HEIDELBERG
UNIVERSITY
HOSPITAL

Heidelberg
Myeloma Center

Bispecific Antibodies in Multiple Myeloma

Prof. Marc S. Raab, MD

Director, Heidelberg Myeloma Center

Dept. of Internal Medicine V (Haematology, Oncology, Rheumatology)

Heidelberg University Hospital &

German Cancer Research Center (DKFZ)

Offenlegung potentieller Interessenkonflikte

1. Anstellungsverhältnis oder Führungsposition

keine

2. Beratungstätigkeit

Amgen, Janssen, BMS, Sanofi, GSK, Oncopeptides, Stemline

3. Aktienbesitz

keiner

4. Honorare

Amgen, Janssen, BMS, Sanofi, GSK

5. Finanzierung wissenschaftlicher Untersuchungen

Janssen, Sanofi, Heidelberg Pharma

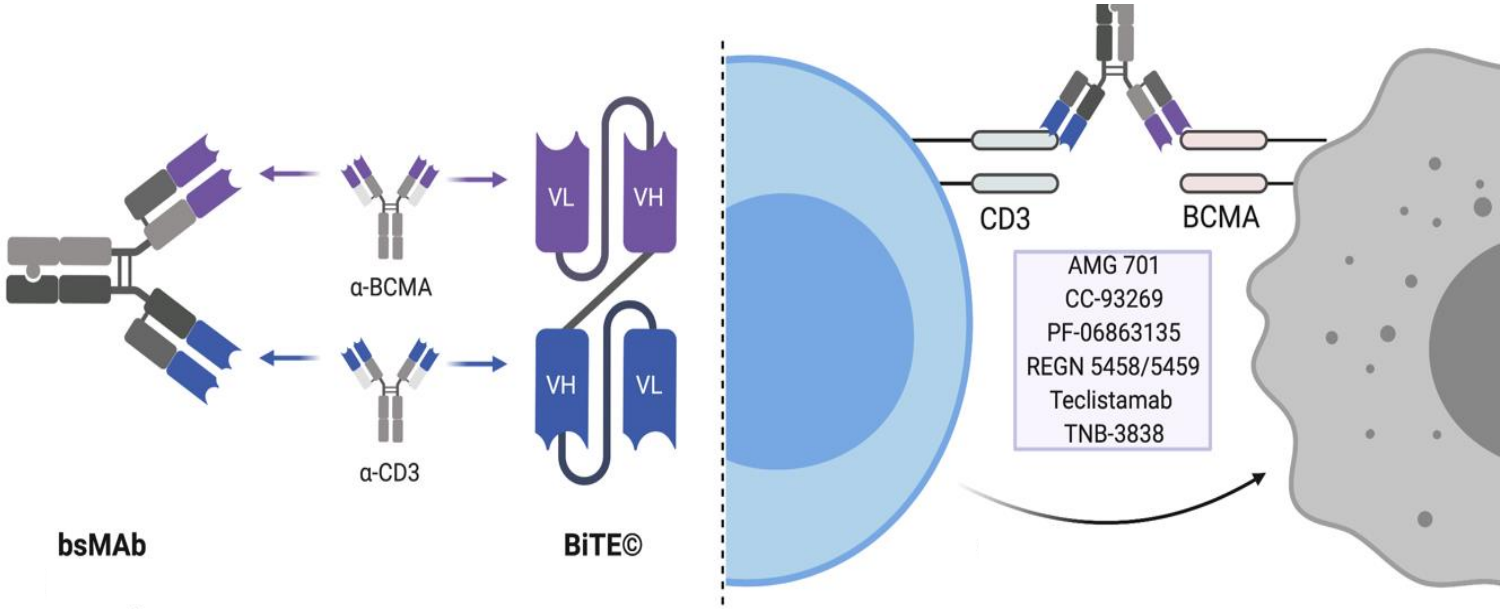
6. Gutachtertätigkeit

keine

7. Andere finanzielle Beziehungen

keine

Novel immunotherapies: Bispecific antibodies



- Bispecific antibody constructs are engineered to have **dual antigen specificity**
- They facilitate **cell-to-cell interactions** between the patients' own **T cells** and the **malignant cells**
- They have specificity for the T-cell receptor **CD3** and **BCMA** on the myeloma cell
- This engagement leads to the **formation** of a **cytolytic synapse** between the T cell and the BCMA-expressing myeloma cell, and the subsequent **lysis of the myeloma cell**

- BCMA, B-cell maturation antigen; BiTE, bispecific T-cell engager; MM, multiple myeloma; mAb, monoclonal antibody; TCR, T-cell receptor.
- Shah N, et al. *Leukemia.* 2020; 34:985-1005.

Helpful Information for Daily Practice

- **BCMAxCD3-binding: Teclistamab and Elranatamab**
- **GPRC5DxCD3-binding: Talquetamab**

Focus:

- **Adverse Events of Special Interest,**
- **Risk of Infection**
- **Prophylactic Measures**

Debate: In Favor of TCEs (vs. CARs)

Overview of Bispecific Antibodies at ASCO/EHA 2023

Endpoint	GPRC5D	BCMA						Combination	
	Talquetamab	ABBV-383	Alnuctamab	Linvoseltamab	Elranatamab	Teclistamab		Talq + Tec	Talq
	Talq[1]	ABBV-383[2]	Alnu SC[3]	Linvos[4]	Elran[5]	Tec QW[6]	Tec + Len[7]	Talq + Tec[8]	Talq + Dara[9]
	MonumenTAL-1 QW: n=143 Q2W: n=145	NCT03933735 N=164 (all doses, overall cohort)	NCT03486067 N=73 (all doses)	LINKER-MM1 50 mg: n=104 200 mg: n=117	MagnetisMM-3 N=123	MajesTEC-1 N=165	MajesTEC-2 N=31 (all doses)	RedirecTT N=93 (all doses)	TRIMM-2 QW: n=14 Q2W: n=51
Median prior LoT (range)	QW: 5 (2-13) Q2W: 5 (2-17)	5 (3-15)	4 (3-11)	50 mg: 6 (3-14) 200 mg: 5 (2-14)	5 (2-22)	5 (2-14)	4 (2-9)	4 (1-11)	QW: 5.5 (4-16) Q2W: 5.0 (2-14)
ORR, %	QW: 74.1 Q2W: 71.1	56	53 63 (3/6/30 dose)	50 mg (n=104): 50 200 mg (n=117): 71	61.0	63.0	74.2	86.6	QW: 71.4 Q2W: 84.0
≥CR, %	QW: 33.6 Q2W:38.7	25	Not reported	50 mg: 21 200 mg: 30 (rec dose)	35.0	45.5	35.5	40.2	QW: 42.9 Q2W: 52.0
Median follow-up, mo (range)	QW: 18.8 Q2W: 12.7	2.8 (0.6-19.2)	4.3 (0.5-16)	50 mg: 7.7 (0.3-31.3) 200 mg: 5.6 (0.2-28.2)	14.7 (0.2-25.1)	23	10.8 (1.1-16.8)	13.4 (0.3-25.6)	QW: 16.8 (1.9-31.0) Q2W: 15.0 (1.0-23.3)
Discontinuation due to AEs, %	QW: 4.9 Q2W: 8.3	6	3	50 mg: 11.5 200 mg: 16.2	13.8	Not reported	16.1	6.5	1.5%
Median DoR, mo [95% CI]	QW: 9.5 (6.7-13.3) Q2W: NR (13.0-NE)	Not reported	NR	NR (3.2-NE)	NR (NE-NE)	21.6 (16.2-NE)	NR	NE	QW: NR Q2W: 20.3
Median PFS, mo [95% CI]	QW: 12-mo: 34.9% Q2W: 12-mo: 54.4%	Not reported	Not reported	50 mg: 7.9 (2.1-12.9) 200mg: NR	NR	11.3 (8.8-16.4)	Not reported	20.9 (13.0-NE)	QW: NR (2.73- NE) Q2W: 19.4 (12.5-NE)
Median OS, mo [95% CI]	QW: 12-mo: 76.4% Q2W: 12-mo: 77.4%	Not reported	Not reported	Not reported	NR	21.9 (15.1-NE)	Not reported	Not reported	QW: 12-mo: 92.3% Q2W: 12-mo: 91.5%
CRS, any gr / gr ≥3, %	QW: 79.0 / 2.1 Q2W: 74.5 / 0.7	60 / 1	56/0	50 mg: 54.8 / 1.9 200 mg: 45.3 / 0.9	57.7/ 0	72.1 / 0.6	67.7 / 3.2	76.3 / 3.2	QW: 71.4 / 0 Q2W: 80.4 / 0
Time to onset, days	Not reported	1 (1-7)	3 (1-20)	50 mg: 8.1 hr (0-42) 200 mg: 14.8 hr (0-177)	Not reported	Not reported	2 (1-4)	2 (1-5)	QW: 3 (2-8) Q2W: 2 (1-4)
Duration, days	Not reported	2 (1-10)	2 (1-11)	50 mg: 14.3 hr (0-96) 200 mg: 16.5 hr (1-144)	Not reported	Not reported	2 (1-15)	2 (1-8)	QW: 2 (1-10) Q2W: 2 (1-9)
Toci, %	Not reported	17	54	50 mg: 24.0 200 mg: 13.7	Not reported	Not reported	Not reported	26.9	QW: 50.0 Q2W: 41.2
Anemia, any gr / gr ≥3, %	QW: 44.8 / 31.5 Q2W: 45.5 / 27.6	34 / 16	41 / 25	50 mg: 40.4 / 35.6 200 mg: 27.4 / 23.9	48.8 / 37.4	54.5 / 37.6	38.7 / 19.4	50.5 / 34.4	QW: 64.3 / 35.7 Q2W: 49.0 / 25.5
Neutropenia, any gr / gr ≥3, %	QW: 35.0 / 30.8 Q2W: 28.3 / 22.1	24 / 15	49 / 42	50 mg: 27.9 / 26 200 mg: 32.5 / 30.8	48.8 / 48.8	71.5 / 65.5	74.2 / 67.7	65.6 / 61.3	QW: 42.9 / 28.6 Q2W: 39.2 / 27.5
Thrombocytopenia, any gr / gr ≥3, %	QW: 27.3 / 20.3 Q2W: 29.7 / 18.6	27 / 8	33 / 14	50 mg: 17.3 / 13.5 200 mg: 17.1 / 13.7	30.9 / 23.6	42.4 / 22.4	35.5 / 16.1	43.0 / 29.0	QW: 42.9 / 28.6 Q2W: 37.3 / 19.6
ICANS, any gr / gr ≥3, %	QW: 10.7 / - Q2W: 11.0 / -	5 / 0.1	3 / 0	5.9 / 1.8	3.4 / 0	3.0 / 0	6.5 / 0	3.2 / 1.1	4.6 / -
Infections, any gr / gr ≥3, %	QW: 58.7 / 19.6 Q2W: 66.2 / 14.5	- / 22	47 / 10	50 mg: 61.5 / 34.6 200 mg: 59.8 / 36.8	69.9 / 46.3	80.0 / 67.9	80.6 / 45.2	83.9 / 52.7	QW: 57.1 / 21.4 Q2W: 72.5 / 25.5
TEAE-related deaths, % (n)	Not reported	2 (3)	1 (1)	50 mg: 6.7 (7) 200 mg: 5.1 (6)	20.3 (25)	4.2 (7)	9.7 (3)	6.5 (6)	2.0 (1)

