Comprehensive Cancer Center
Tübingen-Stuttgart

Multiples Myelom – CAR-T-Zellen, bispezifische Antikörper & Co

Dr. Britta Besemer

26. Juni 2025

EBERHARD KARLS
UNIVERSITÄT
TÜBINGEN

Comprehensive
Cancer Center
Tübingen - Stuttgart

Universitätsklinikum
Tübingen

Disclosure of conflicts of interest

1. **Employment or Leadership Position**
   None

2. **Advisory Role or Expert Testimony**
   None

3. **Stock Ownership**
   None

4. **Patent, Copyright, Licensing**
   None

5. **Honoraria**
   Janssen-Cilag, GSK, Sanofi, Oncopeptides, Pfizer

6. **Financing of Scientific Research**
   None

7. **Other Financial Relationships**
   None

8. **Immaterial Conflicts of Interest**
   None

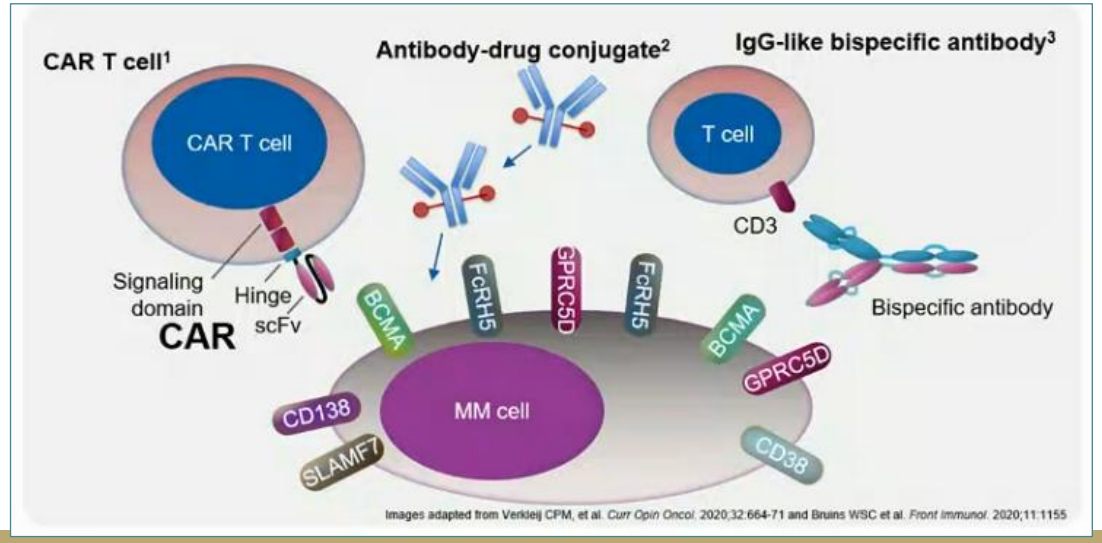
Zelluläre Therapie/“Immuntherapie”

Target bcma

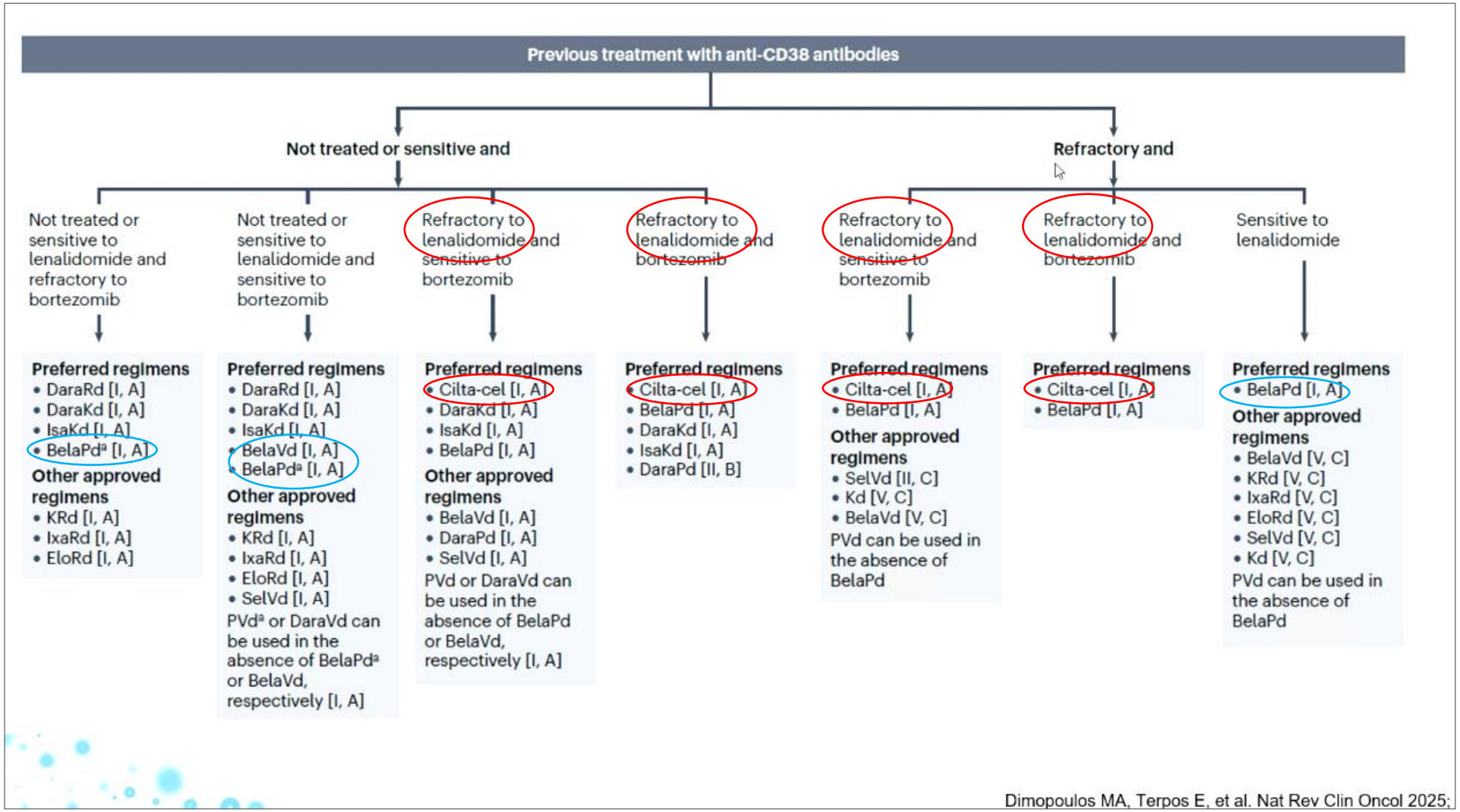
CAR-T-Zelle:	Cilta-cel (*Carvykti*)
Bispezifische Antikörper:	Teclistamab (*Tecvayli*) Elranatamab (*Elrexfio*) Linvoseltamab *(Lynozyfic*)
ADC:	Belantamab mafodotin (*Blenrep*; in Kombination mit Poma/Dex oder Borte/Dex)

