Debate: BsAb >> CART

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Disclosures

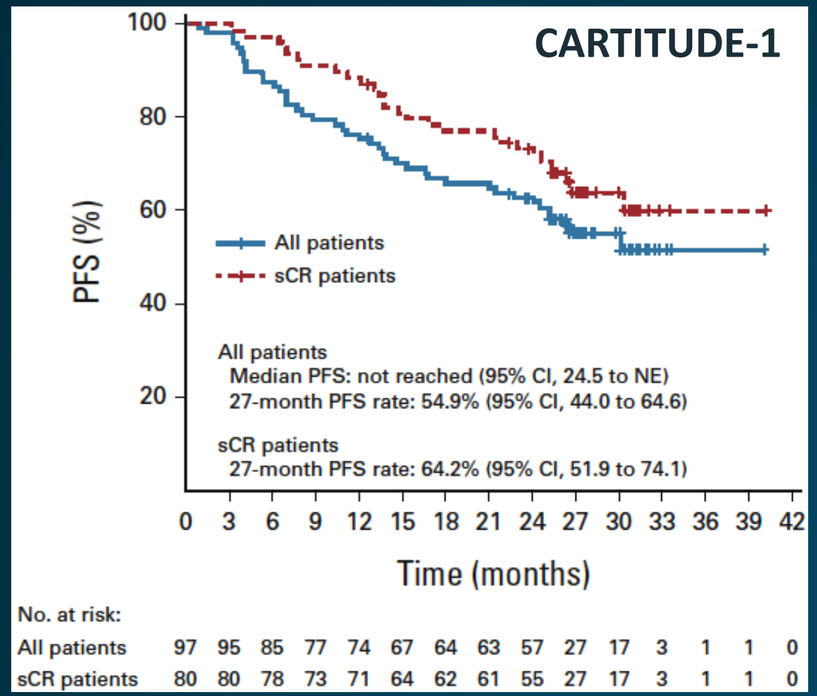
Dr. Hofmeister discloses advisory board involvement with AbbVie, Janssen, Bristol Myers Squibb. He is the primary investigator (PI) for investigator-initiated protocols involving products from Sanofi and is the local PI for company-sponsored protocols from Janssen & Bristol Myers Squibb. He has two patents, one of them surprisingly made some money from Recursion Pharmaceuticals.

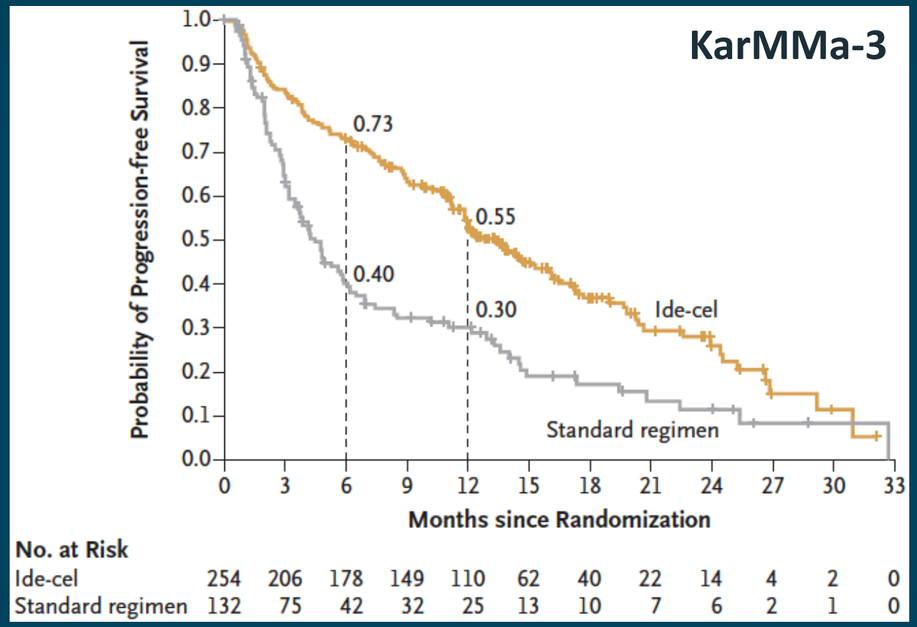
During the course of this lecture, Dr Hofmeister may discuss the use of medications for both FDA-approved and non-approved indications

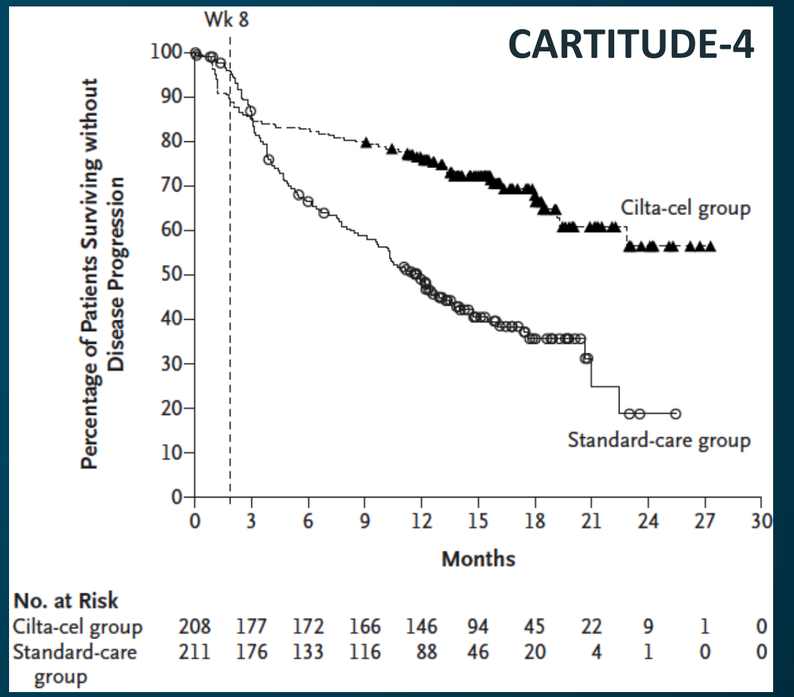
What's the brief and what's my position

Myeloma patient progressing on 4th line therapy, eligible for CART or BsAB

No plateau for CART in Myeloma







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You shouldn’t use CART after alkylator exposure

