Myeloma T-cell Redirecting Therapies/Bispecific Antibodies

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Disclosures

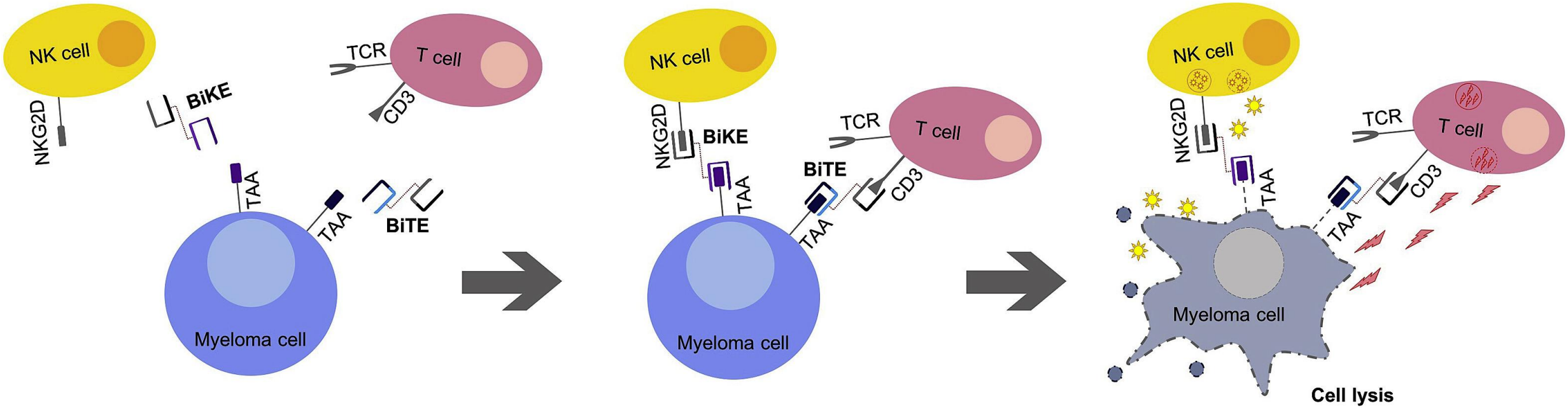
- **Consulting: Bristol Myers Squibb, Celgene, Genentech, Janssen, Karyopharm, Legend Biotech, GlaxoSmithKline, Sanofi, Pfizer, Monte Rosa Therapeutics, Immunitas Therapeutics, Oncopetides, Takeda Pharmaceuticals**

- **Research Funding: Amgen, Janssen, GlaxoSmithSkine, Regeneron, Takeda Pharmaceuticals**

Agenda

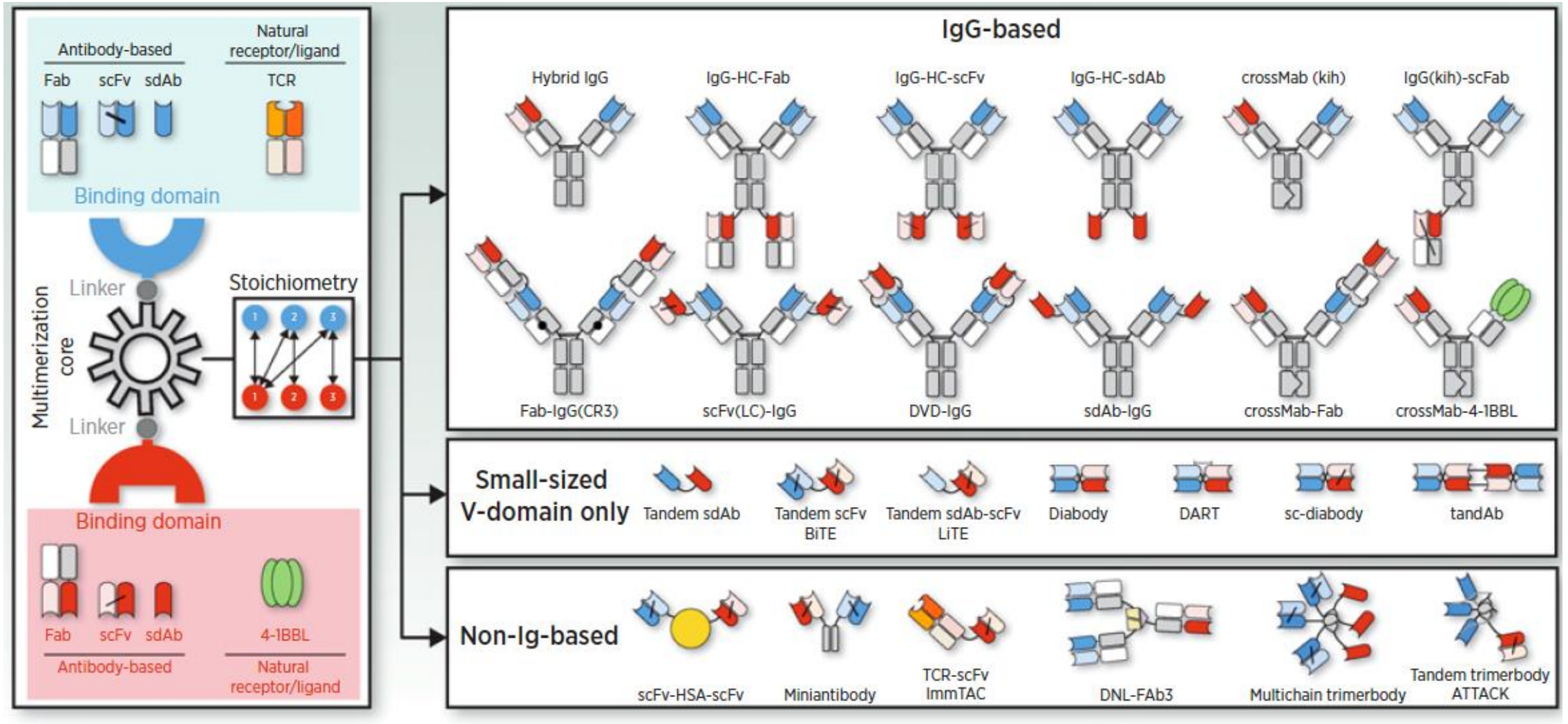
- Bispecific T-cell antibodies
- Bispecific T-cell antibody combination strategies
- Trispecific Antibodies

Bispecific Antibodies



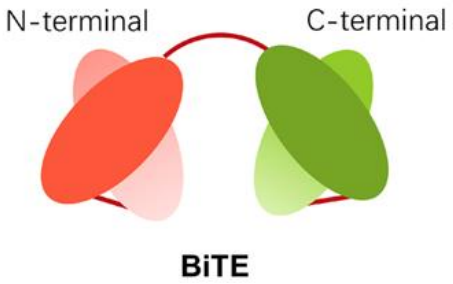
Wudhikarn et al, *Best Pract Res Clin Haematol*, 2020; Yu & Wang, *J Cancer Res Clin Oncol*, 2019

Bispecific Antibody Design



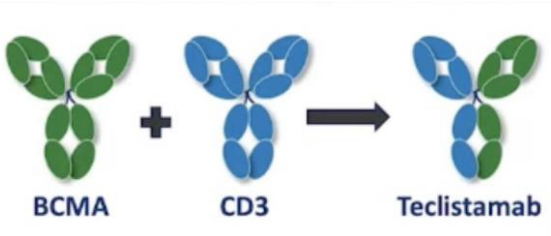
Blanco et al, *Clinical Cancer Research*, 2021

BCMA Bispecific T-Cell Antibodies in Development

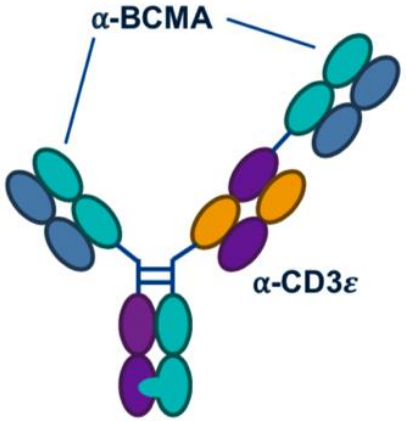


AMG 420

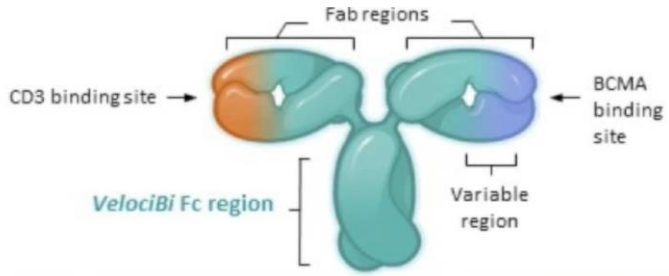
AMG 701



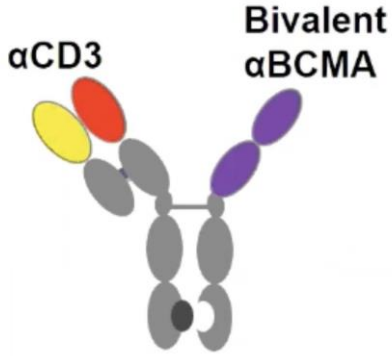
Teclistamab



CC-93269



REGN5458



TNB-383B

Elranatamab

Topp et al, JCO, 2020; Costa et al, ASH 2019; Garfall et al ASH 2020; Rodriguez et al, ASH 2020; Madduri et al, ASH 2020; Harrison et al, ASH 2020; Bahlis et al, ASCO 2021

