10] N.C. Tebbutt,[11] J. Ajani,[12] N. Salimin,[13] G. Ku,[14] J. Gwang Kim,[15] I. Ales Diaz,[16] J. Zhang,[17] F. Pietrantonio,[18] L.-Y. Bai,[19] S. Le Sourd,[20] J. Zhao,[21] C. Hierro,[22] A. Kiberu,[23] F. Van Herpe,[24] Y. Bao,[25] H. Zhang,[26] L. Yang,[26] V. Li,[25] E.M. Gartner,[26] Y. Chen,[25] J. Grim,[26] S.Y. Rha,[27] and L. Shen,[28,29] for the HERIZON-GEA-01 Investigators*

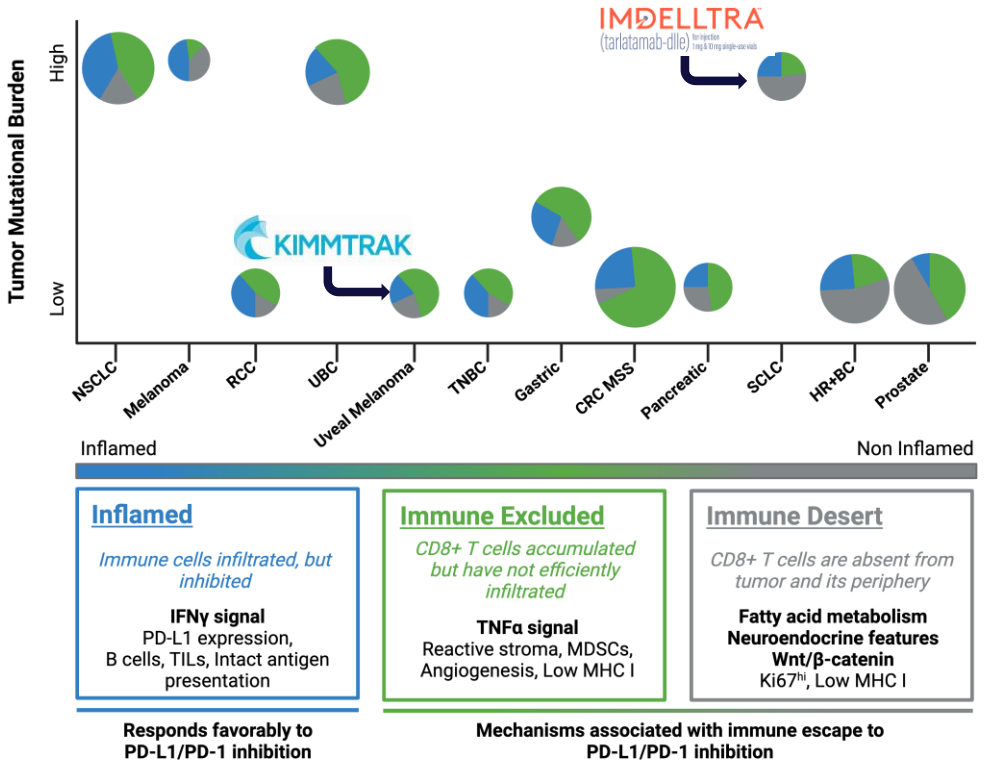
CONCLUSIONS

Zanidatamab plus chemotherapy, both with and without tislelizumab, led to longer progression-free survival than trastuzumab plus chemotherapy among patients with HER2-positive advanced gastroesophageal adenocarcinoma. At this interim analysis, overall survival was longer with zanidatamab–tislelizumab–chemotherapy than with trastuzumab–chemotherapy; further analyses are planned to assess zanidatamab–chemotherapy. Diarrhea was a common adverse event. (Funded by Jazz Pharmaceuticals and others; HERIZON-GEA-01 ClinicalTrials.gov number, NCT05152147.)



Results Support Ziihera® (zanidatamab-hrii) as HER2-Targeted Agent-of-Choice and Ziihera Combination Regimens as New Standard of Care in First-Line HER2-Positive Locally Advanced or Metastatic Gastroesophageal Adenocarcinoma

T cell engagers active in solid tumors but unmet need



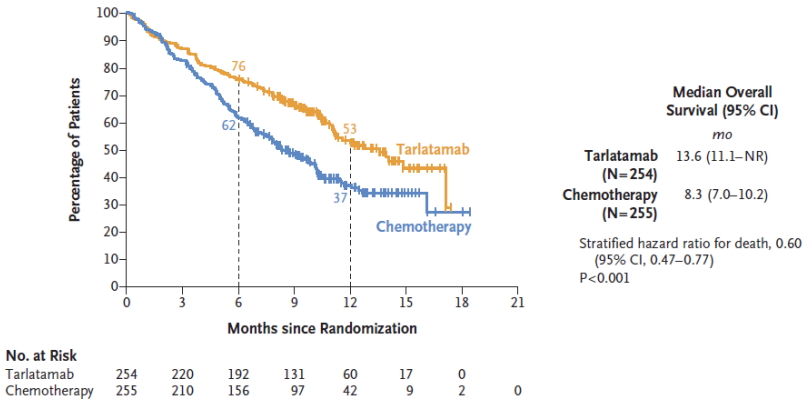
Adapted from Hedge and Chen 2020 Immunity 52

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tarlatamab in Small-Cell Lung Cancer after Platinum-Based Chemotherapy

N ENGL J MED 393;4 NEJM.ORG JULY 24, 2025



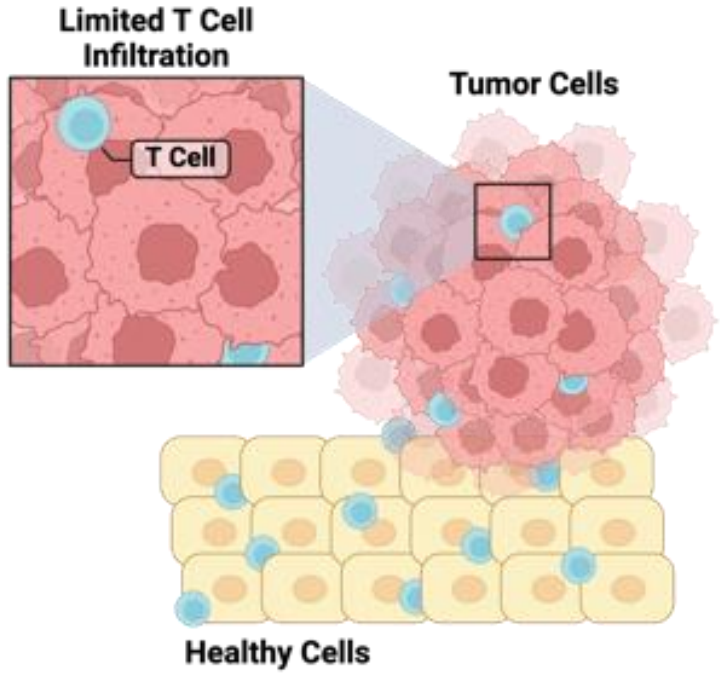
	ORR	PFS	OS	Gr3 AE
Tarlatamab	35%	4.2m	13.6m	54%
Chemotherapy	20%	3.7m	8.3m	80%

Additional targets to broaden responsive tumor types

Complementary MoA to enhance responses rates

Enhancing efficacy and durability of T cell mediated responses in solid tumors through CD28 co-stimulation

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



CD28 profile ideally complements anti-CD3 TCE

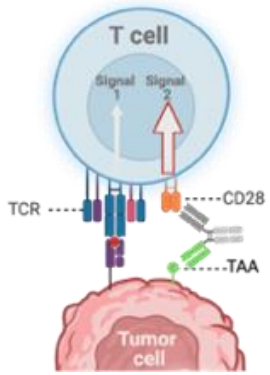
	CD28
Anergy prevention	✓
Ability to expand & maintain T_{pex}	✓
Expressed on activated/naïve / recently recruited T cells	✓
No signaling in absence of Signal 1 (monovalent engagement)	✓
Limited / no detrimental trans-cell interactions	✓
Low TMDD risk	✓
Clinically validated	✓

Arvedson T et al Ann Rev Cancer Biol 2022

[1] Lotze et al., Nature Reviews Immunol 2024; [2] Humblin et al., 2023, Sci. Immunol.; [3] Prokhnevska et al., Immunity 2023; [4] Friedrich et al., Camcer Cell 2023

CD28 co-stimulatory T cell engager approaches

Bispecific CD28 T cell Engagers

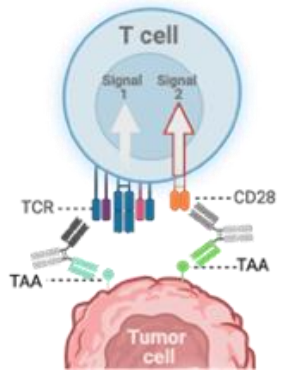


CD28 x TAA +/- PD1

Limitations:

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

Regeneron (PSMAxCD28)



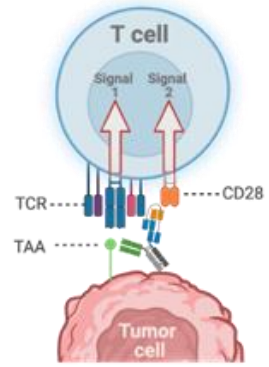
CD28 x TAA + CD3 x TAA

Limitations:

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

Regeneron (MUC16xCD3 + MUC16xCD28, CD20xCD3 + CD22xCD28, PSMAxCD3 + PSMA xCD28)
Janssen (PSMAxCD28 + KLK2xCD3)
Roche (CD20xCD3 + CD19xCD28)

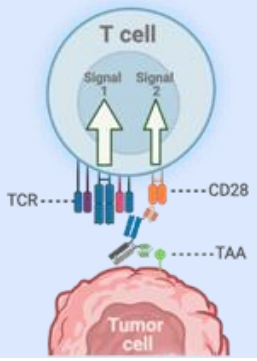
Trispecific CD28 T cell Engagers



First Generation:

