Unlocking novel biologies with bi- and trispecific antibodies: The importance of antibody format

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zymeworks

Discussion Points

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(Combinatorial) Bispecific Antibodies

- Novel biology…Can 1 + 1 > 2?
- Case Study: Anti-HER2 biparatopic zanidatamab
  - Comparisons to parental Ab combinations

(Obligate?) Trispecific Antibodies

- Case Study: Trispecific costimulatory T cell engager ZW209
- Novel biology….Can 1 + 1 + 1 > 3?

Importance of Format

APPROVAL TIMELINE 2014 – 2025

2014
- Blinatumomab

2021
- Aminvantamab

2022
- Teclistamab
- Mosunetuzumab
- Tebentafusp
- Cadonilimab

2023
- Epcortinamab
- Glofitamab
- Talquetamab
- Elranatamab

2024
- Odronextamab (EMA)
- Tarlatamab
- Zanidatamab
- Zenocutuzumab
- Ivonescimab

2025
- Catumaxomab (EMA)

BISPECIFIC ANTIBODY APPROVALS IN ONCOLOGY

LIQUID / BLOOD CANCERS
Hematologic malignancies

8 agents

✓ Blinatumomab	CD19	×	CD3	2014
✓ Teclistamab	BCMA	×	CD3	2022
✓ Mosunetuzumab	CD20	×	CD3	2022
✓ Epcoritamab	CD20	×	CD3	2023
✓ Glofitamab	CD20	×	CD3	2023
✓ Talquetamab	GPRC5D	×	CD3	2023
✓ Elranatamab	BCMA	×	CD3	2023
✓ Odronextamab	CD20	×	CD3	2024 EMA only

SOLID TUMORS
Solid tumor malignancies

8 agents

✓ Amivantamab	EGFR	×	cMET	2021
✓ Tebentafusp	gp100	×	CD3	2022
✓ Cadonilimab	PD-1	×	CTLA-4	2022 NMPA only
✓ Tarlatamab	DLL3	×	CD3	2024
✓ Zanidatamab	HER2	×	HER2	2024
✓ Zenocutuzumab	HER2	×	HER3	2024
✓ Ivonescimab	PD-1	×	VEGF	2024 NMPA only
✓ Catumaxomab*	EpCAM	×	CD3	2025 EMA only

* Approved to treat malignant ascites

Nina E. Weisser

Data current through Feb 2026 | FDA / EMA / NMPA | For Educational Use

- Hematologic Malignancy
- Solid Tumor Malignancy
- EMA only – European approval only
- NMPA only –
- R/R =
- i.p.=

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Approved Bispecific Antibody Modalities in Oncology

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LIQUID / BLOOD CANCERS
Hematologic malignancies

8 agents

8 / 8	CD3 engaging T cell engagers

SOLID TUMORS
Solid tumor malignancies

8 agents

3 / 8	CD3 engaging T cell engagers
3 / 8	Dual-RTK Inhibition or Biparatopic
2 / 8	Dual Checkpoint Inhibition or Checkpoint + VEGF Blockade

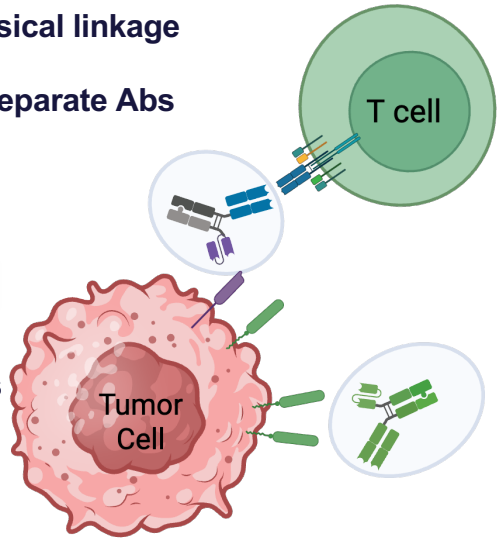
Obligate Bispecific[1]

- **Activity dependent on physical linkage of two specificities**
- **Cannot be achieved with separate Abs with same specificities**
  - **e.g. T cell engager**

Combinatorial Bispecific[1]

- **Activity can also be obtained by combining Abs with same specificities**

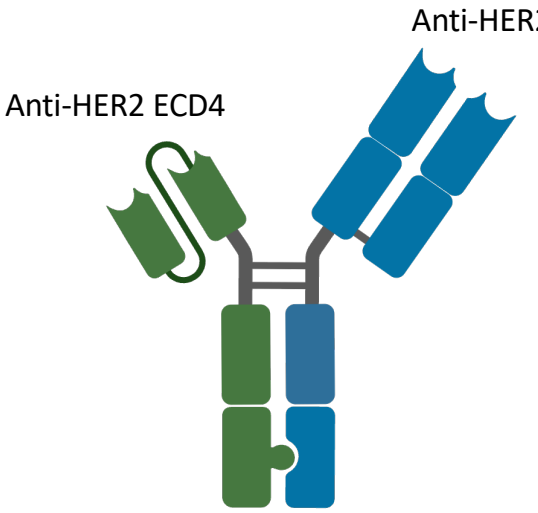
e.g. Dual-RTK Inhibition, Dual Checkpoint Inhibition



Can combinatorial bispecific show unique MOA or benefit vs. parental Ab combination?
Can 1 + 1 > 2?

1. Labrijn et al. 2019 Nat Rev Drug Discov. 18(8):585-608

Zanidatamab is the First (and only) Approved Biparatopic Antibody



zanidatamab

- Anti-HER2 ECD2 x HER2 ECD4 biparatopic
- Approved for 2L treatment of advanced HER2-positive (IHC 3+) biliary tract cancer (BTC)#
- Positive Phase 3 1L gastric/GEA readout, ASCO GI 2026
- Ongoing Phase 3 trials in 1L BTC and in BC post T-DXd
- Ongoing Phase 2 trials in neoadjuvant/adjuvant BC, neoadjuvant locally advanced BC and other HER2+ solid tumors

#Continued approval for the 2L BTC indication is contingent upon verification and description of clinical benefit in a confirmatory trial