Feature	Cluster 1	Cluster 2	Cluster 3	Cluster 4
Prior therapies	Recent alkylator, PI, TI ↑ Prior regimens	Recent alkylator, PI, TI	Recent alkylator, PI ↓ Prior regimens	Distant alkylator, PI, TI
Tumor burden	↑ sBCMA/M-protein	↑ sBCMA/M-protein ↑ LDH	↓ sBCMA/M-protein	↓ sBCMA/M-protein
Immune profile	↓ ALC ↑ Mono:Leuk	↑ ALC ↑ Mono:Leuk	↓ ALC ↓ Mono:Leuk	↑ ALC ↓ Mono:Leuk
Patient fitness	↓ Albumin ↓ Creatinine clearance	↓ Creatinine clearance	↑ Creatinine clearance	↑ Albumin ↓ Creatinine clearance
PBMC material	↓ CD3%	↓ CD4:CD8	↑ CD4:CD8 High quality phenotype	↑ CD3%
In-process	↓ Yield ↓ Early cell size	↓ Yield	↑ Yield ↑ Early cell size	↑ Yield
Drug product	↓ CD3/CAR% ↓ VCN	↓ CD3/CAR%	↑ CD3/CAR%	↑ CD3/CAR% ↑ VCN
Efficacy	mPFS: 3 mo CRR: 18%	mPFS: 7.9 mo CRR: 32%	mPFS: 11.7 mo CRR: 50%	mPFS: 14.5 mo CRR: 61%

Low tumor burden, high ALC count, high cell yield, high CD3 count in the cell product, high % of CAR and distant alkylator therapy (ideally > 9 months) were associated with better outcomes after Ide-Cel

Why do CART cells walk off the job in Myeloma?

1) Lymphodepleting chemotherapy
2) CAR design including type of costimulatory domains
3) T-cell culture conditions (mode of gene transfer)
4) Functionality & phenotype of input T-cells (number of prior therapies, diversity)
5) Cell product composition
6) CAR signaling
7) Stromal cells protect MM against CART in tumor microenvironment
8) Immune-mediated rejection (You can’t retreat with Ide-Cel or Cilta-Cel)

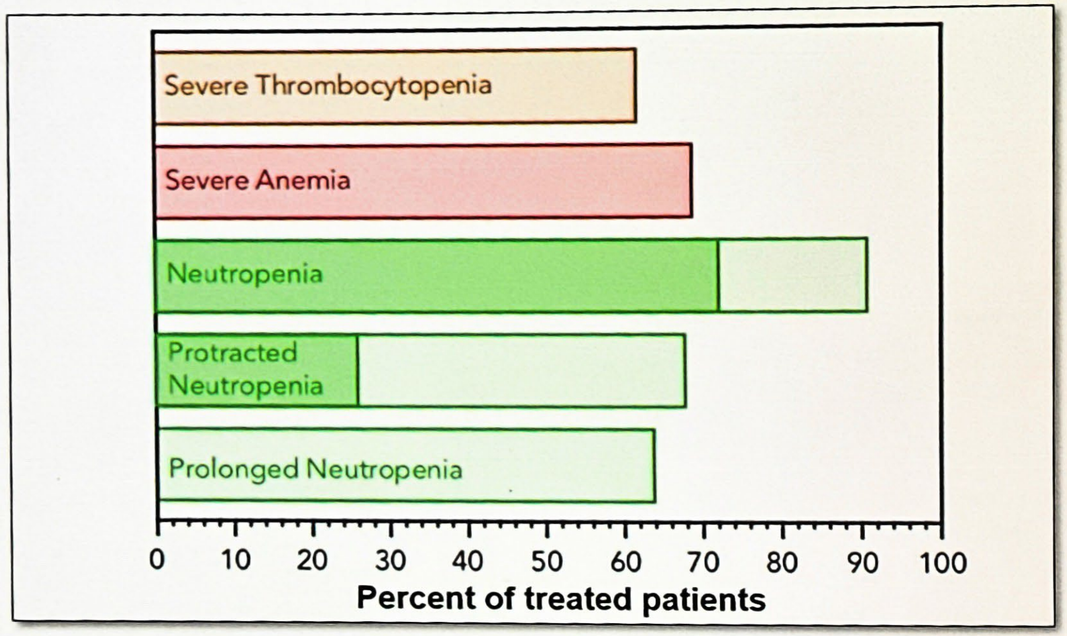
Munshi NEJM 2021, Table S16

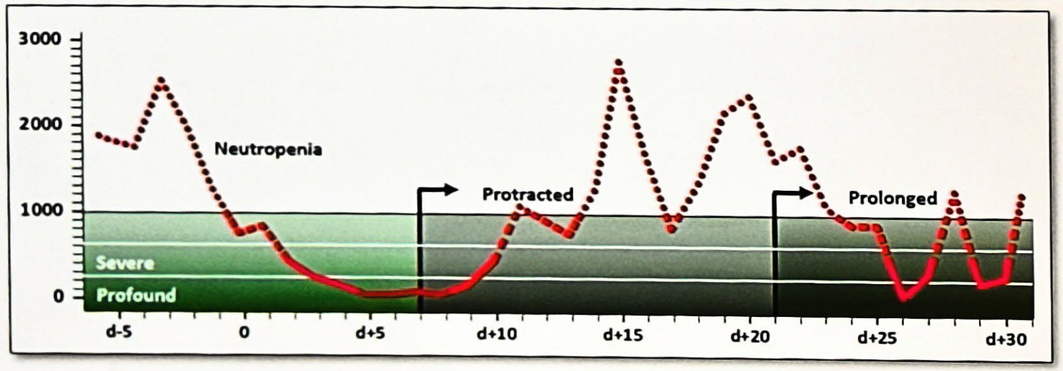
What is the Achilles heel for ‘real world’ CART?