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

Sanofi (HER2xCD3xCD28; CD38xCD3xCD28)



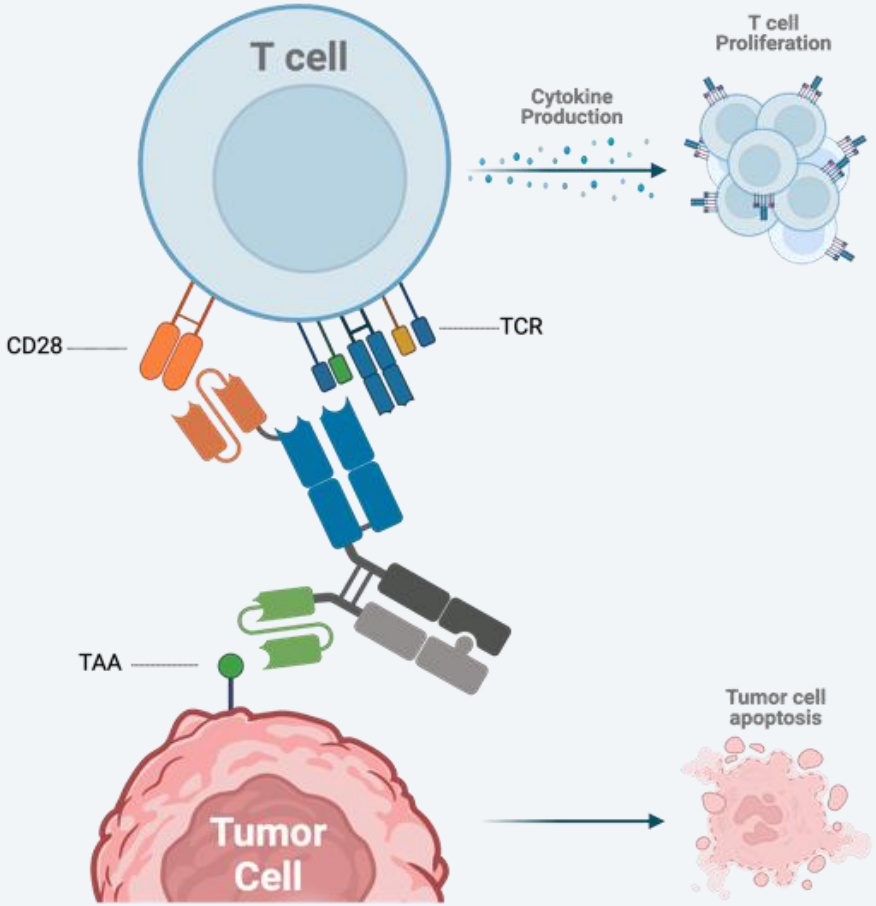
Zymeworks' Next Generation Solution:

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

[1]Stein et al., Journal Clinical Oncology (2023); [2]Seung et al., Nature (2022); [3] Promsote et al., Nature Communications (2023)
TAA: tumor-associated antigens, TMDD: Target-mediated drug disposition

Desired TriTCE co-stim design features

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

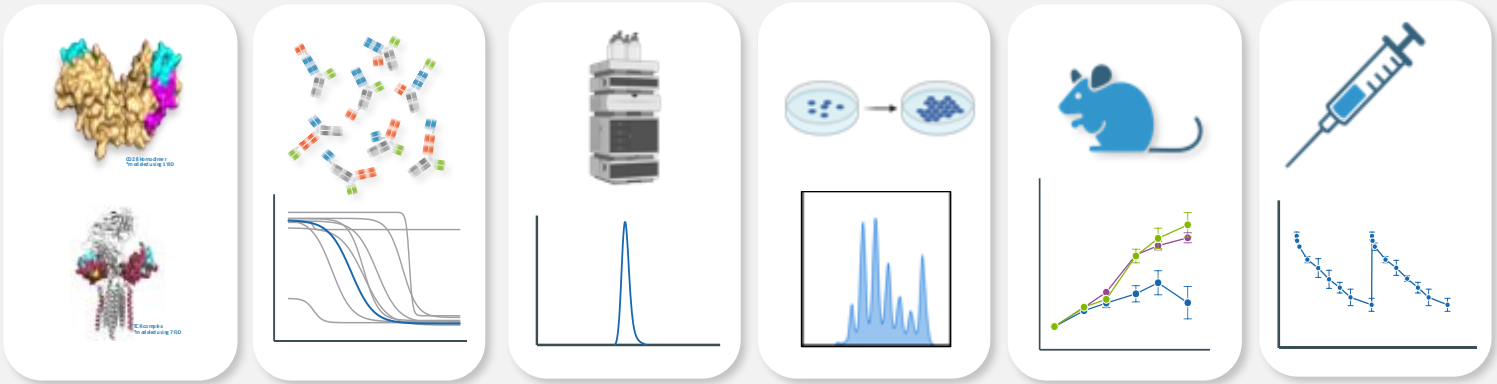


	Design Feature	Expected Benefit
1	**Balanced activation of CD3 and CD28**	Potential to provide more durable responses and activate T cell responses in 'cold' tumors with lower T cell infiltration
2	**Low affinity CD3 and CD28 binding**	Prevents overactivation of T cells and reduces risk of CRS and irAEs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

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

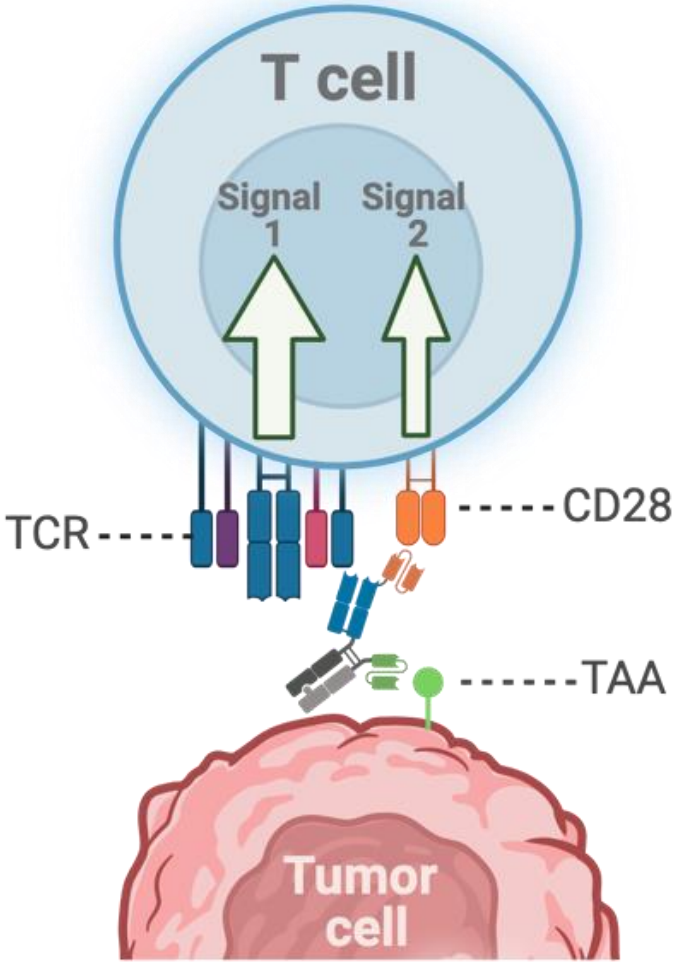
TriTCE co-stim platform development

TriTCE Co-stim Platform Workflow



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

TriTCE Co-stim Lead Format Selection

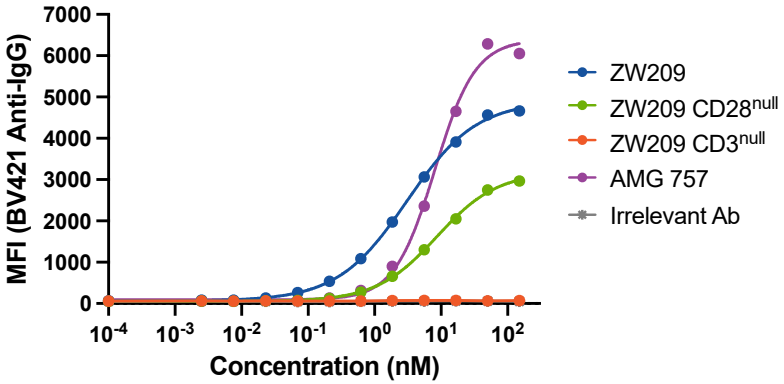


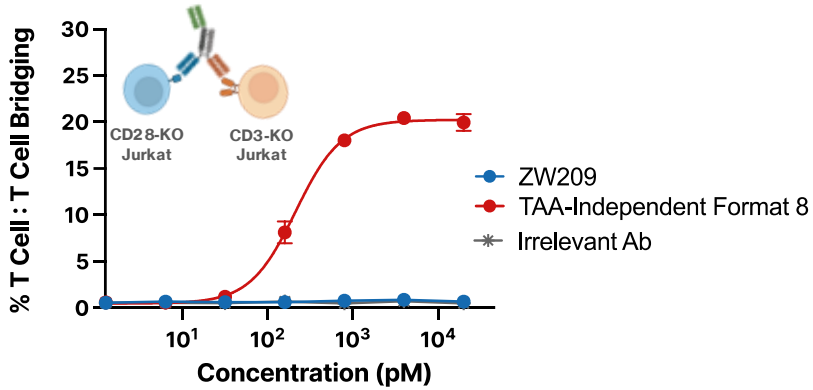
ZW209: DLL3 x CD3 x CD28 trispecific T cell engager designed for treatment of small cell lung cancer

