2026 ESMO TAT

Targeted Anticancer Therapies

Engineering trispecific and multivalent molecules: Design for selectivity and potency

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DECLARATION OF INTERESTS

Nina E. Weisser is an employee and shareholder of Zymeworks Inc.

What is a Tri- or Multispecific Antibody?

An antibody with more than one targeted specificity, excluding the Fc!

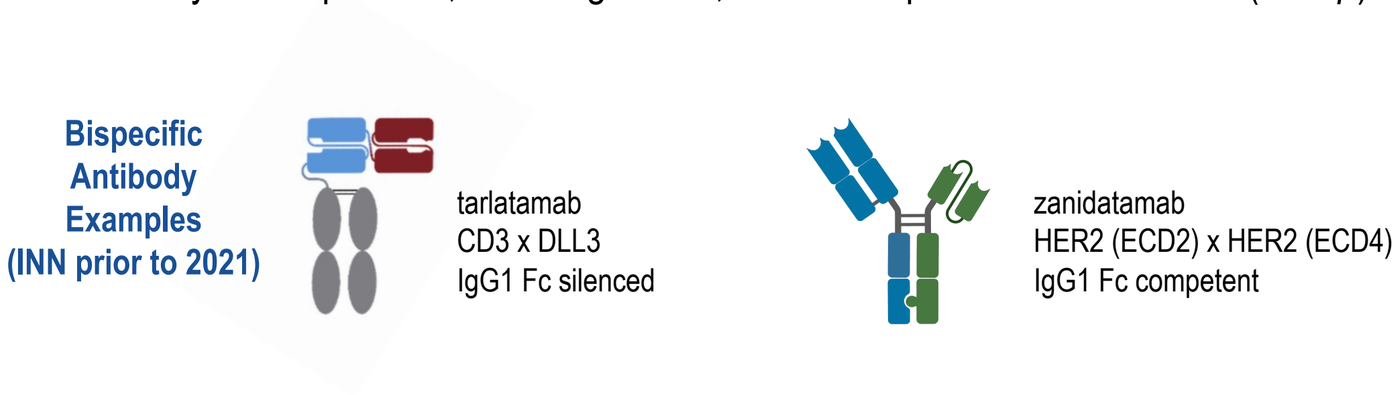
New international nonproprietary names (INN) nomenclature adopted in 2021

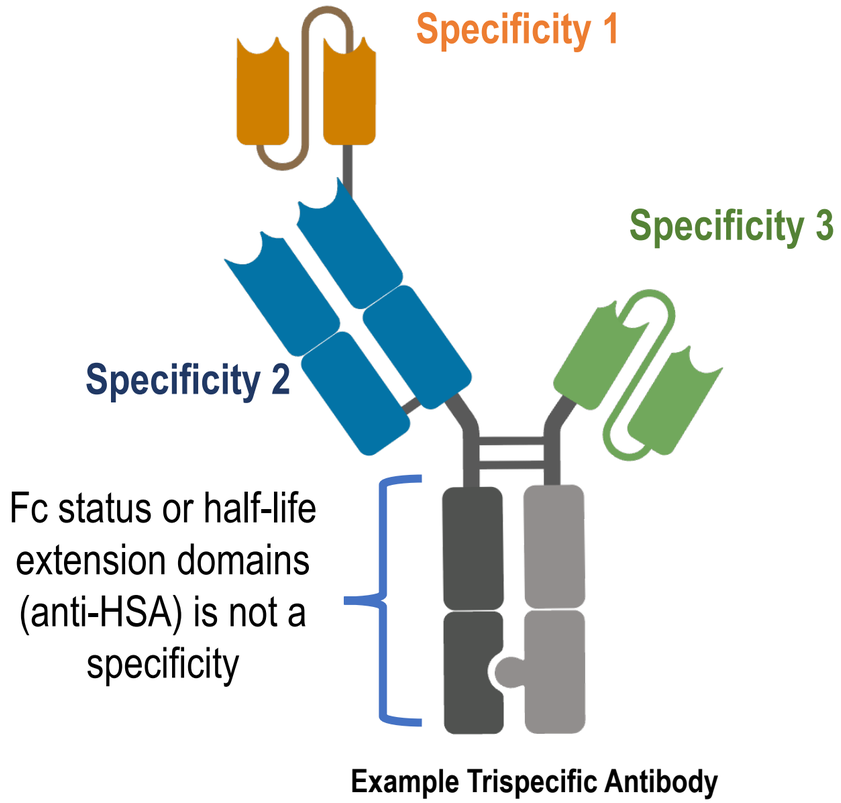
'**mig**' introduced, stands for multispecific immunoglobulin

'**mig**' covers all antibodies with **more than one specificity, regardless of format, type, or shape**

'mig' does not define whether Fc is present, engineered or effector silenced/enhanced

Antibody fusion proteins, including bsAbs, use fusion protein nomenclature (*-afusp*)





Example Trispecific Antibody

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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	BLINCYTO (blinatumomab)	AMGEN	CD19 × CD3	2014
✓ Teclistamab	TECVAYLI (teclistamab-cqyv)	janssen	BCMA × CD3	2022
✓ Mosunetuzumab	Lunsumio (mosunetuzumab-axgb)	Roche	CD20 × CD3	2022
✓ Epcoritamab	epkinly (epcoritamab-bysp)	abbvie Genmab	CD20 × CD3	2023
✓ Glofitamab	COLUMVI (glofitamab-gxbm)	Roche	CD20 × CD3	2023
✓ Talquetamab	TALVEY (talquetamab-tgvs)	janssen	GPRC5D × CD3	2023
✓ Elranatamab	ELREXFIO (elranatamab)	Pfizer	BCMA × CD3	2023
✓ Odronextamab	ORDSPONO	REGENERON	CD20 × CD3	2024 EMA only