Target GPRC5D

CAR-T-Zelle:	-
Bispezifische Antikörper:	Talquetamab (*Talvey*)
ADC:	-



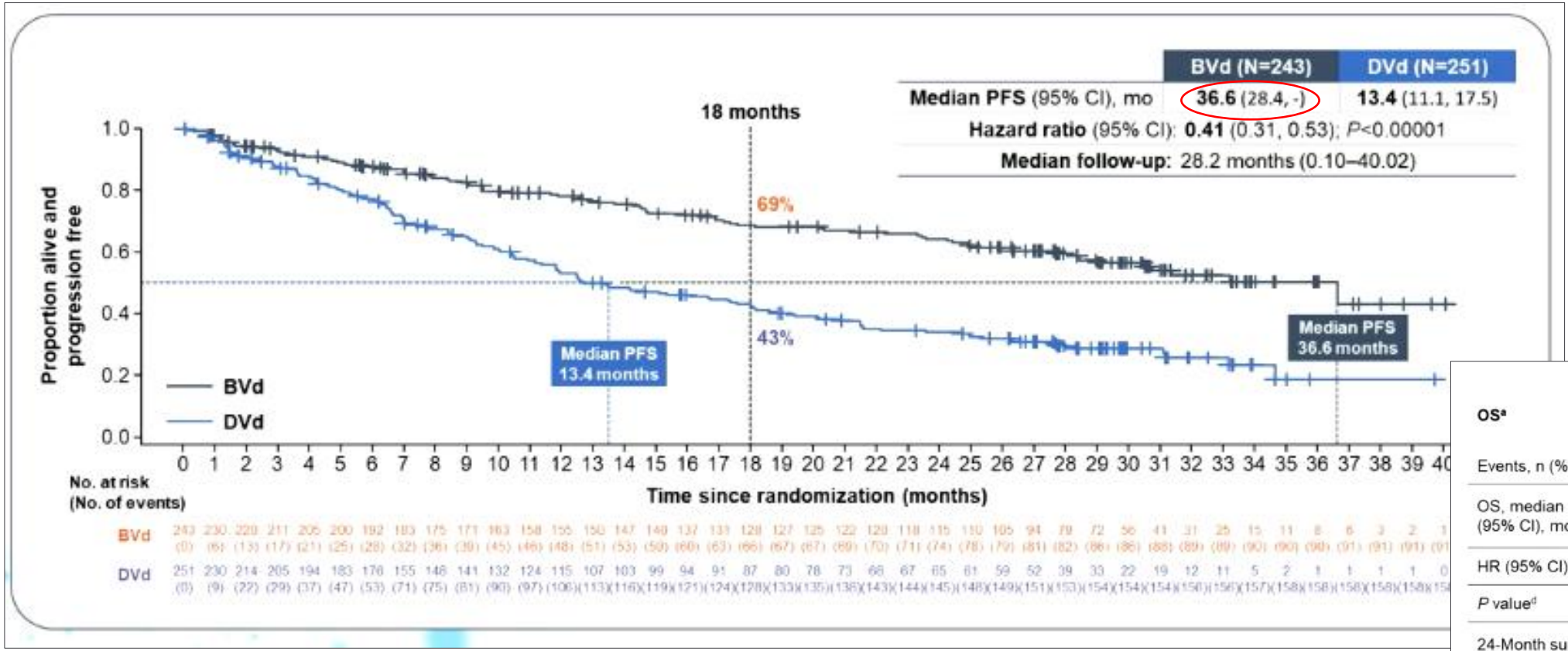
EHA/EMN Guidelines 2025 - Secondline Therapie



Dimopoulos MA, Terpos E, et al. Nat Rev Clin Oncol 2025;

Secondline Therapie

DREAMM-7: BelaVd vs DaraVd (Len refr 33%)

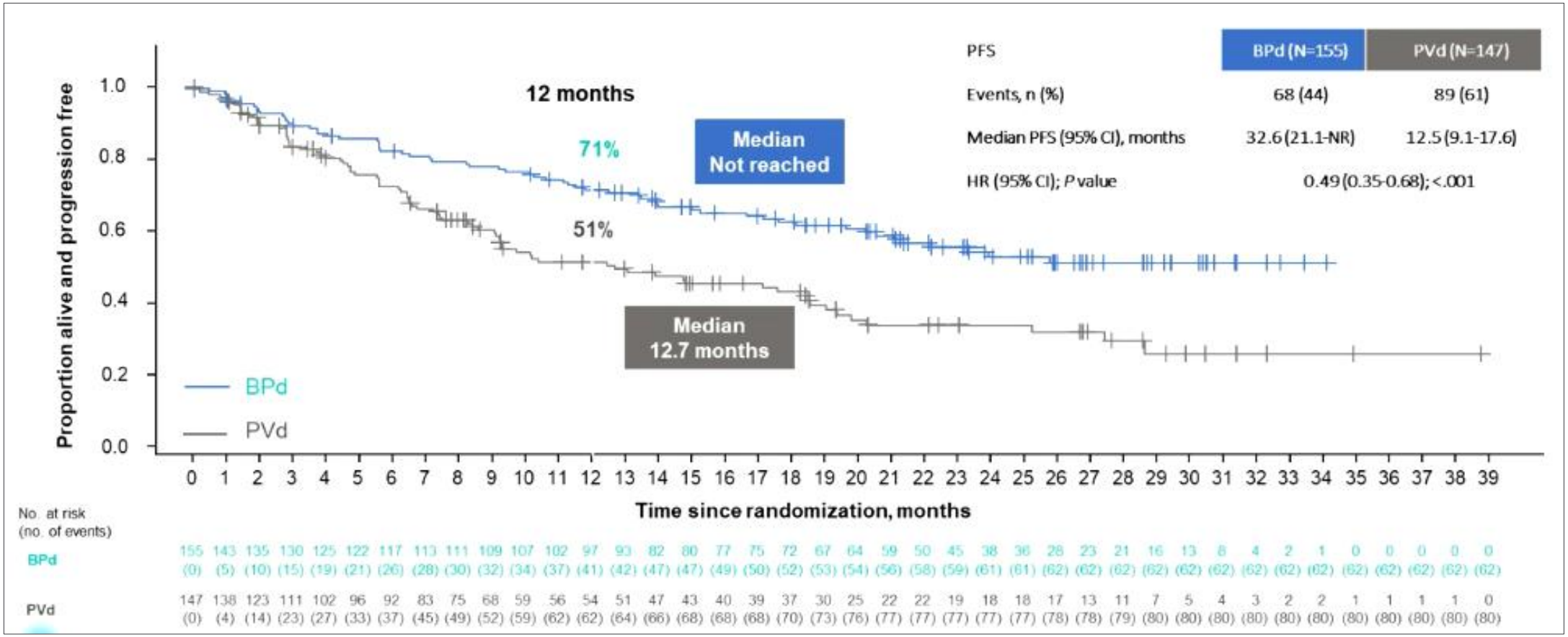


OS[a]	BVd (N=243)	DVd (N=251)
Events, n (%)	68 (28)	103 (41)
OS, median (95% CI), months[b]	NR (NR-NR)	
HR (95% CI)[c]	**0.58 (0.43-0.79)**	
P value[d]	**.00023**	
24-Month survival (95% CI), %	79 (73-84)	67 (61-73)
36-Month survival (95% CI), %	74 (68-79)	60 (54-66)