ZW209 design facilitates desirable T cell engagement

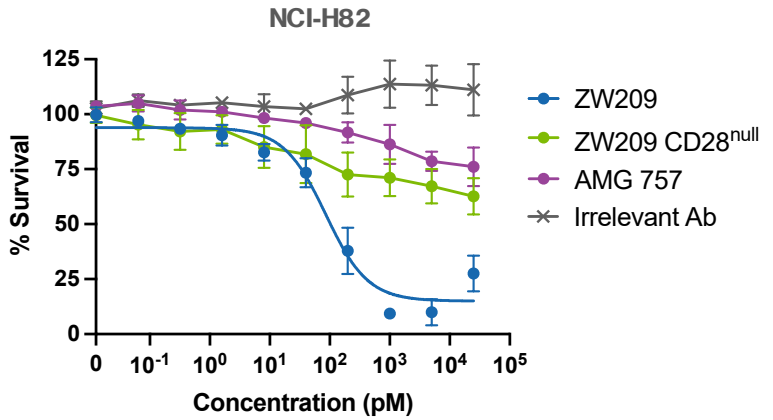
Design Feature
☑ Balanced activation of CD3 and CD28
☑ Low affinity, Conditional CD28 engagement
☑ Obligate *cis*-T cell (CD3xCD28) binding
☑ Target-dependent activity

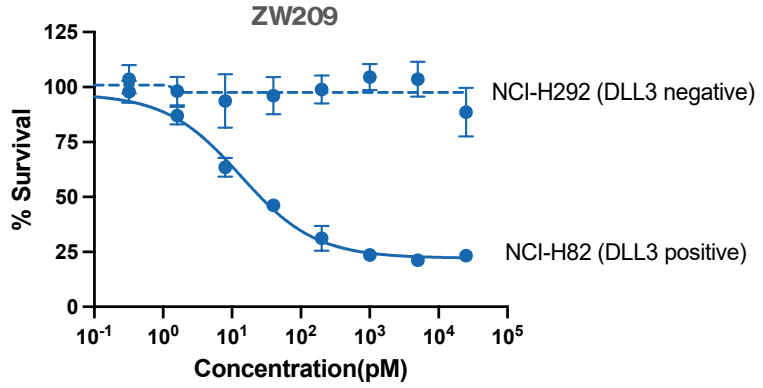
Conditional Binding of CD28, Requiring Co-engagement of CD3; Obligate Cis Binding



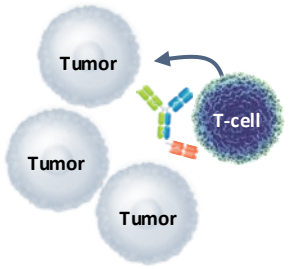


Improved Cytotoxicity Over Bispecifics in Low E:T Conditions



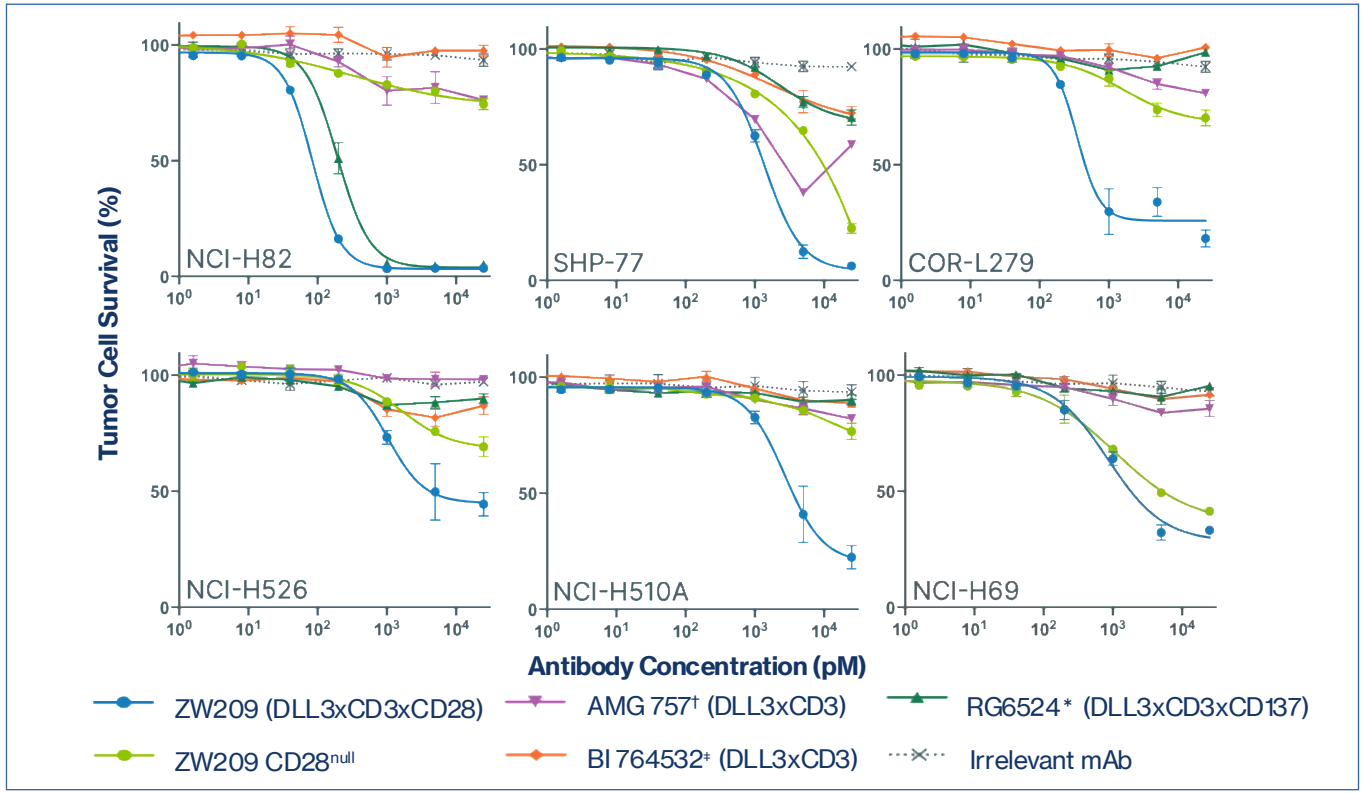


ZW209 exhibits improved potency relative to bispecific and trispecific clinical benchmarks at low effector: target ratios



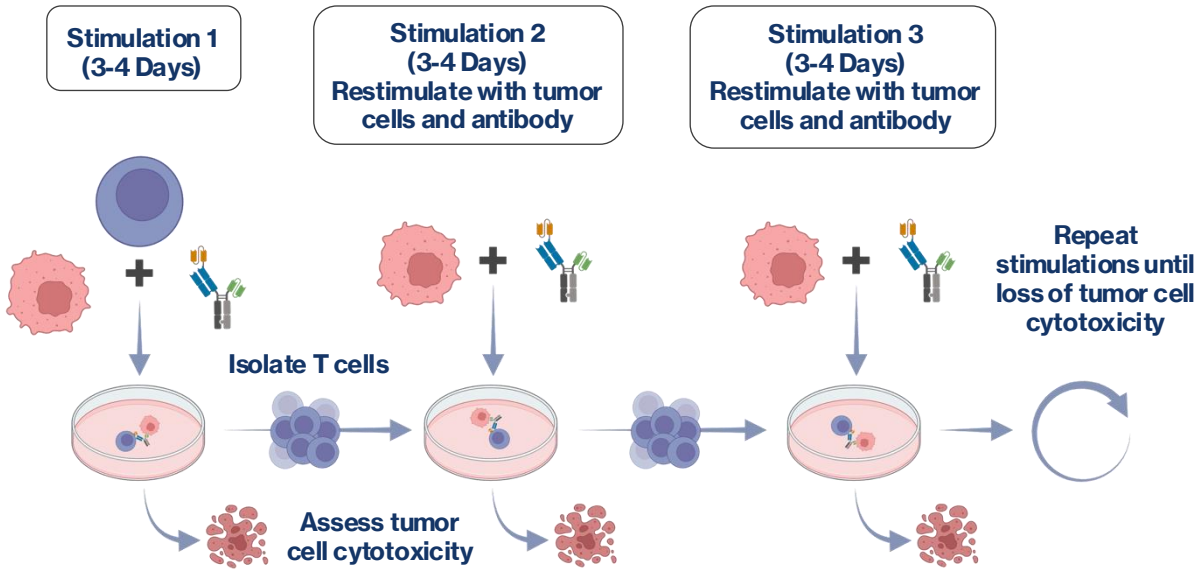
Low E:T Assay System

Cytotoxicity and T cell proliferation

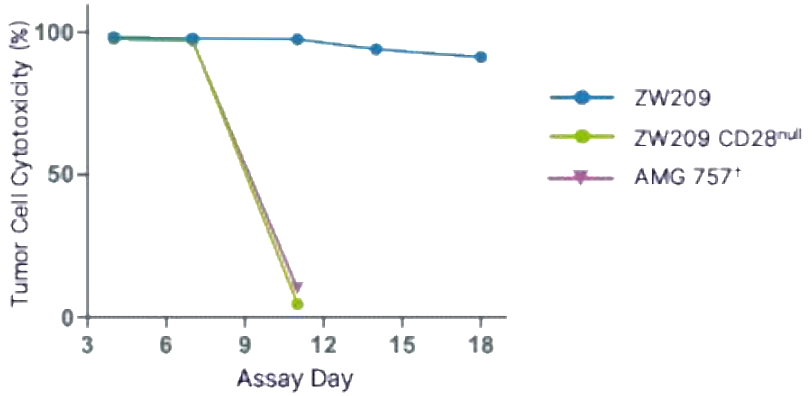


Test articles were incubated with T cells co-cultured with DLL3-expressing SCLC tumor cell lines at low E:T ratio for 7 days and evaluated for cytotoxicity.