SOLID TUMORS
Solid tumor malignancies

8 agents

✓ Amivantamab	RYBREVANT (amivantamab-vmjw)	janssen	EGFR × cMET	2021
✓ Tebentafusp	KIMMTRAK (tebentafusp-tebn)	IMMUNOCORE	gp100 × CD3	2022
✓ Cadonilimab	Lukina®	Akesobio	PD-1 × CTLA-4	2022 NMPA only
✓ Tarlatamab	IMDELLTRA	AMGEN	DLL3 × CD3	2024
✓ Zanidatamab	ZIIHERA (zanidatamab-hrii)	BeOne Jazz zymeworks	HER2 × HER2	2024
✓ Zenocutuzumab	Bizengri zenocutuzumab-zbco	Merus	HER2 × HER3	2024
✓ Ivonescimab	Summit therapeutics	Akesobio	PD-1 × VEGF	2024 NMPA only
✓ Catumaxomab*	Korjuny	LINDIS	EpCAM × CD3	2025 EMA only

* Approved to treat malignant ascites

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

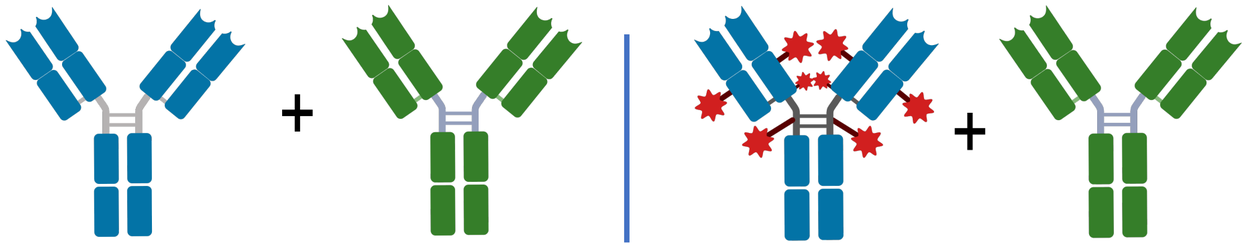
- Hematologic Malignancy
- Solid Tumor Malignancy
- EMA only – European approval only
- NMPA only – China approval only
- R/R = Relapsed/Refractory
- i.p.= Intraperitoneal

ESMO

Alternative Paths to Multispecific Antibody Therapy

Monospecific and Bispecific Combinations

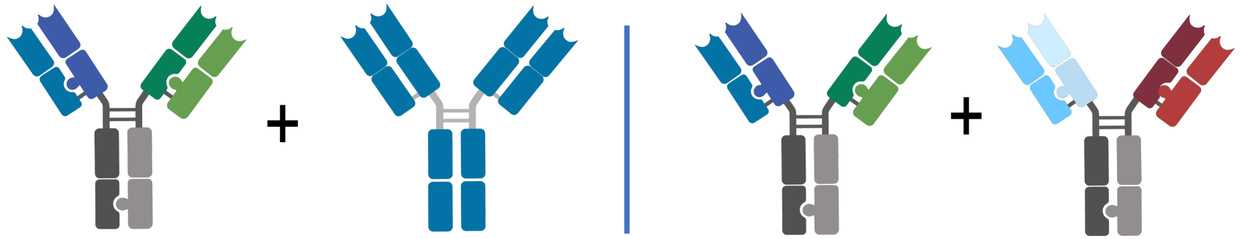
Monospecific Combinations



Approved Monospecific Combination Examples:

- **Dual RTK Inhibition**: HER2 + HER2 - Trastuzumab + Pertuzumab
- **Targeted Therapy**: SLAMF + CD38 - Elotuzumab + Daratumumab
- **Dual checkpoint inhibition**: PD-1 + CTLA-4 – Nivolumab + Ipilimumab
  PD-1 + LAG-3 – Nivolumab + Relatlimab
- **ADC + checkpoint inhibition**: Nectin-4 + PD-1 – Enfortumab vedotin + Pembro
  HER2 + PD-1 – Trastuzumab deruxtecan + Pembro

Bispecific + Monospecific or Bispecific Combinations



Investigational Bispecific Combination Examples:

- **TCE + checkpoint inhibition**: gp100/pMHC x CD3 + PD-L1 – tebentafusp + durva
  DLL3x CD3 + PD-L1 – tarlatamab + atezo/durva
- **TCE + TCE**: CD3 x BCMA + CD3 x GPRC5D
  CD3 x KLK2 + CD28 x PSMA

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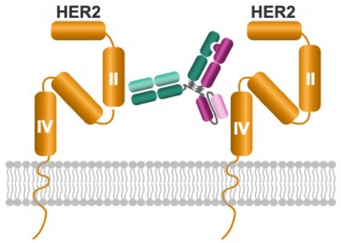
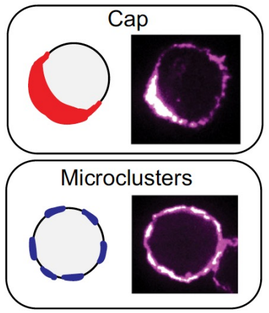
Multispecific Antibodies Can Unlock Novel Biologies

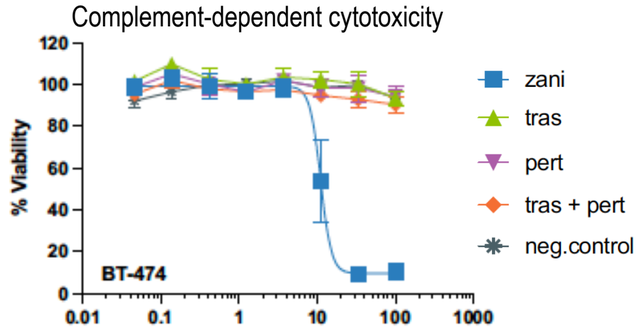
‘Non-obvious’ Bispecific Case Study: 1 + 1 > 2