Hungria V, et al. N Engl J Med. 2024 Aug 1;391(5):393-407; Hungria V, et al. ASH 2024; abstract 772 (oral presentation

Secondline Therapie

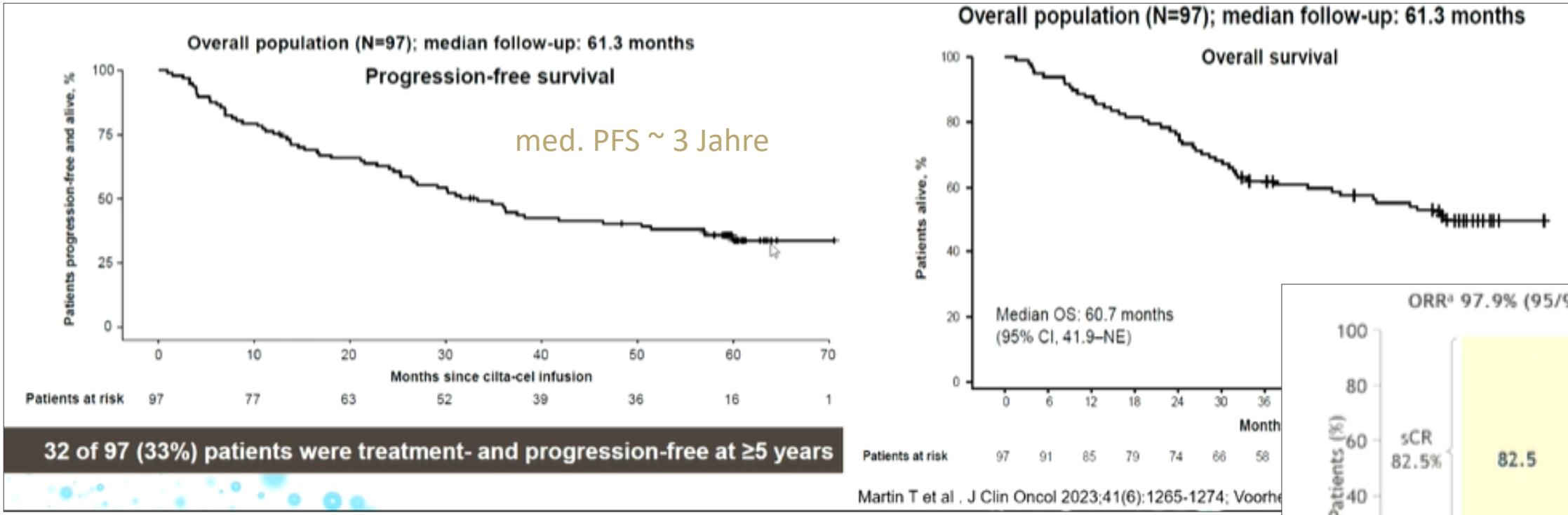
DREAMM-8: BelaPd vs PVd (Len refr 80%, antiCD38 refr 23%)



Dimopoulos MA, et al. N Engl J Med. 2024 Aug 1;391(5):408-421; Trudel S, et al. ASCO 2025; oral presenta

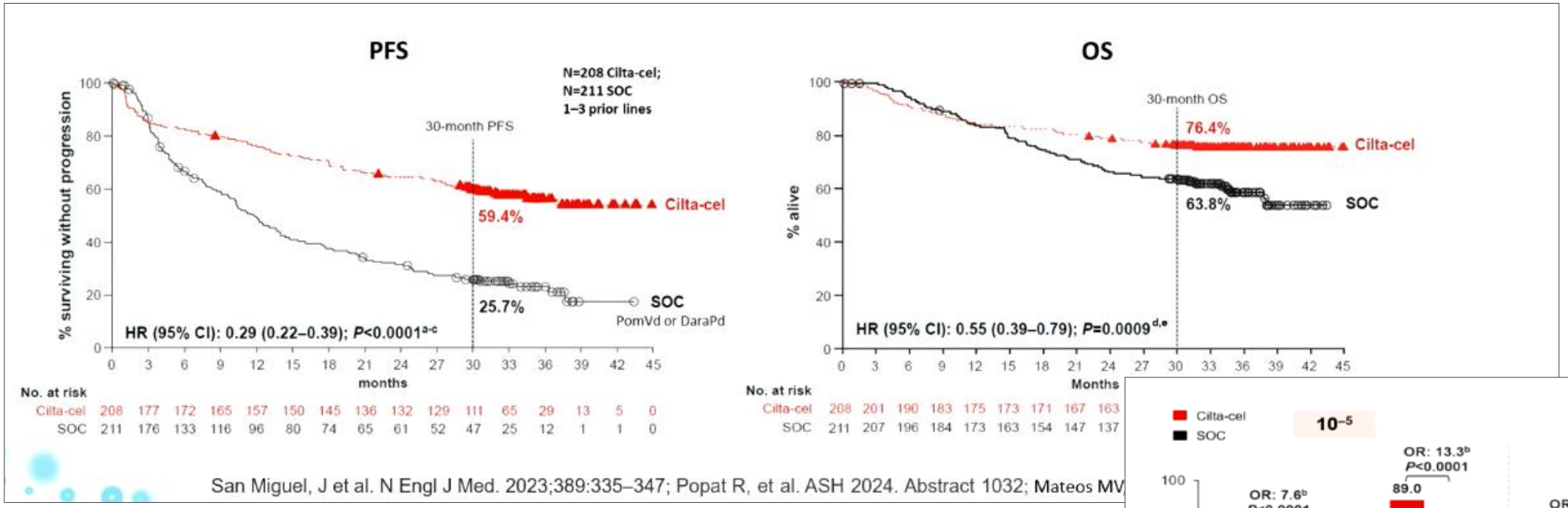
Secondline Therapie – Lenalidomid refraktär

Cartitude-1: Cilta-cel in TCE RRMM (TCR 87%)