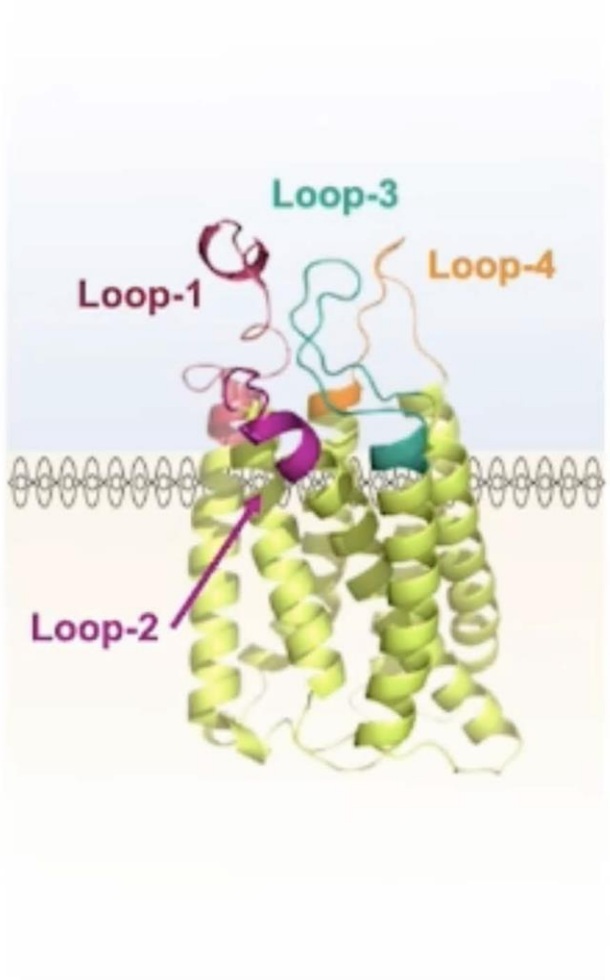
BCMA Bispecific T-Cell Antibodies in Development

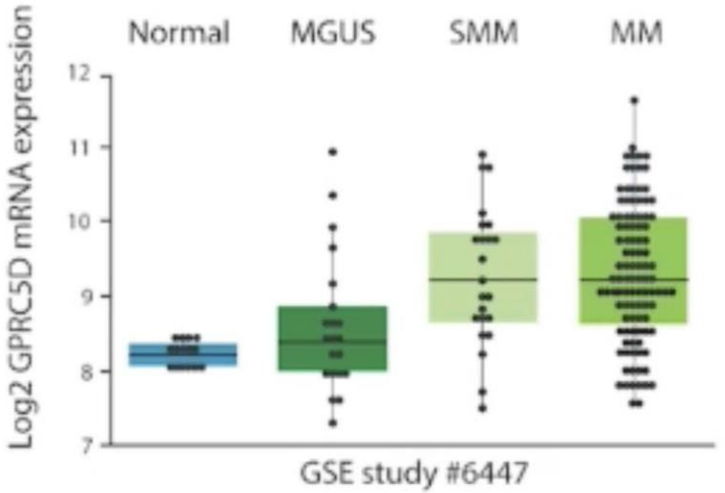
Drug	N	Route/Schedule	ORR at RP2D or higher doses tested to-date	CRS	Comments
AMG 420 (no longer in clinical development)	42	4-week continuous IV	70% (400 ug/day, N=10)	All grade (38%), grade 3/4 (2%)	Grade 3 peripheral neuropathy (2); 1 death due to hepatic failure (adenovirus)
CC-93269	30	IV q week	89% (10 mg, N=9)	All grade (77%), grade 3/4 (0%), grade 5 (3%, 1 patient at 10 mg dose)	2 BCMA binding domains
Teclistamab	165	SC q week	62%, 58% ≥ VGPR (1.5 mg/kg, N=150)	All grade (72%), Grade 3/4 (1%)	9-month PFS 58.5% Median DOR not reached
TNB-383B (ABBV-383)	75	IV q3 weeks	60%, 40% ≥ VGPR (≥40 mg, N=60)	All grade (69%), grade 3/4 (4%)	No step-up dosing; 2 BCMA binding domains
REGN5458	73	IV q week, then q2 weeks starting week 16	75%, 58% ≥ VGPR (200-800 mg, N=24)	All grade (38%), grade 2 (4%), grade 3/4 (0%)	
AMG 701	85	IV q week	83%, 50% ≥ VGPR (18 mg, N=6)	All grade (65%), grade 3 (9%), grade 4 (0%)	
Elranatamab	55	SC q week	70% (≥215 ug/kg, N=20)	All grade (87%), grade 3/4 (0%)	7/10 responders in prior BCMA-exposed

Topp et al, JCO, 2020; Costa et al, ASH 2019; Moreau et al ASH 2021; Kumar et al, ASH 2021; Zonder et al, ASH 2021; Harrison et al, ASH 2020; Sebag et al, ASH 2021

G Protein-Coupled Receptor Class C Group 5 Member D (GPRC5D)

- Orphan G protein-coupled receptor of unknown function
- Limited expression in healthy human tissue, primarily in plasma cells and hair follicles[1-2]
- Highly expressed in myeloma cells and associated with poor prognostic factors in multiple myeloma (MM)[1-3]
- No known shed peptides or extracellular domain shedding (reduced risk for sink effect)
- Ideal target for CD3 redirection

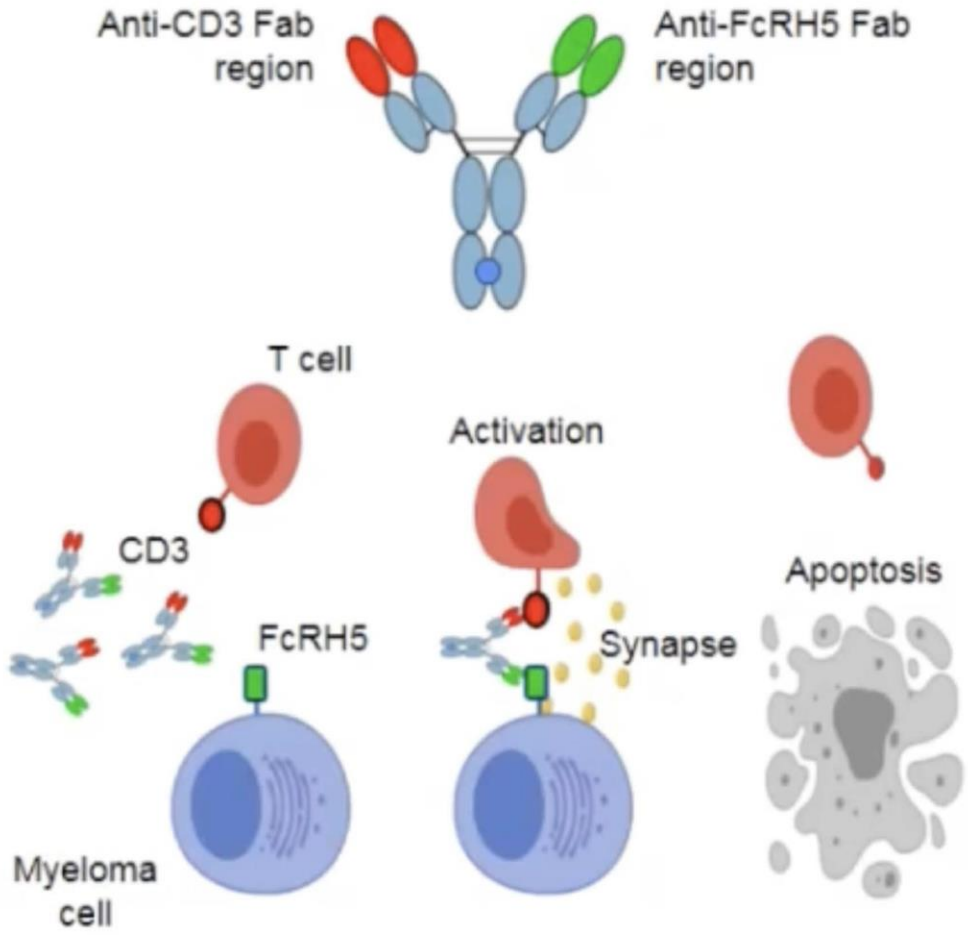




Chari et al, *ASH Annual Meeting,* 2020

Fc receptor-homolog (FcRH5)