zanidatamab[1]: Anti-HER2 biparatopic



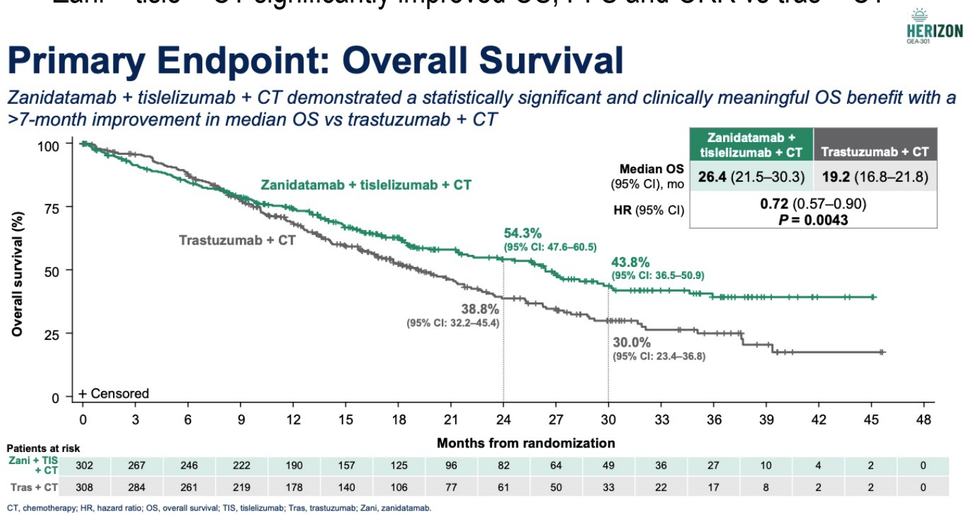
- Anti-ECD2 x ECD4 (like trastuzumab + pertuzumab)
- Cooperative *trans* HER2 binding and clustering
- Enhanced antitumor activity vs. mAb combo
- CDC competent vs. inactive in mAbs and combo
- Antibody format important. Some formats agonistic!





Pivotal Phase 3: First line HER2-positive gastroesophageal adenocarcinoma[2]

Zani + tisle + CT significantly improved OS, PFS and ORR vs tras + CT



- Interim analysis of zanidatamab + CT showed significant improvement of PFS and ORR and strong trend toward significance for OS vs. trastuzumab + CT

In comparison

- tras + pert + CT vs. tras + CT did not meet primary endpoint in JACOB trial[3]

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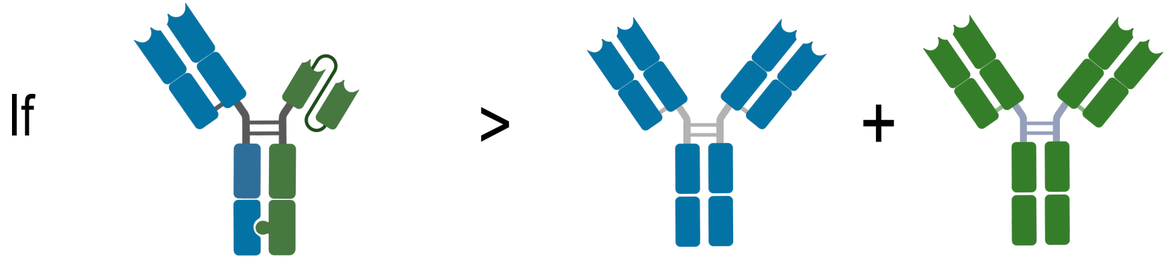
1. Weisser N et al., Nature Communications 2023; 2. Elimova J Clin Oncol 44, LBA285, 2026;
3. Tabernero J, et al. The Lancet Oncology, 2018

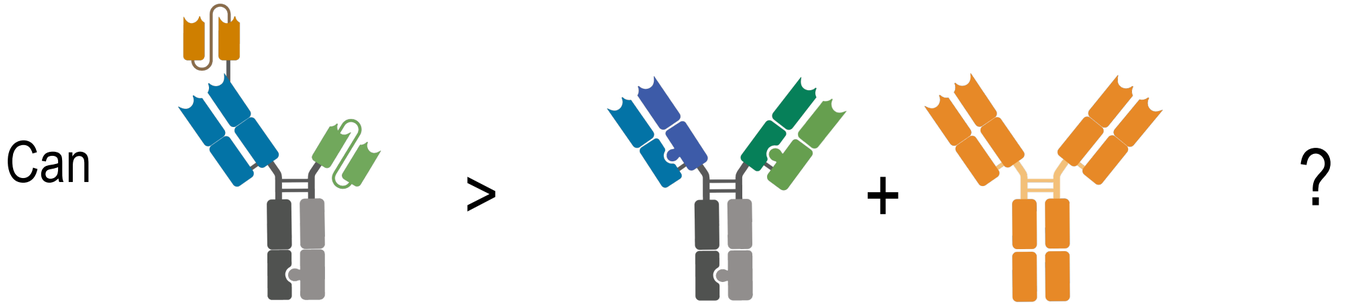
Multispecific Antibodies: Can 1 + 1 + 1 > 3?

Potential for Improvement in Efficacy and/or Safety

Bispecific vs. Monospecific Combinations



Tri or Multispecific vs. Bispecific Combinations



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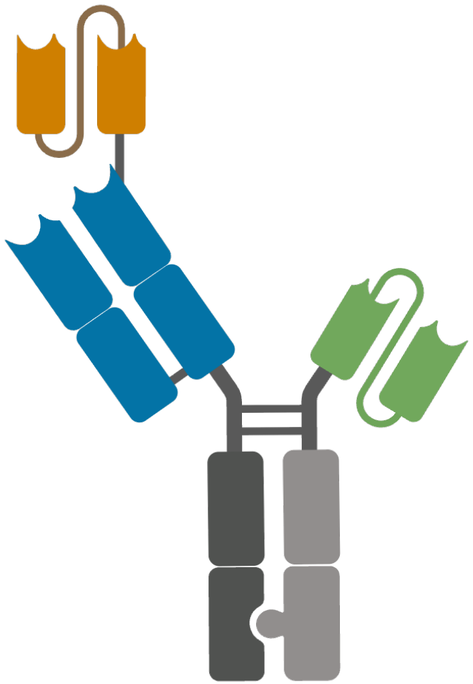
Why Increase Antibody Complexity?