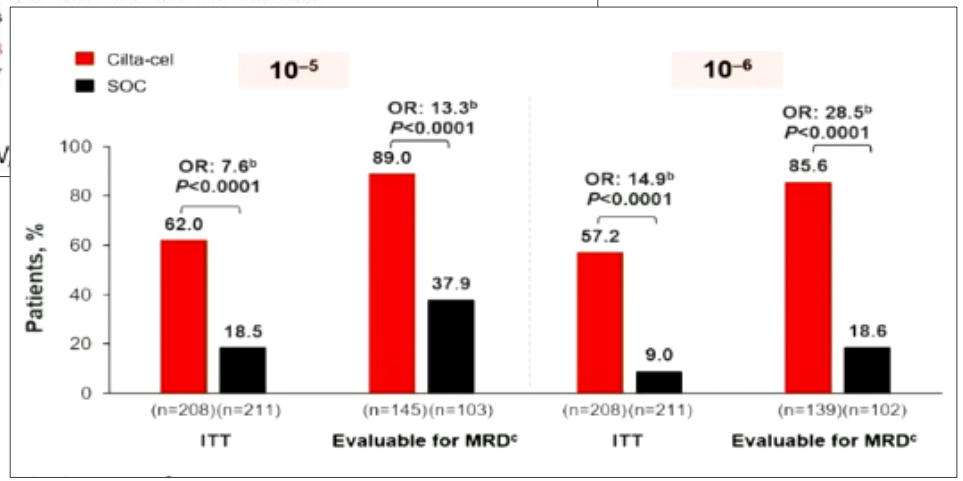


Secondline Therapie – Lenalidomid refraktär

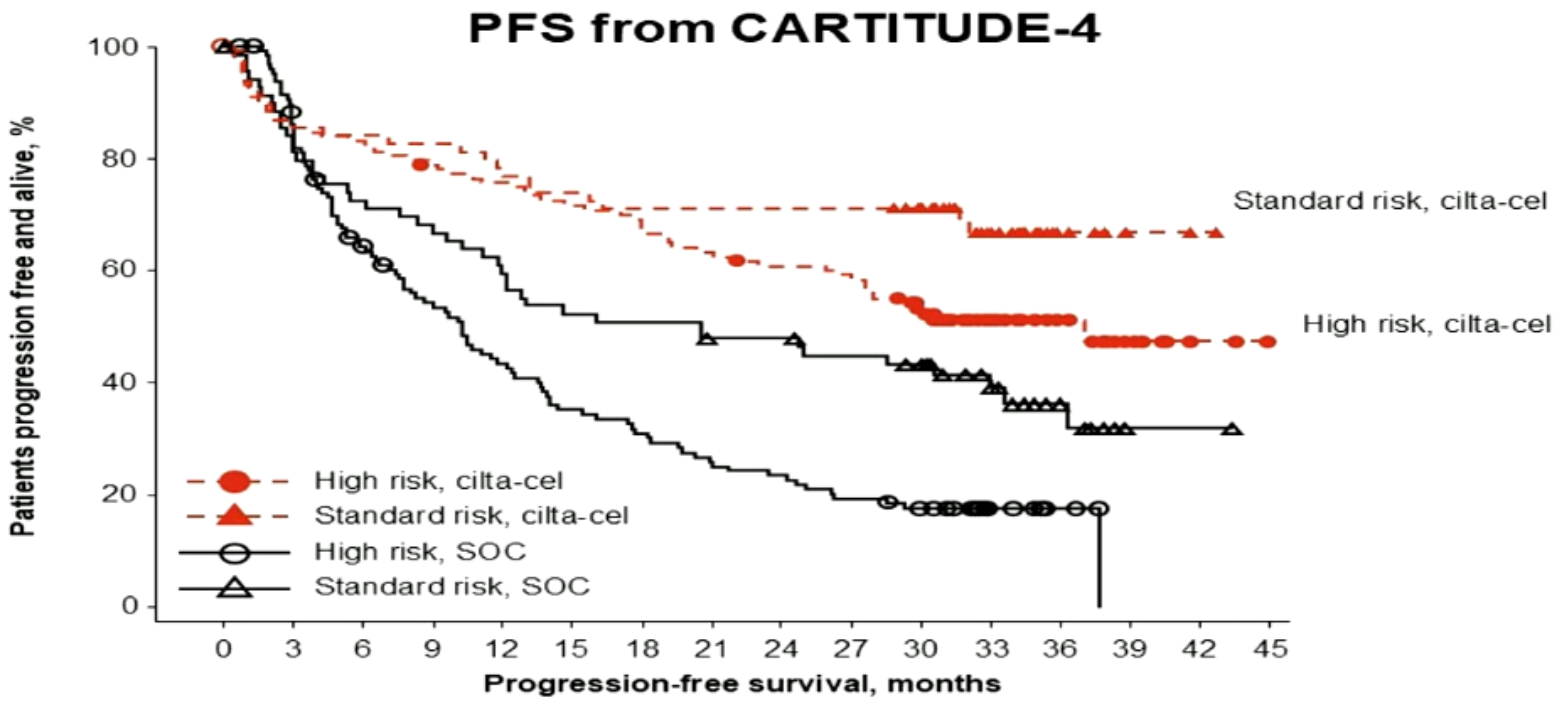
Cartitude-4: Cilta-cel vs Soc (PomVd or DPd) in **early RRMM** (len refr, antiCD38 refr 24%)



San Miguel, J et al. N Engl J Med. 2023;389:335–347; Popat R, et al. ASH 2024. Abstract 1032; Mateos MV



Secondline Therapie – Lenalidomid refraktär



Patients at risk

High risk, SOC	132	111	79	65	52	42	37	31	28	23	20	7	3	0	0	0
High risk, cilta-cel	123	106	102	96	92	87	84	76	73	70	55	31	14	7	2	0
Standard risk, SOC	70	58	50	47	41	36	35	32	32	29	27	18	9	1	1	0
Standard risk, cilta-cel	69	59	58	57	53	51	49	49	49	49	46	27	9	2	1	0

[Poster 7539: Sidana S, et al. Cilta-cel vs SOC in Patients With RRMM: CARTITUDE-4 Survival Subgroup Analyses. June 1, 2025; 9AM–12PM CDT]

Neurotoxicity in earlier vs later lines

There was a **lower incidence and severity** of certain neurotoxicities in CARTITUDE-4 vs CARTITUDE-1, including grade 3/4 delayed neurotoxicities[1–4]

Incidence of MNTs was likely lower due to **patient management strategies** implemented to mitigate the risk[1]

Management considerations for delayed neurotoxicities[5,6]

Bridging

Using bridging therapy before CAR-T cell infusion to reduce disease burden may potentially **lower the risk of neurotoxicity** (compared with no bridging)[5,6]

Monitoring and awareness

Patients, their caregivers, and CAR-T cell treatment centres should be **educated** on incidence, signs, and symptoms of delayed neurotoxicities[5,6]