References: 1. Schinke C et al. ASCO 2023. #8036. 2. Weisel K et al. EHA 2023. #P862. 3. Wong S et al. EHA 2023. #P883. 4. Lee H et al. ASCO 2023. #8006. 5. Mohty M et al. ASCO 2023. #8039. 6. van de Donk N et al. ASCO 2023. #8011. 7. Tan C et al. EHA 2023. #P865. 8. Cohen YC et al. ASCO 2023. #8002. 9. Dholaria B et al. ASCO 2023. #8003.

Overview of Bispecific Antibodies at ASCO/EHA 2023

Endpoint	GPRC5D	BCMA						Combination	
	Talquetamab	ABBV-383	Alnuctamab	Linvoseltamab	Elranatamab	Teclistamab		Talq + Tec	Talq
	Talq[1]	ABBV-383[2]	Alnu SC[3]	Linvos[4]	Elran[5]	Tec QW[6]	Tec + Len[7]	Talq + Tec[8]	Talq + Dara[9]
	MonumenTAL-1 QW: n=143 Q2W: n=145	NCT03933735 N=164 (all doses, overall cohort)	NCT03486067 N=73 (all doses)	LINKER-MM1 50 mg: n=104 200 mg: n=117	MagnetisMM-3 N=123	MajesTEC-1 N=165	MajesTEC-2 N=31 (all doses)	RedirecTT N=93 (all doses)	TRIMM-2 QW: n=14 Q2W: n=51
Median prior LoT (range)	QW: 5 (2-13) Q2W: 5 (2-17)	5 (3-15)	4 (3-11)	50 mg: 6 (3-14) 200 mg: 5 (2-14)	5 (2-22)	5 (2-14)	4 (2-9)	4 (1-11)	QW: 5.5 (4-16) Q2W: 5.0 (2-14)
ORR, %	QW: 74.1 Q2W: 71.1	56	53 63 (3/6/30 dose)	50 mg (n=104): 50 200 mg (n=117): 71	61.0	63.0	74.2	86.6	QW: 71.4 Q2W: 84.0
≥CR, %	QW: 33.6 Q2W:38.7			50 mg: 21				40.2	QW: 42.9 Q2W: 52.0
Median follow-up, mo (range)	QW: 18.8 Q2W: 12.7							13.4 (0.3-25.6)	QW: 16.8 (1.9-31.0) Q2W: 15.0 (1.0-23.3)
Discontinuation due to AEs, %	QW: 4.9 Q2W: 8.3							6.5	1.5%
Median DoR, mo [95% CI]	QW: 9.5 (6.7-13.3 Q2W: NR (13.0-NE							NE	QW: NR Q2W: 20.3
Median PFS, mo [95% CI]	QW: 12-mo: 34.9% Q2W: 12-mo: 54.4%							20.9 (13.0-NE)	QW: NR (2.73- NE) Q2W: 19.4 (12.5-NE)
Median OS, mo [95% CI]	QW: 12-mo: 76.4% Q2W: 12-mo: 77.4%							Not reported	QW: 12-mo: 92.3% Q2W: 12-mo: 91.5%
CRS, any gr / gr ≥3, %	QW: 79.0 / 2.1 Q2W: 74.5 / 0.7							76.3 / 3.2	QW: 71.4 / 0 Q2W: 80.4 / 0
Time to onset, days	Not reported							2 (1-5)	QW: 3 (2-8) Q2W: 2 (1-4)
Duration, days	Not reported							2 (1-8)	QW: 2 (1-10) Q2W: 2 (1-9)
Toci, %	Not reported							26.9	QW: 50.0 Q2W: 41.2
Anemia, any gr / gr ≥3, %	QW: 44.8 / 31.5 Q2W: 45.5 / 27.6							50.5 / 34.4	QW: 64.3 / 35.7 Q2W: 49.0 / 25.5
Neutropenia, any gr / gr ≥3, %	QW: 35.0 / 30.8 Q2W: 28.3 / 22.1							65.6 / 61.3	QW: 42.9 / 28.6 Q2W: 39.2 / 27.5
Thrombocytopenia, any gr / gr ≥3, %	QW: 27.3 / 20.3 Q2W: 29.7 / 18.6	27 / 8	33 / 14	50 mg: 17.3 / 13.5 200 mg: 17.1 / 13.7	30.9 / 23.6	42.4 / 22.4	35.5 / 16.1	43.0 / 29.0	QW: 42.9 / 28.6 Q2W: 37.3 / 19.6
ICANS, any gr / gr ≥3, %	QW: 10.7 / - Q2W: 11.0 / -	5 / 0.1	3 / 0	5.9 / 1.8	3.4 / 0	3.0 / 0	6.5 / 0	3.2 / 1.1	4.6 / -
Infections, any gr / gr ≥3, %	QW: 58.7 / 19.6 Q2W: 66.2 / 14.5	- / 22	47 / 10	50 mg: 61.5 / 34.6 200 mg: 59.8 / 36.8	69.9 / 46.3	80.0 / 67.9	80.6 / 45.2	83.9 / 52.7	QW: 57.1 / 21.4 Q2W: 72.5 / 25.5
TEAE-related deaths, % (n)	Not reported	2 (3)	1 (1)	50 mg: 6.7 (7) 200 mg: 5.1 (6)	20.3 (25)	4.2 (7)	9.7 (3)	6.5 (6)	2.0 (1)

Response rates 60-70%

PFS 12-16 months

in triple-class refractory MM

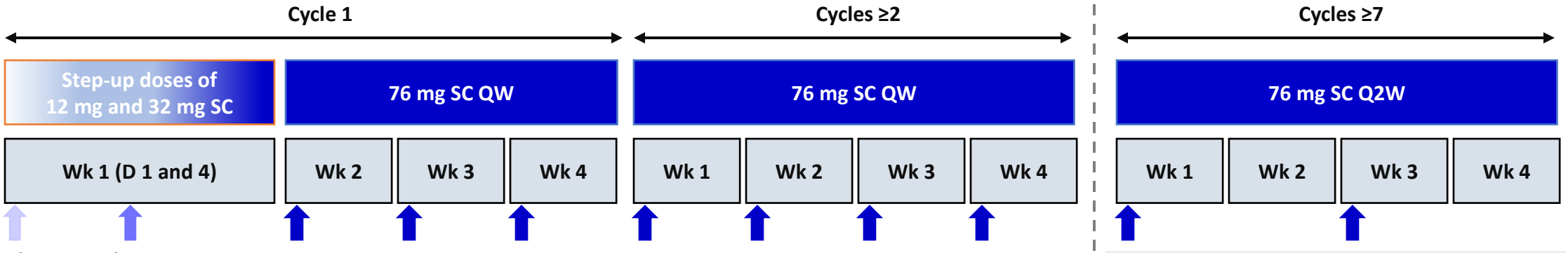
References: 1. Schinke C et al. ASCO 2023. #8036. 2. Weisel K et al. EHA 2023. #P862. 3. Wong S et al. EHA 2023. #P883. 4. Lee H et al. ASCO 2023. #8006. 5. Mohty M et al. ASCO 2023. #8039. 6. van de Donk N et al. ASCO 2023. #8011. 7. Tan C et al. EHA 2023. #P865. 8. Cohen YC et al. ASCO 2023. #8002. 9. Dholaria B et al. ASCO 2023. #8003.

Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results

Lesokhin AM, Tomasson MH, Arnulf B, Bahlis NJ, Miles Prince H, Niesvizky R, Rodríguez-Otero P, Martinez-Lopez J, Koehne G, Touzeau C, Jethava Y, Quach H, Depaus J, Yokoyama H, Gabayan AE, Stevens DA, Nooka AK, Manier S, Raje N, Iida S, Raab MS, Searle E, Leip E, Sullivan ST, Conte U, Elmeliegy M, Czibere A, Viqueira A, Mohty M.