Rationale for Tri- or Multispecific Antibody Therapy



- Combine multiple mechanisms in one molecule
- Address challenges with bsAb therapy e.g. improve tumor selectivity and/or potency
- Controlled exposure vs. independent exposure of two molecules
- Potential for unique mechanisms of action, not attainable with Ab combinations
- Potential for improved tolerability profile compared to single agents or combinations
- Simplified clinical trial design and CMC
- Challenges:
  - More complex engineering required
  - Potential increased risk in immunogenicity
  - Fixed dosing of one molecule may limit tox mitigation

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Limitations of Mono & Bispecific Antibody Therapy

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

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Increasing Clinical Development of Multispecific Abs

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

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Trispecific Dual Tumor Antigen Targeting T cell Engagers

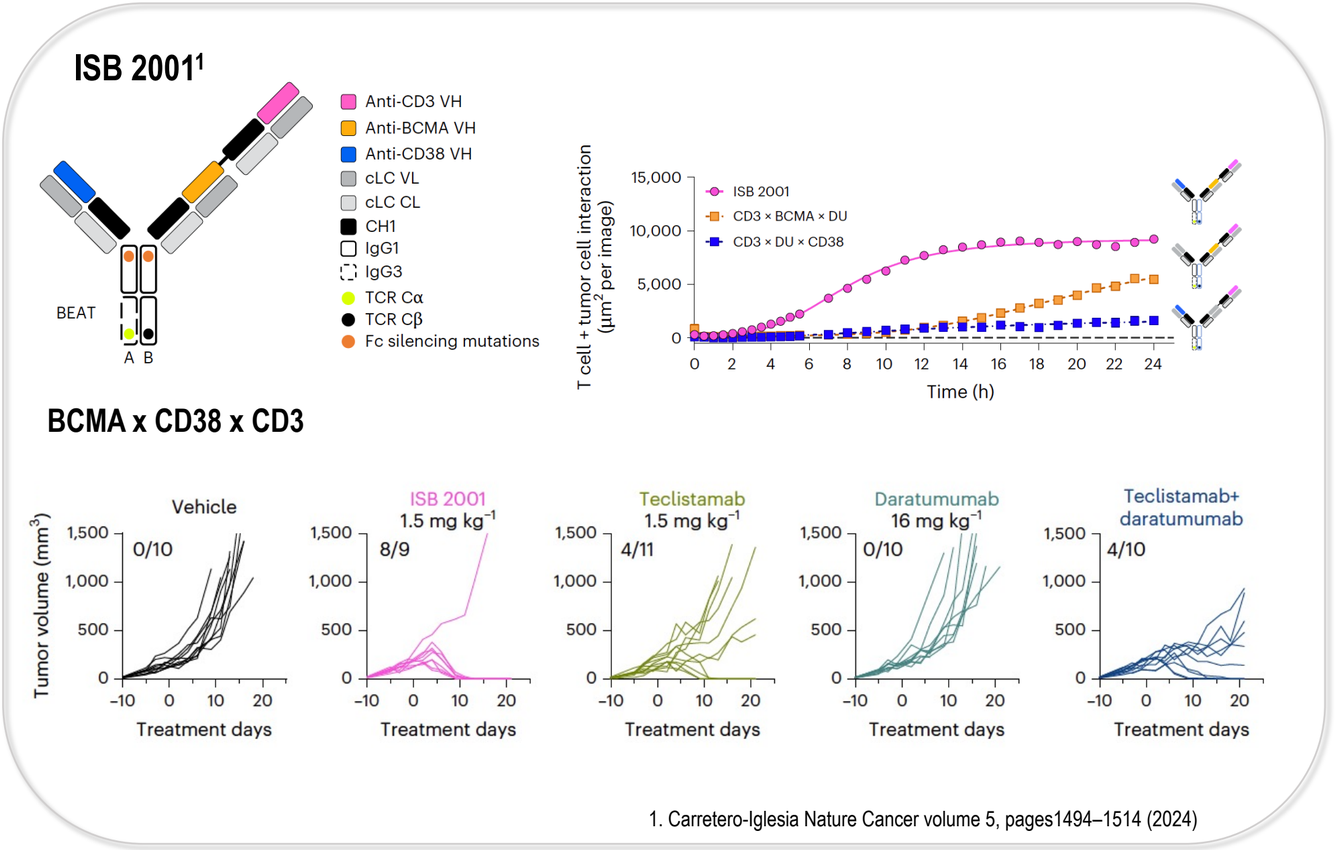
Addressing Tumor Heterogeneity and Prevention of Antigen Loss

Dual tumor antigen targeting 1 2

- **Reduce antigen escape resistance**
- **Enhance potency in heterogenous tumors**
- **Improve tumor selectivity through avidity**

Indication	Trispecific Targets	No. Molecules in Clinical Development#
Multiple Myeloma	BCMA × GPRC5D × CD3 BCMA × CD38 × CD3	4 1
B-cell cancers*	CD79b × CD20 × CD3 CD19 × CD20 × CD3	2 1

Molecules in Phase 1 or Phase 1 / 2
BCMA x GPRC5D x CD3: Ramantamig (J&J); MBS314 (Mabworks);SIM0500 (Simcere); IBI3003 (Innovent)
BCMA x CD38 x CD3: ISB 2001 (Ichnos Science)
CD79b x CD20 x CD3: JNJ-80948543, JNJ-95566692 (J&J)
CD19 x CD20 x CD3: CMG1A46 (GSK)
2 additional solid tumor targeting molecules include SOA101 and alveltamig; * B-NHL, B-ALL and/or CLL