Prompt neurological assessment should be initiated following identification of signs and symptoms[5,6]

Treatment

Guillain-Barré syndrome: consider IVIG treatment and escalation to plasmapheresis, depending on severity[6]

Peripheral neuropathy and cranial nerve palsies: consider a short course of systemic corticosteroids, depending on severity and symptom progression[6]

ALC expansion – prophylactic dexamethasone

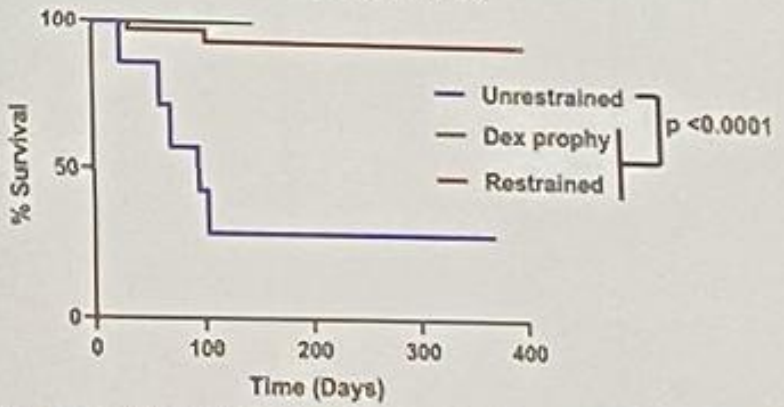
ALC is an early biomarker for identifying patients at risk for MNT and CNP after CAR-T cell therapy and may help guide closer monitoring and pre-emptive interventions[2]

Unrestrained expansion of ALC after CAR-T cell infusion may be associated with ICANS and CRS[1]

Adverse events[1]

AE, n (%)	Restrained ALC (n=34)	Unrestrained ALC (n=7)	Unrestrained ALC with prophylactic dex (n=8)
Any-grade CRS	24 (70.6)	7 (100)	8 (100)
Any-grade ICANS/MNT	2 (5.9)	5 (71.4)	0 (0)

Overall survival[1]



Expansion of absolute lymphocyte count (ALC) peaks post-CAR-T infusion; unrestrained expansion of ALC refers to ALC >5x10³/µl post-CAR-T cell infusion

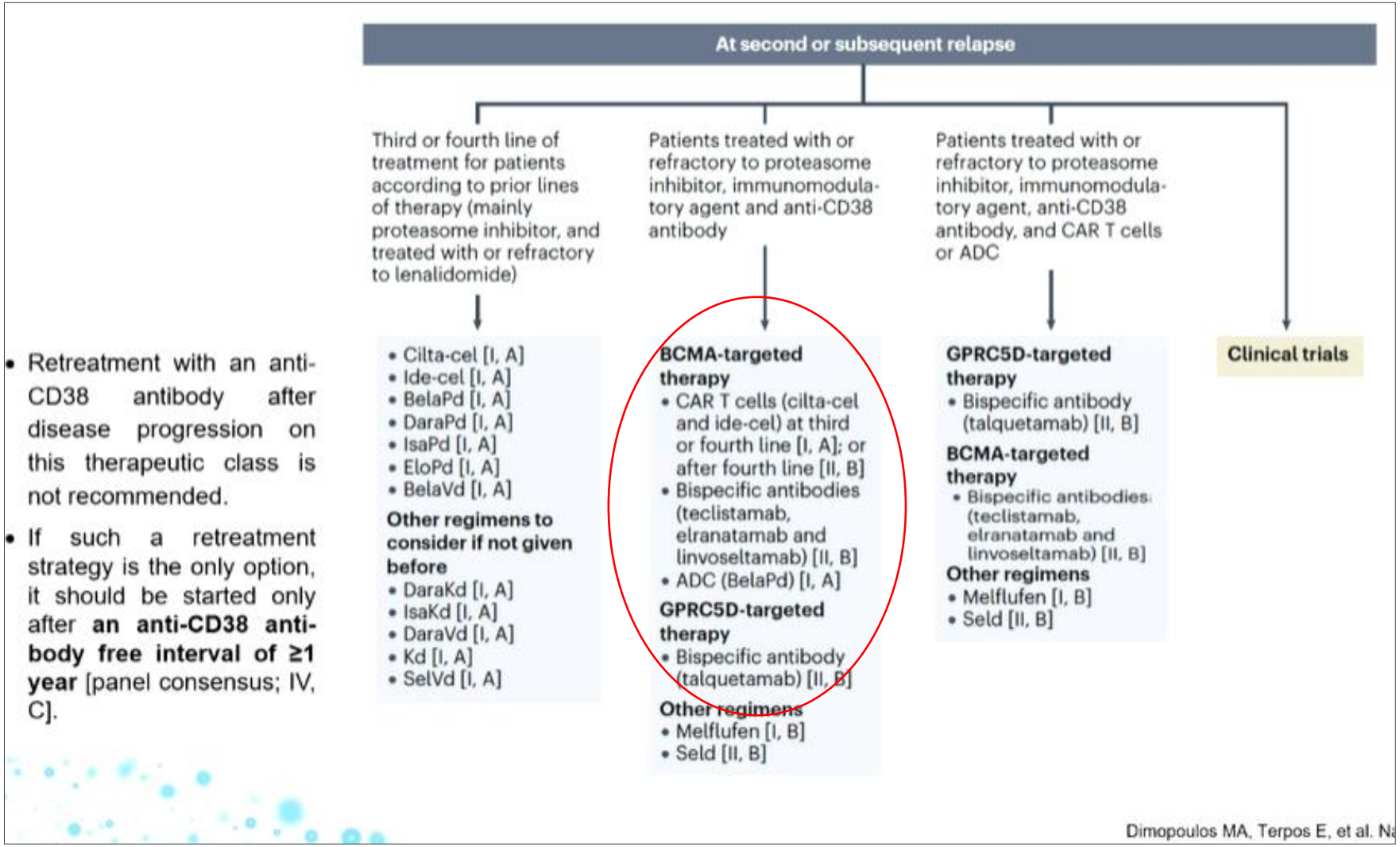
100% of patients treated with prophylactic dexamethasone did not develop ICANS/Parkinsonism[1]

AE, adverse event; ALC, absolute lymphocyte count; CRS, cytokine release syndrome; dex, dexamethasone; ICANS, immune effector cell-associated neurotoxicity; MNT, movement and neurocognitive treatment emergent AE; RRMM, relapsed/refractory multiple myeloma; RW, real-world; US, United States.
1. Turner JA, et al. Tandem Meetings 2025 (Abstract No. 290 – poster). 2. Lin Y et al. EHA 2025 (Abstract No. PS1728 - abstract).