- Fc receptor-homolog 5 (FcRH5)
  - Expressed on myeloma cells with near 100% prevalence[1]
  - Expression on myeloma and plasma cells > normal B cells[1]
- Cevostamab
  - Humanized IgG-based T-cell-engaging bispecific antibody[1]
  - Targets FcRH5 on myeloma cells and CD3 on T cells[1]
- Ongoing Phase I dose-escalation and expansion trial (NCT03275103) is evaluating the safety and activity of cevostamab monotherapy in patients with RRMM[2]



Cohen et al, *ASH Annual Meeting,* 2020

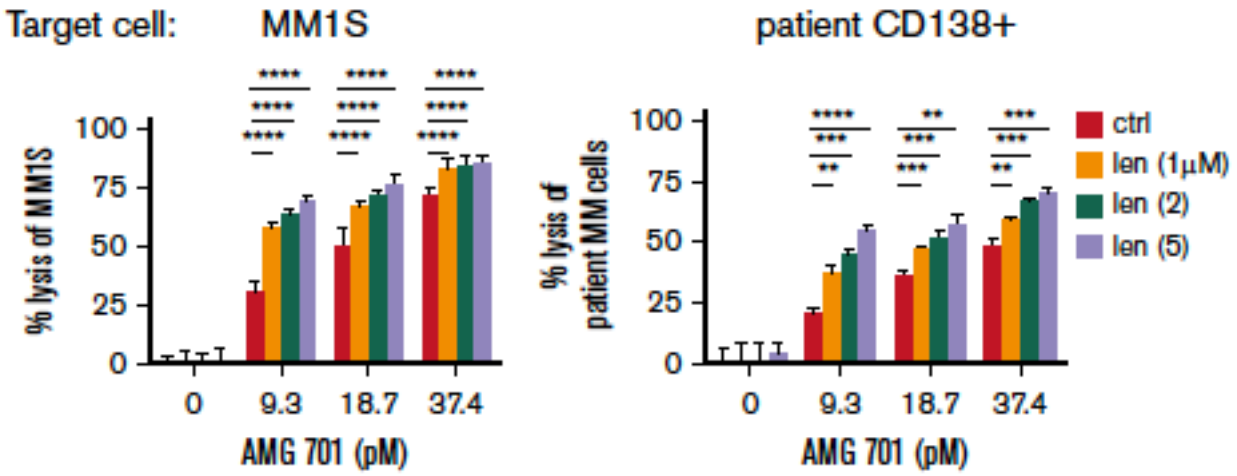
Non-BCMA Bispecific T-Cell Antibodies in Clinical Development

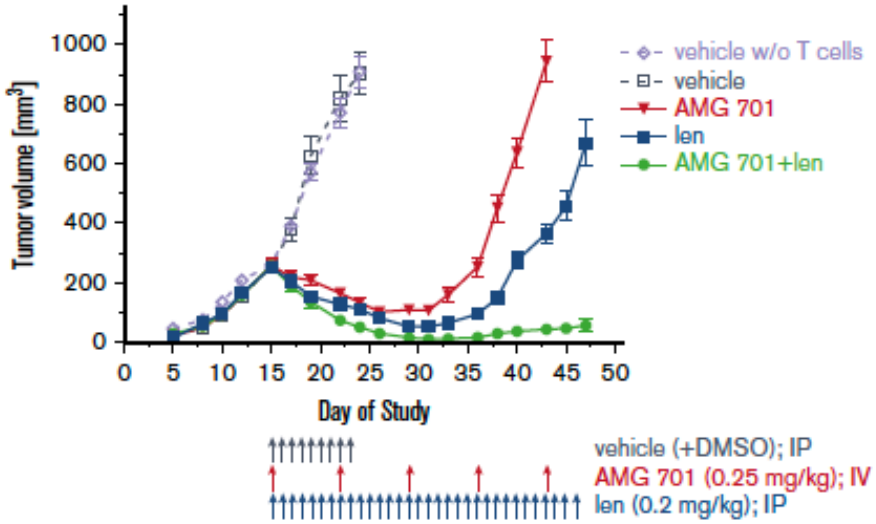
Drug	N	Route/Schedule	ORR at RP2D or higher doses tested to-date	CRS	Comments
Talquetamab (GPRC5D x CD3)	55	SC qweek or q2 weeks	70%, 60% ≥ VGPR (405 ug/kg q week SC, N=30) 67%, 52% ≥ VGPR (800 ug/kg q2 weeks SC, N=21)	77% All grade, 1% grade 3/4 (405 ug/kg q week SC) 72% All grade, 0% grade 3/4 (800 ug/kg q2 weeks SC)	Other unique AEs: dysgeusia, skin exfoliation, nail disorders 22% prior BCMA exposed
Cevostamab (FcRH5 x CD3)	161	IV q3 weeks x 17 cycles	57% (132-198 mg, N=60)	All grade (81%) Grade 3/4 (1%)	14% ICANS (all grade 1/2) 33% prior BCMA exposed

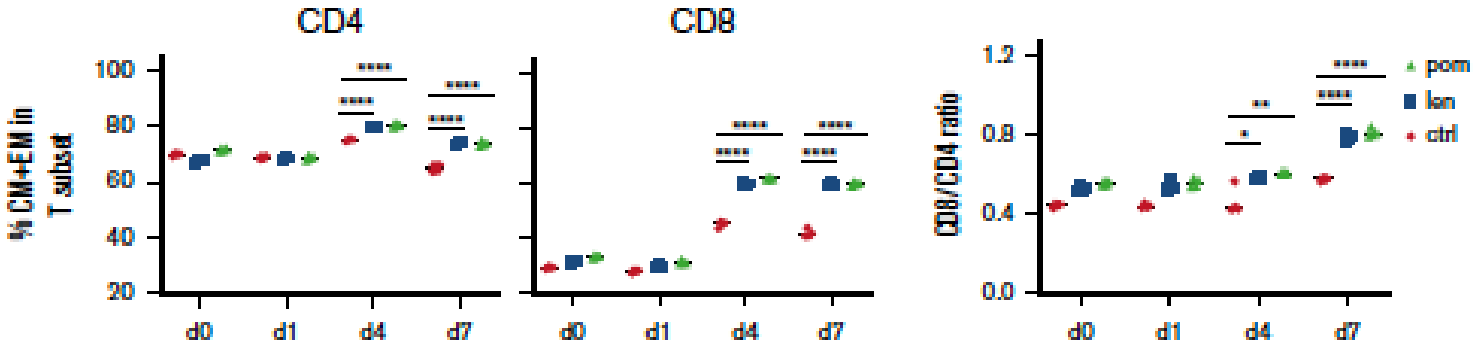
Krishnan et al, *ASH* 2021; Trudel et al, *ASH* 2021