Lesokhin et al., Nat Med. 2023 Sep;29(9):2259-2267

MagnetisMM-3: Elranatamab Dosing Schedule



For patients receiving ≥6 cycles and achieving partial response or better with responses persisting for ≥2 mo, the dosing interval will be changed to Q2W

Premedication:

60 min (±15 min) prior to the first 3 doses of elranatamab

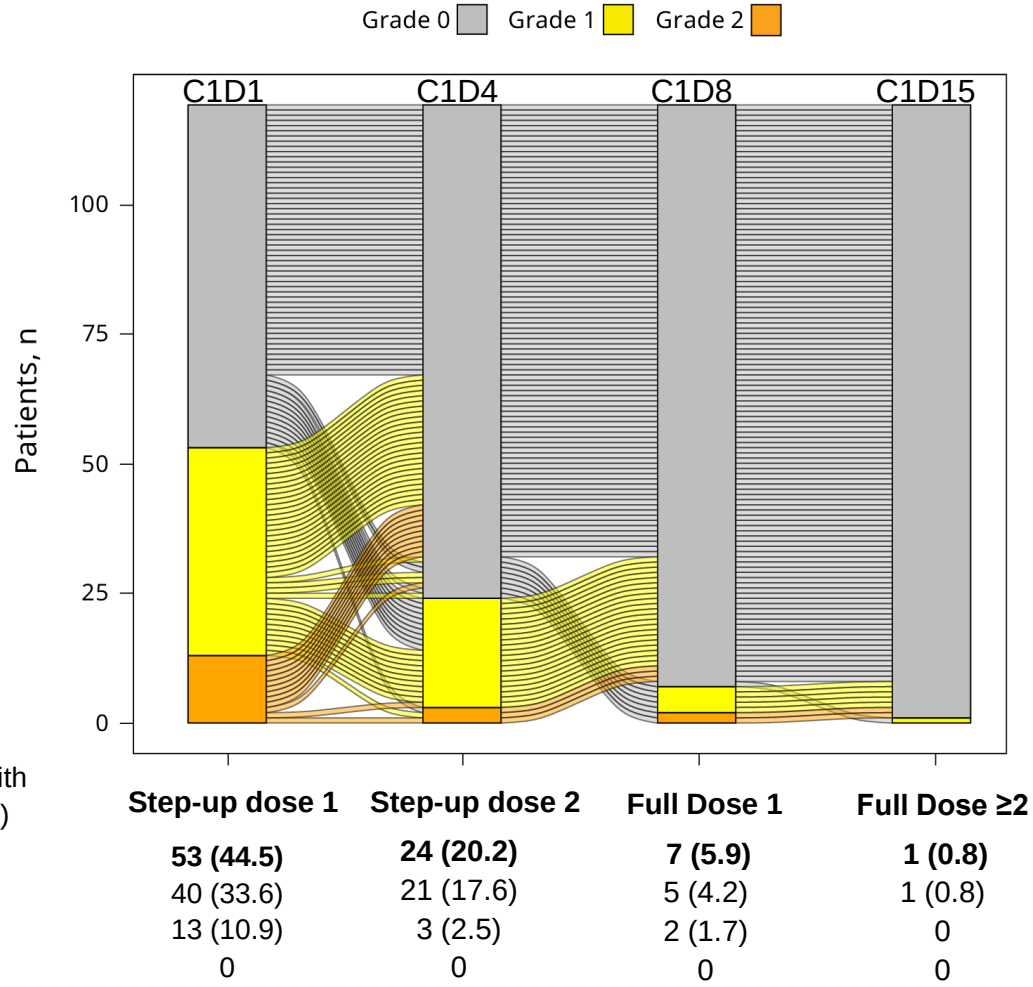
- Acetaminophen 650 mg (or paracetamol 500 mg)
- Diphenhydramine 25 mg (or equivalent), oral or IV
- Dexamethasone 20 mg (or equivalent), oral or IV

IV=intravenous; QW=once weekly; Q2W=once every 2 weeks; SC=subcutaneous

AEs of Special Interest: CRS and ICANS

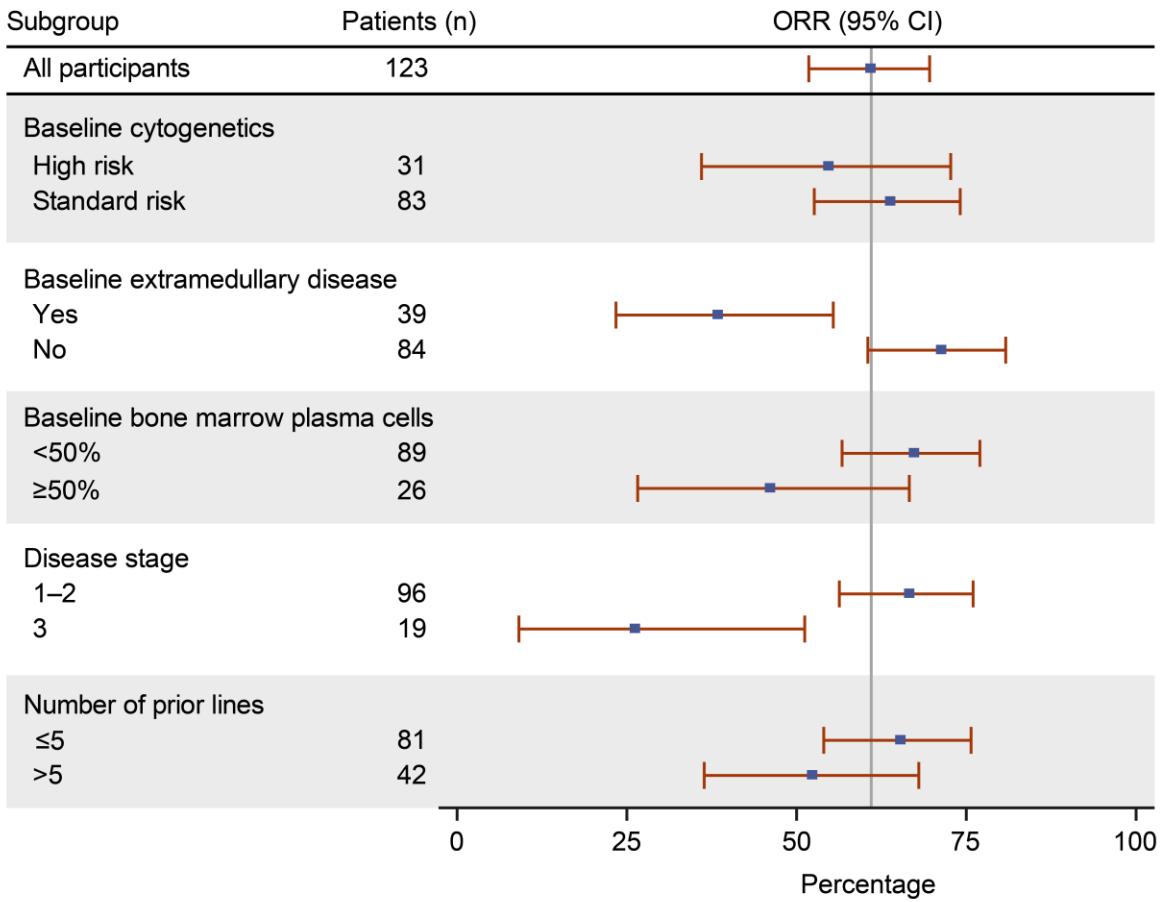
TEAE of special interest	12/32 mg step-up regimen (n=119)[a] CRS	ICANS
Patients with TEAE, n (%)	67 (56.3)	4 (3.4)
Maximum Grade 1	50 (42.0)	1 (0.8)
Maximum Grade 2	17 (14.3)	3 (2.5)
Maximum Grade ≥3	0	0
Patients with >1 TEAE, n (%)	18 (15.1)	1 (0.8)
Median time to onset of TEAE, d (range)	2.0 (1.0–9.0)	2.5 (1.0–4.0)
Median time to resolution of TEAE, d (range)	2.0 (1.0–19.0)	2.0 (1.0–6.0)
Patients who received tocilizumab[b] or steroids, n (%)		
Tocilizumab	27 (22.7)	2 (1.7)
Steroids	10 (8.4)	2 (1.7)
Permanent discontinuation due to AE, n (%)	0	0

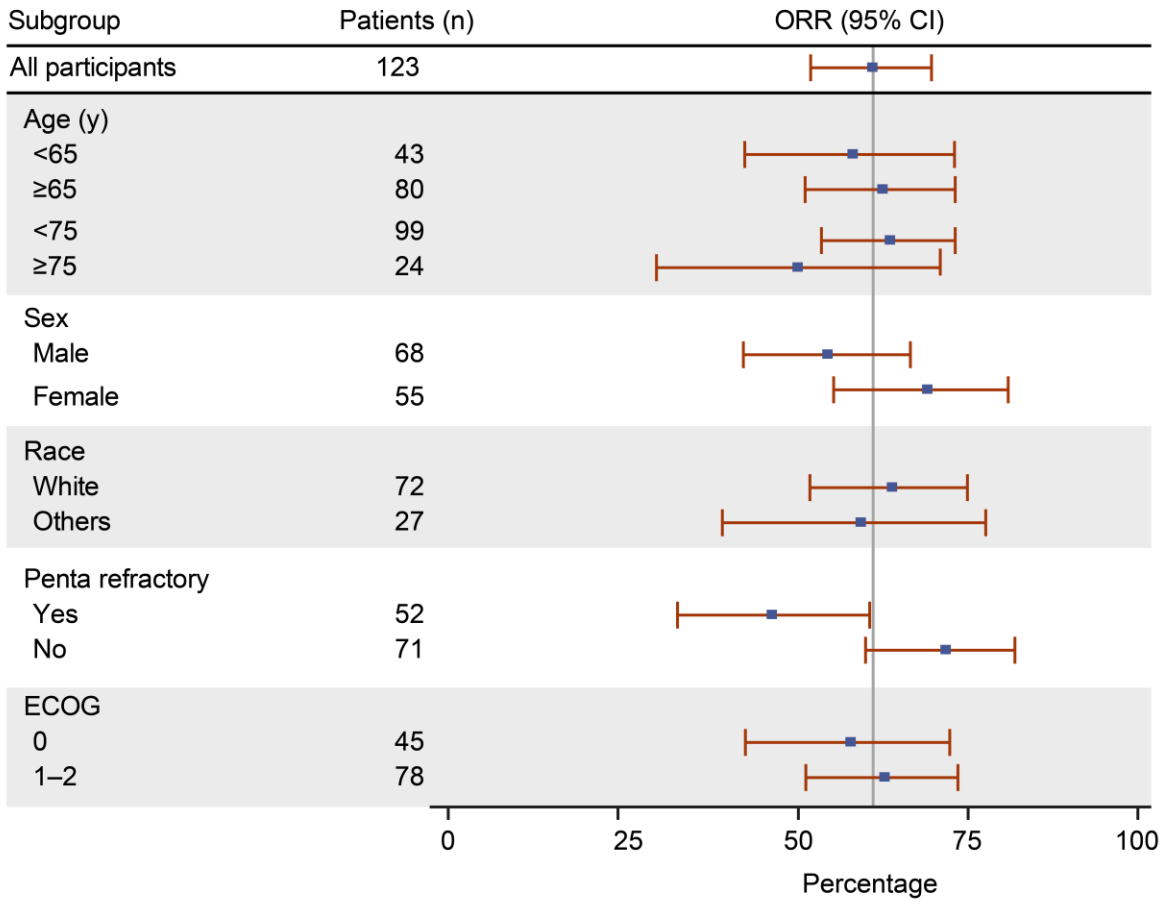
The 2 step-up priming regimen of 12/32 mg successfully mitigated the rate and severity of CRS, and the CRS profile was predictable