MNT: neurocognitive movement disorders
CNP: Cranial nerve palsies

EHA/EMN Guidelines 2025 – Second/subsequent relapse

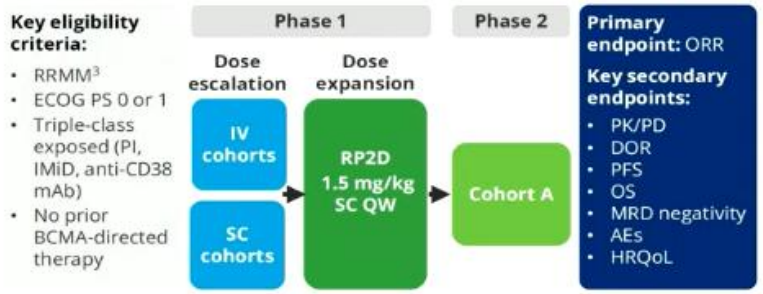
- Retreatment with an anti-CD38 antibody after disease progression on this therapeutic class is not recommended.
- If such a retreatment strategy is the only option, it should be started only after **an anti-CD38 antibody free interval of ≥1 year** [panel consensus; IV, C].



Dimopoulos MA, Terpos E, et al. Na

MajesTEC-1: Teclistamab in TCE RRMM

Trial design and dosing schedule

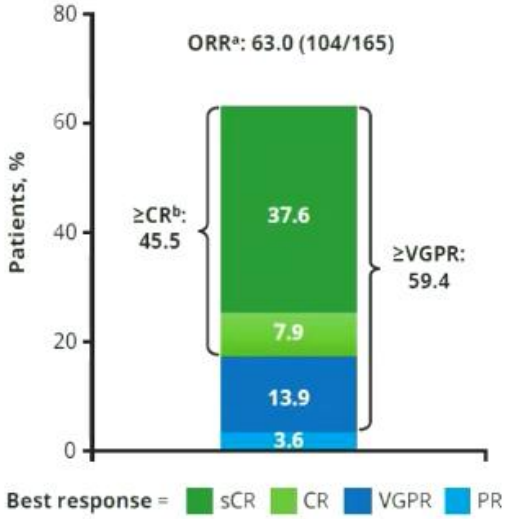


Teclistamab dosing schedule: QW; option to switch to Q2W after ≥4 cycles (Phase I) if ≥PR or after 6 months (Phase II) if ≥CR[2]

Baseline characteristics, n=165

Extramedullary disease, n (%)	28 (17.0)
High-risk cytogenetics, n (%)	38 (25.7)
ISS stage III, n (%)	20 (12.3)
Prior lines of therapy, median (range)	5 (2–14)
Refractory status, n (%)	
Triple-class refractory	128 (77.6)
Penta-drug refractory	50 (30.3)

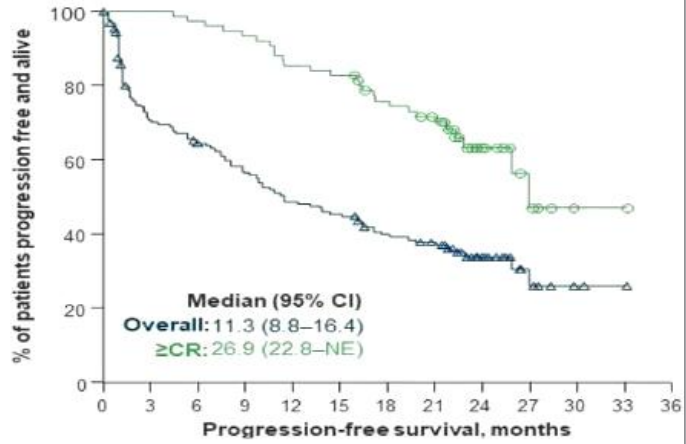
Response rates

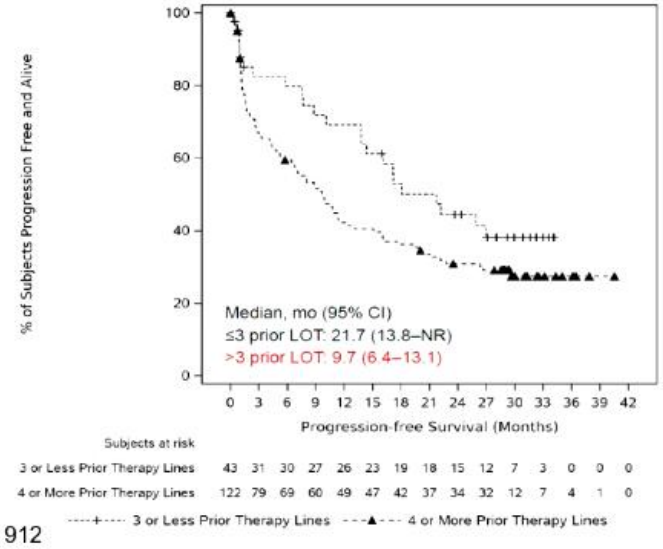


Median time to first response: 1.2 months
Median time to ≥CR: 4.6 months

MRD-negativity rate (10^{-5}): 27%

Progression-free survival





Van de Donk NWCJ, et al. ASCO 2023:abstract 8011; Costa L, et al. HEMO 2024:abstrac t 912

MagnetisMM-3: Elranatamab in TCE RRMM

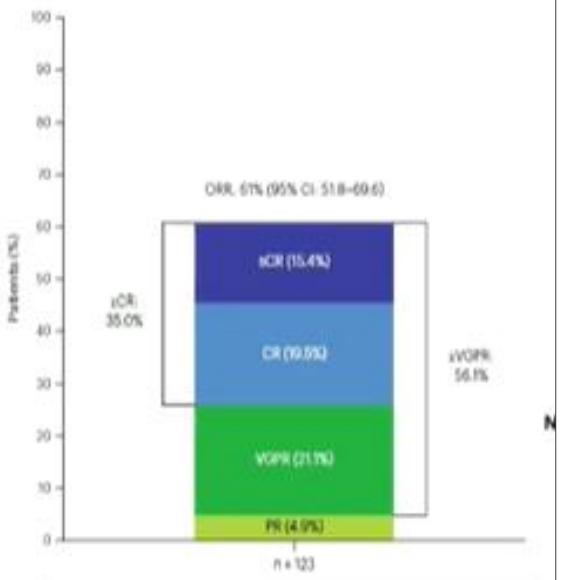
Elranatamab dosing schedule

QW cycles 1–6; Q2W cycles 7+ for patients with ≥PR

Baseline characteristics, Cohort A (N=123)

Extramedullary disease by BICR,† n (%)	39 (31.7)
Bone marrow plasma cells, n (%)	
<50%	89 (72.4)
≥50%	26 (21.1)
Missing	8 (6.5)
Prior lines of therapy, median (range)	5 (2–22)
Prior stem cell transplant, n (%)	87 (70.7)
Exposure status, n (%)	
Triple-class	123 (100.0)
Penta-drug	87 (70.7)
Refractory status, n (%)	
Triple-class	119 (96.7)
Penta-drug	52 (42.3)
Refractory to last line of therapy, n (%)	118 (95.9)