Myeloma Bispecific T-Cell Antibodies Combination Strategies

Myeloma Bispecific BCMAxCD3 (AMG 701) + IMiDs

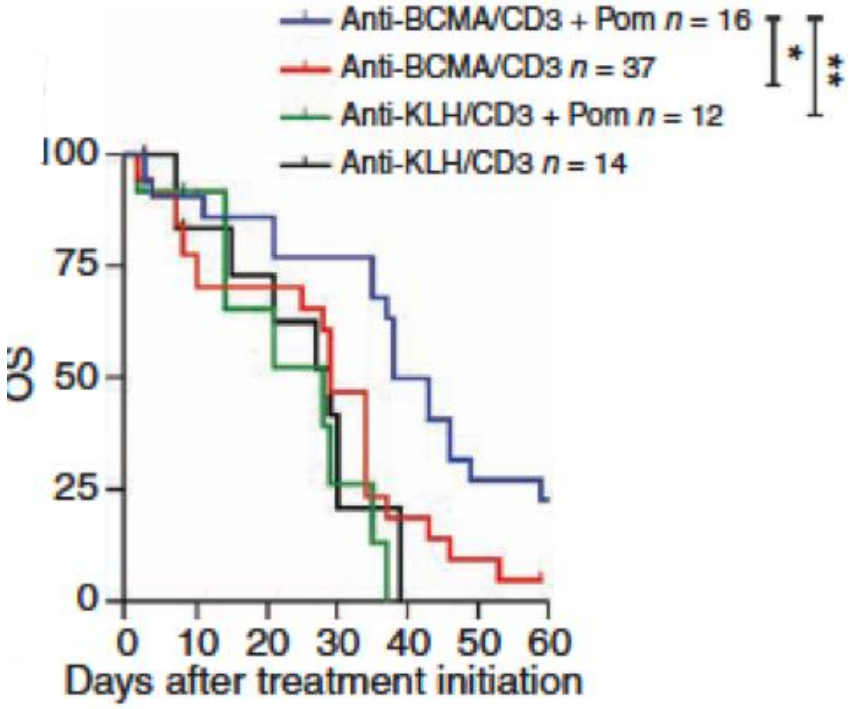


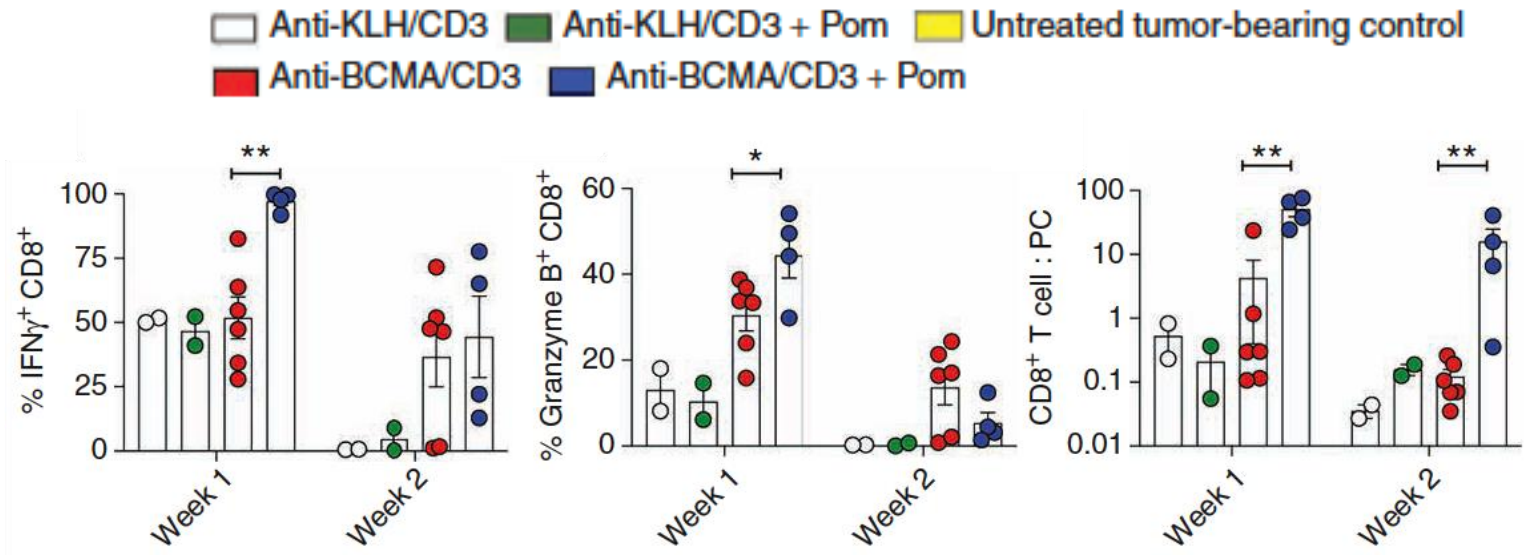




Cho et al, *Blood Advances* 2020

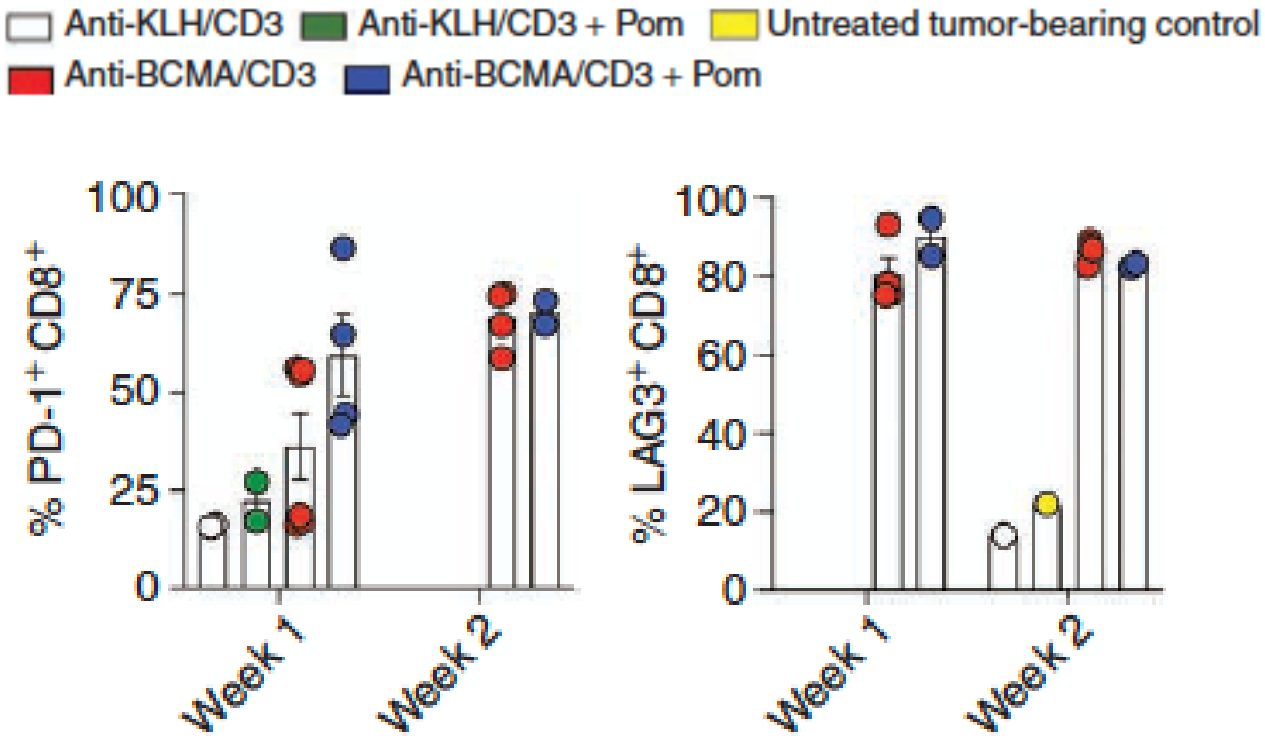
Myeloma Bispecific BCMAxCD3 + Pomalidomide