Zanidatamab Shows Enhanced & Differentiated Activity vs. mAbs and mAb combos

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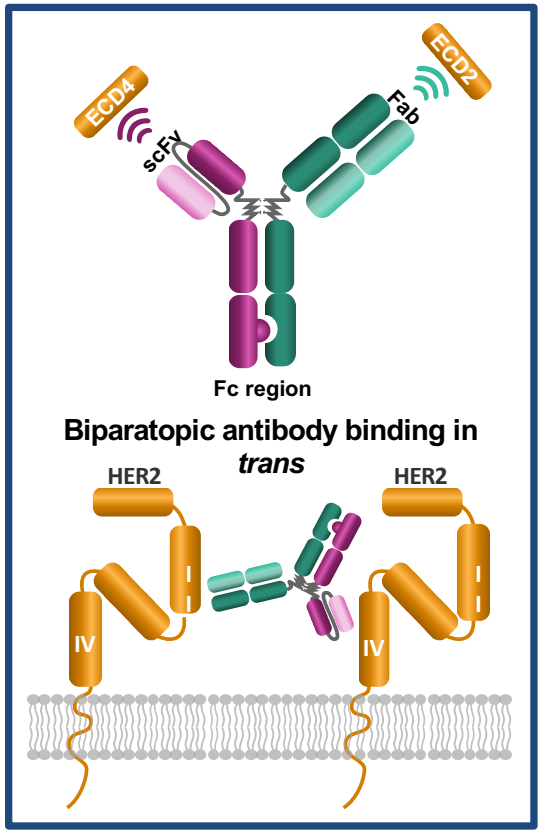

- Zanidatamab is a dual HER2-targeted bispecific IgG1-like antibody that binds to ECD2 and ECD4 on HER2 in a *trans* configuration
- This biparatopic binding enables zanidatamab to crosslink neighboring HER2 proteins, leading to receptor clustering
- In preclinical studies, zanidatamab enhanced HER2 internalization, reduced downstream signaling, and promoted immune-mediated cytotoxicity (CDC, ADCC, ADCP)

- Anti-HER2 ECD2 x ECD4 (like trastuzumab + pertuzumab)
- In preclinical studies, zanidatamab showed enhanced and differentiated activity vs. tras, pert and tras + pert

Weisser NE et al., Nature Communications 2023

Understanding Potential Differentiation from Tras + Pert was Developmentally Important

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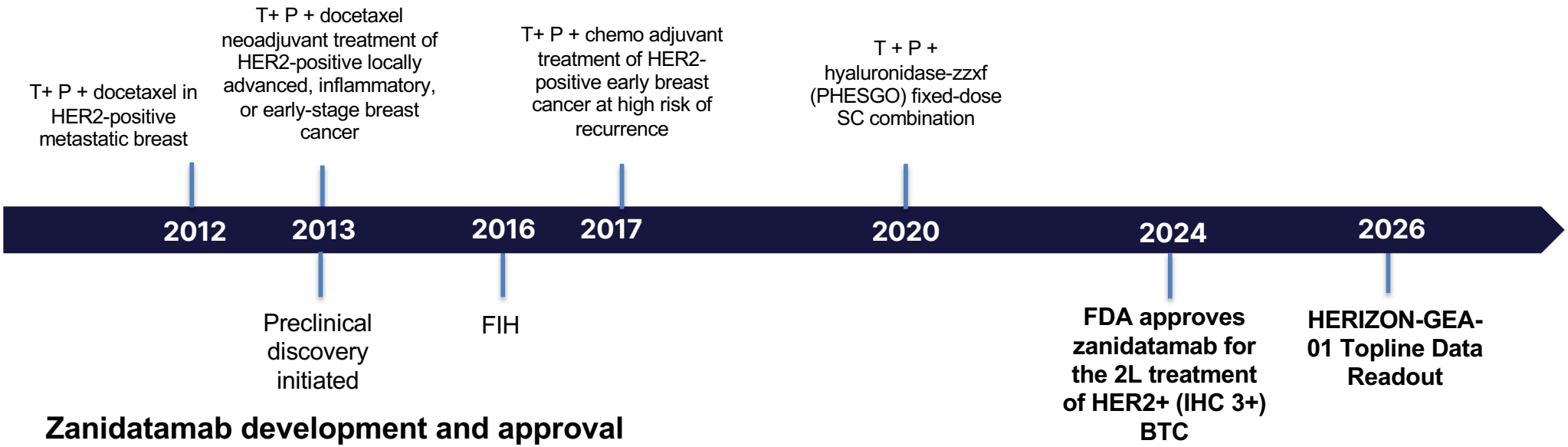
Trastuzumab in combination with pertuzumab approvals



Zanidatamab development and approval

Selected biparatopic papers with comparisons to parental antibody combo

Year, Author, verdict vs. combo

2012 Kelton	2020 DaSilva	2020 Cheng	2021 Kast
Similar to combo	Enhanced antitumor activity	Enhanced antitumor activity	Enhanced antitumor activity

Kelton 2012, Arch Biochem Biophys 526(2); DaSilva 2020 Clin Cancer Res 6(6); Cheng 2020 Antibodies (Basel) 9(3):49; Kast et al. 2021 Nat Commun 12, 3790 (2021)

Zanidatamab Mediates *trans* HER2 Binding and High Cell Surface Decoration

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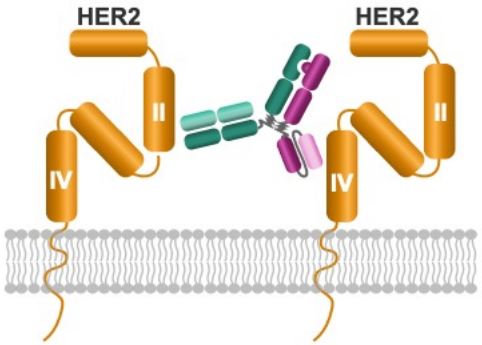