[a] Patients who received 1 step-up priming dose of 44 mg in Wk 1 were excluded from this CRS and ICANS analysis (n=4); [b] Includes tocilizumab and siltuximab
CRS and ICANS were graded by American Society for Transplant and Cellular Therapy criteria (Lee DW, et al. Biol Blood Marrow Trans 2019;25:62)
AE=adverse event; CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome; TEAE=treatment-emergent adverse event

Objective Response Rate per BICR Across Subgroups





BICR=blinded independent central review; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; ORR=objective response rate

10

Long-Term Follow-Up From MajesTEC-1 of Teclistamab, a BCMA×CD3Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma

Niels WCJ van de Donk[1], Philippe Moreau[2], Alfred L Garfall[3], Manisha Bhutani[4], Albert Oriol[5], Ajay K Nooka[6], Thomas G Martin[7], Laura Rosiñol[8], María-Victoria Mateos[9], Nizar Bahlis[10], Rakesh Popat[11], Britta Besemer[12], Joaquín Martínez-López[13], Amrita Krishnan[14], Michel Delforge[15], Danielle Trancucci[16], Raluca I Verona[17], Tara Stephenson[17], Katherine Chastain[16], Surbhi Sidana[18]

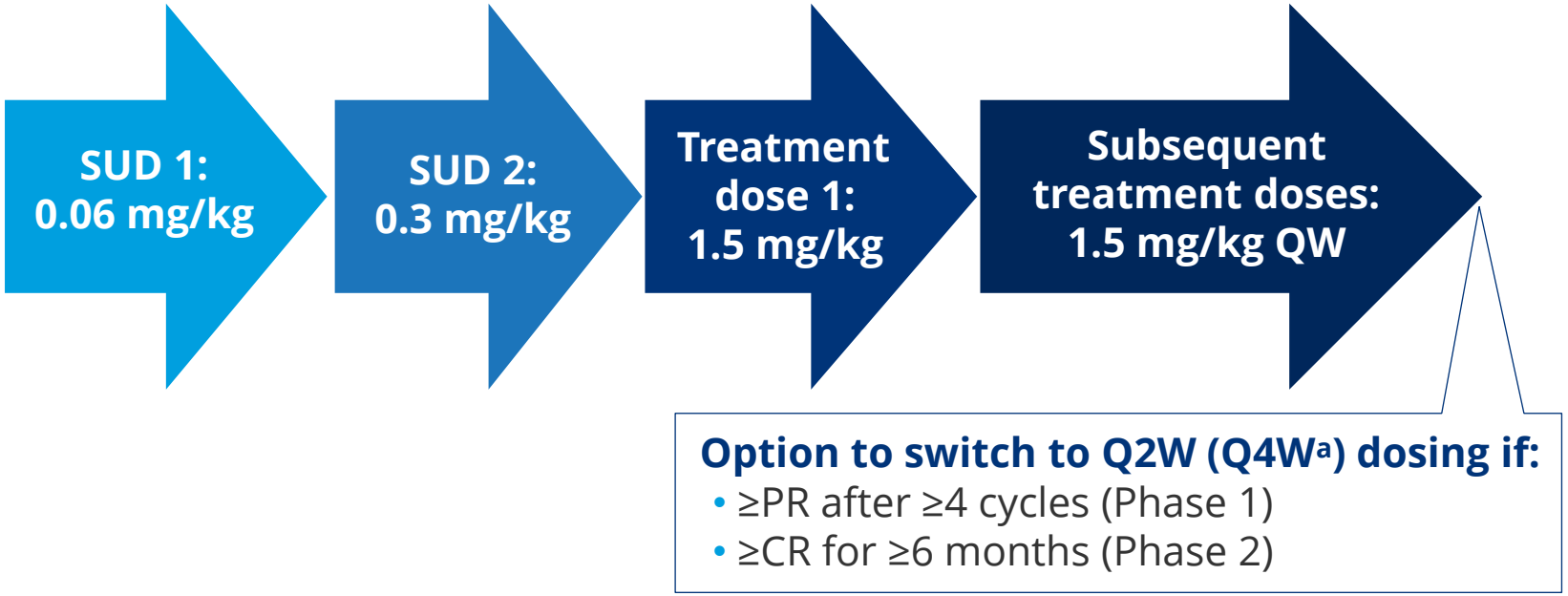
[1]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands; [2]Hematology Clinic, University Hospital Hotel-Dieu, Nantes, France; [3]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [4]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA; [5]Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; [6]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [7]University of California, San Francisco, San Francisco, CA, USA; [8]Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain; [9]University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Salamanca, Spain; [10]Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada; [11]University College London Hospitals, NHS Foundation Trust, London, UK; [12]University of Tübingen, Tübingen, Germany; [13]Hematología Hospital 12 de Octubre, Madrid, Spain; [14]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [15]University of Leuven, Leuven, Belgium; [16]Janssen Research & Development, Raritan, NJ, USA; [17]Janssen Research & Development, Spring House, PA, USA; [18]Stanford University School of Medicine, Stanford, CA, USA.

CA-SFM-1693

Presented at American Society of Clinical Oncology (ASCO) Annual Meeting; June 2-6, 2023; Chicago, Illinois (hybrid).

MajesTEC-1: Teclistamab Dosing

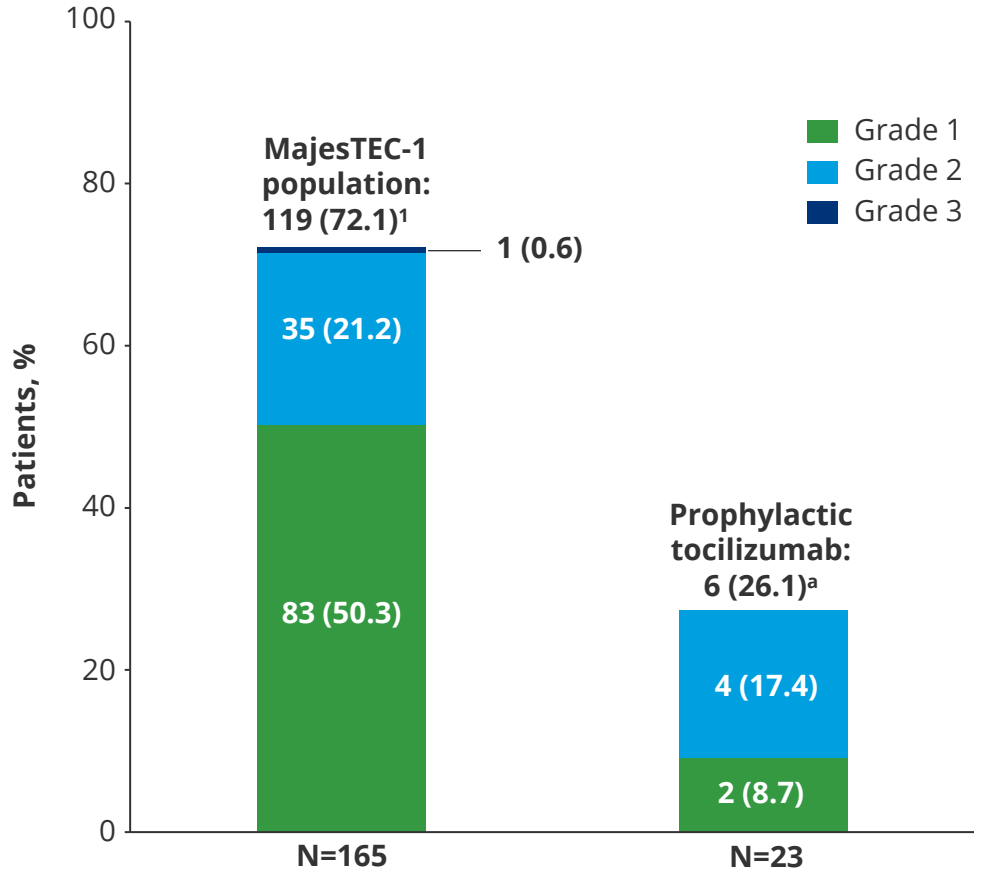
- Eligible patients received teclistamab at the RP2D, with the option to switch to Q2W or Q4W dosing



2–4 days were allowed between SUD 1, SUD 2, and treatment dose 1. [a]Patients could further switch to monthly dosing if they demonstrated continued response on the Q2W schedule.
CR, complete response; PR, partial response; Q2W, every other week; Q4W, every 4 weeks; QW, once weekly; RP2D, recommended Phase 2 dose; SUD, step-up dose.

Prophylactic Tocilizumab: CRS Incidence and Severity

- Prophylactic tocilizumab reduced the incidence of CRS to 26.1% (6/23 patients)
  - 2 patients had grade 1 CRS
  - 4 patients had grade 2 CRS
  - No grade ≥3 CRS was observed



N indicates number of patients; grade indicates maximum toxicity grade of CRS. [a]As of April 28, 2023.
CRS, cytokine release syndrome.
1. Martin TG, et al. *Cancer* 2023; Mar 29 [online ahead of print].