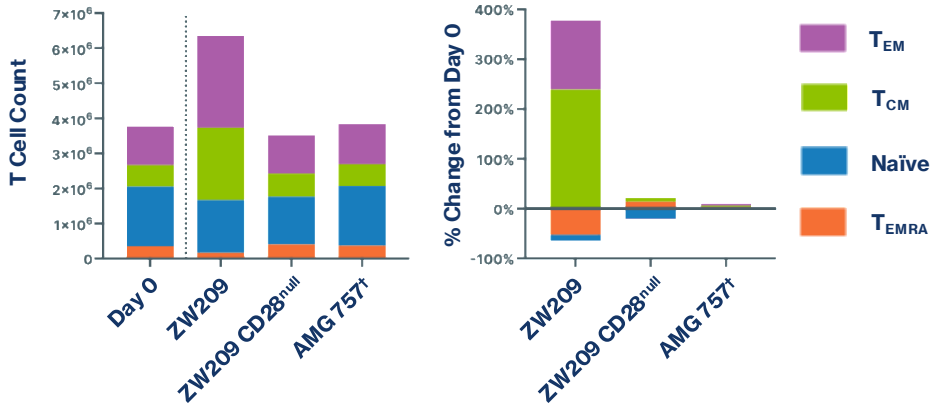
ZW209 demonstrates prolonged T cell cytotoxicity in repeat challenge assay



Sustained cytotoxicity relative to bispecific TCEs

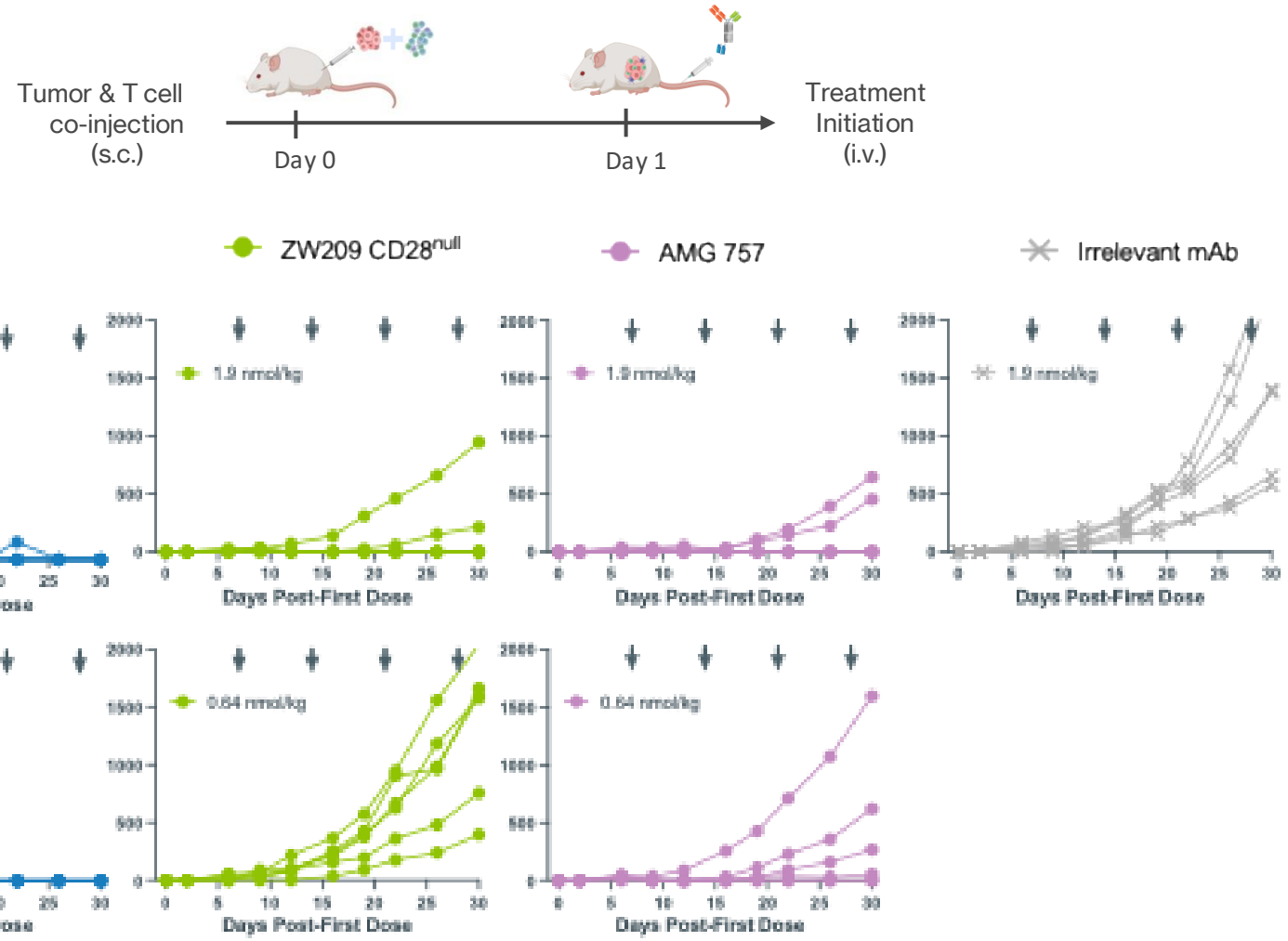


Expanded effector memory (T_{EM}) and central memory (T_{CM}) T cell populations after 2nd stimulation (Day 7)



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

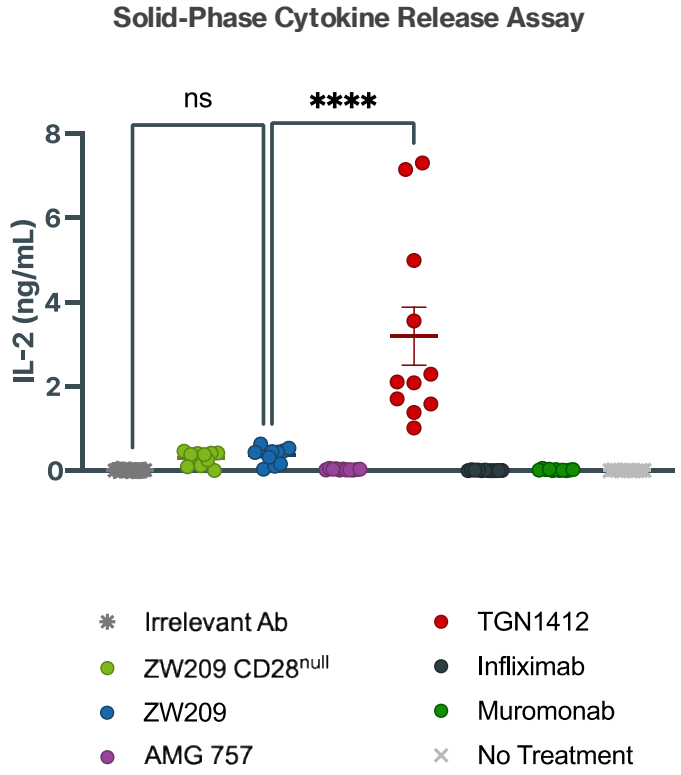
ZW209 mediates enhanced antitumor activity compared to bispecific and benchmark antibody



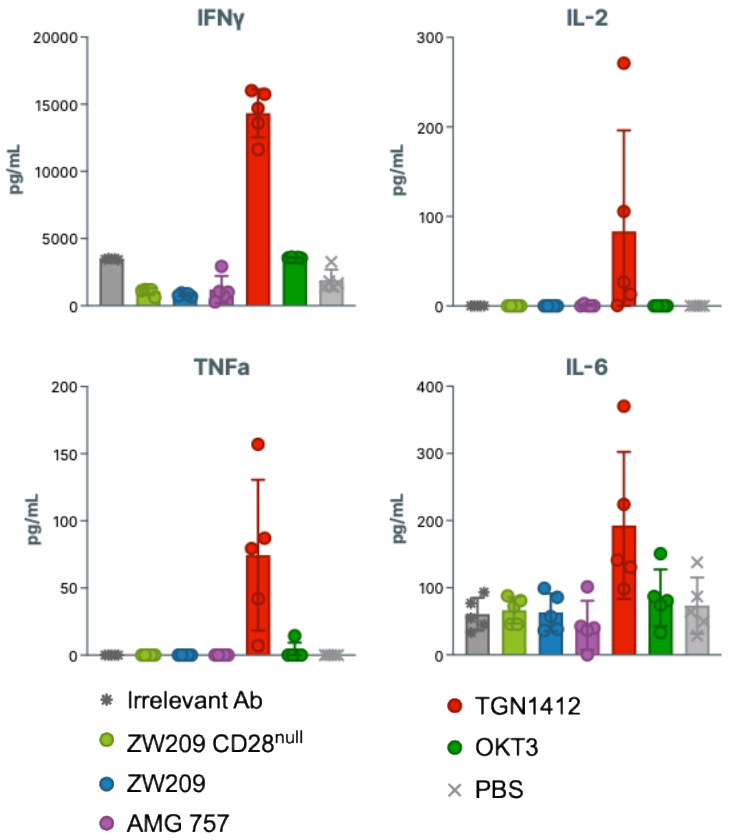
ZW209 shows superior anti-tumor activity compared to the bispecific and benchmark antibody in NCI-H82 admixture xenograft model