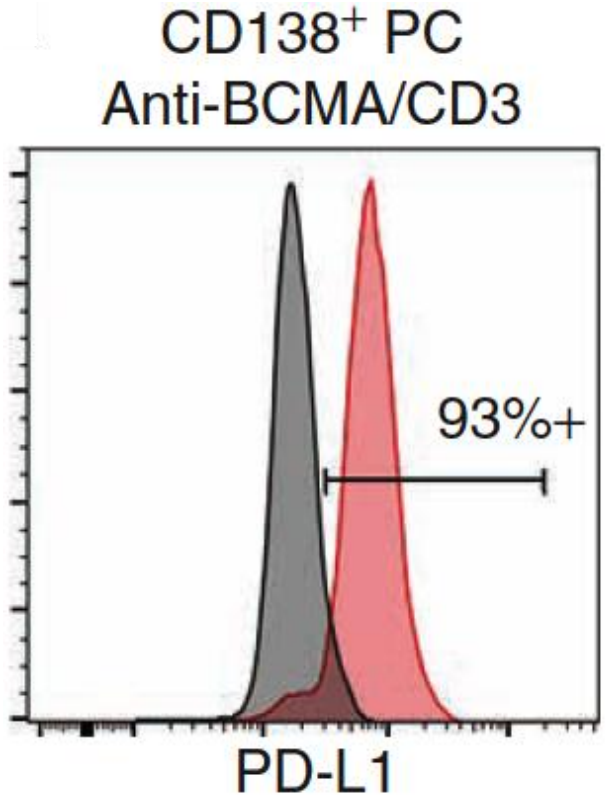




Meermeier et al, *Cancer Discovery,* 2021

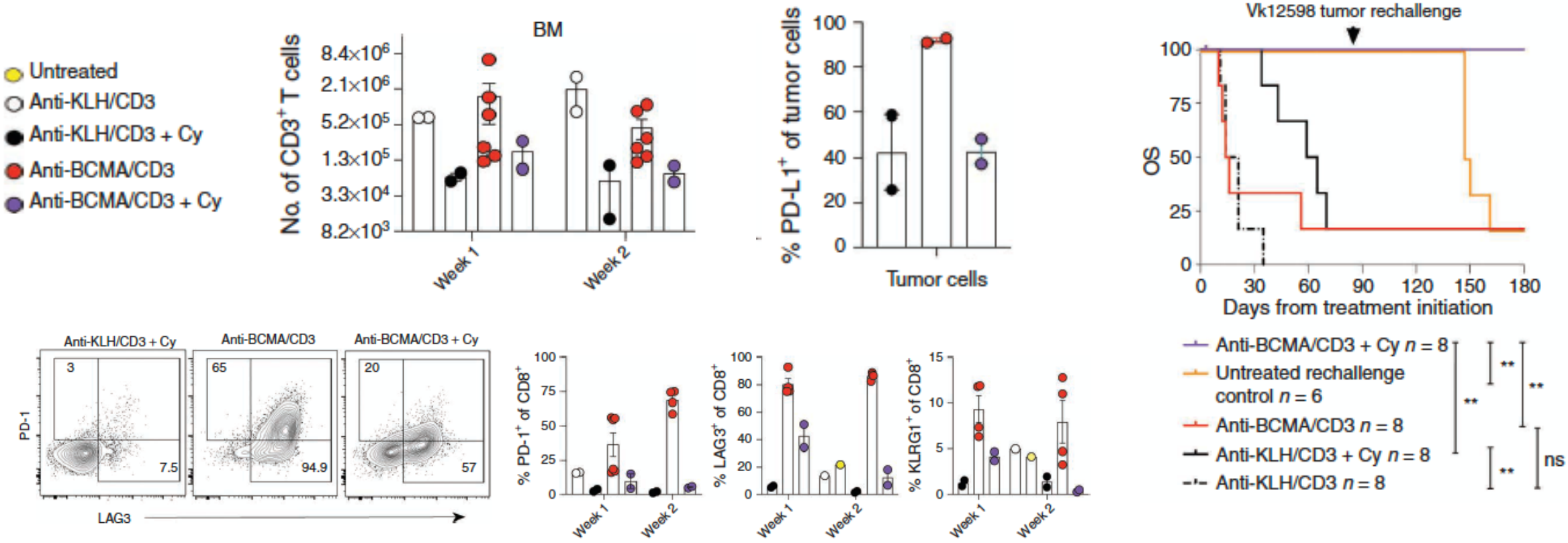
T-cell Exhaustion with BCMAxCD3 Treatment





Meermeier et al, *Cancer Discovery,* 2021

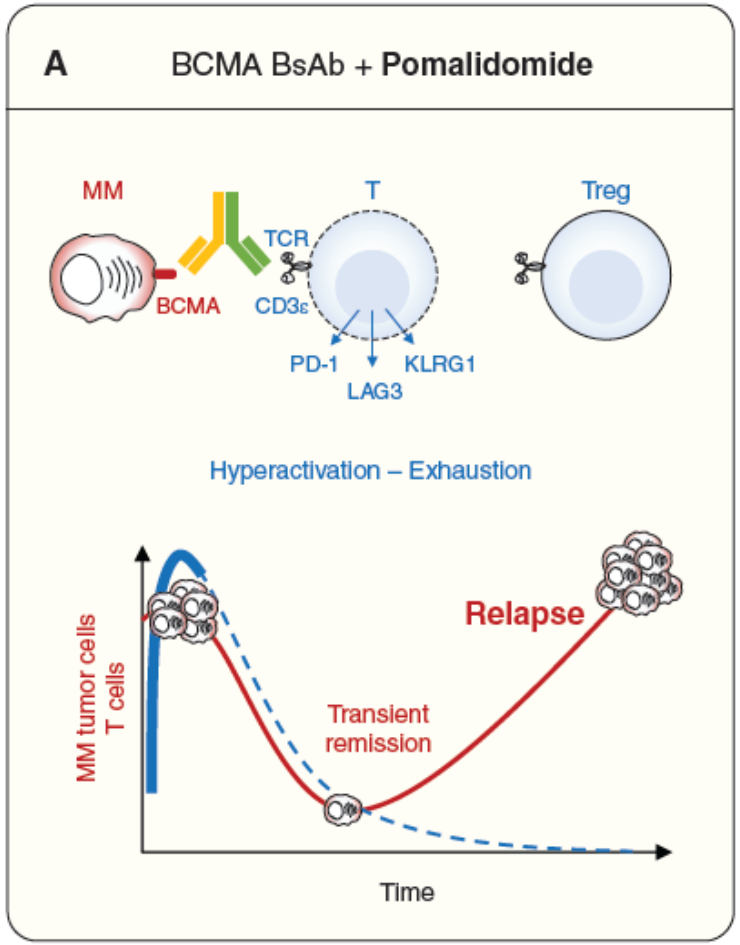
BCMAxCD3 + Cyclophosphamide

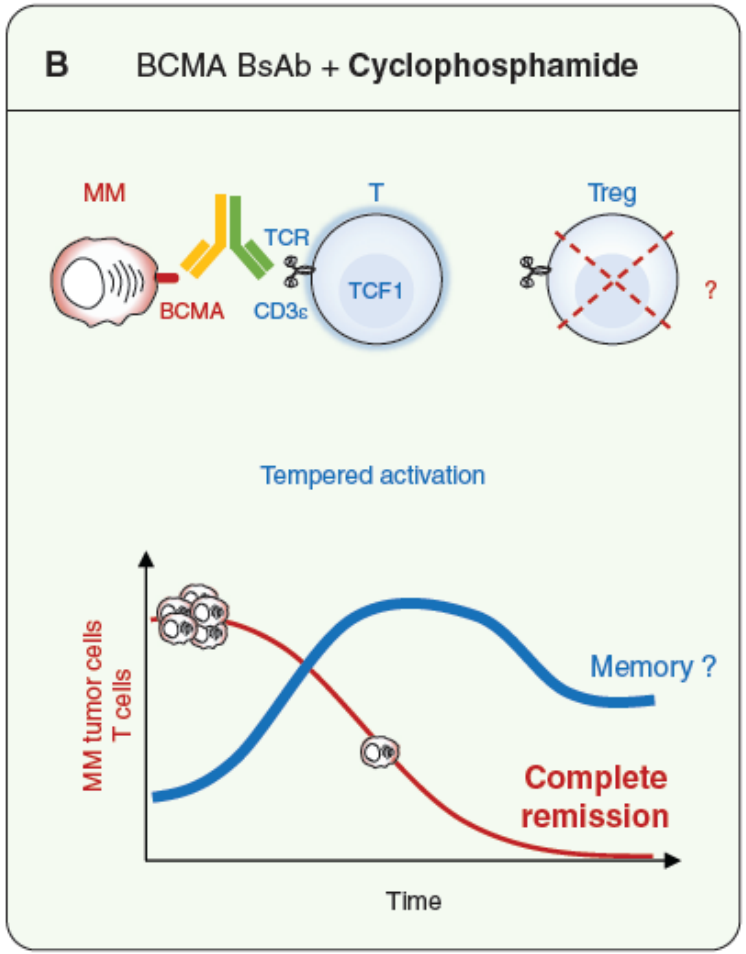


Potential role for debulking and downregulating Tregs with cyclophosphamide for sustaining myeloma tumor response