Incidence and Severity of Clinically Relevant Infections During Teclistamab Treatment

- Majority of grade ≥3 infections were COVID-19 and respiratory infections
  - Study enrollment overlapped with peak of the COVID-19 pandemic
  - 13/165 (7.9%) patients received a COVID-19 vaccine prior to the first teclistamab dose
  - 18/165 (10.9%) patients died due to COVID-19
- All 7 PJP infections were grade 3/4 and all resolved No PJP prophylaxis in 4/7 patients
- Most viral, GI, and fungal infections were grade 1/2

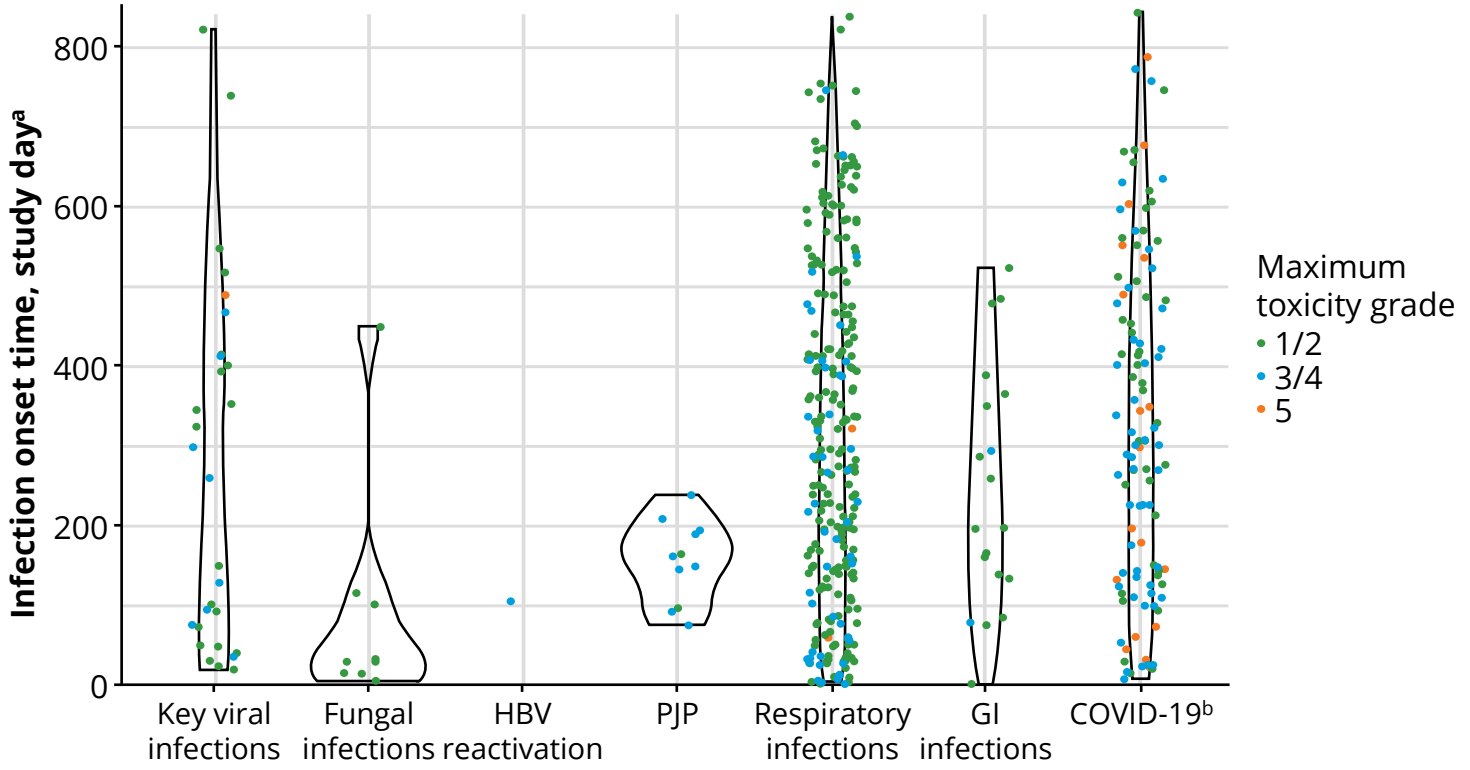
Patients, n (%)	N=165		
	Any Grade	Grade 3/4	Grade 5
Any Infection	132 (80.0)	91 (55.2)	21 (12.7)
Respiratory Infections	95 (57.6)	32 (19.4)	2 (1.2)
COVID-19 infections	48 (29.1)	35 (21.2)	18 (10.9)
Key viral infections[a]	20 (12.1)	7 (4.2)	1 (0.6)
GI infections	15 (9.1)	2 (1.2)	0
Fungal infections[b]	9 (5.5)	0	0
PJP	7 (4.2)	7 (4.2)	0
HBV reactivation	1 (0.6)	1 (0.6)	0

Infections were selected based on categories of clinically relevant infections typically occurring in patients with RRMM using MedDRA v24.0. Patients were counted once for any given event, regardless of the number of times they experienced the event. [a]ExcludingCOVID-19. [b]Excluding PJP.

GI, gastrointestinal; HBV, hepatitis B virus; MedDRA, Medical Dictionary for Regulatory Activities; PJP, *Pneumocystis jirovecii* pneumonia; RRMM, relapsed/refractory multiple myeloma.

Timing and Maximum Toxicity Grade of Clinically Relevant Infections During Teclistamab Treatment Was Variable

- Respiratory infections occurred throughout the study (mostly grade 1/2)
- COVID-19 infections of all grades were observed throughout the study
- Most viral infections occurred during the first 12 months
- GI infections were seen throughout the study
- Most fungal and PJP infections were observed early



Continued monitoring throughout treatment is recommended, although improvements are expected with increased awareness and vigilance, new expert management guidelines, and additional strategies

Infections were selected based on categories of clinically relevant infections typically occurring in patients with RRMM using MedDRA version 24.0. Each point on the plot represents an individual infection (ie, patients were included for every infection event they experienced within these categories), colored according to maximum toxicity grade (1/2, 3/4, or 5). Key viral infections included parvovirus B19 infection, adenovirus infection and reactivation, adenoviral pneumonia, oral herpes, herpes zoster virus infection, cytomegalovirus viremia and reactivation, BK virus infection, and progressive multifocal leukoencephalopathy.

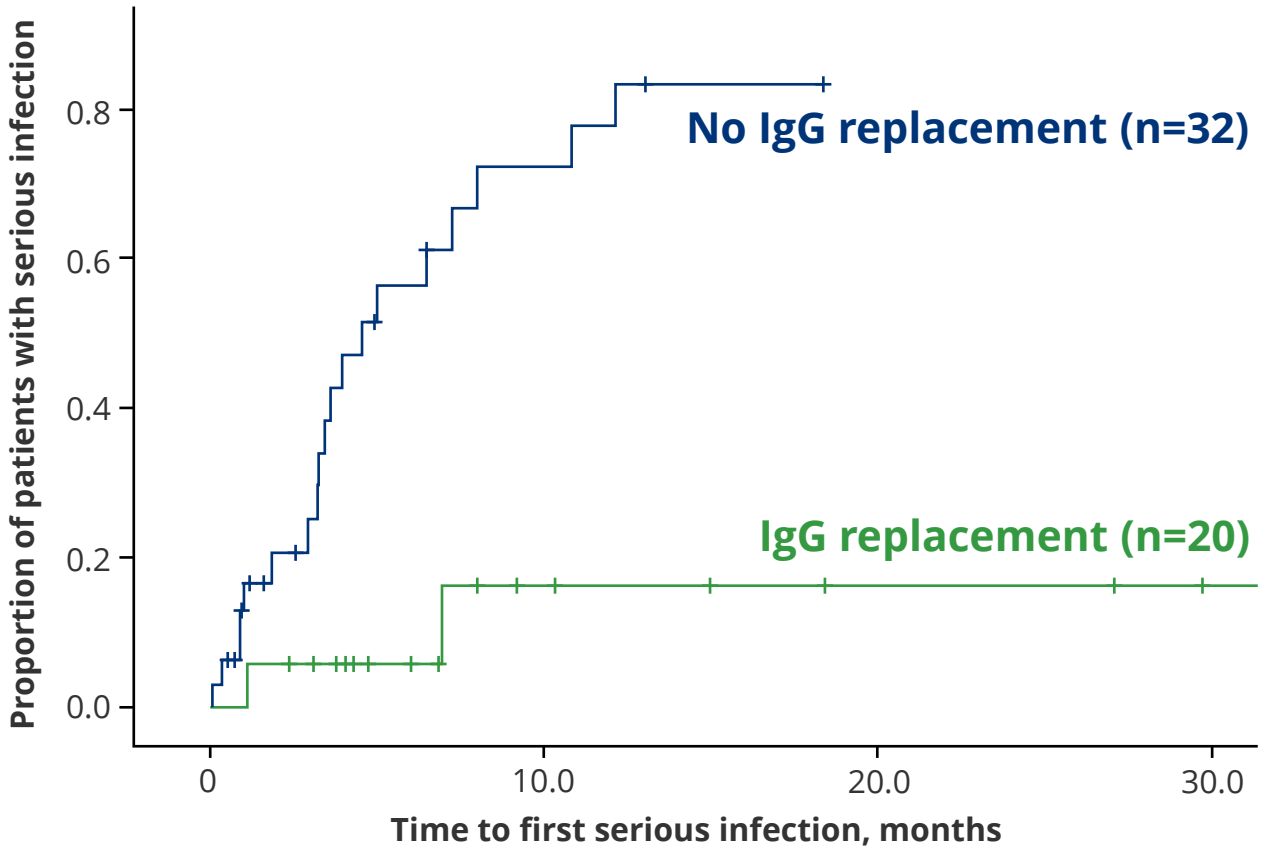
[a]Relative to each patient based on their individual treatment start date. Days 200, 400, 600, and 800 correspond with 6.6, 13.2, 19.7, and 26.3 months, respectively.

[b]Most patients were enrolled before COVID-19 vaccines were available; 99 (60.0%) patients received at least 1 COVID-19 vaccination dose during the study, including 13 of the 18 patients who died from COVID-19.

GI, gastrointestinal; HBV, hepatitis B virus; MedDRA, Medical Dictionary for Regulatory Activities; PJP, *Pneumocystis jirovecii* pneumonia.