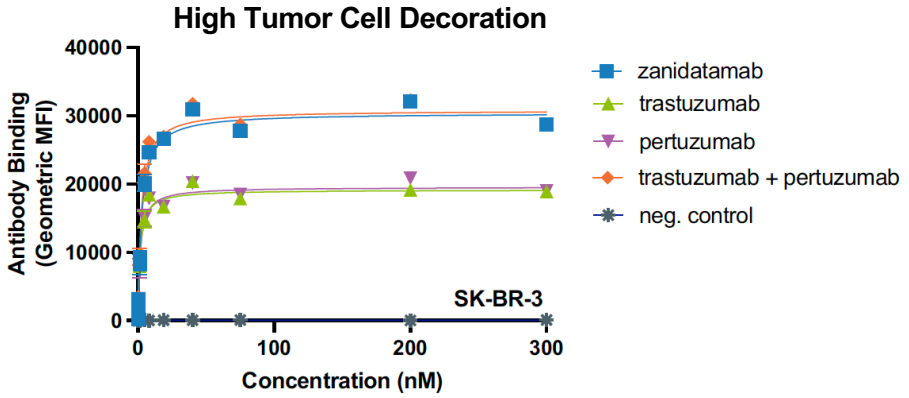

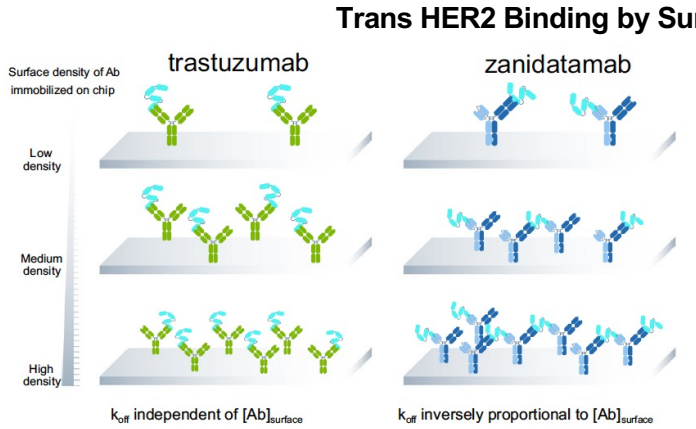

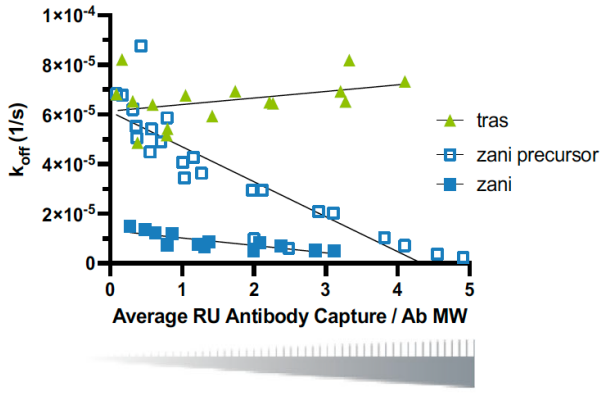

Weisser NE et al., Nature Communications 2023

trans Binding Mediates HER2 Clustering

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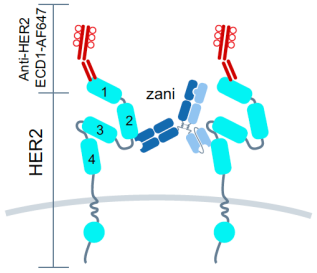

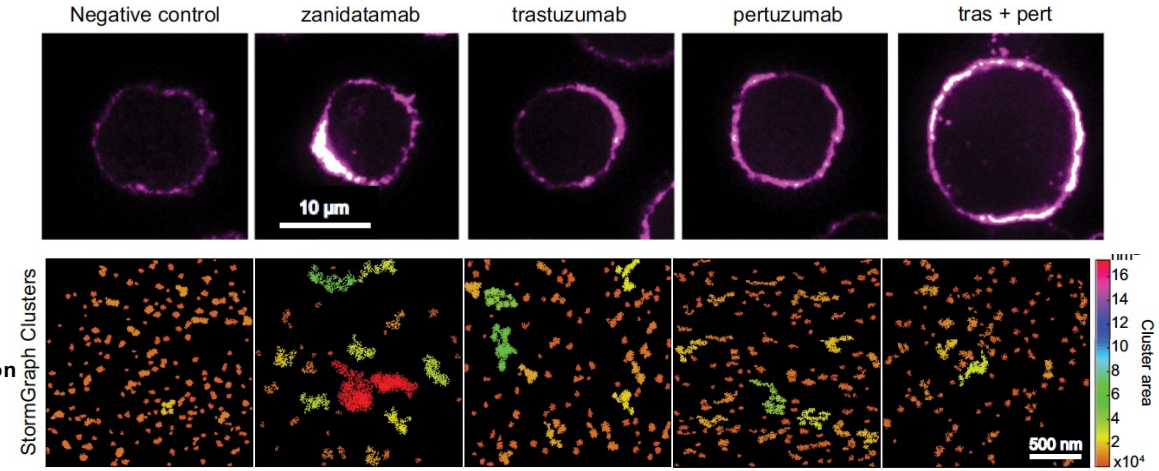

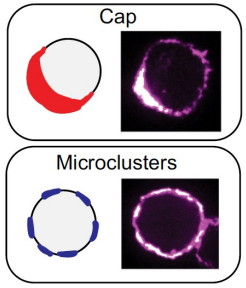

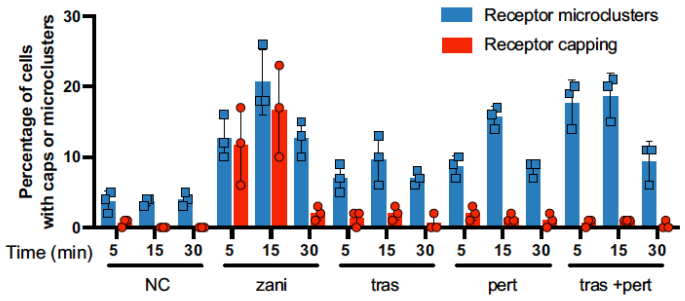

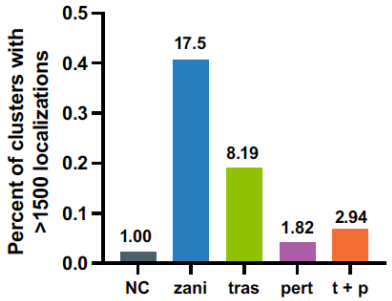

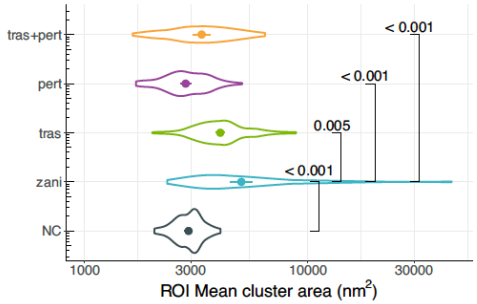

Weisser NE et al., Nature Communications 2023

CDC is a Rapid and Differentiating MOA of zanidatamab facilitated by HER2 Clustering