Response

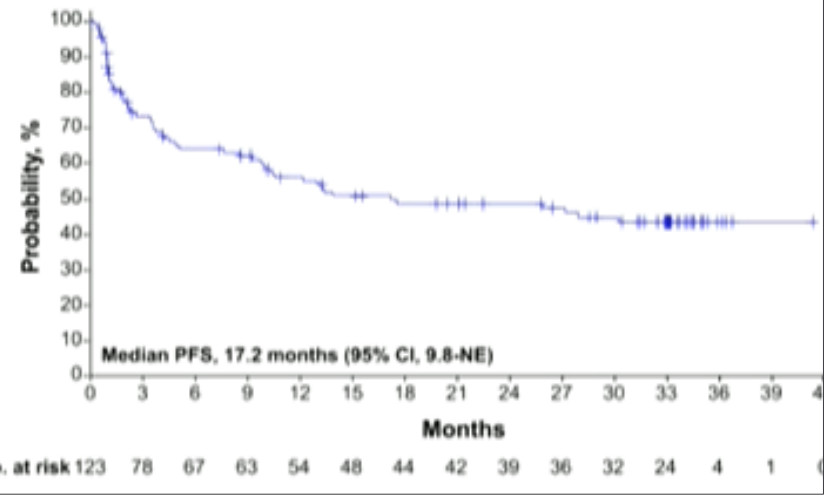


Median time to first response: 1.2 months

Median time to ≥CR: 6.1 months

Median follow-up-33.9 months

Progression-free survival



Lesokhin AM, et al. Nat Med 2023;29:2259-2267; Prince M, et al. ASH 202

MonumenTAL-1: Talquetamab in TCE RRMM

Trial design

RP2D 0.4 mg/kg QW SC
- Prior BCMA-targeting ADC treatment allowed
- Prior T-cell redirecting therapy-naïve

(n=143; n=21 Phase I and n=122 Phase II)

RP2D 0.8 mg/kg Q2W SC
- Prior BCMA-targeting ADC treatment allowed
- Prior T-cell redirecting therapy-naïve

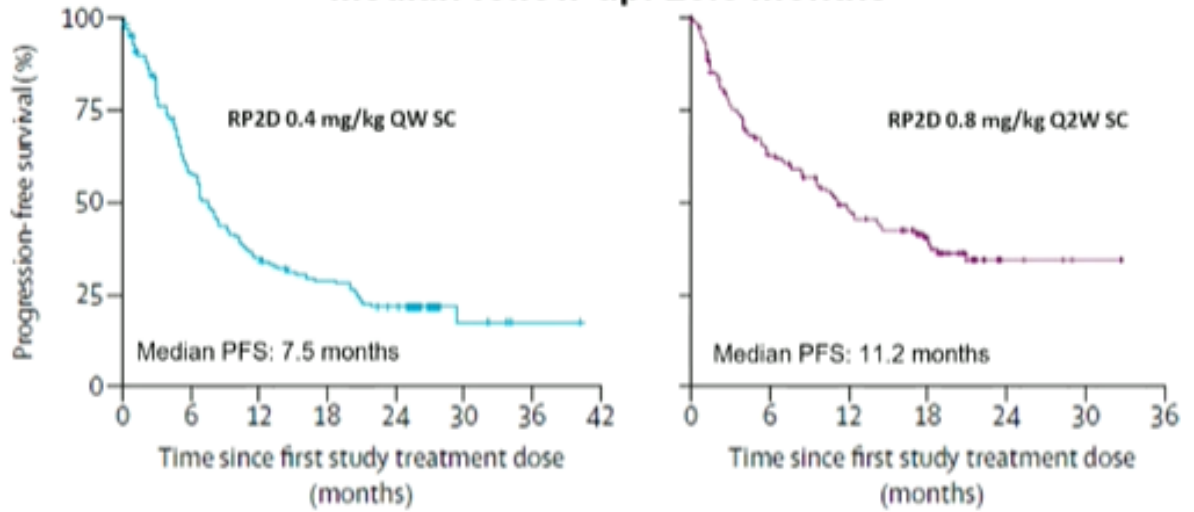
(n=145; n=36 Phase I and n=199 Phase II)

Prior T-cell redirection (QW and Q2W)
- Patients received either 0.4 mg/kg QW or 0.8 mg/kg talquetamab

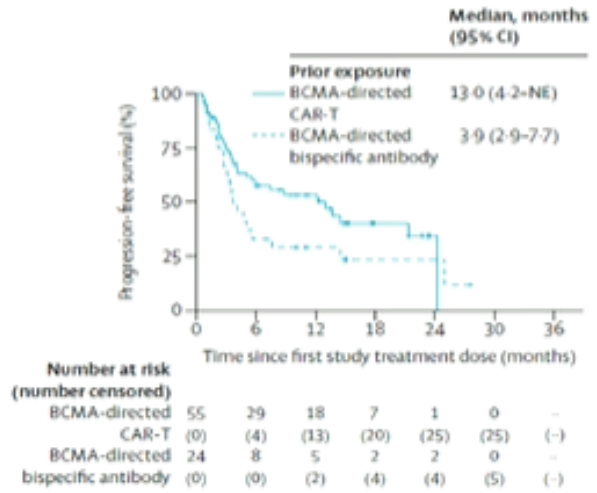
(n=51; n=17 Phase I and n=34 Phase II)

100% triple-class exposed
69–74% triple-class refractory

Median follow-up: 25.6 months



Response rates



Chari A, et al. N Engl J Med 2022;387:2232-2244; Chari A, et al. Lancet Haematol 2025;12:e269-e281;

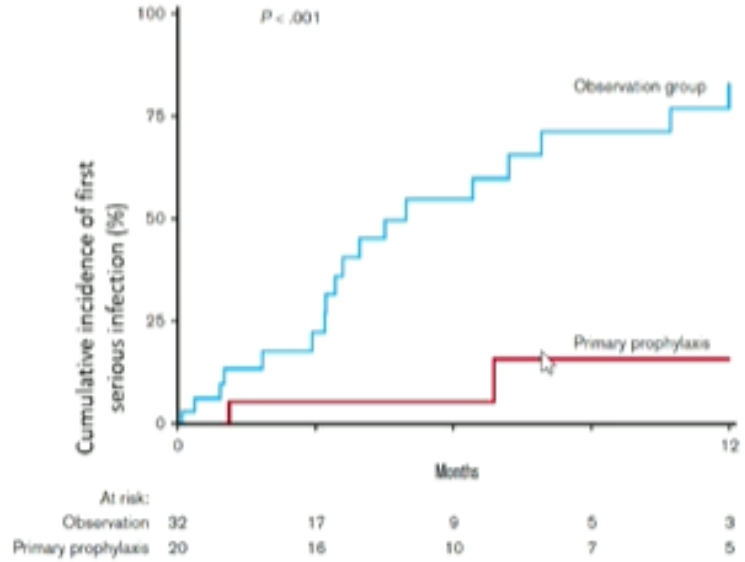
Bispezifische Antikörper in der Praxis

Managing infections

IMWG guidelines recommend specific measures:[1]