IgG Replacement Significantly Reduced the Risk of Developing Grade ≥3 Infections in a Single-Center, Retrospective Analysis

- In a retrospective analysis of 52 patients at Amsterdam UMC:
  - Low baseline polyclonal IgG levels further decreased after starting teclistamab[1]
- Monthly IgG replacement significantly reduced the risk of grade ≥3 infections
  - Mostly lower respiratory tract infections caused by gram-negative bacteria
- Consistent with another study of BCMA-targeted bispecific antibodies, showing 80% reduction in grade ≥3 infections with IgG replacement[2]



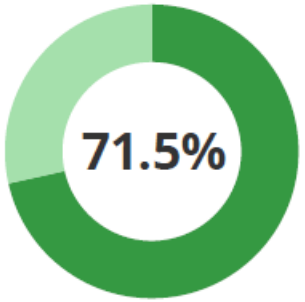
IgG, immunoglobulin G.

1. Frerichs K, et al. *HemaSphere* 2023;7(S3)2922-3. . 2. Lancmann G, et al. *Blood* 2022;140(suppl 1):10073-4.

Neutropenia Peaked Approximately 2 Months After Starting Teclistamab and Was Managed with Growth Factors

Any grade neutropenia

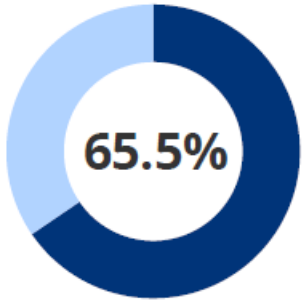
Overall incidence



Median duration: 1.2 months

Grade 3/4 neutropenia

Overall incidence

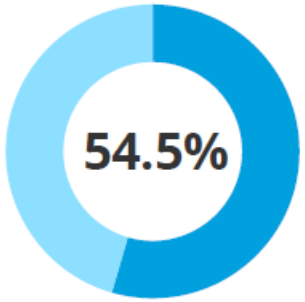


Median duration: 0.8 months[a]

Median time to onset[a]

G-CSF use

Prophylaxis and management



[a]Grade 3/4 neutropenia or febrile neutropenia
G-CSF, granulocyte colony-stimulating factor.

Summary of Key Recommendations for Managing Infections During Teclistamab Treatment

Based on experience from MajesTEC-1[1,2] and in line with recently published consensus guidelines[3-5]

Before starting teclistamab, patients should be up to date with all vaccinations and screened for HBV, HCV, and HIV

Teclistamab should not be initiated in patients with any active infections

Prophylaxis for PJP, HSV, and VZV should be given to all patients

Other prophylactic antimicrobials should be administered per institutional guidelines

IgG replacement should be used to maintain IgG ≥400 mg/dL

IgG replacement should be administered prophylactically and/or for treatment of life-threatening infections, and for serious or recurrent infections, per institutional guidelines

Growth factors should be considered for grade ≥3 neutropenia with infection/fever and grade 4 neutropenia

Growth factors should not be given during step-up dosing or during cytokine release syndrome

Patients should be closely monitored for a range of infections during treatment to facilitate prompt investigation and intervention

Teclistamab should not be given to patients with any active infections

HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; IgG, immunoglobulin G; PJP, *Pneumocystis jirovecii* pneumonia; VZV, varicella-zoster virus. 1. Moreau P, et al. *N Engl J Med* 2022;387:495-505. 2. van de Donk NWCJ, et al. *J Clin Oncol* 2023;41(16 Suppl):8011. 3. Raje N, et al. *Lancet Haematol* 2022;9:143-61. 4. Ludwig H, et al. *Lancet Oncol* 2023;24:e255-69. 5. Raje N, et al. *Blood Cancer J* 2023;13:116.

Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D × CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma: Phase 1/2 Results From MonumenTAL-1

Ajai Chari[1], Cyrille Touzeau[2], Carolina Schinke[3], Monique C Minnema[4], Jesus G Berdeja[5], Albert Oriol[6], Niels WCJ van de Donk[7], Paula Rodriguez-Otero[8], Elham Askari[9], María-Victoria Mateos[10], Luciano J Costa[11], Jo Caers[12], Leo Rasche[13], Amrita Krishnan[14], Deeksha Vishwamitra[15], Xuewen Ma[15], Xiang Qin[15], Katharine S Gries[16], Michela Campagna[17], Tara Masterson[15], Brandi Hilder[15], Jaszianne Tolbert[15], Thomas Renaud[18], Jenna D Goldberg[18], Christoph Heuck[15], Jesús San-Miguel[8], Philippe Moreau[19]

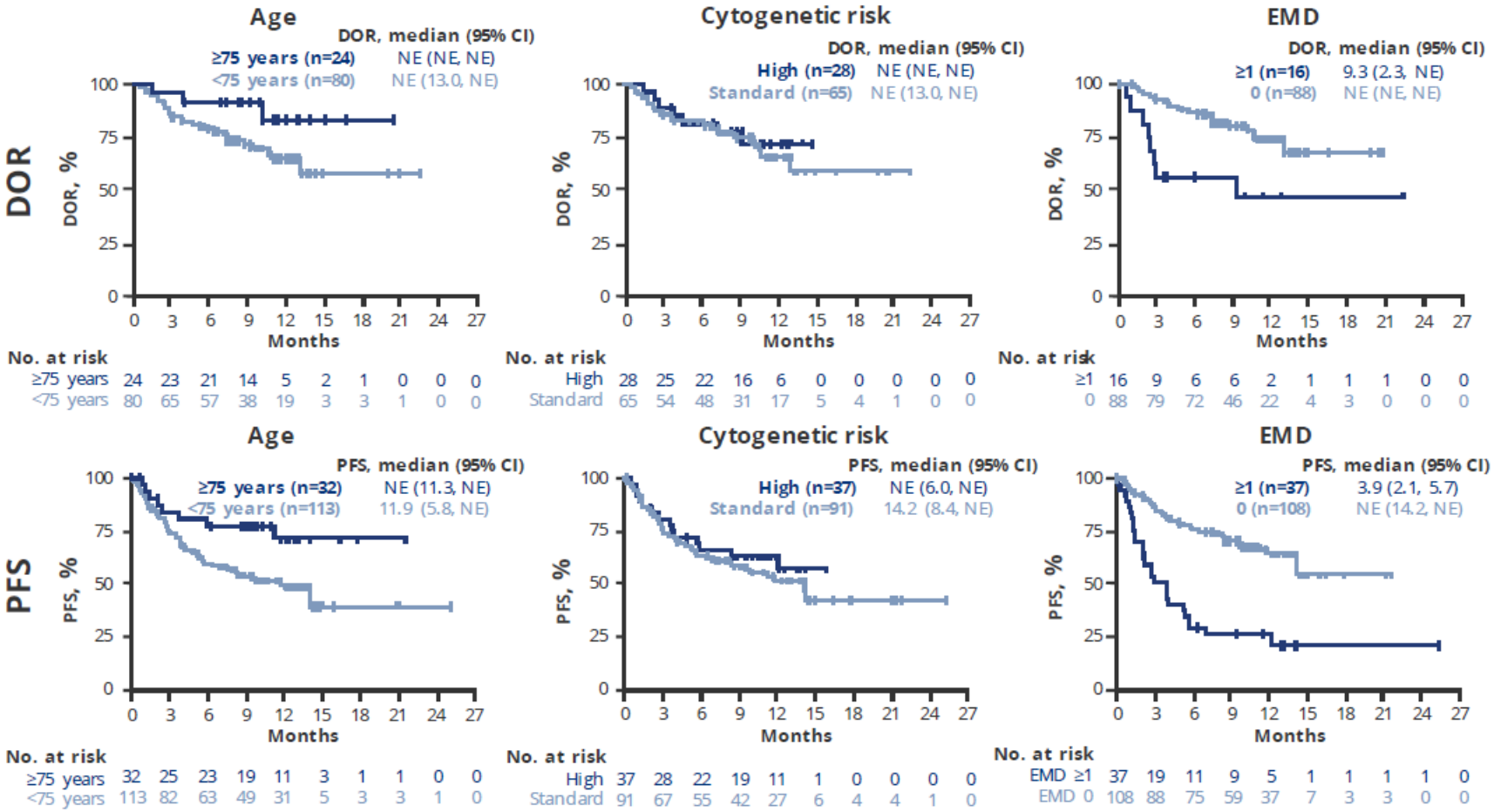
[1]Mount Sinai School of Medicine, New York, NY, USA; [2]Centre Hospitalier Universitaire de Nantes, Nantes, France; [3]Myeloma Center, University of Arkansas for Medical Sciences, Little Rock, AR, USA; [4]University Medical Center Utrecht, Utrecht, Netherlands; [5]Sarah Cannon Research Institute, Nashville, TN, USA; [6]Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias I Pujol, Badalona, Barcelona, Spain; [7]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands; [8]University of Navarra, Pamplona, Spain; [9]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [10]University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Salamanca, Spain; [11]University of Alabama at Birmingham, Birmingham, AL, USA; [12]University of Liège, Liège, Belgium; [13]University Hospital of Würzburg, Würzburg, Germany; [14]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [15]Janssen Research & Development, Spring House, PA, USA; [16]Janssen Global Services, Raritan, NJ, USA; [17]Janssen-Cilag, Madrid, Spain; [18]Janssen Research & Development, Raritan, NJ, USA; [19]University Hospital Hotel-Dieu, Nantes, France

Presented at the 64th American Society of Hematology (ASH) Annual Meeting; December 10–13, 2022; New Orleans, LA, USA.