ZW209 has a favorable safety profile *in vitro* and in animal studies

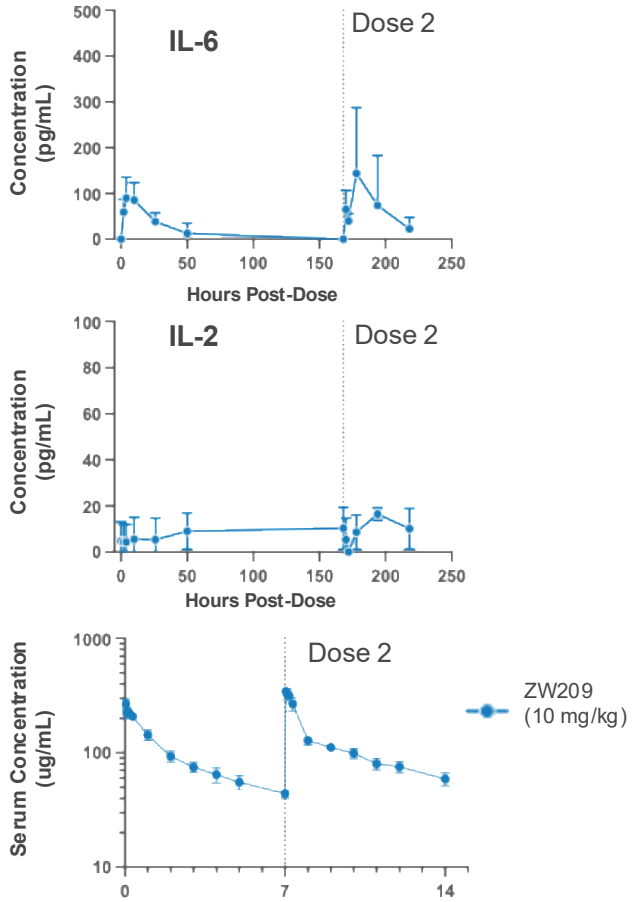
No Cytokine Activation With PBMCs Alone



Induces Minimal Systemic Cytokine In An *In Vivo* Cytokine Release Model



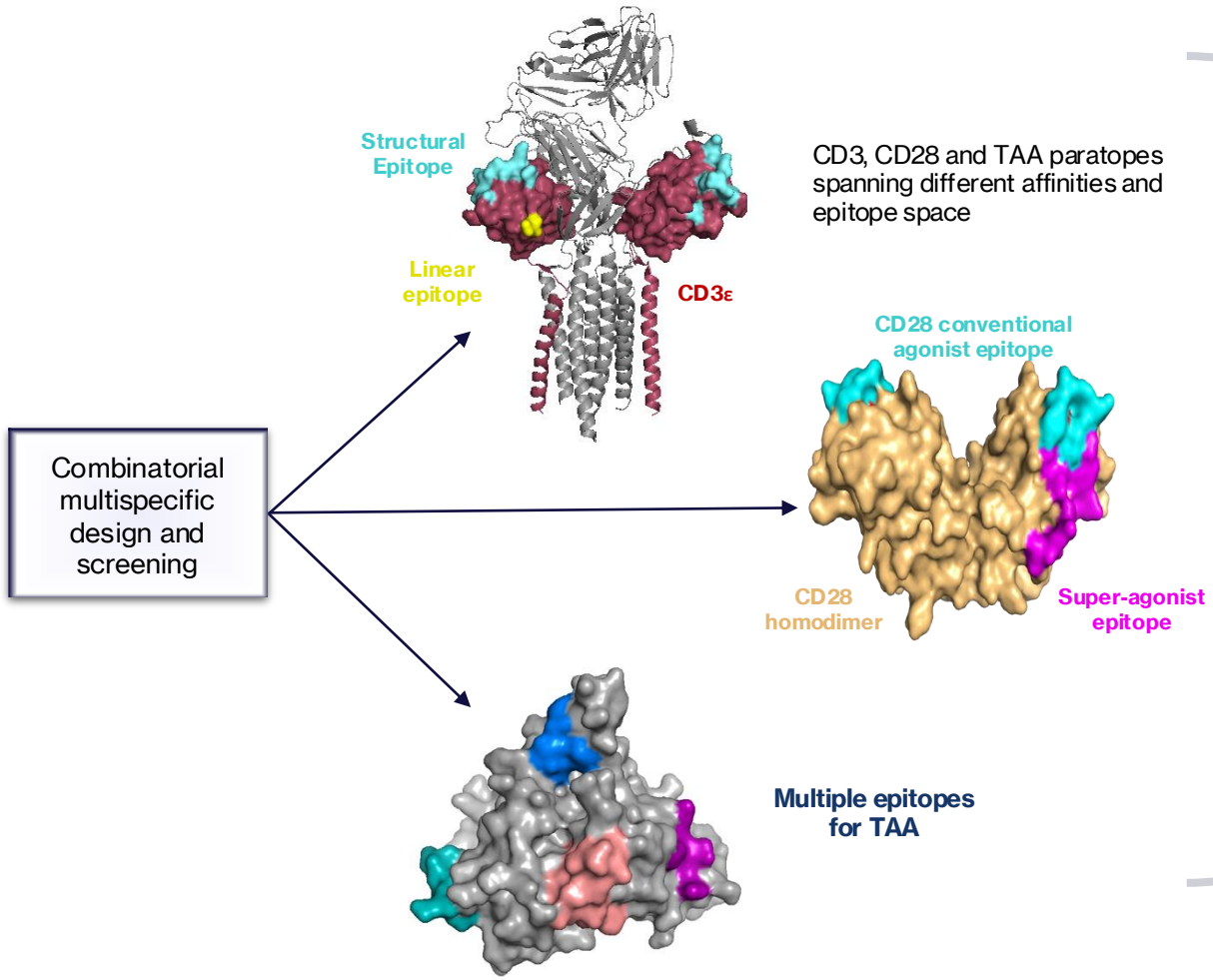
Well-Tolerated In Cynomolgus Monkeys



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

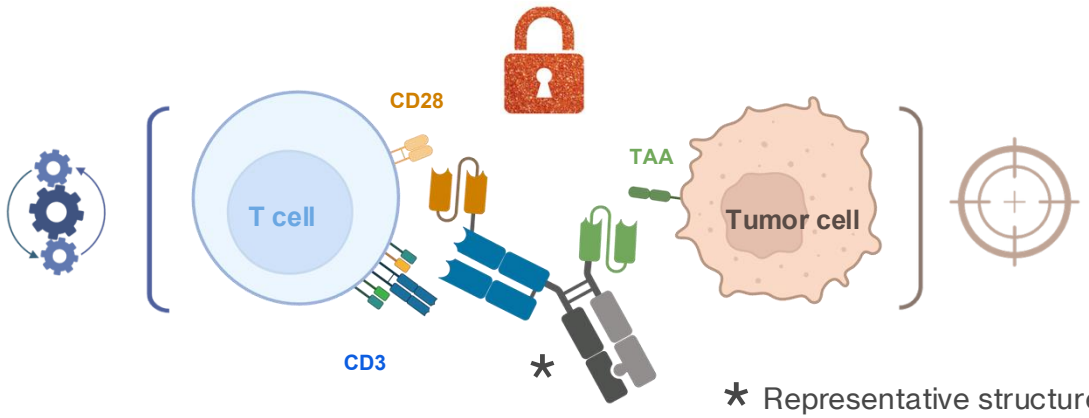
Extensive paratope and format exploration enables discovery of optimal multispecific TCEs

Selection of Diverse Paratopes and Affinities



CD3, CD28 and TAA paratopes spanning different affinities and epitope space

Locked CD3/CD28 geometry:
optimized for efficient conditional *cis* CD28 co-stimulation and strict TAA dependence



* Representative structure

Fine-tune CD3 and CD28 affinity:

- Cytotoxic potency
- T cell activation
- Cytokine production
- T cell proliferation

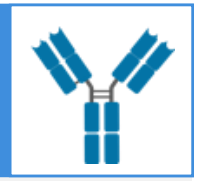
Versatile tumor targeting solutions:

- Monovalent/bivalent Fab, scFv, VHH
- Multi-TAA logic-gated designs
- pMHC targeting

Selection of desired antibody format for ADCs

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

Monospecific



Binds to single epitope on a single target

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

Biparatopic

Binds to two distinct epitopes on a single target

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

Bispecific

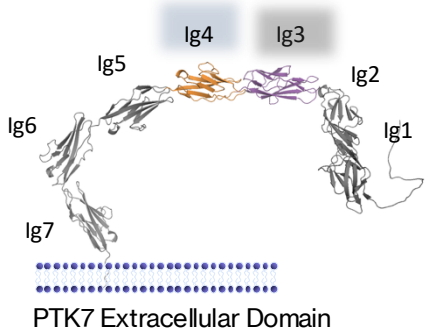
Binds to two distinct targets

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

ZW418 is a PTK7-targeting biparatopic RASi ADC for application in NSCLC

A novel approach to NSCLC therapy, comprising a rapidly internalizing PTK7-targeting biparatopic antibody conjugated to a potent and well tolerated pan-RAS inhibitor.

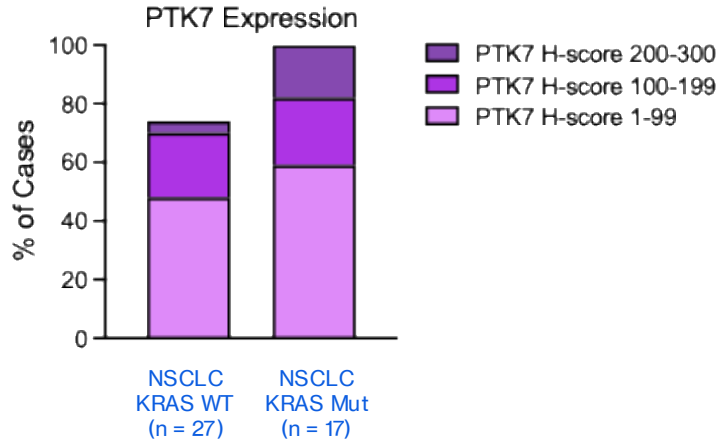
In-house biparatopic antibody is uniquely optimized for ADC properties



Antibody	Paratopes	Epitopes
Lead Biparatopic Azymetric™ Het-Fc & Het-Fab	P1 x P2	Ig4 x Ig3/4
Monoparatopic #1	P1 x P1	Ig4 x Ig4
Monoparatopic #2	P2 x P2	Ig3/4 x Ig3/4
Lead Monoparatopic Internal Benchmark	P3 x P3	Ig4 x Ig4