High incidence of severe and prolonged cytopenia post CD19 CART in RWE

Clinical features: CAR T-cell mediated hematotoxicity	Pooled (n = 235)
Severe Thrombocytopenia (PLT Count < 50 G/l)	145 (62%)
Anemia (Hb <8 g/dl or requiring transfusion)	162 (69%)
Neutropenia*	
Severe (ANC ≤ 500/µl)	213 (91%)
Profound (ANC ≤ 100/µl)	169 (72%)
Protracted, severe (ANC ≤ 500/µl, ≥ 7 days)	160 (68%)
Protracted, profound (ANC ≤ 100/µl, ≥ 7 days)	60 (26%)
Prolonged (ANC ≤ 1000/µl measured ≥ 21 days after CAR transfusion)	151 (64%)

*According to IDSA consensus guidelines for cancer-related infection risk (Taplitz et al, JCO 2018)





Rejeski et al, Blood 2021

CAR-HEMATOTOX SCORE

Features	0 Point	1 Point	2 Points
Platelet Count	> 175.000/µl	75.000 - 175.000/µl	< 75.000/µl
Absolute Neutrophil Count (ANC)	> 1200/µl	< 1200/µl	-
Hemoglobin	> 9.0 g/dl	< 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	> 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650-2000 ng/ml	> 2000 ng/ml
Low: 0-1 **High: ≥ 2**			

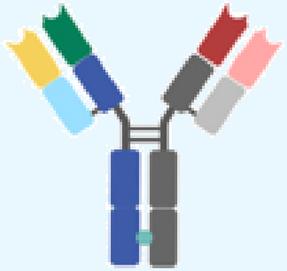
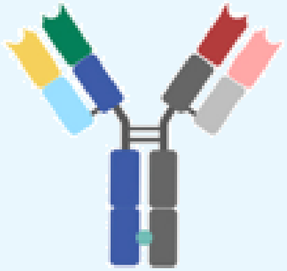
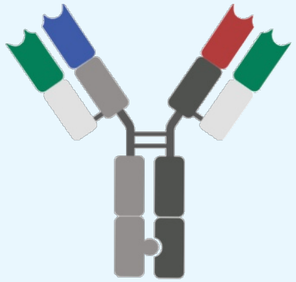
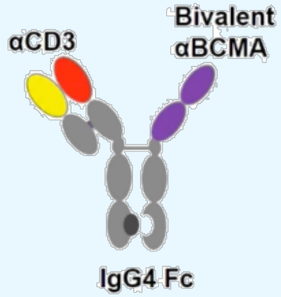
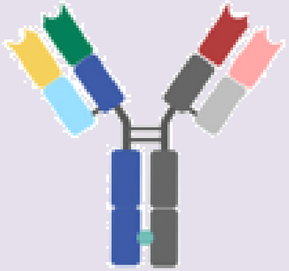
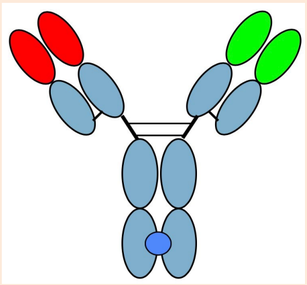
Low Risk (HT 0-1)

High Risk (HT 2-7)

	LBCL (n=235)	MCL (n=103)	MM (n=113)
Median duration of severe neutropenia (ANC<500/µL, D0-60)	5.5 days (95% CI 5-8 days)	6 days (95% CI 5-7 days)	3 days (95% CI 2-5 days)
Aplastic Phenotype	2.6%	0%	3%
Severe Infection Rate	8%	5%	5%
Severe Bacterial Infection Rate	0.9%	5%	3%

	LBCL (n=235)	MCL (n=103)	MM (n=113)
Duration of severe neutropenia (ANC <500/µL day 0-60)	12 days (95% CI 10-16 days)	14 days (95% CI 9-18 days)	9 days (95% CI 7-13 days)
Aplastic Phenotype	36%	47%	32%
Severe Infection Rate	40%	30%	40%
Severe Bacterial Infection Rate	27%	28%	34%

Overview of Bispecific Antibodies in Multiple Myeloma

Elranatamab (anti-BCMA)	Teclistamab* (anti-BCMA)	Linvoseltamab (anti-BCMA)	TNB-383B (anti-BCMA)	Talquetamab (anti-GPRC5D)	Cevostamab (anti-FcRL5/FcRH5)
IgG2a Fc	IgG1 Fc	Fc region Fab arms	IgG4 Fc	IgG1 Fc	IgG1 Fc
					

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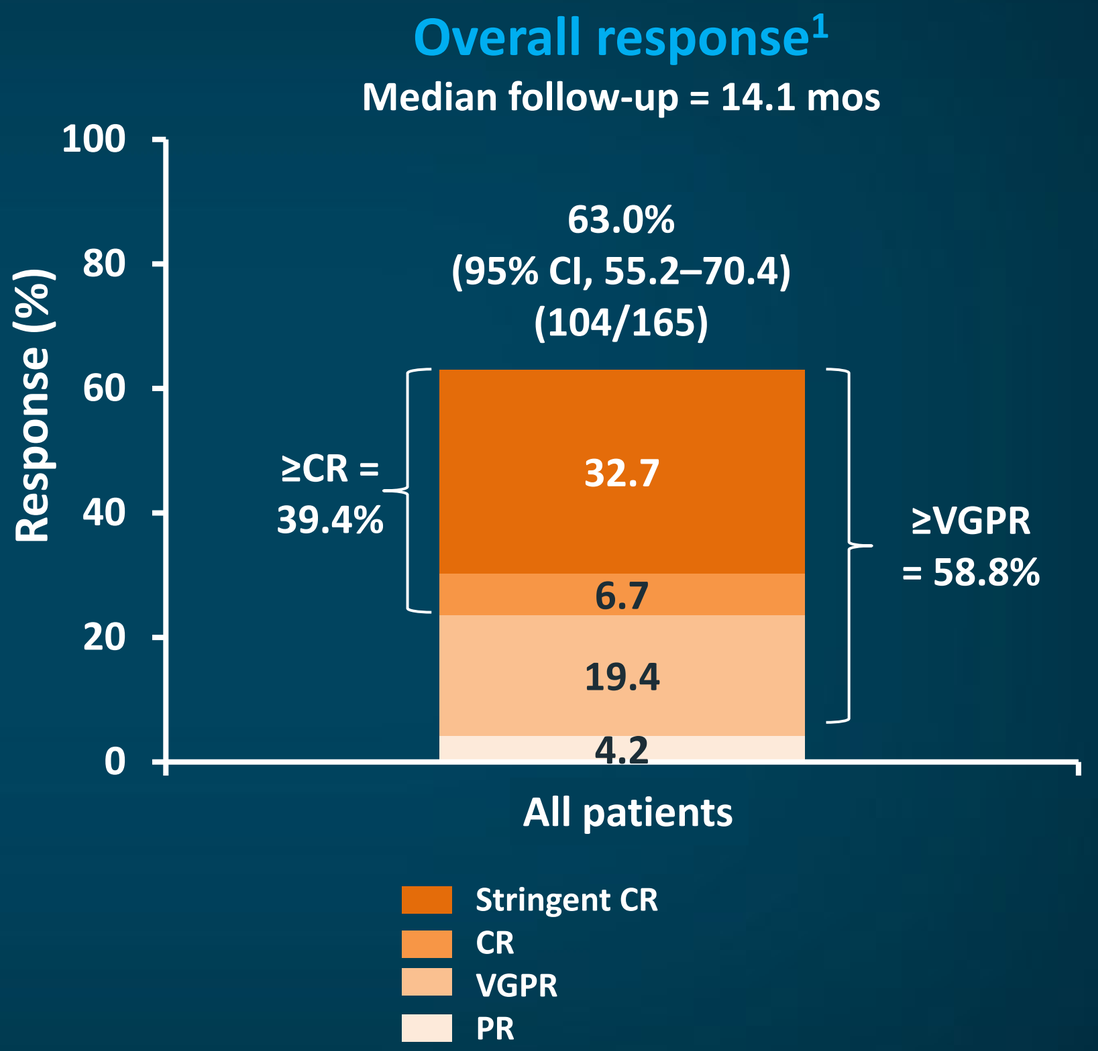
Teclistamab: MajesTEC-1 Trial Efficacy Results