1. Carretero-Iglesia Nature Cancer volume 5, pages1494–1514 (2024)

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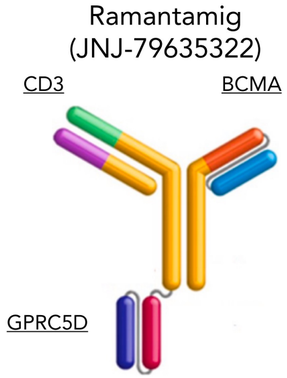
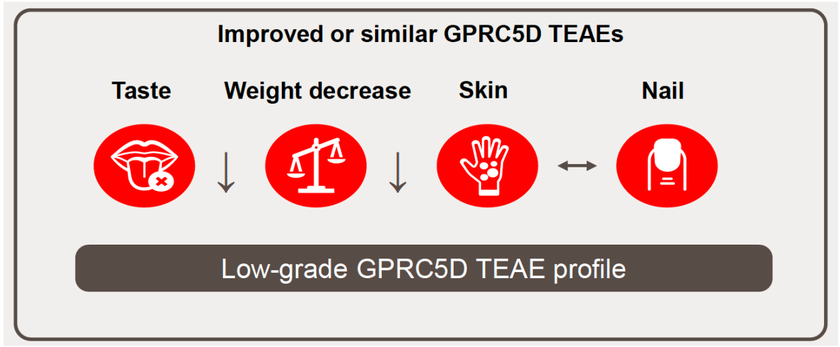
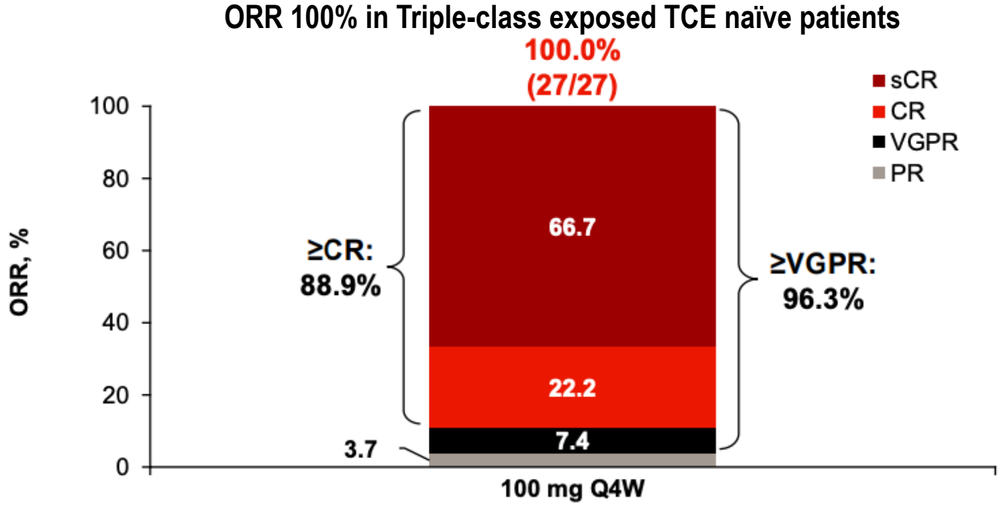
Trispecific Dual Tumor Antigen Targeting T cell Engagers

Ramantamig Shows Promising Phase 1 Clinical Efficacy and Safety







- Ramantamig showed enhanced antitumor activity with ramantamig over combination of bispecific antibodies in primary patient BM samples[1]
- At RP2D: **ORR of 86.1%** (n=36), ≥ CR rat of 75%, and MRD negativity of 100.0% at 10^{-5} (n=10/10) and 10^{-6} (n=7/7)[2]
- At RP2D, triple-class exposed patients naïve to TCE therapies achieved an **ORR of 100%**[2]
- Improved or similar TEAE[2,3]

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1. O Neil *Blood* (2025) 146 (Supplement 1): 3922.
2. Krishnan *Blood* (2025) 146 (Supplement 1): 4042.
3. van de Donk,,J Clin Oncol 43, 7505(2025)

Trispecific TCE with Integrated Co-Stimulation

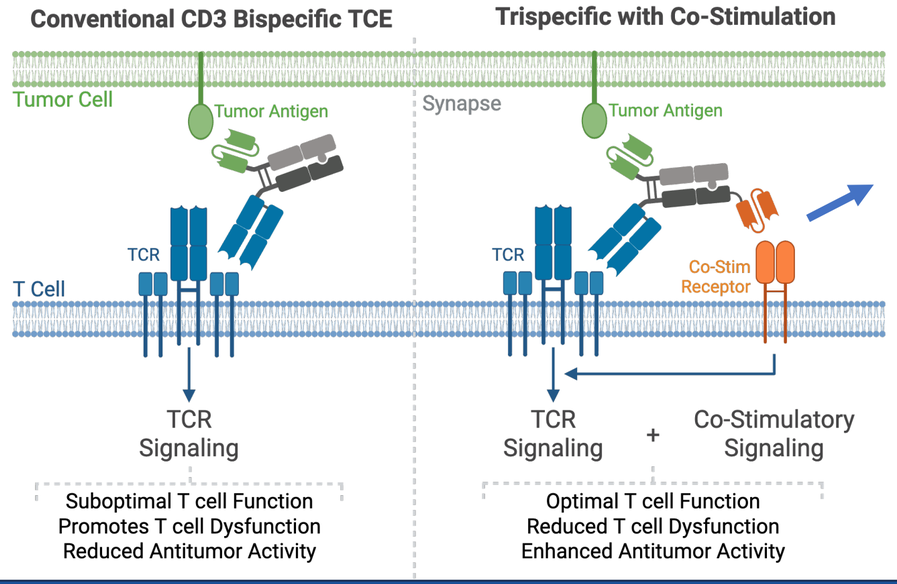
Enhancing T cell Fitness to Increase Antitumor Activity

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



Co-Stimulatory Targets

- CD28
- 4-1BB
- CD2

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?

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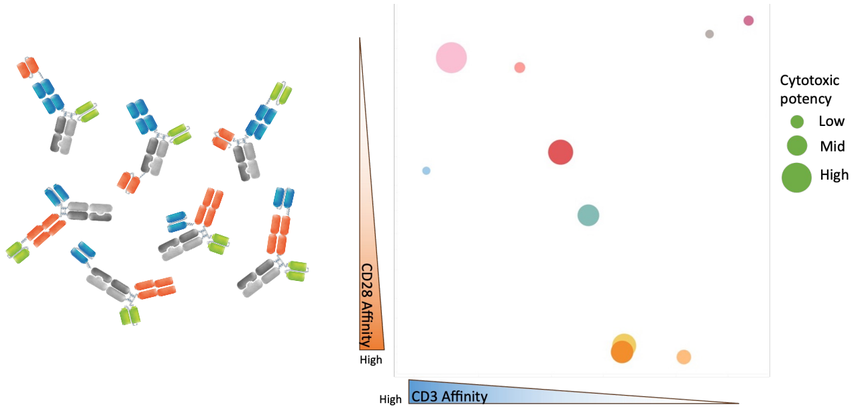
Trispecific TCE with Integrated Co-Stimulation