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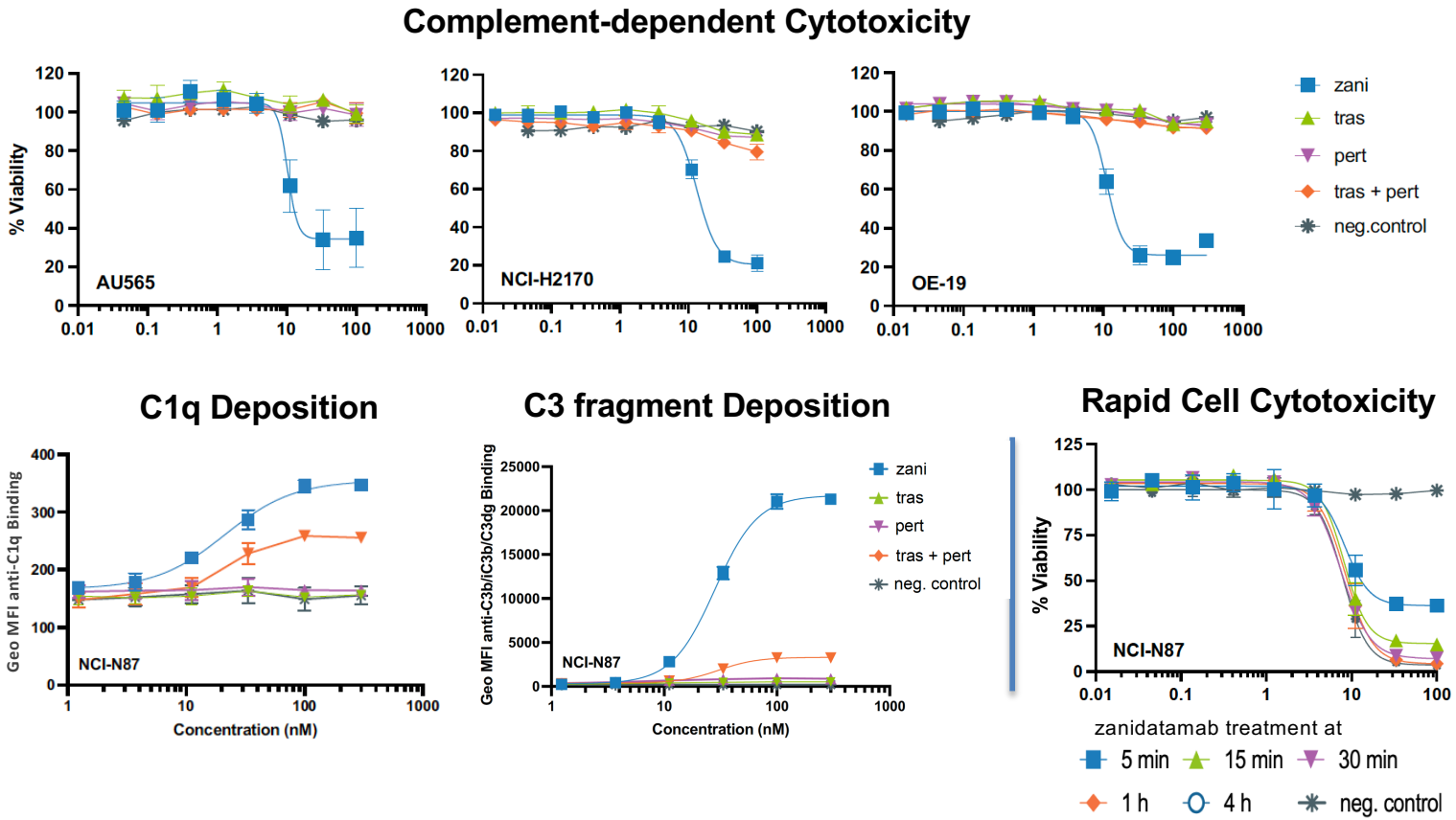

Weisser NE et al., Nature Communications 2023

Zanidatamab Mediates Tumor Regression in BTC PDX Model

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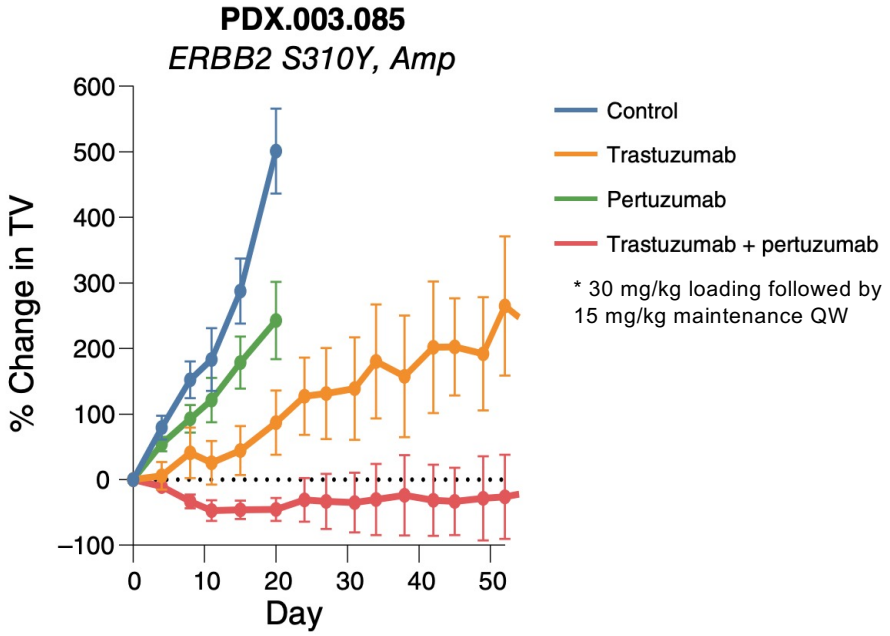

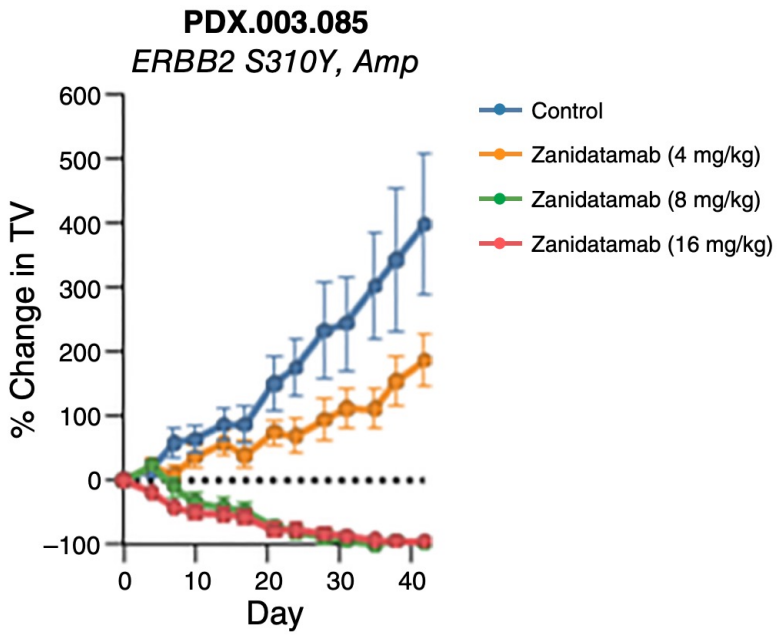

DiPeri T.P. et al. Clin Cancer Res 2025;31(2):387-402

Zanidatamab has Multiple MOA

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Comparative MOA & Activity Scorecard

	trastuzumab	pertuzumab	tras + pert	zanidatamab
Saturating Tumor Cell Binding	Moderate	Moderate	Strong	Strong
HER2 Clustering	No effect	No effect	No effect	Strong
HER2 Internalization	Moderate	Moderate	Strong	Strong
HER2 Downregulation	No effect	No effect	Moderate, Strong	Moderate, Strong
Signal Inhibition	No effect, Weak	No effect, Weak	Moderate, Strong	Moderate, Strong
Ligand-indep. Growth Inhibition	Weak, Moderate	No effect, Weak	Moderate	Moderate, Strong
Ligand-dep. Growth Inhibition	No effect	Moderate	Strong	Strong
ADCC and ADCP	Strong	Strong	Strong	Strong
CDC	No effect	No effect	No effect	Strong
In vivo Antitumor Activity	Weak	Weak	Moderate	Strong