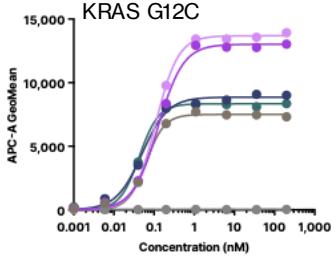
PTK7 targeting by RASi-ADC:

- PTK7 is prevalently overexpressed in NSCLC and has **clinical PoC** as an ADC target[1]
- Expression of PTK7 in NSCLC is high **regardless of KRAS mutation**



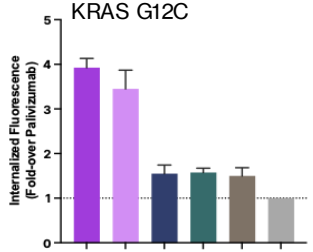
Superior binding

H358
Lung Carcinoma Cell Line
KRAS G12C



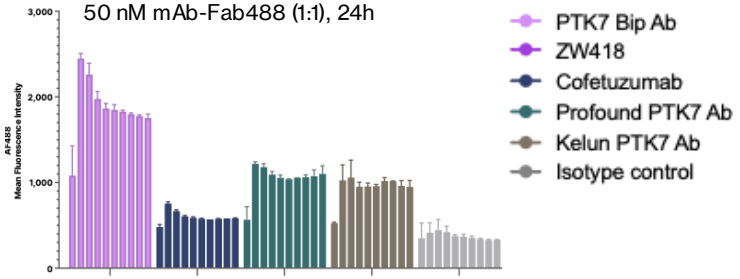
Higher internalization

H358
Lung Carcinoma Cell Line
KRAS G12C



Better Spheroid Penetration

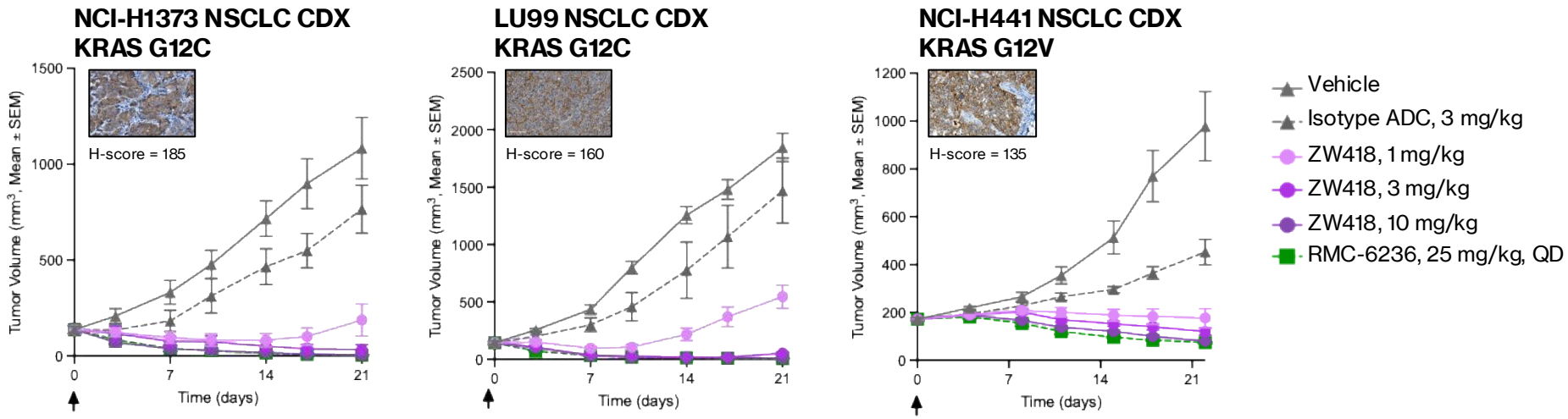
H446 Spheroid
50 nM mAb-Fab488 (1:1), 24h



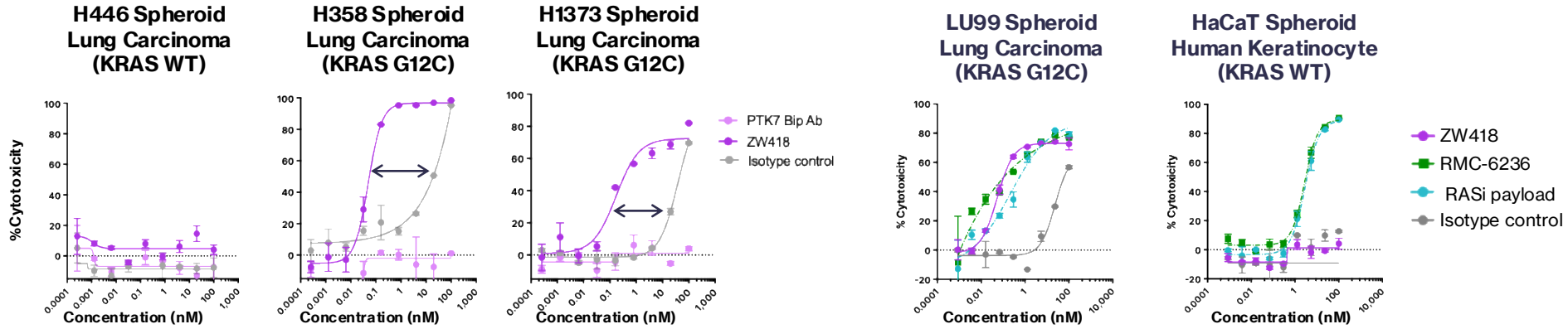
1. BC. Cho et al. *Lung Cancer* 202 (2025): 108492.

ZW418 exhibits robust and selective anti-tumor activity in non-small cell lung cancer

ZW418 has strong anti-tumor activity in NSCLC xenograft models



ZW418 exhibits target-dependent cytotoxicity, while sparing normal tissues



ZW1528

Bispecific Designed to Address Respiratory Inflammation

On track for regulatory submission in 2027

Optimized design

- IL-4Rα x IL-33 bispecific molecule that inhibits multiple pathways within complex pathophysiology of inflammation in diseases such as mixed-type COPD
- In-house antibody discovery of novel anti-IL4Rα and IL-33 paratopes
- Native IgG-like geometry

Differentiated profile

- Potently blocks two complementary pathways of respiratory inflammation: IL-4Rα and IL-33
- Targets three cytokines in a single biologic
- Offers a unique approach that leverages clinically validated targets
- Demonstrates high manufacturability and incorporates half-life extending Fc modifications
- Aligns with requirements for successful AIID therapeutics

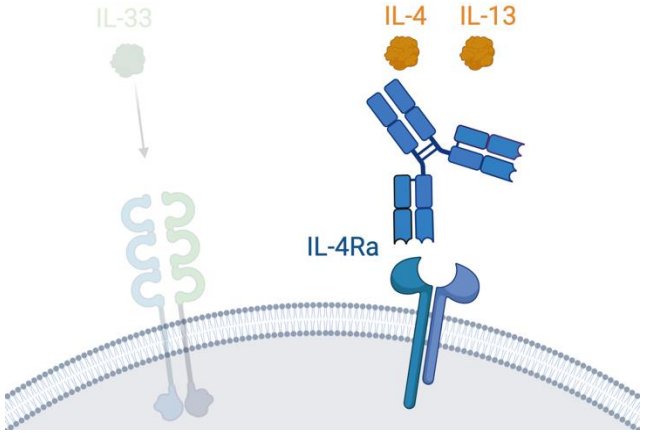
Significant patient need

- Mixed-type COPD patients are hospitalized 2-3.6 times more often than those with other COPD phenotypes[1]

1. https://pubmed.ncbi.nlm.nih.gov/25844673/#:~:text=Measurements%20and%20main%20results:%20Of,%3C%200.05%20for%20all%20comparisons).
AIID: Autoimmune and inflammatory disease, COPD: Chronic obstructive pulmonary disease

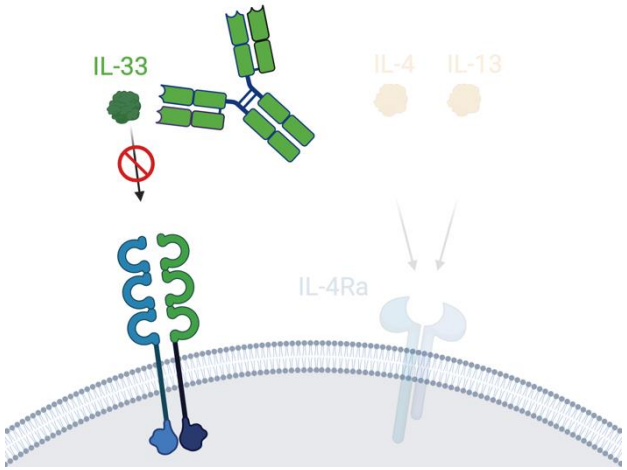
Anti-IL4Rα and anti-IL-33 therapeutics are being developed to target different aspects of COPD pathology

Dupilumab blocks IL-4Ra



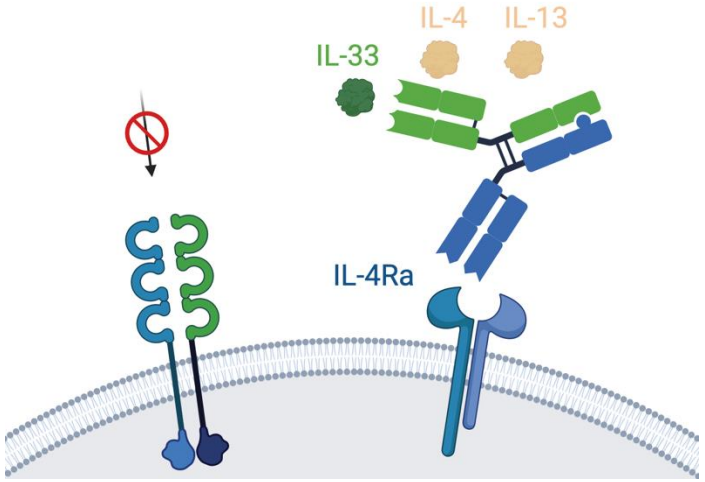
Type 2 inflammation suppression.