- MajesTEC-1
  - 2 step-up doses of 0.05 mg/kg and 0.3 mg/kg; then 1.5 mg/kg SC weekly
  - ORR = 63.0%; 39.4% had CR or better[1]
  - Median DoR = 18.4 mos[1]
  - Median PFS = 11.3 mos[1]
- In separate study of 38 patients with prior BCMA-targeted treatment, ORR = 40% but 26% developed grade 3–4 infections[2]

Teclistamab was **approved** on October 25, 2022 under accelerated approval for adult patients with RRMM who have received **at least 4 prior lines of therapy**, including a PI, an IMiD, and an anti-CD38 monoclonal antibody[3]

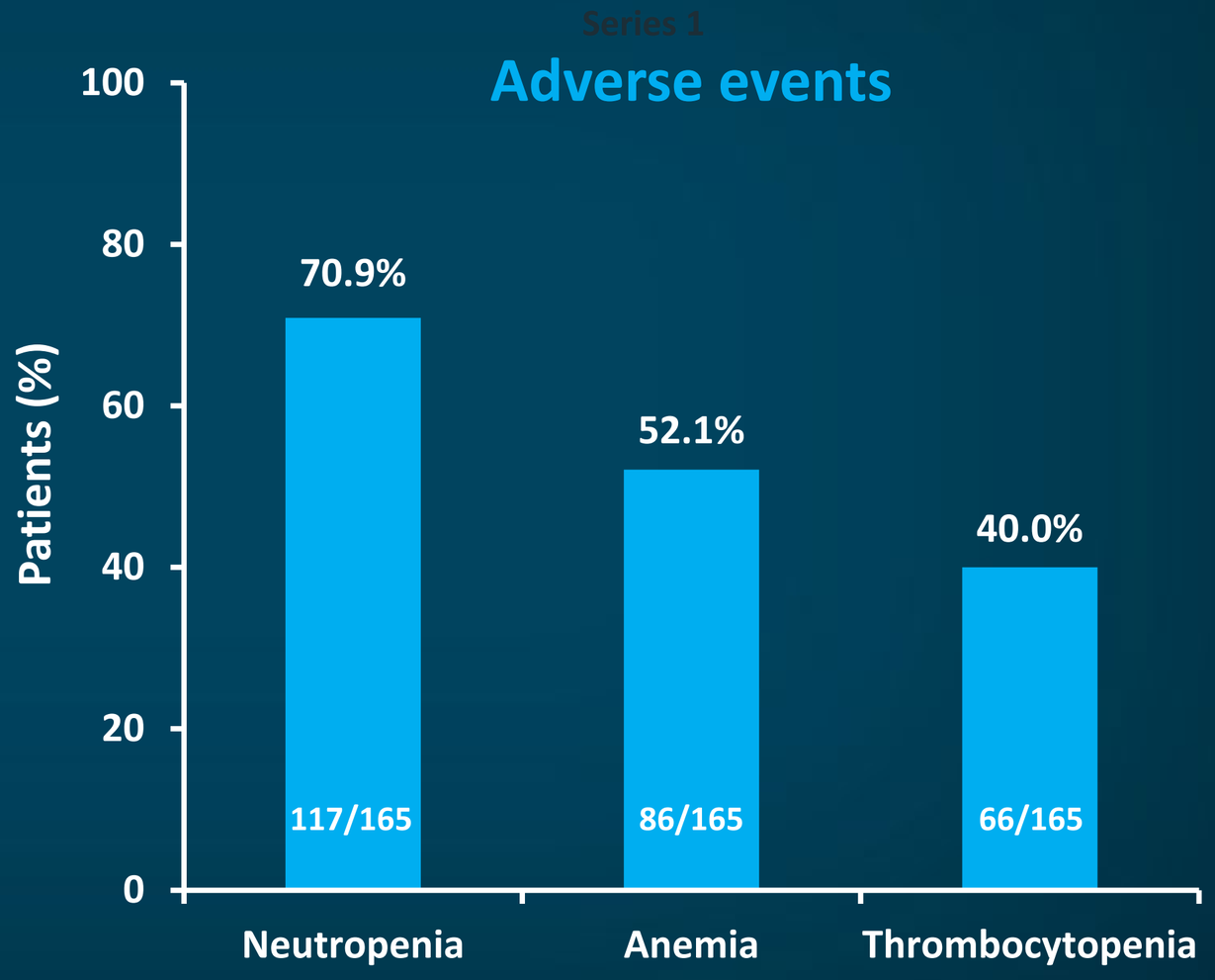


SC = subcutaneous(ly).

1. Moreau P, et al. *N Engl J Med*. 2022;387:495-505. 2. Touzeau C, et al. *J Clin Oncol*. 2022;40(16 suppl): abstract 8013. 3. United States (US) Food and Drug Administration (FDA). Teclistamab approval 10/25/2022 (www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-teclistamab-cqyv-relapsed-or-refractory-multiple-myeloma). Accessed 2/21/2023.