Meermeier et al, *Cancer Discovery,* 2021

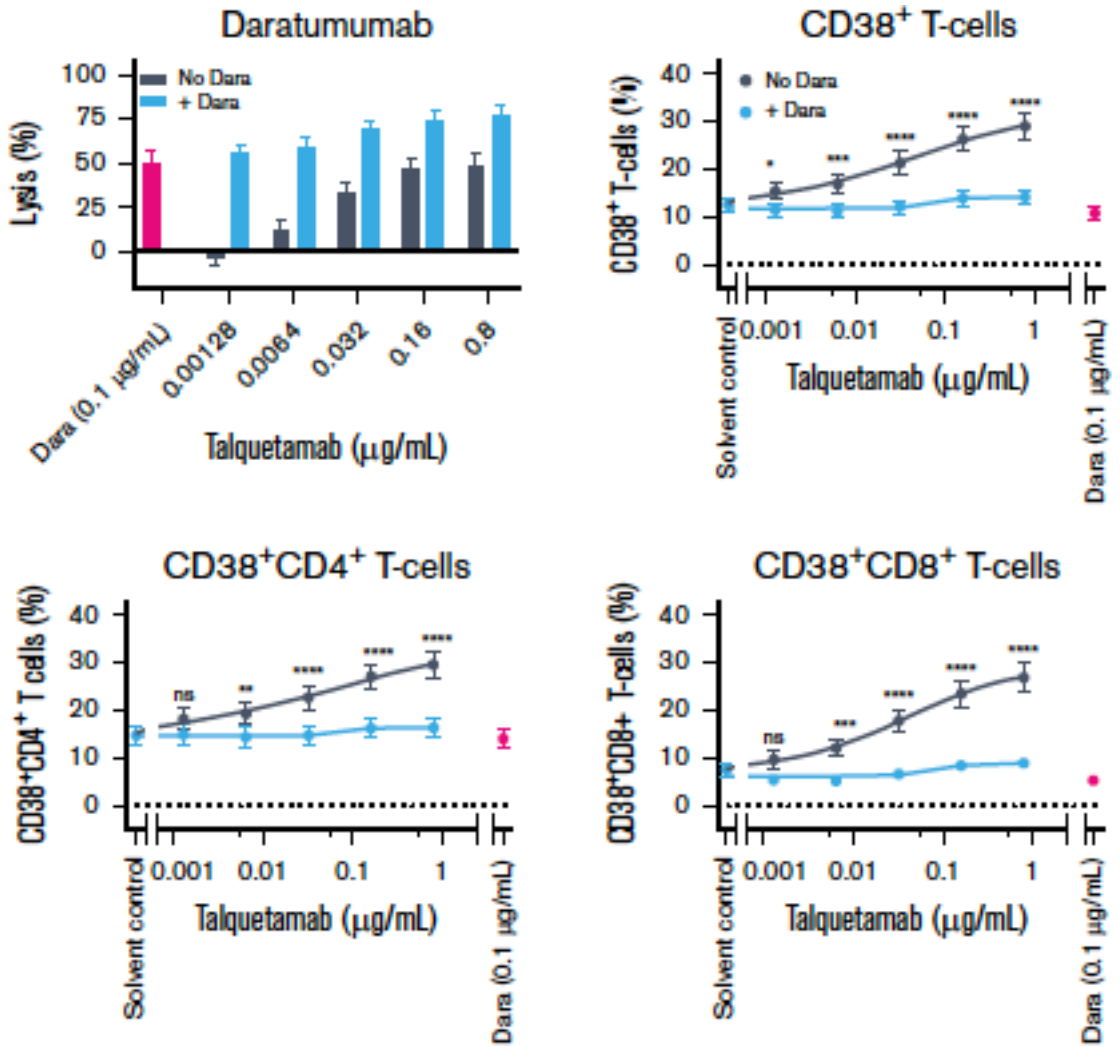
Pacing T-cell Activation





Louvet et al, *Cancer Discovery*, 2021

GRC5DxCD3 (Talquetamab) + anti-CD38 (daratumumab)



Verkleij et al, *Blood Advances*, 2021

GPRC5DxCD3 (talquetamab) + anti-CD38 (daratumumab)

Tal	Dara SC	Patients enrolled to date (n)
400 µg/kg SC Q2W	1800 mg SC Cycles 1-2: QW Cycles 3-6: Q2W Cycles 7+: monthly	5
400 µg/kg SC QW		9
800 µg/kg SC Q2W		15

Characteristic	Tal + Dara SC[a] (n=29)
Prior lines of therapy, median (range)	6 (2-18)
Prior stem cell transplantation, n (%)	18 (62.1)
Exposure status, n (%)	
Prior BCMA therapy[e]	16 (55.2)
Anti-CD38[f]	23 (79.3)
IMiD[g]	28 (96.6)
Triple-class[h]	23 (79.3)
Penta-drug[i]	19 (65.5)
Refractory status, n (%)	
Anti-CD38[f]	19 (65.5)
IMiD[g]	19 (65.5)
Triple-class[h]	15 (51.7)
Penta-drug[i]	9 (31.0)
To last line of therapy	19 (65.5)

Chari et al, *ASH*, 2021

GPRC5DxCD3 (talquetamab) + anti-CD38 (daratumumab)

Tal + Dara SC[a] (n=29)		
AE (≥20%), n (%)	Any Grade	Grade 3/4
Nonhematologic		
CRS	16 (55.2)	0 (0)
Dysgeusia	14 (48.3)	N/A
Dry mouth	10 (34.5)	0 (0)
Pyrexia	8 (27.6)	1 (3.4)
Skin exfoliation	8 (27.6)	0 (0)
Decreased appetite	7 (24.1)	0 (0)
Fatigue	7 (24.1)	0 (0)

Response Categories	Evaluable patients[a], n (%)		
	Dara 1800 mg SC: Cycle 1-2: QW, Cycles 3-6: Q2W; Cycles 7+: monthly		
	Tal 400 µg/kg SC Q2W (n=5)	Tal 400 µg/kg SC QW (n=7)	Tal 800 µg/kg SC Q2W (n=9)
ORR[b]	**4 (80.0)**	**6 (85.7)**	**7 (77.8)**
sCR/CR	1 (20.0)	2 (28.6)	1 (11.1)
VGPR	2 (40.0)	3 (42.9)	5 (55.6)
PR	1 (20.0)	1 (14.3)	1 (11.1)
MR	0 (0)	0 (0)	0 (0)
SD	0 (0)	1 (14.3)	2 (22.2)
PD	1 (20.0)	0 (0)	0 (0)