Importance of Engineering & Format Screening For Optimal T cell Engagement

ZW209 (DLL3 x CD3 x CD28) Screening

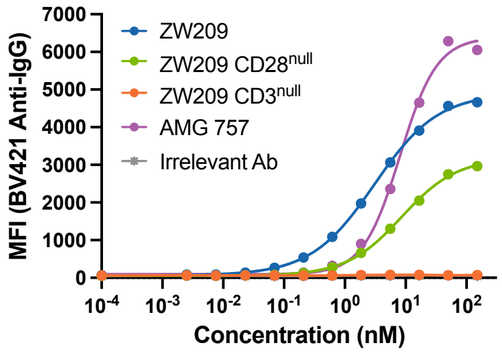


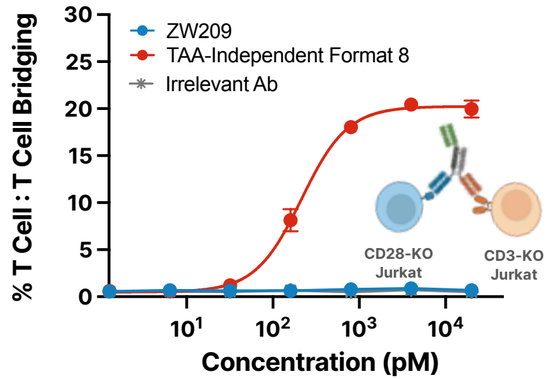
DLL3 Co-stim Molecule	1	2	3	4	5	6	7	8	9	10
Cytotoxicity										
Target-Dependent	✓	✓	✓	X	X	X	X	X	✓	✓

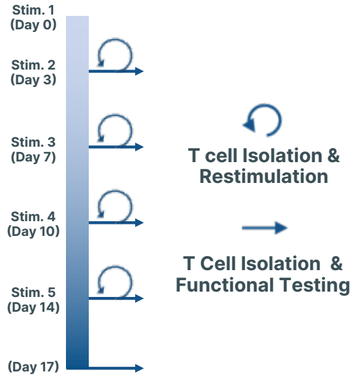
Cytotoxicity

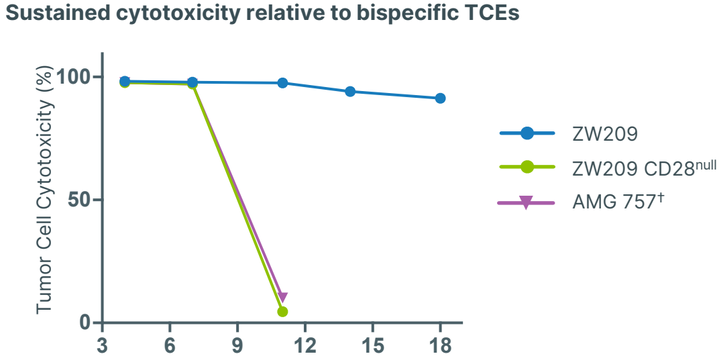
- Placement of CD3 and CD28 paratope affects binding affinity, potency and biological profile
- Many formats failed screen for strict target-dependent activity

ZW209: Obligate Cis & Conditional CD28 Binding, Requiring Co-engagement of CD3









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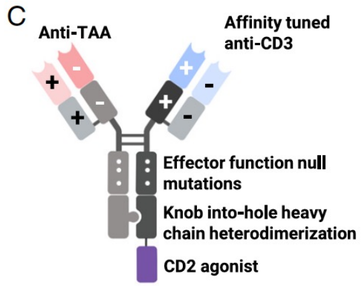
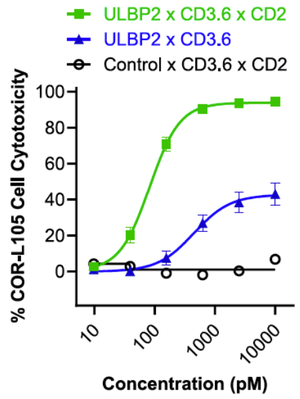
Repenning, Cancer Res (2024) 84 (6_Supplement): 6719.
Lau, Cancer Res (2025) 85 (8_Supplement_1): 7318.

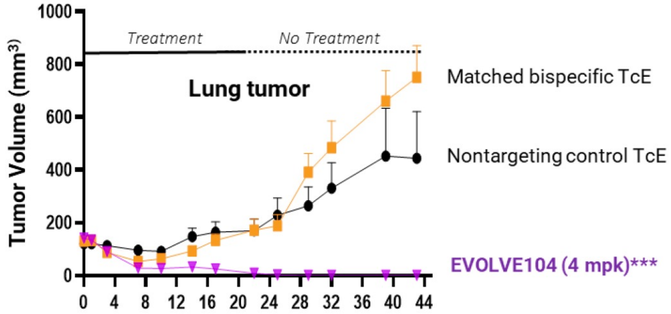
Trispecific TCE with Integrated Co-Stimulation

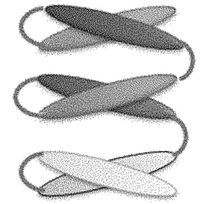
Differentiated Activity vs. Bispecific TCE & Preliminary Clinical Data



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

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Sergeeva et al 2025 PNAS 122 (47) e2510829122 (EvolveImmune)
Huang et al. 2025 AACR (Cytocares)

Dual-Checkpoint Inhibition with VEGF Blockade

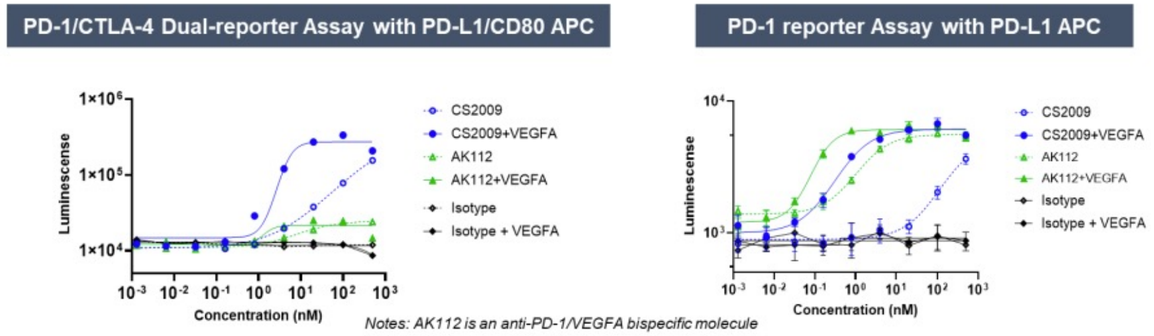
Capture CTLA-4 Benefit While Limiting Systemic CTLA-4 Toxicity