Strong Moderate Weak No effect

zanidatamab is the first biparatopic antibody to demonstrate unique cytotoxic functionality vs. combination of parental antibodies

Weisser NE et al., Nature Communications 2023

Major findings to date: JACOB vs. HERIZON-GEA-01 in HER2+ advanced GEA

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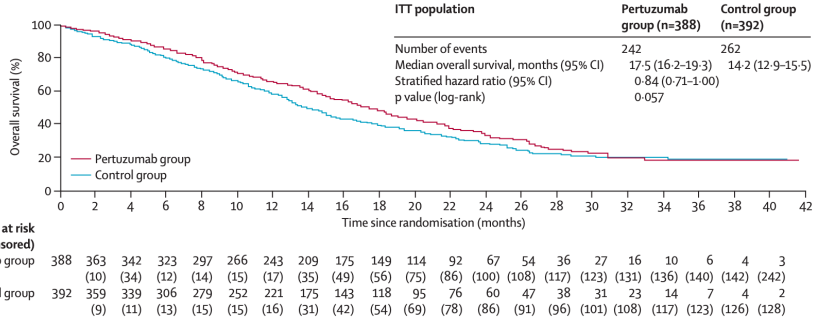
Not head-to-head; populations and background standard differed across trials

JACOB (pertuzumab + trastuzumab + CT)

Trial frame

Phase 3, double-blind; n=780
1L HER2+ metastatic gastric/GEJ adenocarcinoma
Pertuzumab + trastuzumab + cisplatin/fluoropyrimidine vs trastuzumab + CT



ITT population	Pertuzumab group (n=388)	Control group (n=392)
Number of events	242	262
Median overall survival, months (95% CI)	17·5 (16·2–19·3)	14·2 (12·9–15·5)
Stratified hazard ratio (95% CI)	0·84 (0·71–1·00)	
p value (log-rank)	0·057	

Number at risk (number censored)

Pertuzumab group	388	363 (10)	342 (34)	323 (12)	297 (14)	266 (15)	243 (17)	209 (35)	175 (49)	149 (56)	114 (75)	92 (86)	67 (100)	54 (108)	36 (117)	27 (123)	16 (131)	10 (136)	6 (140)	4 (142)	3 (242)
Control group	392	359 (9)	339 (11)	306 (13)	279 (15)	252 (15)	221 (16)	175 (31)	143 (42)	118 (54)	95 (69)	76 (78)	60 (86)	47 (91)	38 (96)	31 (101)	23 (108)	14 (117)	7 (123)	4 (126)	2 (128)

Primary endpoint: OS
17.5 vs 14.2 mo
HR 0.84; P=.057
Numerical gain, not statistically significant

Secondary activity
PFS 8.5 vs 7.0 mo (HR 0.73)
ORR 56.7% vs 48.3%

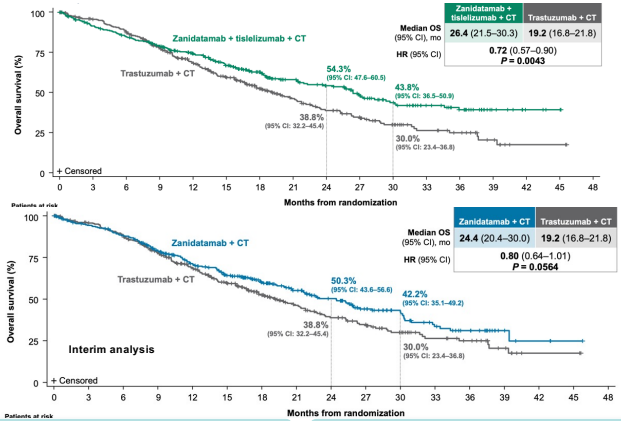
Bottom line: biologic activity, but not practice-changing in 1L GEA

Tabernero J, et al. The Lancet Oncology, 2018; Elimova J Clin Oncol 44, LBA285, 2026

HERIZON-GEA-01 (zanidatamab-based)

Trial frame

Phase 3, open-label; n=914
1L HER2+ unresectable/metastatic GEA including stomach, GEJ and esophagus
Zanidatamab + CT; zanidatamab + tislelizumab + CT; trastuzumab + CT



Zanidatamab + CT
PFS 12.4 vs 8.1 mo
HR 0.65; P<.0001
OS 24.4 vs 19.2 mo
HR 0.80; P=.0564
Strong OS trend; interim analysis

Zanidatamab + tislelizumab + CT *
PFS 12.4 vs 8.1 mo
HR 0.63; P<.0001
OS 26.4 vs 19.2 mo
HR 0.72; P=.0043
Statistically significant OS benefit

***The PFS and OS benefits were observed in patients with PD-L1 TAP scores <1% and ≥1%**

Bottom line: first phase 3 program to outperform trastuzumab with a new HER2-directed backbone in 1L HER2+ GEA.

Biparatopic Format Comparison

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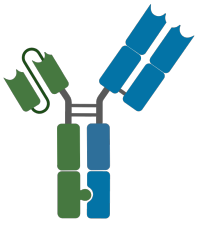
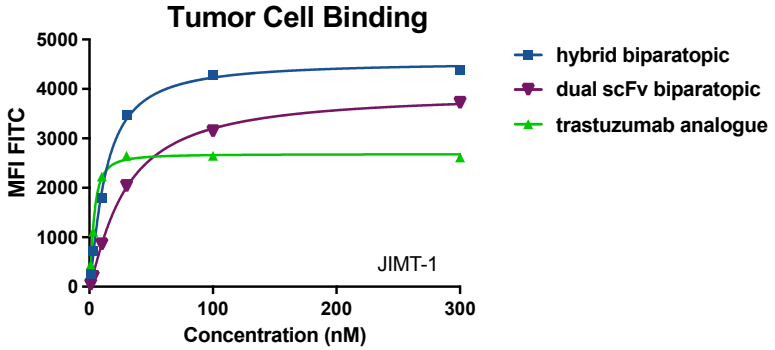
'Minor' format differences can yield different and non-desirable biological profiles