Itepekimab/tozorakimab block IL-33



Type 2 and non-Type 2 inflammation suppression. Improved tissue remodelling.

Dual blockade by ZW1528



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

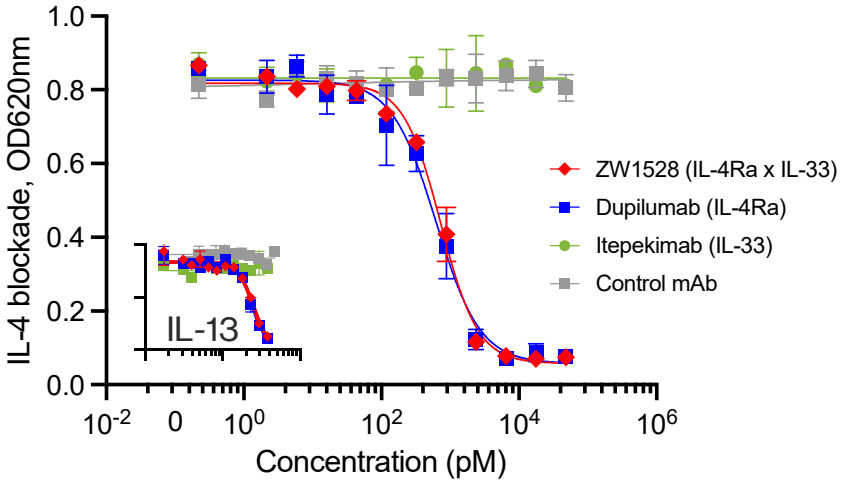
Potential for increased efficacy in monotherapy-responsive patients

ZW1528 effectively blocks both IL-4/13 and IL-33 comparable to benchmark mAbs

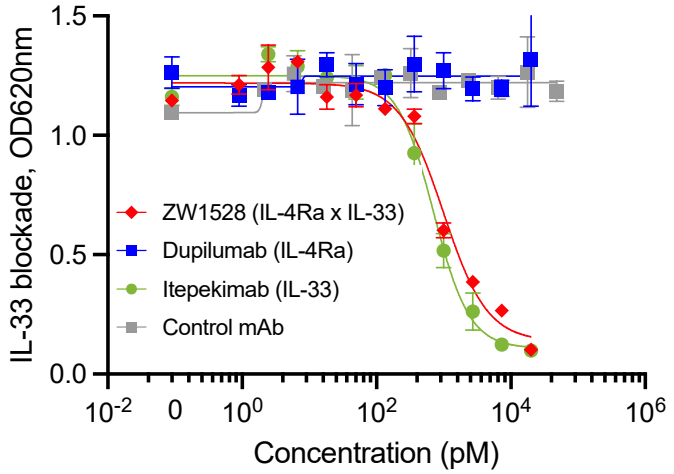
Anti-IL4Rα

Anti-IL-33

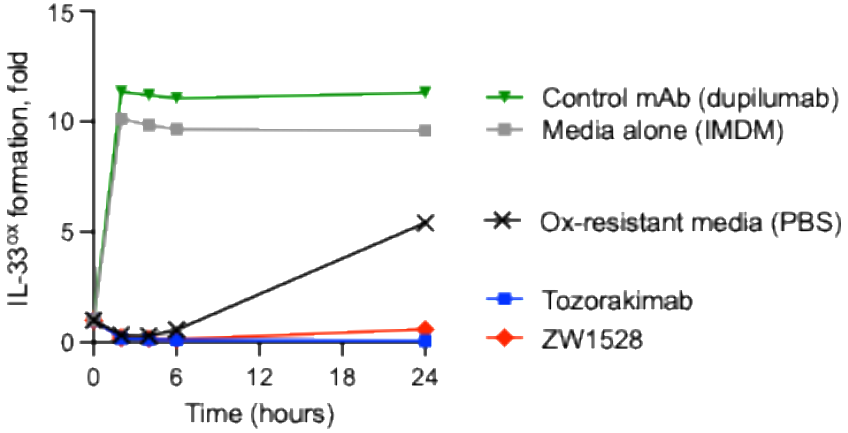
Blockade of IL-4/13 Signaling

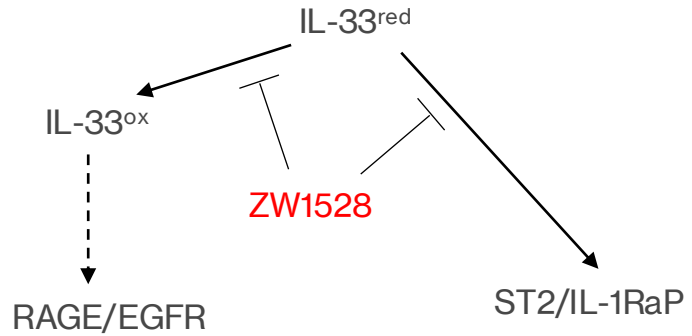


Blockade of IL-33 Signaling



Blockade of IL-33 Oxidation



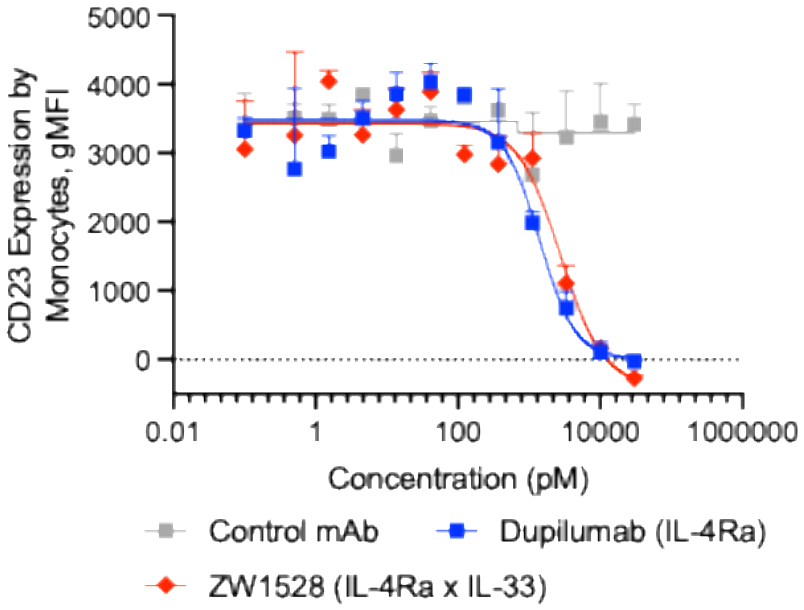


ZW1528 blocks two complementary pathways of airway inflammation in primary cells of COPD patients

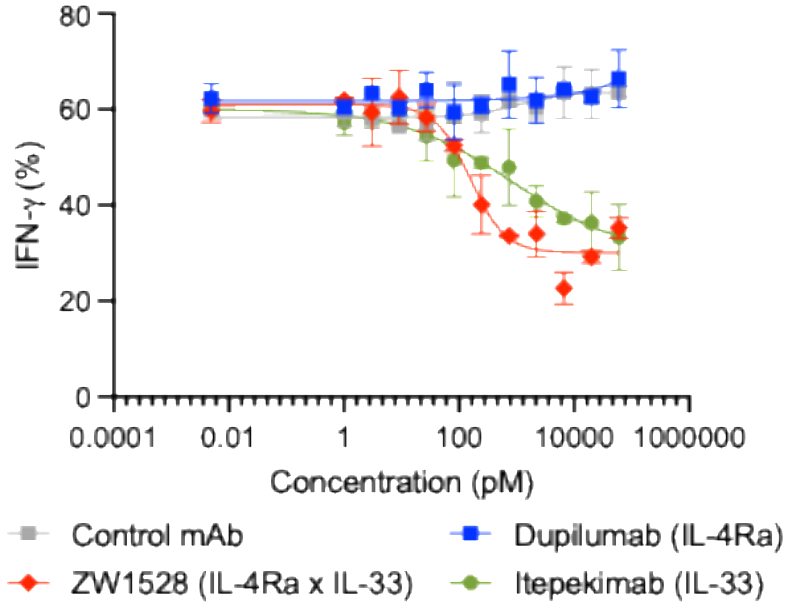
Anti-IL4Rα

Anti-IL-33

Blockade of IL-4



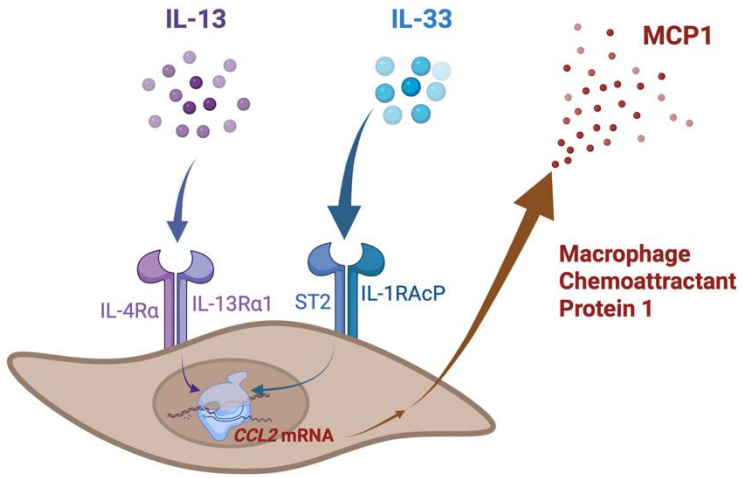
Blockade of IL-33



- ZW1528 effectively blocks IL-4Ra and IL-33 in PBMC of COPD patients in vitro
- Enhanced blockade of IL-33 axis