Results

- In high-risk vs standard-risk patients, DOR and PFS outcomes were similar for cytogenetic risk and showed differences for age and EMD subgroups in the Q2W cohort. Similar data were observed in the QW cohort, except age, in which analyses were not performed
- In total, 92 (64.3%) and 99 (68.3%) patients had ≥2 high -risk features in QW and Q2W cohorts, respectively; among these patients, ORR was 66.3% and 46.9%, respectively

FIGURE 2: Outcomes among select high-risk subgroups in Q2W cohort



NE, not estimable

Talquetamab after prior T-cell redirecting therapies

Eligibility criteria

Phase 1:
- Measurable MM
- Intolerant to or progressed on established therapies
- ECOG PS ≤1

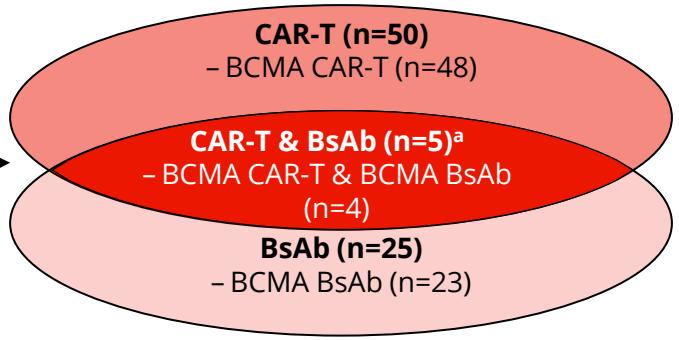
Phase 2:
- Measurable MM
- ≥3 prior LOT (≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb)
- ECOG PS ≤2

TCR naïve: 0.4 mg/kg SC QW → Prior BCMA ADC allowed **(n=143)**

Prior TCR: 0.4 mg/kg SC QW or 0.8 mg/kg SC Q2W → Prior BCMA, ADC, CAR-T, and/or BsAb allowed (n=70)

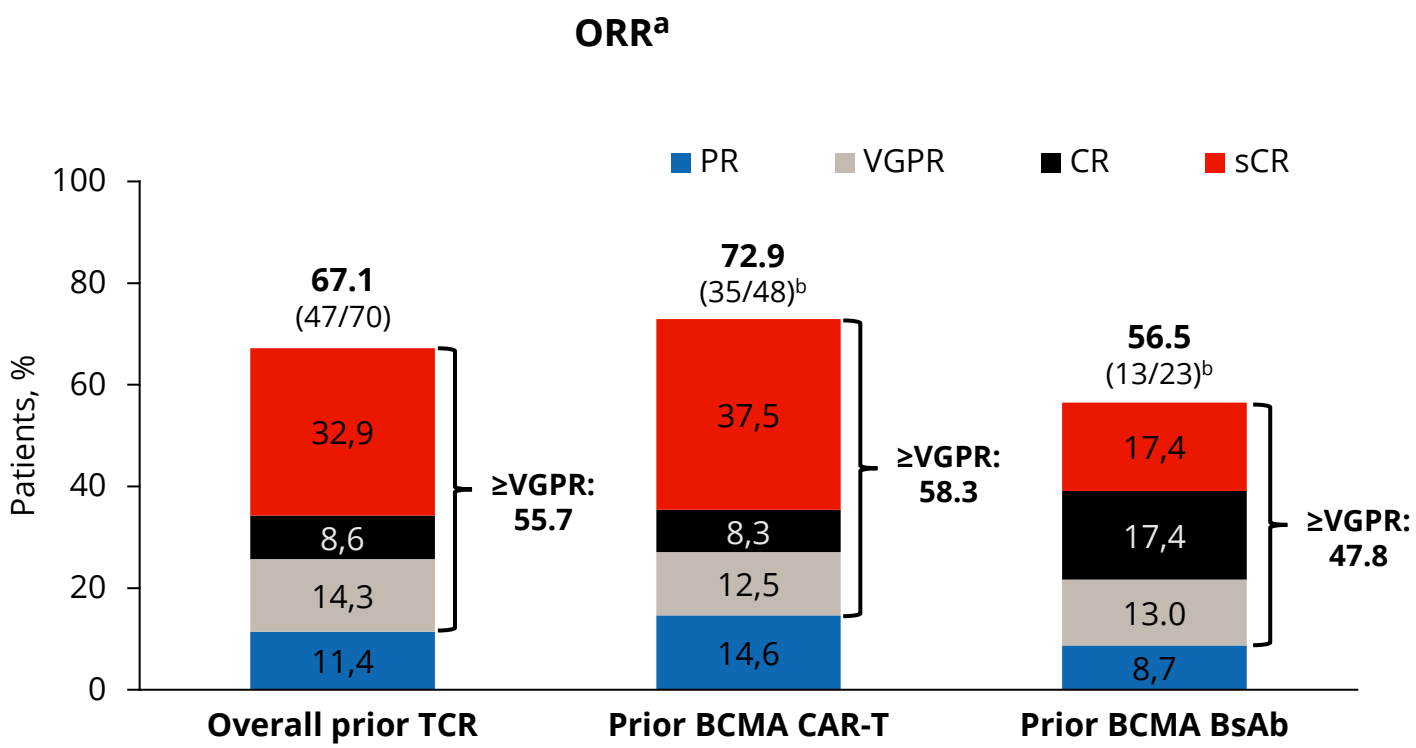
TCR naïve: 0.8 mg/kg SC Q2W → Prior BCMA ADC allowed **(n=154)**

Prior TCR received in 70 patients



MonumenTAL-1 ClinicalTrials.gov identifiers: NCT03399799/NCT04634552.
[a]Among the overall prior TCR group (N=70), 5 patients treated with both prior CAR-T and BsAb were also counted in each of the respective overall CAR-T (n=50) and BsAb (n=25) groups.
ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; BsAb, Bispecific antibody; CAR, chimeric antigen receptor; CD, cluster of differentiation; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; LOT, line of therapy; mAb, monoclonal antibody; MM, multiple myeloma; PI, proteasome inhibitor; Q2W, every other week; QW, weekly, SC, subcutaneous; TCR, T-cell redirecting

MonumenTAL-1 Prior TCR Patients: ORR Trended Higher with Prior BCMA CAR-T vs BCMA BsAb



Date cut-off date: October 11, 2023

[a]Due to rounding, individual response rates may not sum to the ORR. [b]4 patients received both BCMA CAR-T and BCMA BsAb.

BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CAR, chimeric antigen receptor; CR, complete response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response; TCR, T-cell redirection therapies; VGPR, very good partial response

Management of Key Toxicities Specific to Talquetamab

Based on own experience, MonumenTAL-1 and Chari et al., ASH2023

Taste loss/changes

Inform patient

Reversible

Consider longer intervals

Difficulties to swallow

Consider nutritional supplements

Usually only first few weeks

Weight loss

Most pronounced in the first 2-3 months

Even without taste changes

Consider nutritional supplements

Typically stabilizes over time

Nail disruption/loss

Inform patient

Improves over time

Artificial nails

Skin dry/desquamation

Topical moisturizing lotions

Topical steroids of iching

Consider longer intervals if severe

HEIDELBERG
UNIVERSITY
HOSPITAL

Heidelberg
Myeloma Center

Debate: In Favour of TCEs

Why TCEs are preferred over CAR-Ts

Key aspects to consider:

- Accessibility 
- Efficacy 
- Toxicity 

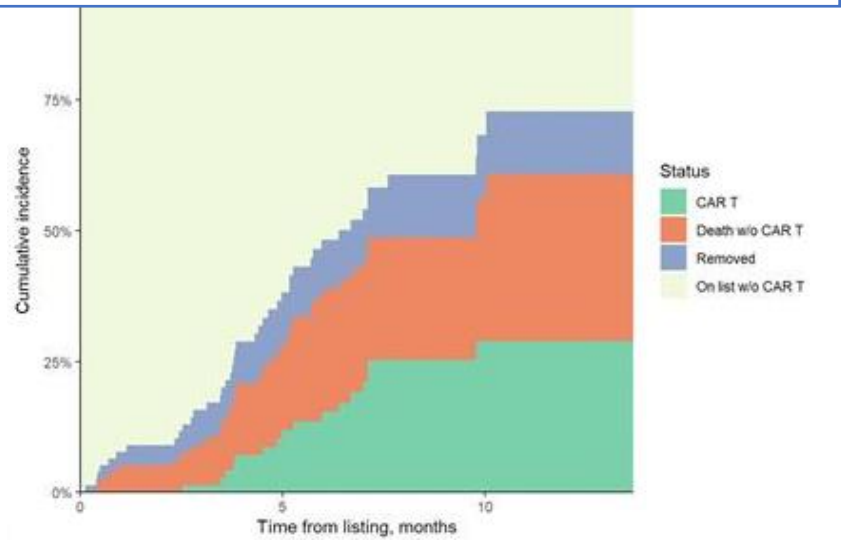
Accessibility: What do you mean, waitlists & slots?

- CAR-T therapy, while effective, is difficult to scale. Approved autologous CAR-T therapies can have waitlists,
- 1-2 month “vein to vein” times,
- 3-4 months “brain to vein” times.

Study #1: 25% of patients on BCMA CAR-T waitlist ultimately went to hospice instead.

Annual CAR T infusions (all diseases, on/off trial) pre-/during COVID	50-100 (<50, 100-300) 50-100 (<50, 100-300)
No. CART infusion volume for MM in 2021	10-50 (<5,50-100)
No. of pts on waiting list since ide-cel approval	20 (5-100)
No. of slots given per site per month	1 (0-4)
Time (months) spent on waiting list prior to apheresis	6 (3-8)
% patients on waiting list receiving: apheresis/CAR T trial/ hospice	25% (0%-64%) 25% (0-50%) 25% (25%-75%)

Study #2: At 12-month mark, 29% got CAR-T while 32% died without CAR-T.



Kourelis T, Bansal R, Patel KK, et al. JCO. 2022. 40(16_suppl):e20021 Al Hadidi S, Szabo A, Esselmann J, et al. Blood. 2022. 140(Suppl_1): 8038-8039.