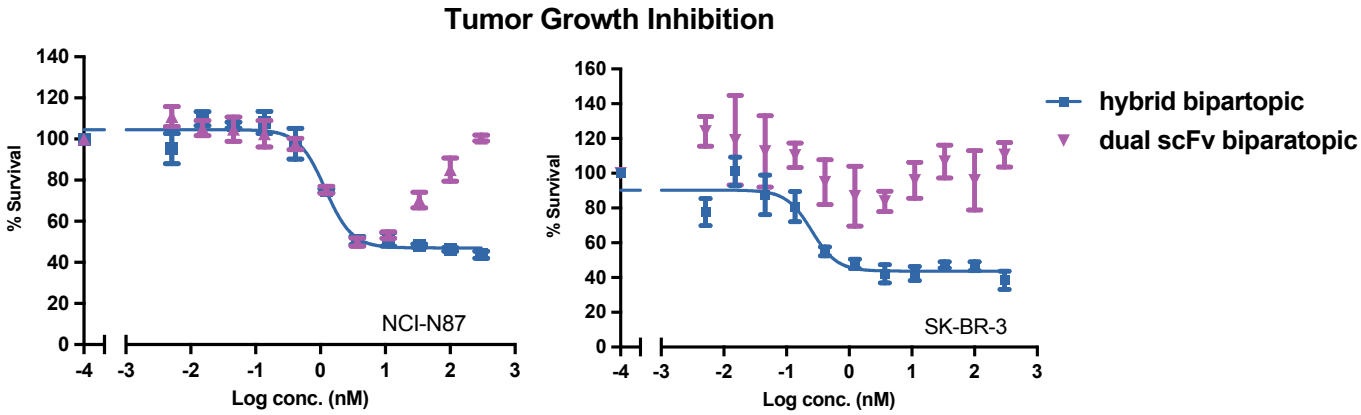


Hybrid
Zani format

Dual scFv



Dual-scFv format showed reduce tumor cell binding vs. hybrid format and loss of anti-tumor growth inhibition (possible agonism)



Addressing Challenges with Multispecific Solutions

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MONOSPECIFIC & BISPECIFIC PROBLEM

1. Antigen escape & tumor heterogeneity
2. On-target toxicity
3. Low T cell function & exhaustion
4. Treatment-related T cell anergy
5. Immunosuppressive microenvironment & cold tumors
6. Innate immunity untapped

MULTI-SPECIFIC SOLUTION

- Dual tumor antigen targeting (1, 2)
- Logic-gating multiple tumor targets (1, 2)
- Conditional activation (2)
- Co-stimulation (3, 4, 5)
- Dual checkpoint + VEGF blockade (3, 5)
- NK cell engagers (5, 6)
- Multi-pathway blockade (1, 5)

Increasing Clinical Development of Multispecific Antibodies

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Addressing Challenges and Targeting Diverse Mechanisms of Action in Oncology

Tri or multispecific antibodies entered, completed or entering Phase 1 2026

T CELL ENGAGER

Dual antigen targeting	10
Co-stimulation	8
CD8 redirection	3
Dual antigen targeting + co-stimulation	5

NK CELL ENGAGER

4

DUAL CPI + VEGF BLOCKADE

3

MULTI PATHWAY INHIBITION

2

MULTI IMMUNE AGONIST

1

Trispecific TCE with Integrated Co-Stimulation

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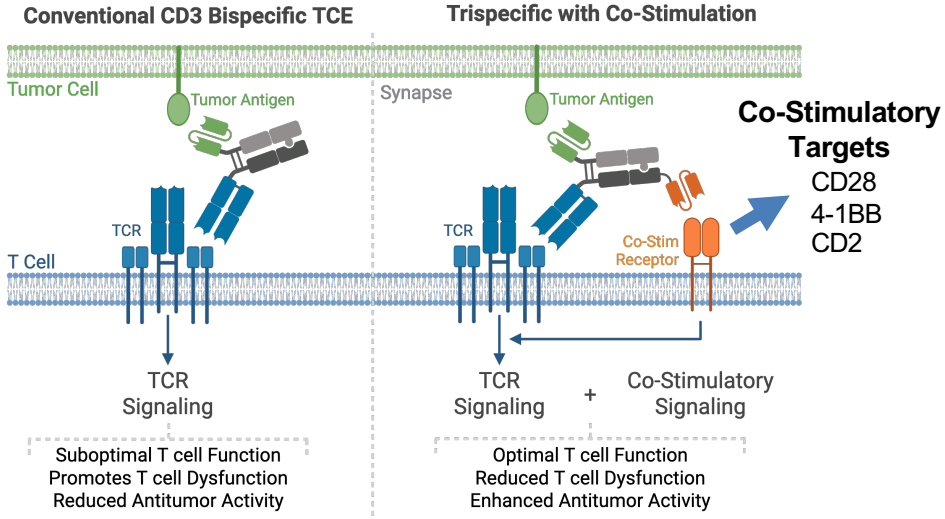
Enhancing T cell Fitness to Increase Antitumor Activity

Co-stimulation 3 4 5

- **Enhance T cell proliferation and survival (signal 1 + signal 2)**
- **Overcome innate or treatment-related T cell anergy**
- **Improve the depth and durability of antitumor response**

Clinical Status	Molecule	Trispecific Targets	Company
Discontinued	SAR442257 SAR443216 SAIL 66 PIT565	CD38 × CD3 × CD28 HER2 × CD3 × CD28 CLDN6 × CD28 × 4-1BB CD19 × CD3 × CD2	Sanofi Sanofi Roche (Chugai) Novartis
Completed	RO7616789	DLL3 × CD3 × 41BB	Roche (Chugai)
Active Phase 1	CC312 EVOLVE104	CD19 x CD3 x CD28 ULBP2/5/6 x CD3 x C2	Cytocares EvolveImmune
Phase 1 - 2026	ZW209	DLL3 x CD3 x CD28	Zymeworks

Active or discontinued molecules in Phase 1 or Phase 1/2



Engineering Challenge:
Optimize T cell binding to avoid T-T bridging and fratricide
- Risk for peripheral T cell activation & reduced antitumor activity

Questions:
- Optimal tumor target? Optimal co-stim target?

ZW209 has Conditional Cis T cell Engagement and Enhanced Antitumor Activity

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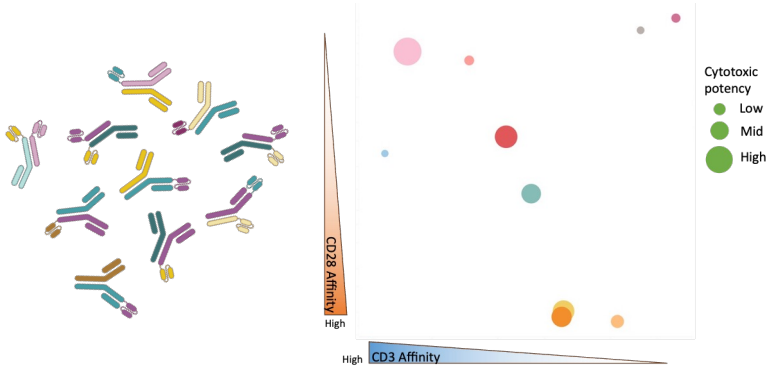
Importance of Engineering & Format Screening For Optimal T cell Engagement & Activity