Chari et al, *ASH*, 2021

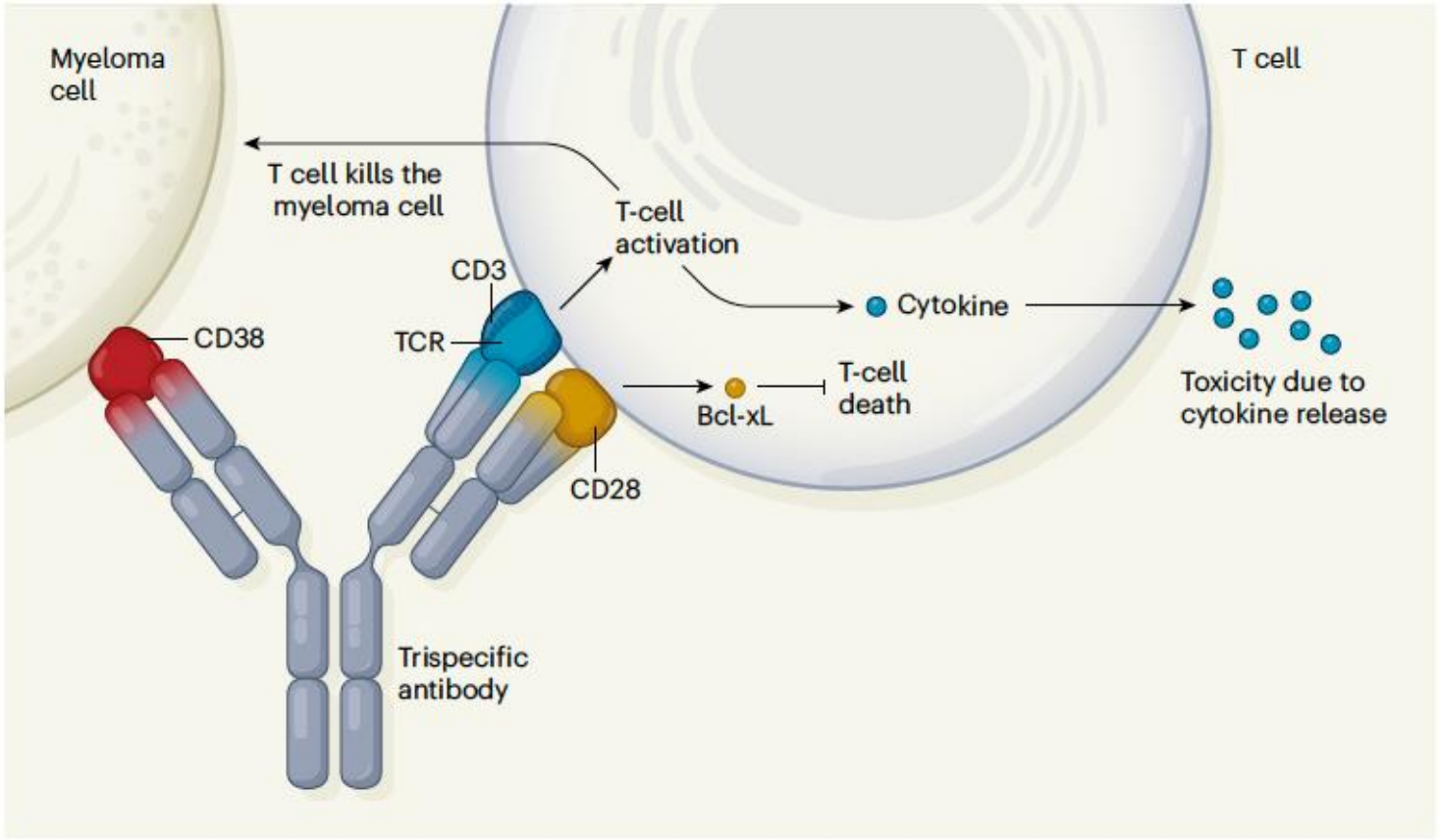
Myeloma Bispecific Antibodies Summary

- **Promising clinical data to date with several BCMA x CD3**
  - "Off-the-shelf" format advantageous over autologous CART products
  - Several BCMA x CD3 bispecifics in clinical development: teclistimab, AMG 701, REGN5458, CC-93269, TNB-383B, and elranatamab
  - Non-BCMA bispecifics: GPRC5D (talquetamab) and FcRH5 (cevostamab)
- **CRS common; Grade 3/4 CRS and neurotoxicity less frequent; severe CRS can be mitigated by step-up dosing strategy**
- **Future directions**
  - Rational combination strategies
    - Gamma secretase inhibitors to increase BCMA antigen density
    - IMiDs to augment immune effector cell function
    - Immune checkpoint blockade to augment T-cell response

    } Need to balance with added CRS risk
  - Maximize CRS mitigation strategies to enhance safety for earlier outpatient administration
  - Interrogate resistance mechanisms (antigen loss, increased Tregs, T-cell exhaustion)
  - Optimal sequencing strategies (induction, consolidation in MRD+ patients, pre- or post- CART?)
  - Multi-antigen targeted T-cell engagers (e.g. tri-specifics); NK-cell bispecifics or trispecifics

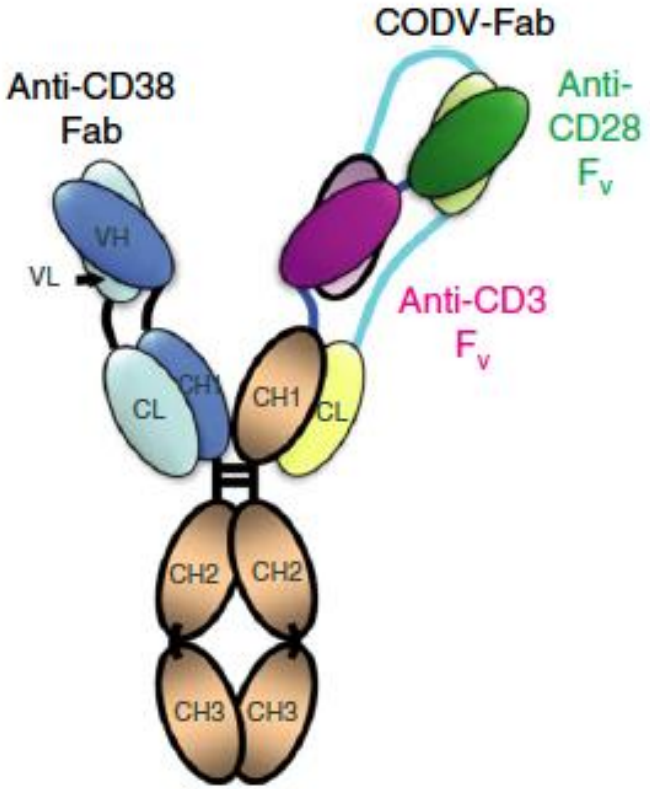
Trispecific Antibodies

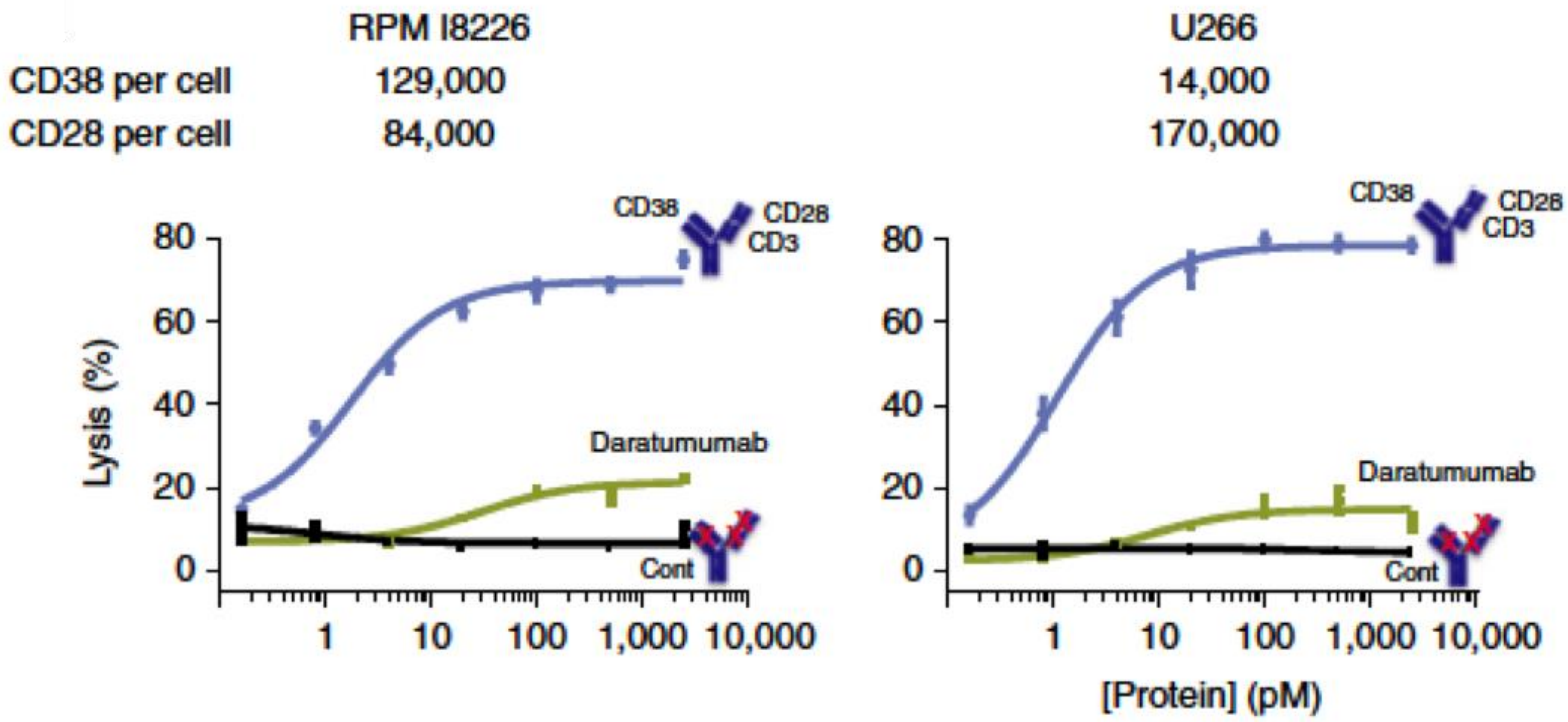
- **Builds on bispecific antibody platform**
- **Allows for recognition of third antigen**
  - Co-stimulation of immune effector cell to mitigate T-cell anergy or exhaustion
  - May also allow for dual targeting of tumor associated antigens