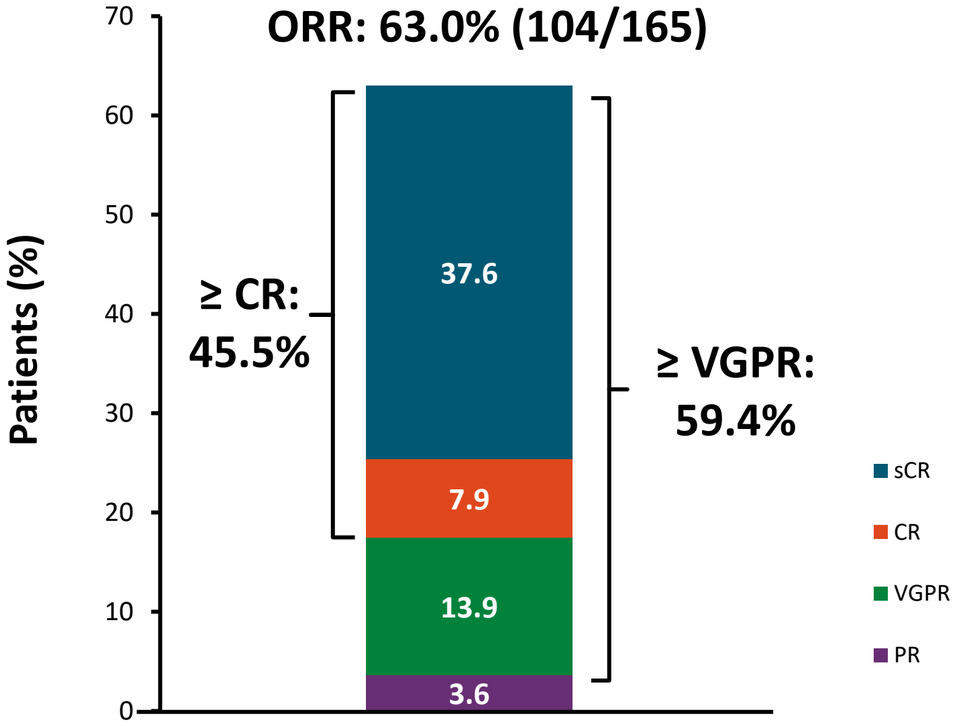
Teclistamab: MajesTEC-1 Trial Safety Results

- Cytokine release syndrome = 72.1%; grade 1 (50.3%), grade 2 (21.2%)
  - 33% of patients had ≥2 CRS events
  - 36.4% of patients with CRS required tocilizumab
- Neurotoxic events: 14.5%
- Infections: 44.8% grade 3–4; 123 patients (74.5%) had evidence of hypogammaglobulinemia
- Cytopenias
  - Neutropenia (grade 3 or 4, 64.2%)
  - Anemia (grade 3 or 4, 37.0%)
  - Thrombocytopenia (grade 3 or 4, 21.2%)

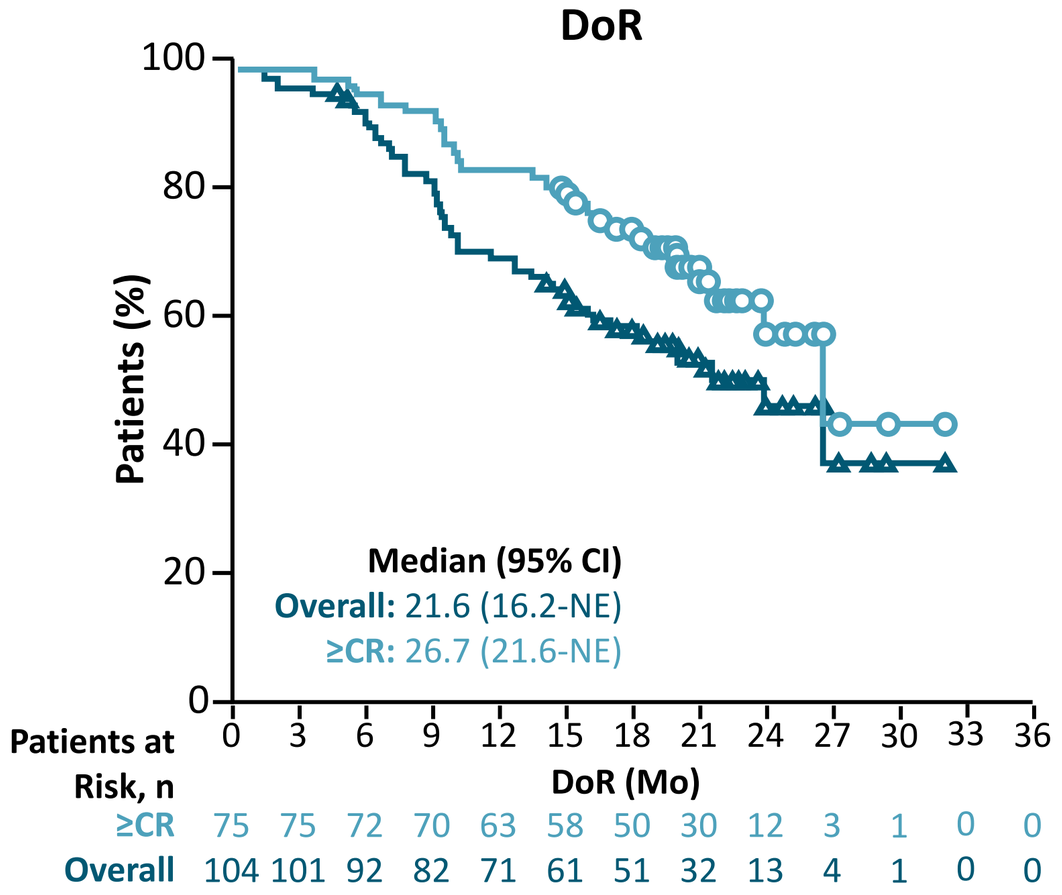


Moreau P, et al. *N Engl J Med*. 2022;387:495-505 and supplement.