ZW209 (DLL3 x CD3 x CD28) Screening

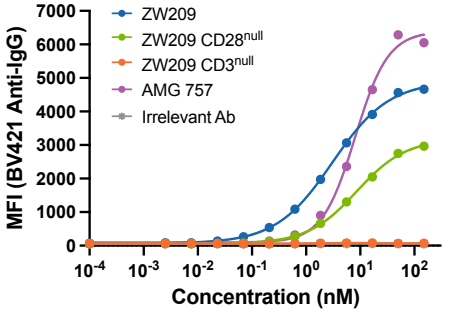


DLL3 Co-stim Molecule	1	2	3	4	5	6	7	8	9	10
Cytotoxicity										
Target-Dependent	✓	✓	✓	X	X	X	X	X	✓	✓

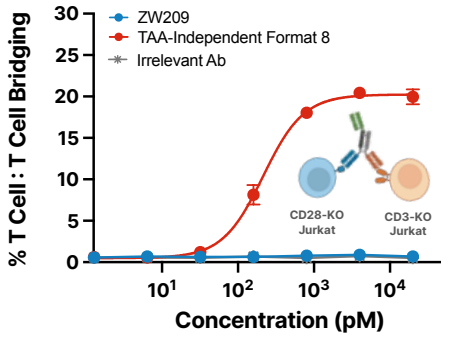
Cytotoxicity

- Placement of CD3 and CD28 paratope affects binding affinity, potency and biological profile
- Many formats failed screen for strict target-dependent activity

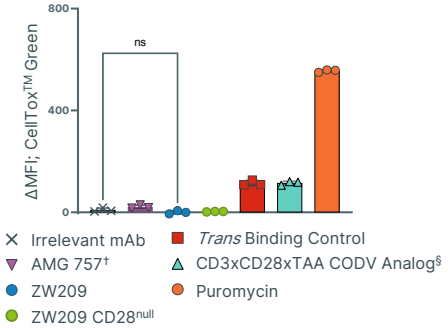
Conditional CD28 engagement



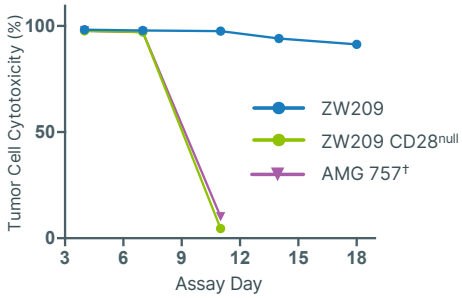
Obligate cis T cell engagement



No T cell Death (Fratricide)



Sustained Cytotoxic Activity



Clinical Stage Molecules: Differentiated Activity vs. Bispecific TCE & Preliminary Clinical Data

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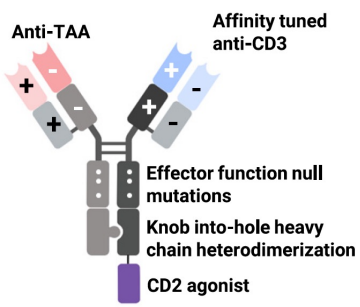
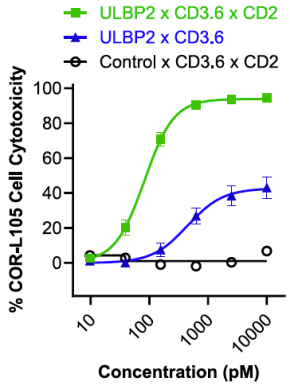
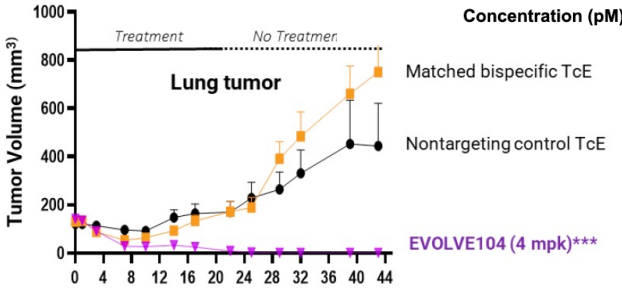
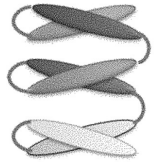
EVOLVE104
(ULBP2/5/6xCD3xCD2)







CC312
(CD19xCD3xCD28)



CC312 is Well Tolerated, and Shows Preliminary Efficacy at Lowest Few Dosages

Table 1. Summary of Safety and Preliminary Efficacy

Dose Level	N	DLT	CRS (Grade)	ICANS(Grade)	BOR	Enrolling Status
0.3 µg	2	0/2	0/2	0/2	SD	Completed
0.6 µg	3	0/3	0/3	0/3	SD	Completed
1.2 µg	2	0/2	0/2	0/2	SD	Completed
2.4 µg	3	0/3	1/3(G1)	0/3	SD(>7 months)	Completed
4.8 µg	2	0/2	1/2(G1)	0/2	PD	Completed
9.6 µg	10	0/10	2/10(G1, G2)	1/10(G1)	PD	Completed
19.2 µg	2	0/2	1/2(G1)	0/2	MR	Ongoing

Two active co-stimulatory trispecific clinical programs in early stages with CC312 showing early signs of tolerability and antitumor activity

Sergeeva et al 2025 PNAS 122 (47) e2510829122
Myers 2025 PEGS Boston
Huang et al. 2025 AACR

How Does Trispecific Ab Compare to Combination?