Garfall & June, *Nature,* 2019

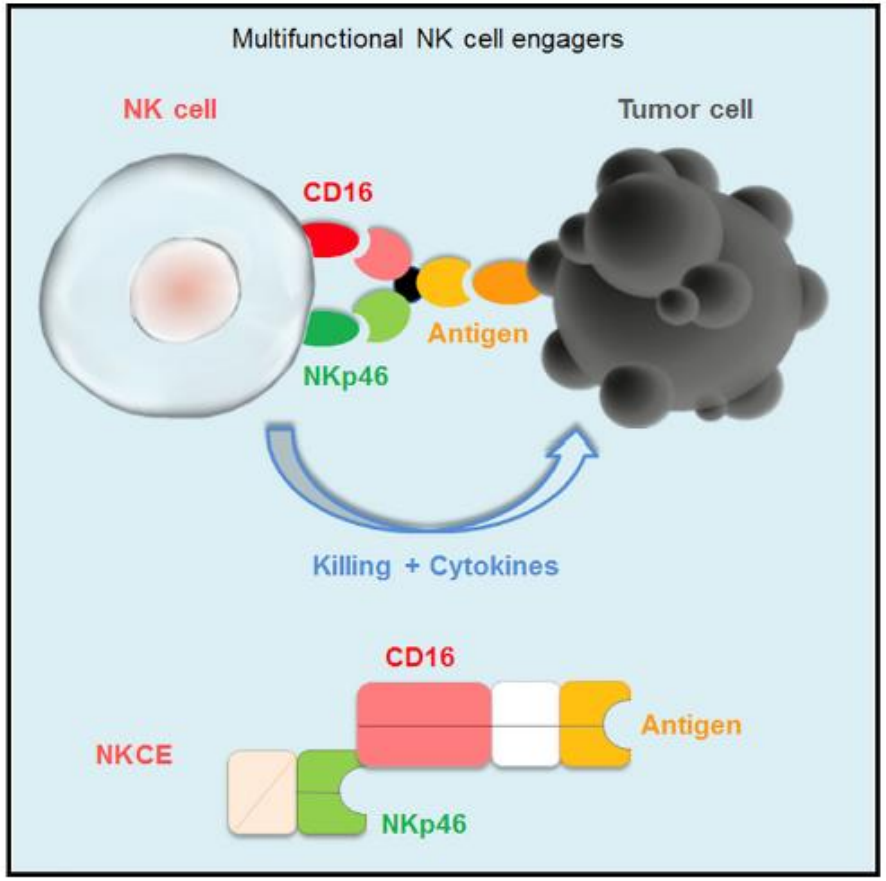
CD38 x CD28 x CD3 Trispecific Antibody

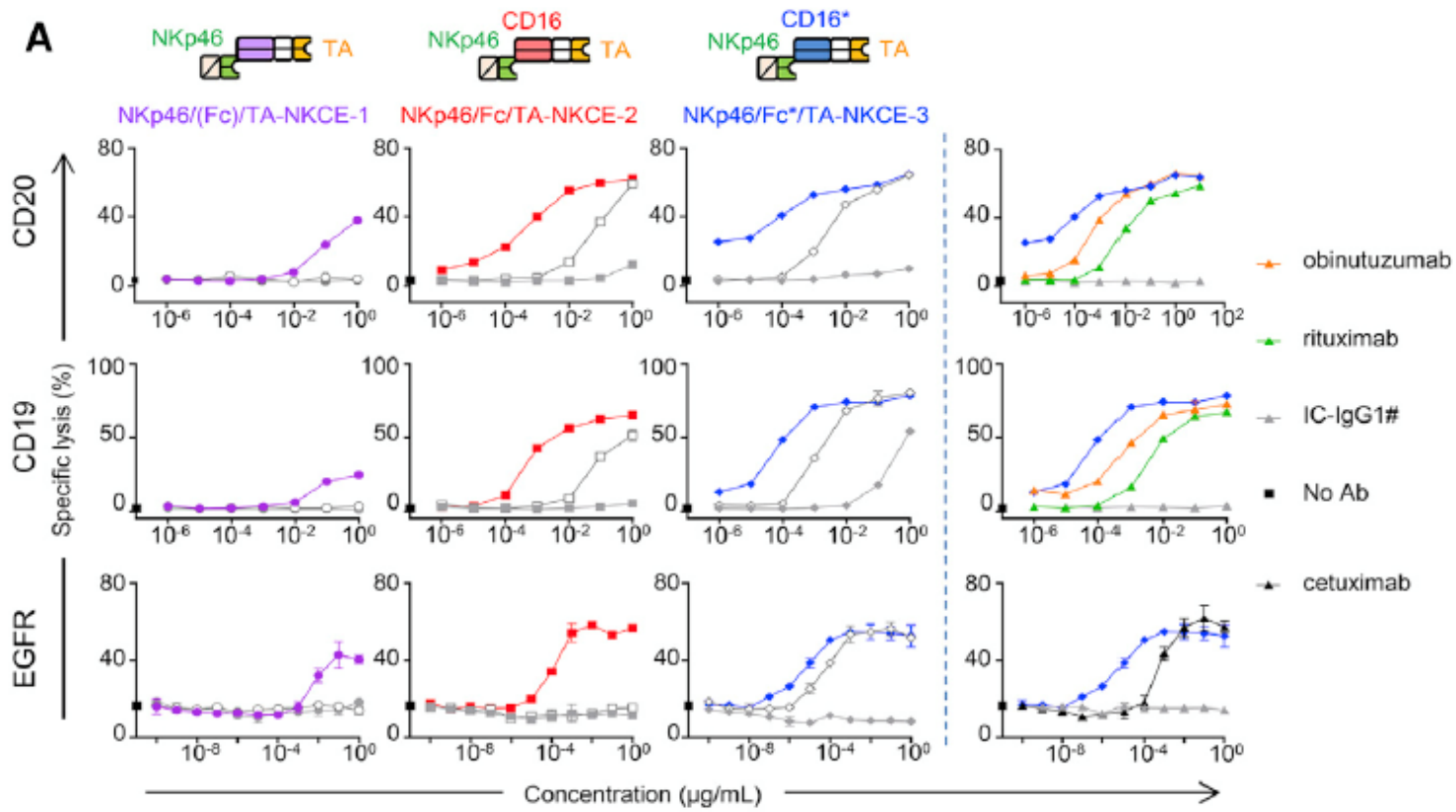




Wu et al, *Nature Cancer,* 2020

Tumor Associated Antigen x CD16 x NKp46





Gauthier et al, *Cell,* 2019

Trispecific Antibodies Summary

- **Allows flexibility to target multiple antigens with single drug rather than using multiple uni-specific antibodies in combination**
- **Very early in clinical development across solid tumors and hematologic malignancies**
  - SAR442257 - CD3xCD28xCD38 (Phase 1, includes myeloma cohort)
  - GTB-3550 - CD16xCD33xIL-15 (Phase 1)
- **Potential to enhance immune effector response and mitigate T-cell anergy or exhaustion**

Myeloma ADCs, Bispecific Antibodies, & CARTs

	ADCs	Bispecific T-cell Antibodies	CARTs
Advantages	▪ Off-the-shelf ▪ Less dependence of endogenous immune effector cells ▪ Can be given in community ▪ No CRS ▪ Can give in elderly/frail patients	▪ Off-the-shelf ▪ Can be given in community ▪ High and deep responses; duration of response yet to be seen	▪ Unprecedented response rates, depth of response, and duration of response with some products ▪ One-time dose (for now)
Disadvantages	▪ Ocular toxicity requiring ancillary ocular supportive care and monitoring ▪ Lower efficacy than bispecifics, CARTs ▪ Continuous therapy	▪ Continuous therapy with more frequent dosing ▪ CRS risk ▪ Hospital admission usually required for first several doses for CRS monitoring ▪ Earlier in development than ADCs and CARTs; long-term outcomes and additional safety data awaited	▪ Not ideal with patients with rapidly progressing disease due to manufacturing time ▪ Cost / **Access** ▪ Bridging therapy often needed ▪ Requires complex infrastructure to administer ▪ CRS, HLH, ICANS risks ▪ Prolonged cytopenias

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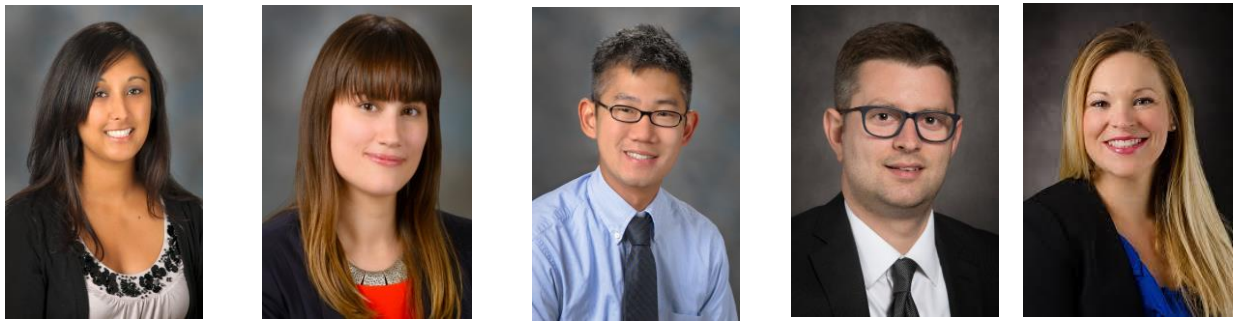
Thank you



MD Anderson Plasma Cell Dyscrasia Group