MajesTEC-1 (ASCO 23 Update)



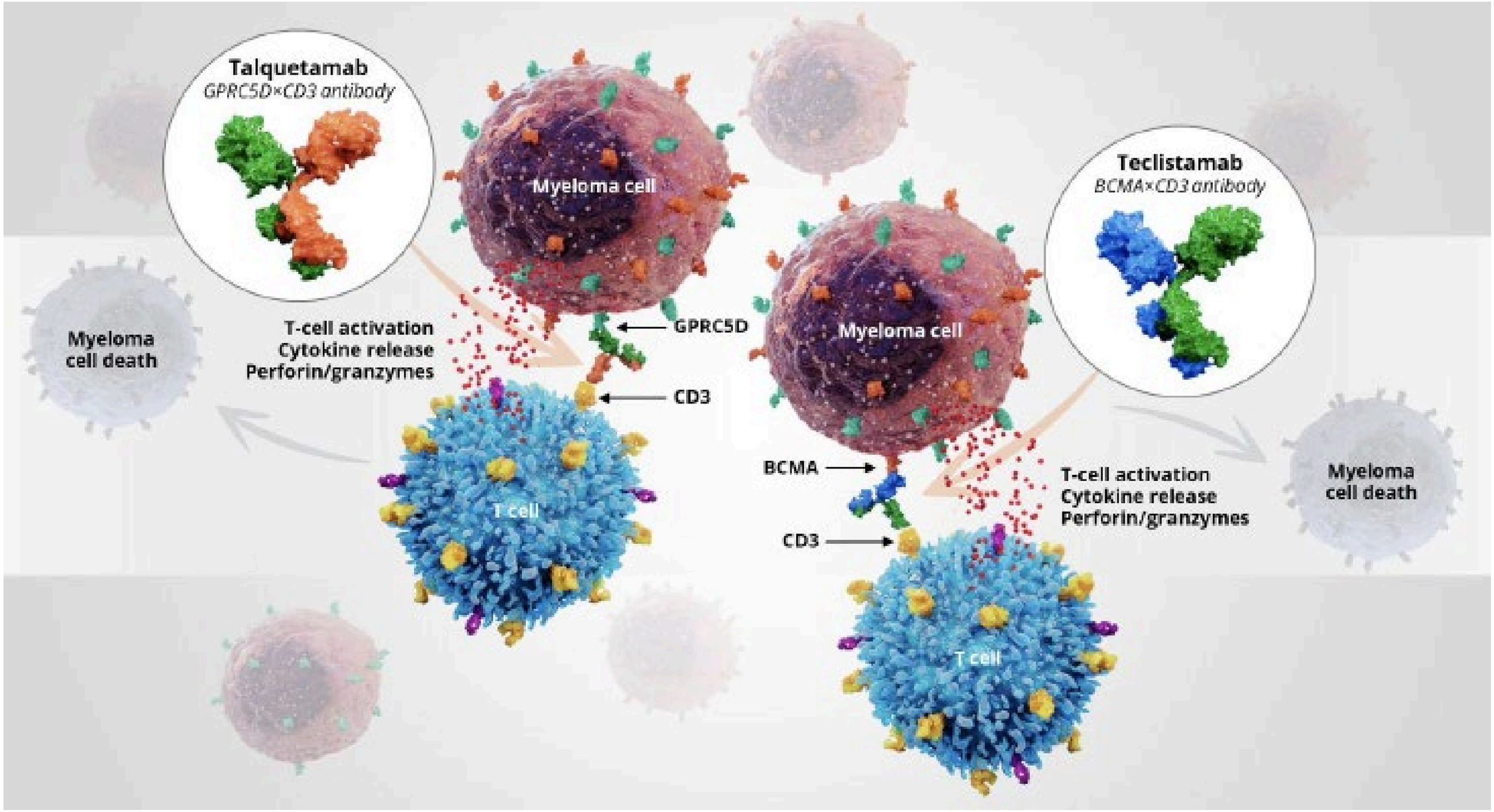
Patient Subgroup	ORR, % (n/N)
≤3 prior lines of treatment	74.4 (32/43)
>3 prior lines of treatment	59.0 (72/122)
High-risk cytogenetics and/or EMD	53.3 (32/60)



- Median time to ≥ CR: 4.6 mo (range: 1.6-18.5)

van de Donk. ASCO 2023. Abstr 8011.