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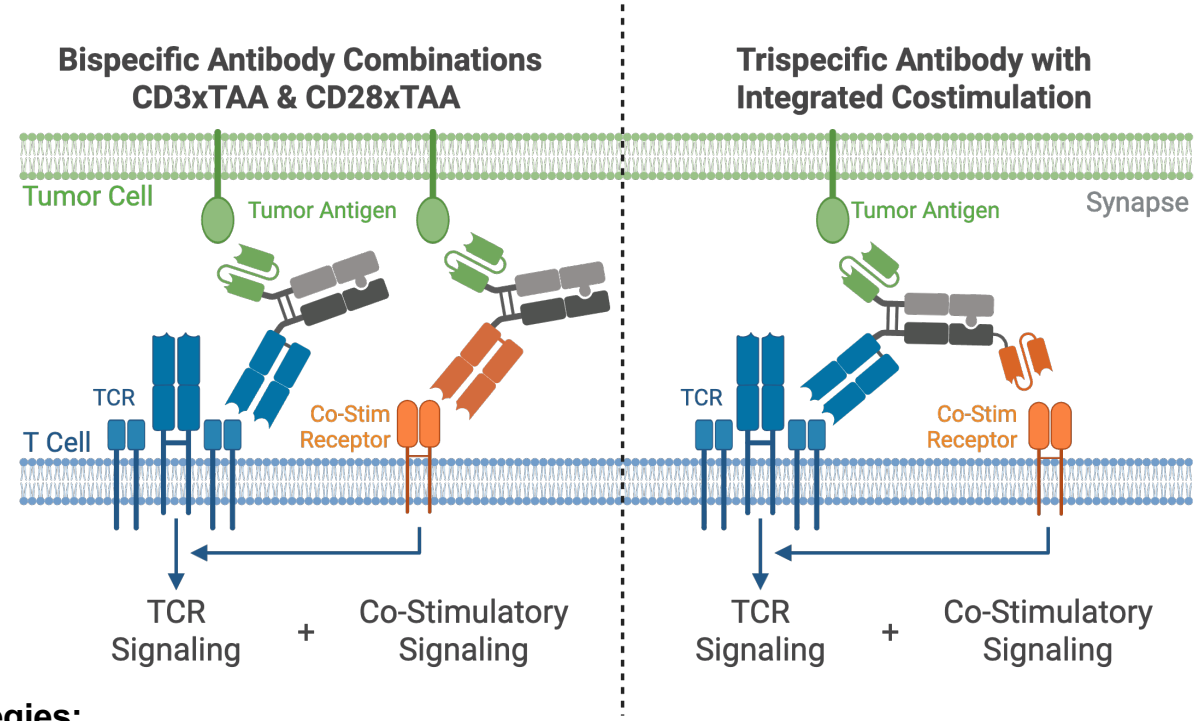

Combination Strategies:

Two different tumor targets: TAA1 x CD3 + TAA2 x co-stim

One tumor target, different epitope: TAA1a x CD3 + TAA1b x co-stim

Majority of Combination Trials Target Two Different Tumor Antigens

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Company	Targets	Name	Indication	Development Stage
Johnson & Johnson	CD28 x PSMA + CD3 x KLK2	JNJ-87189401 + Pasritamig	Advanced Prostate Cancer	Ph1
Johnson & Johnson	CD28 x CD20 + CD3 x CD22	JNJ-87801493 + JNJ-75348780	NHL	Ph1
Regeneron	CD28 x PSMA + CD3 x PSMA	Nezastomig + REGN4336	Advanced Prostate Cancer	Ph1/2
Regeneron	CD28 x MUC16 + CD3 x MUC16	REGN5668 + Ubamatamab	Advanced Ovarian Cancer	Ph1/2
Regeneron	CD28 x CD38 + CD3 x BCMA	REGN7945 + Linvoseltamab	R/R MM	Ph1/2
Regeneron	CD28 x CD22 + CD3 x CD20	REGN5837 + Odronextamab	R/R B-NHL	Ph1
Roche	4-1BBL x CD19 + CD3 x CD20 CD28 x CD19 + CD3 x CD20	Englumafusp alfa + Glofitamab RG6333 + Glofitamab	R/R B-NHL	Ph1 Ph1 (discontinued)

Blue = same tumor target
Green = different tumor targets

Multispecific Antibodies: Can 1 + 1 + 1 > 3?

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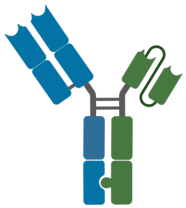
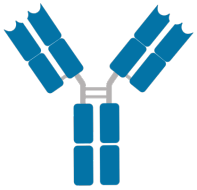
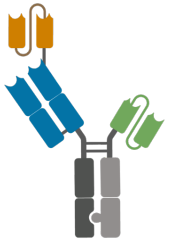
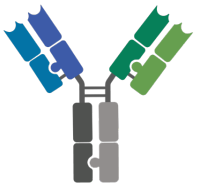
Potential for Improvement in Efficacy and/or Safety

Bispecific vs. Monospecific Combinations

If  >  + 

Tri or Multispecific vs. Bispecific Combinations

Can  >  +  ?

Summary

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- Zanidatamab is approved for 2L treatment of advanced HER2-positive (IHC 3+) biliary tract cancer (BTC)
- Zanidatamab is the first approved biparatopic antibody, and first instance of a biparatopic antibody to demonstrate unique cytotoxic activity compared to parental Ab combination
- Many multispecific antibodies with ≥ 3 specificities are under development and use strategies to address current challenges in the field
- Depending on target biological requirements, some multispecifics require extensive engineering and format evaluation

Acknowledgements

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zanidatamab Preclinical/Non-clinical

Abhishek Mukhopadhyay
Anders Ohrn
Andrea Hernández Rojas
Antonios Samiotakis
Bryant Harbourne
Chi Wing Cheng
Claire E. Atkinson
Duncan Browman
Elizabeth Whalen
Emma E. Smith
Eric Escobar-Cabrera
Gesa Volkers
Gordon Ng
Grant Wickman
Jason Baardsnes
Jason O'Toole
Jodi Wong
Joel Smith
Joseph D. Schrag
Joshua M. Scurll
Joy Guedia
Kate Choi
Leonard G. Presta
Libin Abraham
Liam J. Worrall
Lisa Newhook
Mario Sanches
Matteo Zago-Schmitt
Michael R. Gold
Natalie C. J. Strynadka
Peter W. Y. Chan
Prajwal Raghunatha
Priya Baichoo
Sohyeong Kang
Sonia Black
Surjit Dixit
Patricia Zwierzchowski
Vincent Fung
Desmond Lau
Genevieve Desjardins
Prajwal Raghunatha

Zymeworks' Multispecific Antibody Therapeutics Team

Funda Meric-Bernstam and lab

Jazz Pharmaceuticals

BeOne Medicines

TriTCE Co-Stim & ZW209

Aaron Tieu
Aditi Deshmukh
Akshay Kamath
Alec Robinson
Alexandra Livernois
Anna Von Rossum
Andrew Sharon
Begonia Silva Moreno
Bing Catherine Wu
Caitlin Low
Catherine Wu
Chayne L. Piscitelli
Cindy Park
David Douda
David Kroeger
Desmond Lau
Diana Canals Hernaez
Diego Perez Escanda
Dnyandeo Amberkar
Fisal Elstone
Gavin Storoschuk
Genevieve Desjardins
Gursev Anmole
Hamed Shirvani
Harpreet Bamra
Harsh Pratap
John Zhang
Kesha Patel
Kurt Stahl
Larissa Patlan Ramirez
Lauren Clifford
Lisa Newhook
Liz Halvorsen
Marylou Vallejo
Maya C. Poffenberger
Meghan Verstraete
Nan Nan Liu
Nichole K. Escalante
Nicole Afacan
Patricia Zwierzchowski
Paul A. Moore
Peter Repenning
Polly Shao
Purva Bhojane
Richard Kunze
Stella Kauryzhka
Yun Peng
Thomas Spreter von Kreudenstein

Abstract 4542 –Karmokar et al. Zanidatamab modulates multiple pathways involved in tumor growth and survival and is efficacious post T-DXd