Accessibility: TCEs ready to go

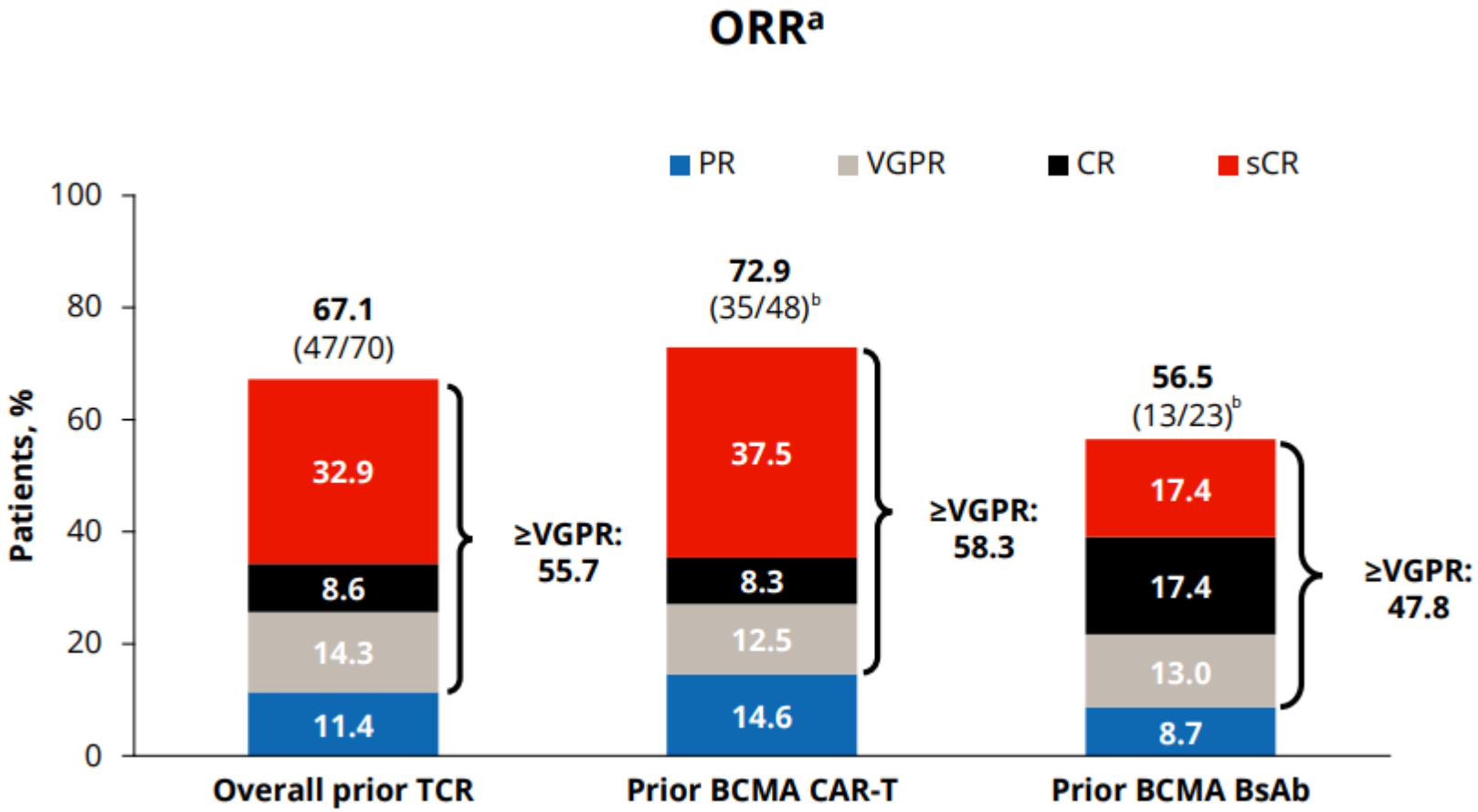
1. **Pre-manufacturing, hence available “off the shelf”**:
   No need for waitlists, slots, or “out-of-spec” drama

2. **Easier to adopt (hopefully soon!) in community settings:**
   Training and experience will come over time

3. **Brain to vein to brain: Do it – adjust it – stop it**
   For example: older frailer patients, with ESRD, with AEs

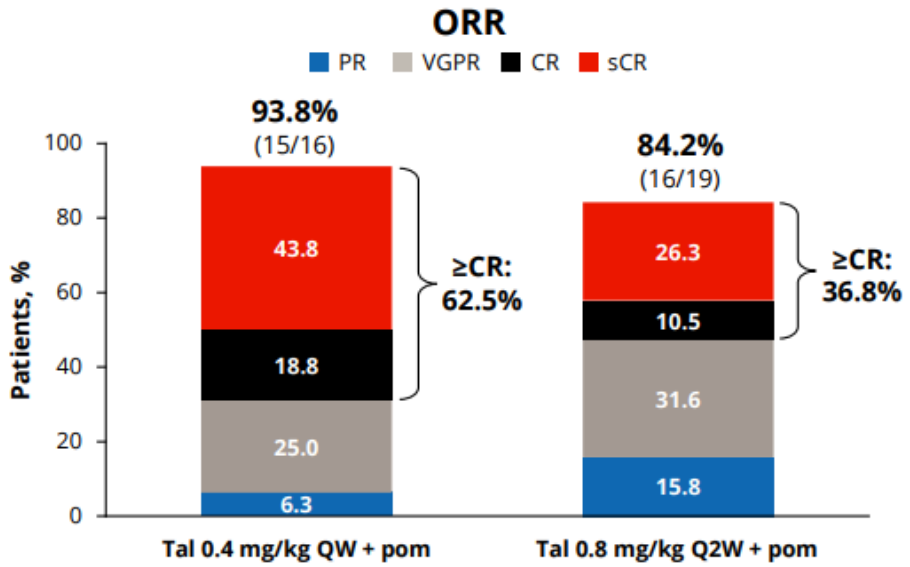
ESRD, End-stage renal disease; Out-of-spec: Out of specification CAR-T product.

Efficacy: TCEs even work after CAR-Ts (so who is the champion?)



Presented by AJ Jakubowiak at the 65th American Society of Hematology (ASH) Annual Meeting; December 9–12, 2023; San Diego, CA, USA

Efficacy: with some help from your friends



	Tal 0.4 mg/kg QW + pom (n=16)	Tal 0.8 mg/kg Q2W + pom (n=19)
Median follow-up, months (range)	15.0 (1.2–19.0)	11.1 (1.2–14.8)
Median time to first response, months (range)	1.7 (0.9–3.3)	1.2 (0–4.8)

- ORRs were consistent across patient subgroups
  - 100% (3/3) in CAR-T–exposed patients in the QW cohort (no patients had CAR-T exposure in Q2W)
  - 100% (5/5 in QW, 3/3 in Q2W) in pomalidomide-exposed patients in both cohorts
  - 50% (1/2 in QW) and 67% (2/3 in Q2W) in patients with EMD
  - 80% (4/5 in QW) and 75% (3/4 in Q2W) in patients with high-risk cytogenetics

Toxicity: Late neurological events

micrographia

shuffling gait

bradykinesia

Berdeja et al. *The Lancet* 2021

Toxicity: Neurological events

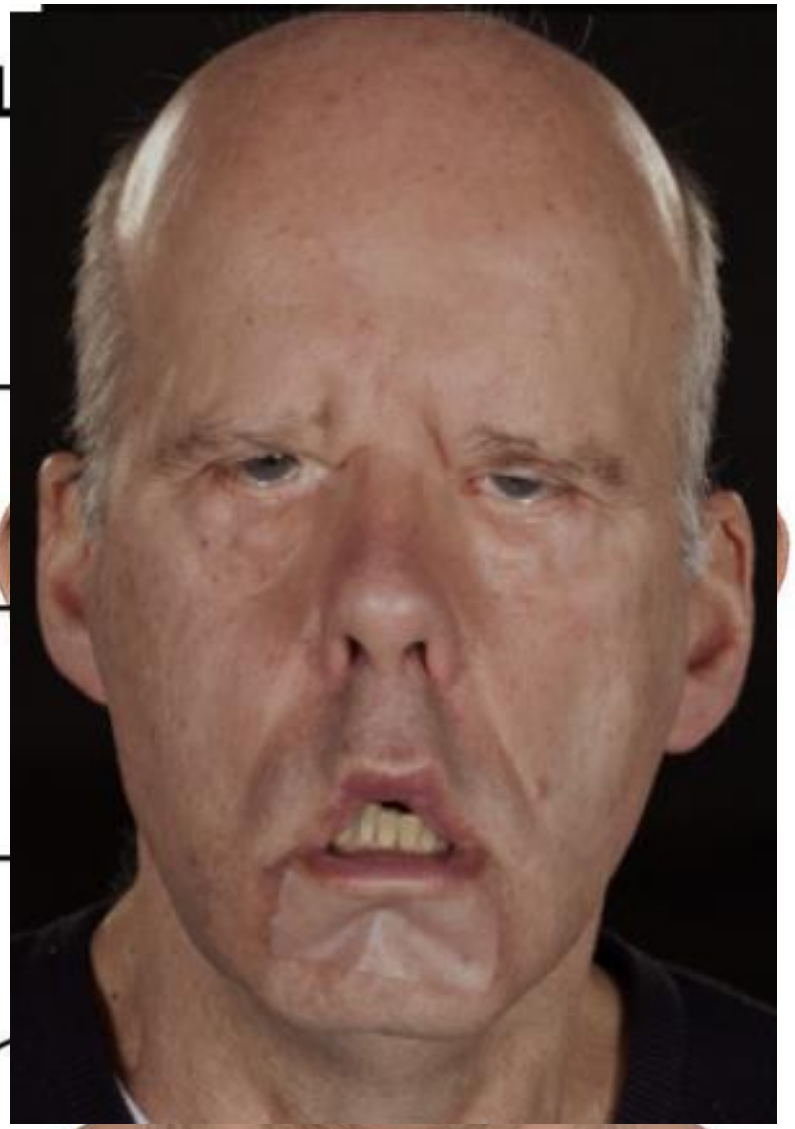
FACIAL NERVE PAL

Inability to wrinkle brow:
The affected person may not be able to raise one eyebrow or wrinkle the forehead on one side

Drooping eyelid, inability to close eye:
The eyelid on one side may droop, making it difficult to close the eye completely.

Asymmetrical smile:
When the person smiles, the affected side of the face may not move as much as the other side, resulting in an uneven or lopsided smile.

Drooping corner of mouth:
The corner of the mouth on one side may droop, causing a lopsided appearance.



www.bergerhenryent.com; Butler et al, 2017

CAR-T vs bsAbs in MM at its essence:

bsAbs	CAR-T
Can be pulled “off the shelf” for anyone	Unpredictable kinetics of expansion
Novel configurations to match individual patient needs	Capable of causing extremely serious toxicities
Easily deliverable to smaller centers	Very difficult to scale to smaller centers

Thanks to Rahul Banerjee for sharing slides!