RedirectTT-1: Teclistamab + Talquetamab

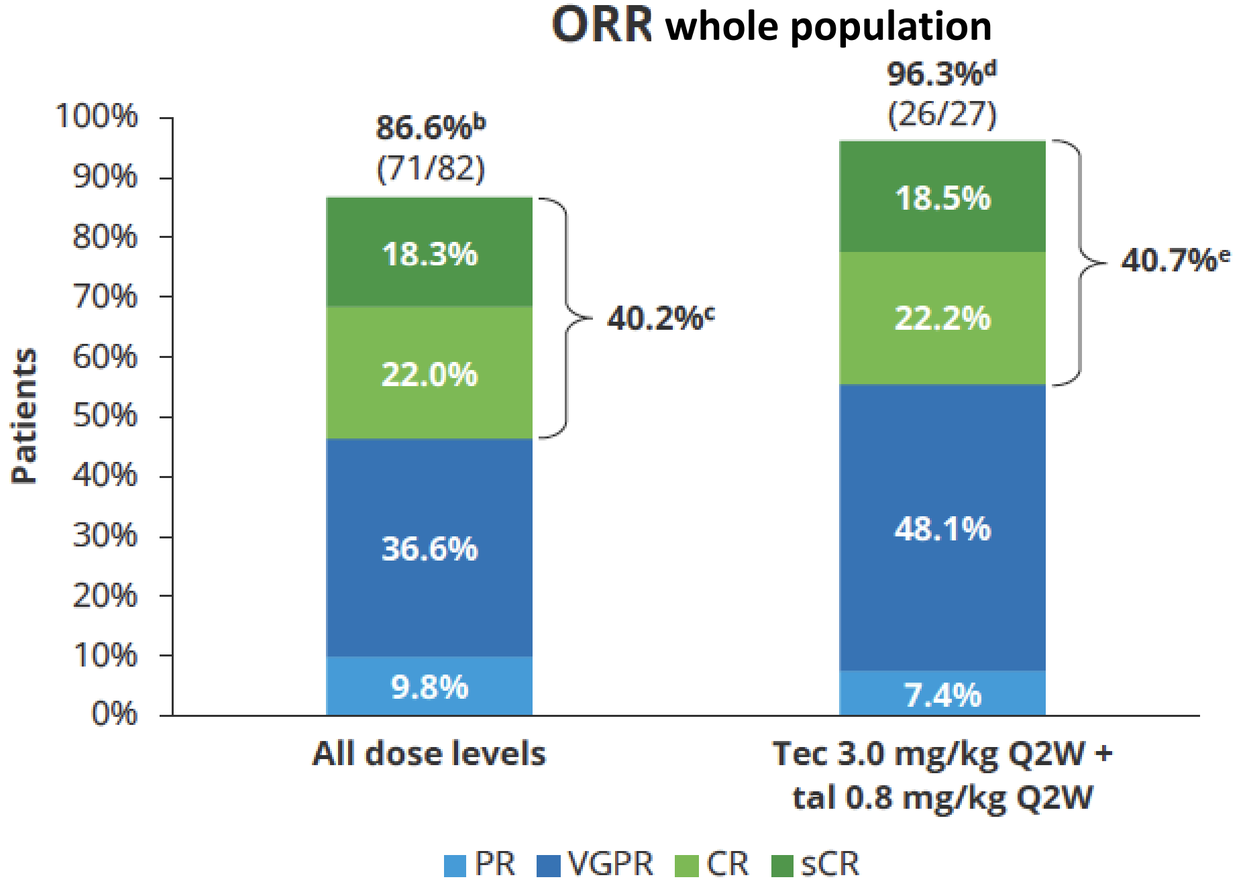


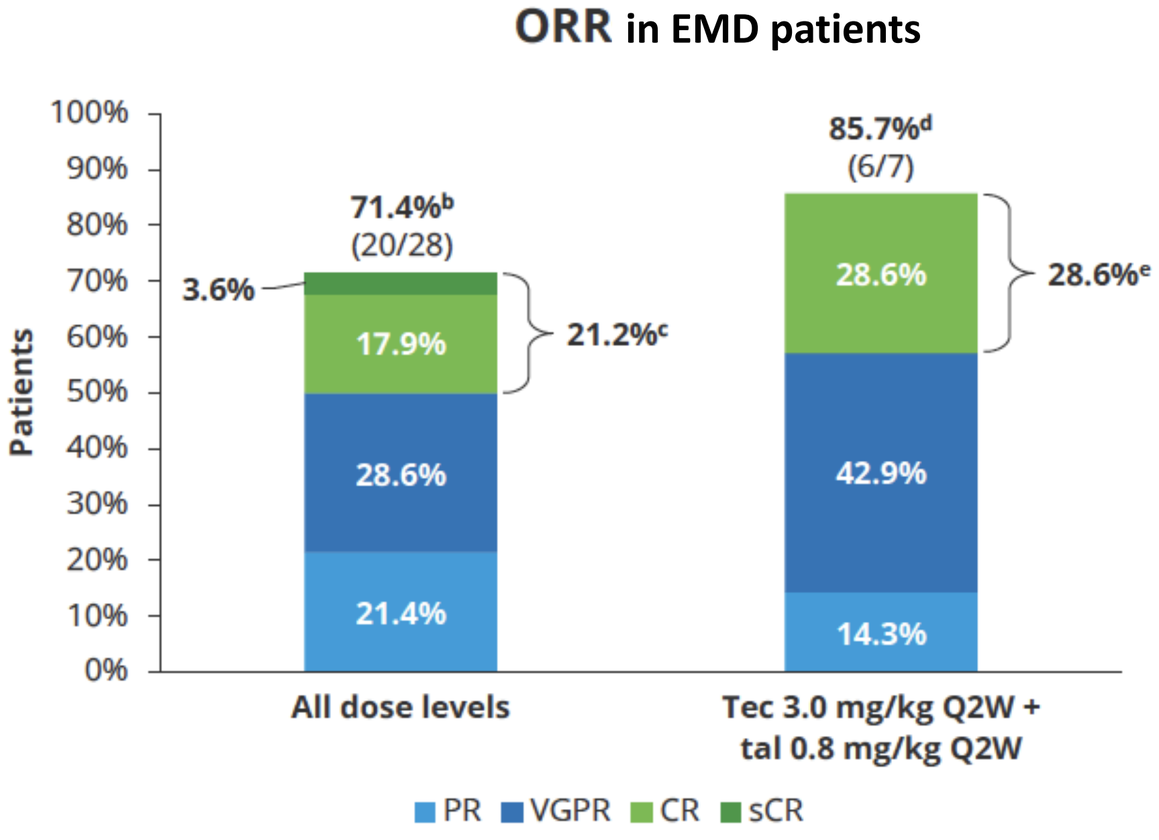
RedirectTT-1: Teclistamab + Talquetamab

TEAE[a] (≥20% overall), n (%)	All dose levels (N=93)		Tec 3.0 mg/kg Q2W + tal 0.8 mg/kg Q2W (n=34)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic TEAEs				
Neutropenia	61 (65.6)	57 (61.3)	19 (55.9)	15 (44.1)
Anemia	47 (50.5)	32 (34.4)	11 (32.4)	8 (23.5)
Thrombocytopenia	40 (43.0)	27 (29.0)	11 (32.4)	8 (23.5)

- Febrile neutropenia in 12.9% of patients across all dose levels, including 8.8% at the RP2R
- No discontinuations due to hematologic TEAEs

RedirectTT-1: Teclistamab + Talquetamab - response





Cohen. ASCO 2023. Abstr 8002.