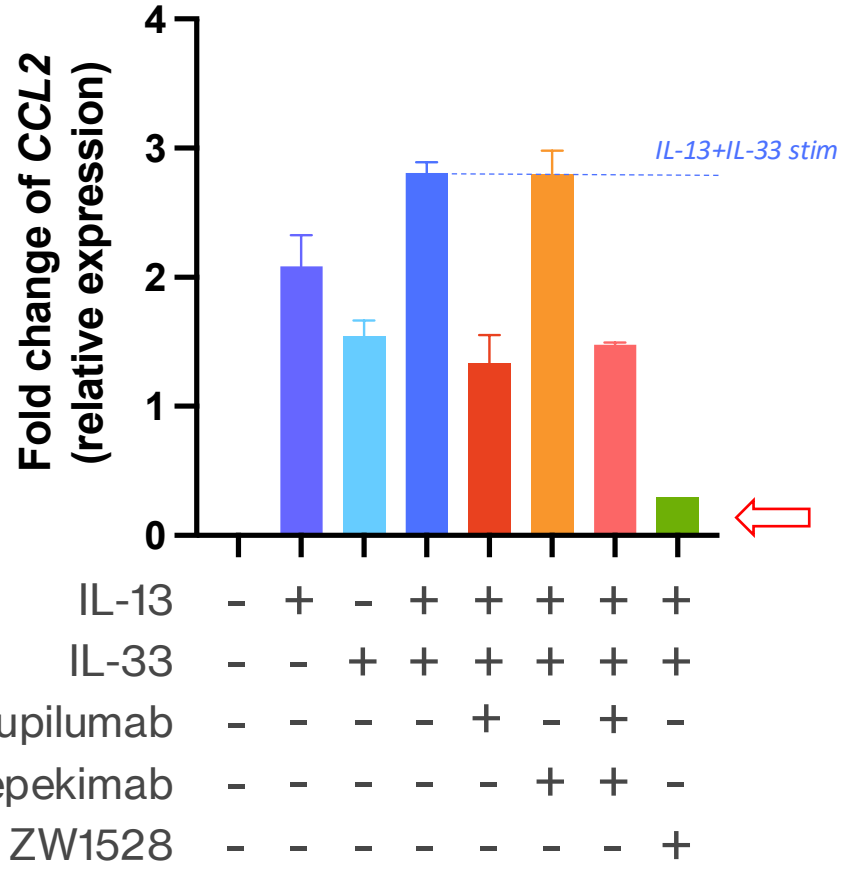
ZW1528-mediated blockade of primary cell activation superior to combination of dupilumab and itepekimab

IL-33 and IL-13 activate human epithelial cells



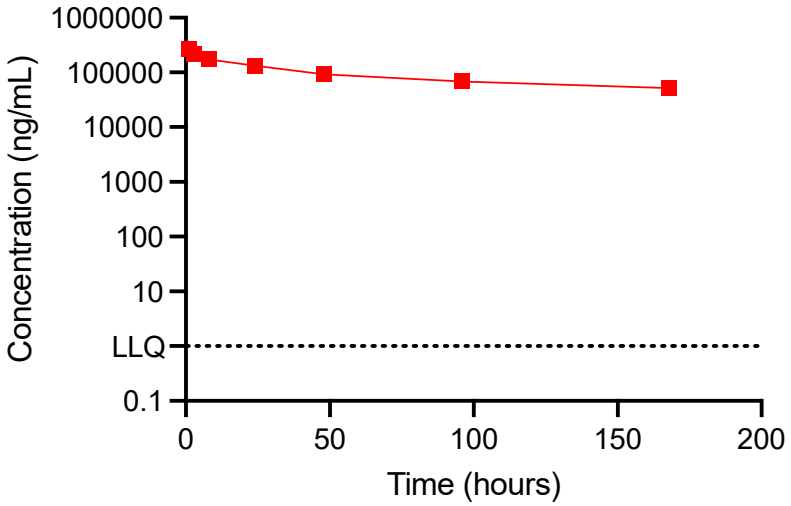
- IL-13 and IL-33 treatment induces disease-relevant genes in primary cells
- ZW1528-mediated blockade is superior to dupilumab, itepekimab and combo

ZW1528 blocks activation



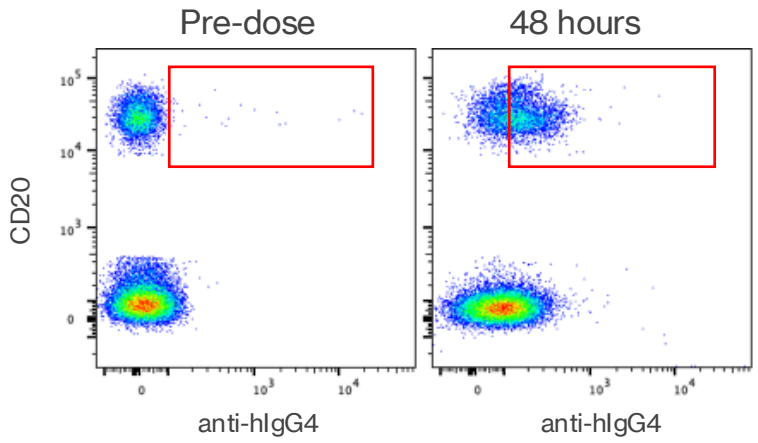
ZW1528 demonstrates biomarkers of IL-4Rα/IL-33 blockade in NHP

Pharmacokinetics

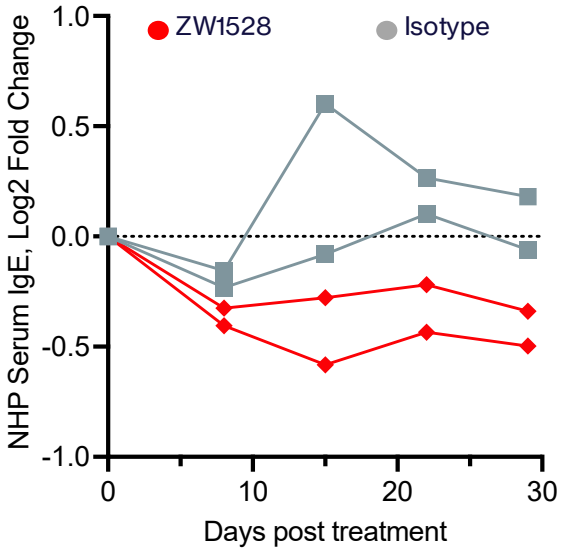


Cynomolgus monkey (N=2) were dosed with ZW1528 i.v. at 10 mg/kg

IL-4Rα Receptor Occupancy



Reduction of Serum IgE

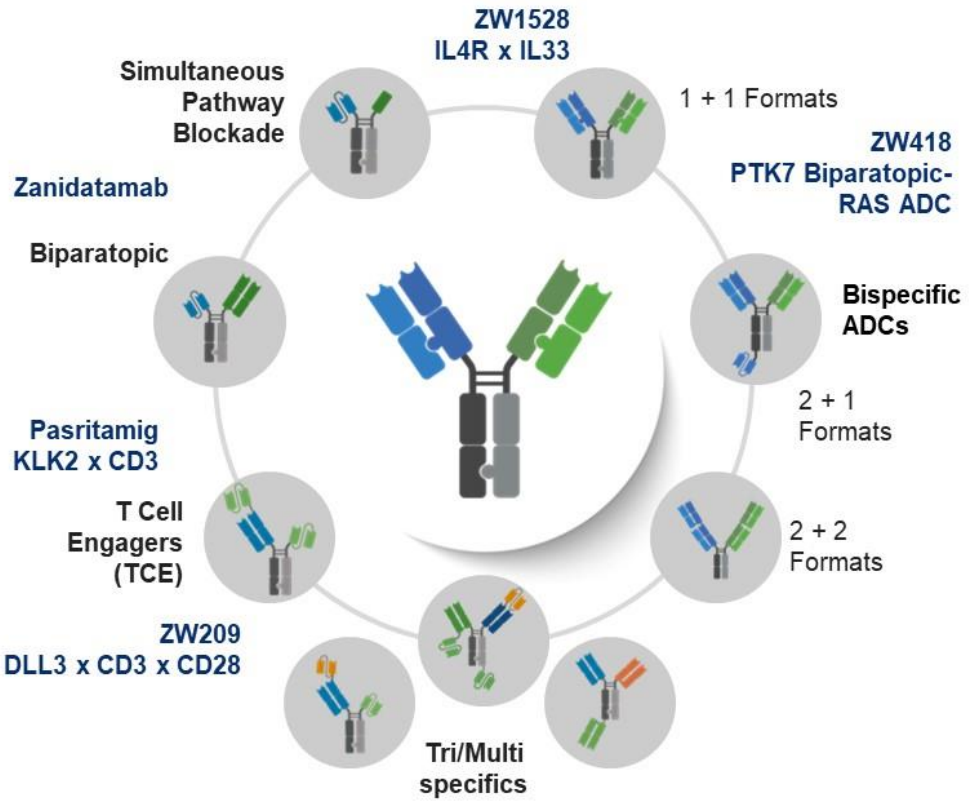


- IgG-like pharmacokinetics in non-human primates (NHP); exposure is maintained.
- Biomarkers of IL-4Rα/IL-33 blockade up to **6 weeks** after single administration
- Well tolerated with no adverse effects up to 200 mg/kg/dose in a multidose study

Optimizing multispecific antibody design for therapeutic application

- Multispecifics provide opportunity for modes of therapeutic intervention not feasible with therapeutic antibodies
- Imperative to their design is the optimal integration of each individual binding component to yield optimal biological activity, while maintaining desired pharmacological and manufacturing properties
- **Multiple Azymetric molecules in development/approved exemplifying importance of matching format to application and potential to uncover novel biology**

Azymetric Platform: Adaptable to different formats & applications



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Acknowledgements…a global team effort

Multispecific Antibody Therapeutics Group

https://www.zymeworks.com/publications/

ADC Therapeutics Group