Dual checkpoint Inhibition + VEGF blockade 3 5

- **Avidity/TME based PD1/CTLA-4 engagement or tuned CTLA-4 blockade**
- **Leverage VEGF-rich TME to enhance local activity and reduce peripheral CTLA-4 effects**
- **Enhanced checkpoint inhibition via VEGFA dimer crosslinking**

Targets	Molecule	Company
PD-1 x CTLA-4 x VEGF	CS2009 GB268 HC010	CStone Pharmaceuticals Genor Biopharma HC Biopharma

Molecules in Phase 1 or Phase 1/2



Notes: AK112 is an anti-PD-1/VEGFA bispecific molecule

- **CS2009** demonstrates enhanced activity on PD1+ / CTLA-4+ cells that is further enhanced with crosslinking by VEGFA dimers[1]
- ESMO 2025 Phase 1[2]:
  - 49 evaluable patients: ORR 12.2%, DCR 71.4%; post-cutoff follow-up ORR 14.3%. Higher activity at tentative RP2D 30 mg/kg: ORR 25.0%.
  - irAE 16.7%, Grade 3 ≥ irAE 4.2 %, Grade ≥3 TRAEs 13.9%, No Grade 4/5 TRAEs

Modality Question:
Can this class of trispecific achieve responses in PD-1 non-responsive setting?

1. Wang *Cancer Res* (2025) 85 (8_Supplement_1): 7299
2. Lemech C SMO Congress 2025; Annals of Oncology. 2025;36(Suppl 2):S923.

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Is There an Increase in Immunogenicity?

Immunogenicity is Molecule Dependent

Most approved bispecific antibodies have ADA incidence of ≤ 10% with a range of 0-25%

Based on disclosed examples, tri- and multispecifics have ADA incident range of ~9 - 63%

Multispecifics are not inherently more immunogenic, construct design, platform, dosing and clinical context play a role

	Molecule	Targets	Format / platform	Status	ADA Incidence
Approved Bispecific - ADA Benchmarks					
Low ADA	Teclistamab	BCMA × CD3	IgG-like (IgG4, Fc-silenced)	Approved	**0.5%** (1/186)*
Mid ADA	Elranatamab	BCMA × CD3	IgG-like (IgG2a, Fc-silenced)		**8.9%** (15/168)* ~5.4% neutralizing
High ADA	Talquetamab	GPRC5D × CD3	IgG-like (IgG4, Fc-silenced)		**18–25% *** Neutralizing Abs observed
Investigational Multispecifics with ADA reported					
Tri- or Multispecific Antibodies	ISB-2001	BCMA × CD38 × CD3	IgG-like (IgG1, Fc-silenced)	Phase 1	**10%** (2/20 evaluable)[1]
	SAR443216	HER2 × CD3 × CD28	IgG-like (IgG4, Fc-silenced)	Phase 1	**27.6%** (2-wk lead-in)[2] **9.1%** (3-wk lead-in)
	SAR444200	GPC3 × GPC3 x CD3	Nanobody-based scaffold	Phase 1/2	**24.2%** (8/33)[3]
	MP0533	CD33 × CD123 × CD70 × CD3	DARPin-based scaffold	Phase 1	**62.9%** (34/54)[4]

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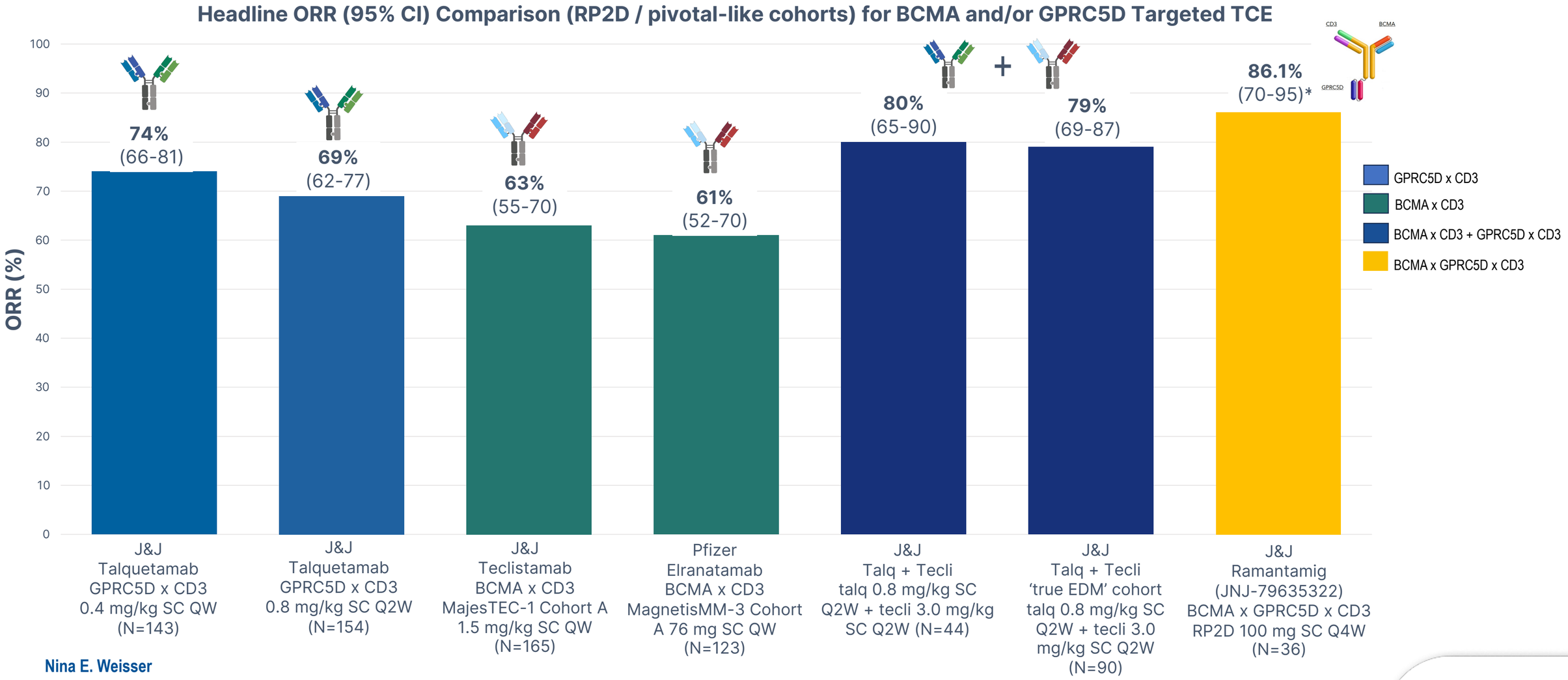
*Associated FDA Label; 1. Quach, ASCO 2025; 2. Calvo, ESMO Open 2025; 3. Chenard-Poirier, ASCO 2024; 4. Bories, ASH 2025