RedirectTT-1: Teclistamab + Talquetamab - toxicity

Adverse Event, n (%)	All Dose Levels n = 93		Tec 3 mg/kg + Tal 0.8 mg/kg Q2W n = 34	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TEAE	90 (97)	82 (88)	32 (94)	27 (79)
CRS	71 (76)	3 (3)	25 (74)	0
Infections	78 (84)	49 (53)	27 (79)	13 (38)
Neutropenia	61 (66)	57 (61)	19 (56)	15 (44)
Anemia	47 (51)	32 (34)	11 (32)	8 (24)
Thrombocytopenia	40 (43)	27 (29)	11 (32)	8 (24)

- The majority of CRS events occurred during step-up dosing or cycle 1
- 5 ICANS events in 3 patients – 1 was grade 3

TEAE[a] (≥25% overall), n (%)	All dose levels (N=93)		Tec 3.0 mg/kg Q2W + tal 0.8 mg/kg Q2W (n=34)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Nonhematologic TEAEs				
CRS	71 (76.3)	3 (3.2)	25 (73.5)	0
Dysgeusia[b,c]	57 (61.3)	–	16 (47.1)	–
Pyrexia	47 (50.5)	2 (2.2)	13 (38.2)	1 (2.9)
Skin toxicity[d]	50 (53.8)	0	18 (52.9)	0
Nail disorders[e]	43 (46.2)	0	14 (41.2)	0
Diarrhea	38 (40.9)	2 (2.2)	14 (41.2)	1 (2.9)

	All dose levels (N=93)	Tec 3.0 mg/kg Q2W + tal 0.8 mg/kg Q2W (n=34)
Patients with CRS,[a] n (%)	71 (76.3)	25 (73.5)
Time to onset (days)[b], median (range)	2 (1–5)	2 (1–4)
Duration (days), median (range)	2 (1–8)	2 (1–4)
Patients who received supportive measures,[c] n (%)		
Tocilizumab[d]	25 (26.9)	7 (20.6)
Steroids	4 (4.3)	0
Oxygen	7 (7.5)	0
Vasopressor	1 (1.1)	0

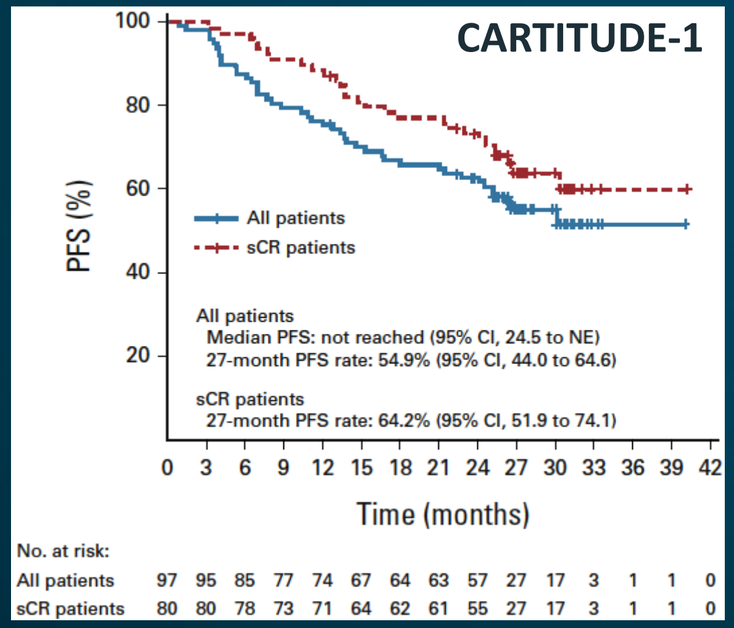
Cohen. ASCO 2023. Abstr 8002.

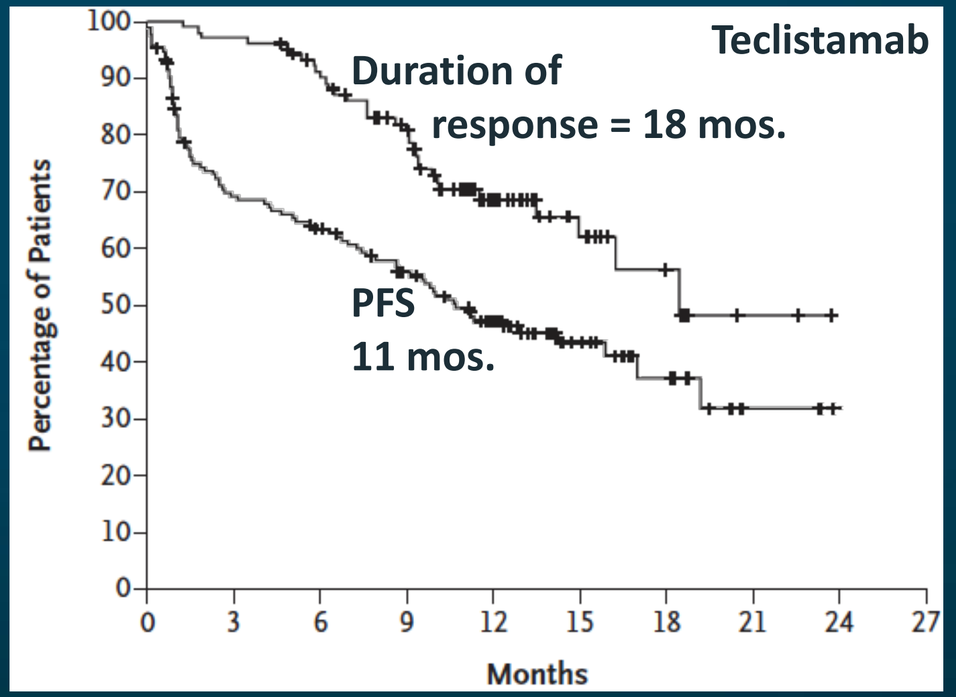
What safety precautions are we taking now with BsAb's?

Condition	Preventative intervention
Viral hepatitis	Check Hep B diagnostic profile (C1D1), then entecavir or similar if HepB Core Ab +ve
Hypogammaglobulinemia	IVIG monthly while on BsAb starting with second outpatient cycle
Neutropenia	• G-CSF (5 mcg/kg) for grade 3+ neutropenia, TIW initially, then dose reduce to achieve trough ANC > 800. If ANC<500, recommend Levaquin; • If patient has allergies, intolerance, or prolonged QTc, then 2nd choice of cefpodime or doxycycline
CMV/EBV	• Check CMV & EBV PCR inpatient cycle 1 day 1, then q2 weeks; at 3 months, decrease to monthly. • At 6 months, just CMV PCR monthly
PJP	• PJP prophylaxis with Bactrim (preferred), Dapsone (2nd line); • If G6PD deficient attempt Atovaquone (preferred) or IV pentamidine monthly (2nd line)

Why should you use Teclistamab and not Cilta-Cel or Ide-Cel?

- No preconditions – they work no matter what you've been on.
- When the going gets tough, these antibodies get to work. CART's lead to prolonged pancytopenia
- CARTITUDE-1 had a selection bias. Your patients deserve treatment **now**.





Thank you!