Trispecific TCE Demonstrate Promising Early Data in MM



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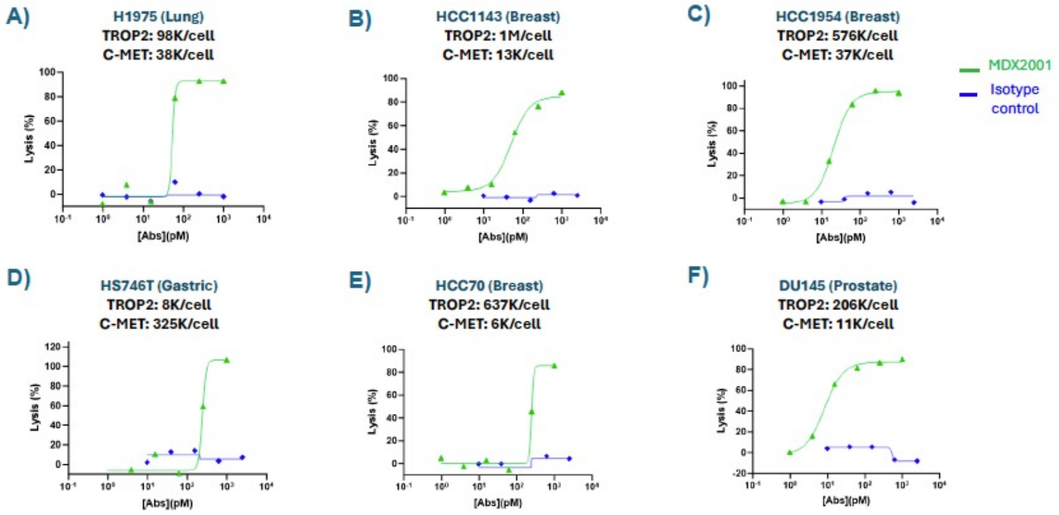
Moreau P, et al. N Engl J Med. 2022; Lesokhin AM, et al. *Nat Med.* 2023; Touzeau C, et al. *HemaSphere (EHA Suppl).* 2023; Popat R, et al. *EHA Congress.* 2025; Krishnan AY, et al. ASH Annual Meeting. 2025; Cohen YC, et al. *N Engl J Med.* 2025; Mateos M-V, et al. *ASH* , 2025; Kumar S, et al. *N Engl J Med.* 2026.

Next Generation Multispecifics Combine Strategies

Dual tumor antigen targeting or Logic-Gating + Co-Stimulation

1 2 3 4 5

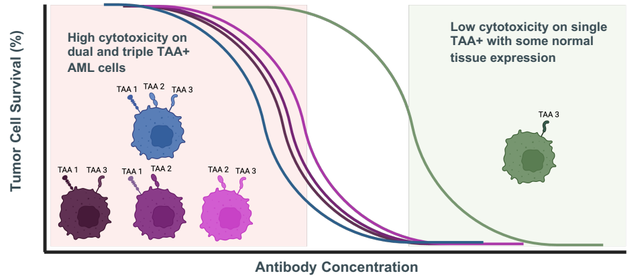
Dual Antigen Targeting + Co-Stimulation

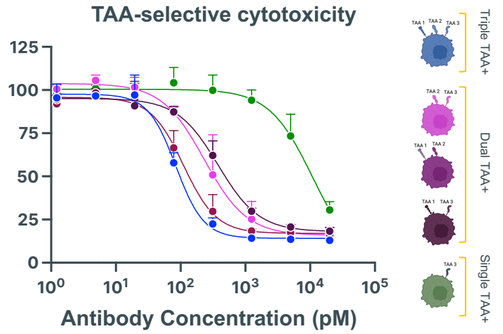


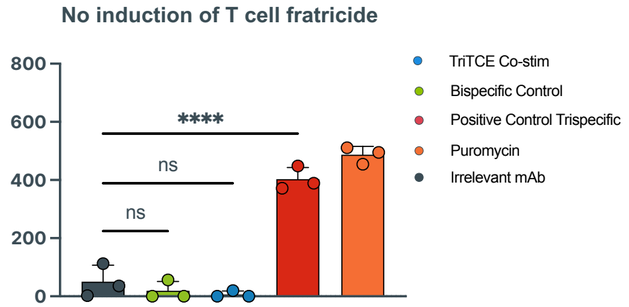
Xu et al. 2024 SITC (Modex)

Logic-Gating + Co-Stimulation

TAA expression profile	TAA	Cytotoxicity
Triple positive	TAA 1 & TAA 2 & TAA 3	✅
Dual positive	TAA 1 & TAA 2 OR TAA 2 & TAA 3 OR TAA 1 & TAA 3	✅
Single positive	TAA 3	❌







Verstraete et al. 2025 SITC (Zymeworks)

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Tri- & Multispecific Antibody Summary

Rapid and Promising Multispecific Antibody Development

- Multispecifics antibodies comprise a class of antibodies that bind more than one target
- Multiple multispecific antibodies that bind 3 or more targets are in Phase 1, Phase 1 / 2 and preclinical development
- Tri- and multispecific strategies are designed to address tumor or treatment-specific challenges
  - 4 main classes engineered for increased selectivity and potency
    - TCE – various strategies
    - Dual-CPI + VEGF blockade
    - NK engagers
    - Multipathway Blockade
- Tri- and multispecifics show enhanced preclinical activity compared to clinically approved bispecifics
- Trispecific antibodies have shown early and promising antitumor activity and safety
- Depending on the target biological requirements, certain multispecifics may require more extensive engineering assessments

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Thank you