- Antivirals, antibacterials or antifungals
- Vaccinations
- Monthly IVIg treatment in patients with IgG concentration <400 mg/dL

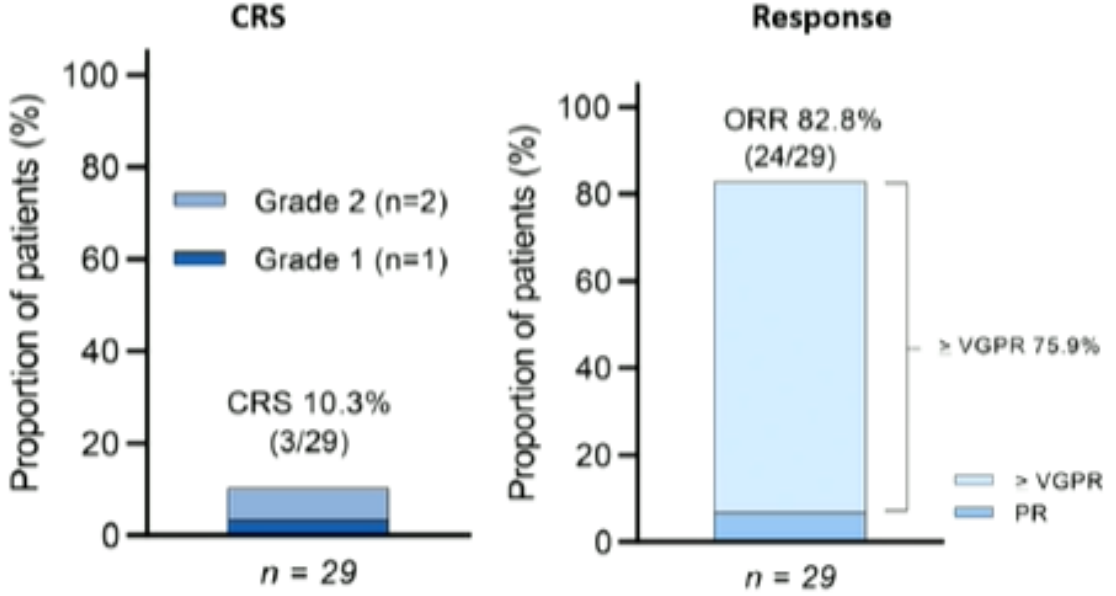
Impact of prophylactic IVIg on infection[2]



Managing CRS

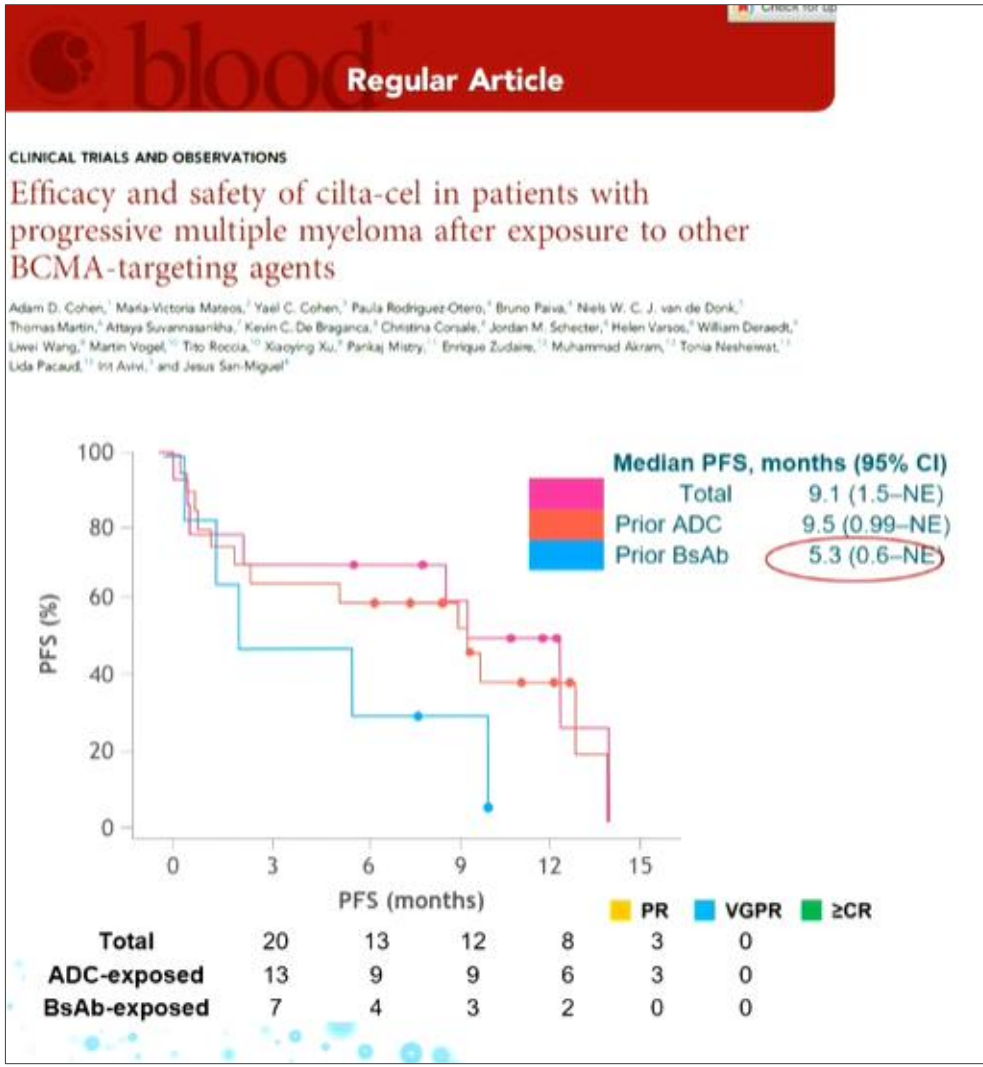
- Prophylactic tocilizumab may be used to prevent CRS[3]

Impact of prophylactic tocilizumab on CRS and response[3]



1. Rodriguez-Otero P, et al. Lancet Oncol 2024;25:e205–e216; 2. Frerichs KA, et al. Blood Adv 2024;8:195–206; 3. Korst CLBM, et al. Hemasphere 2024;8:e132.

Sequencing

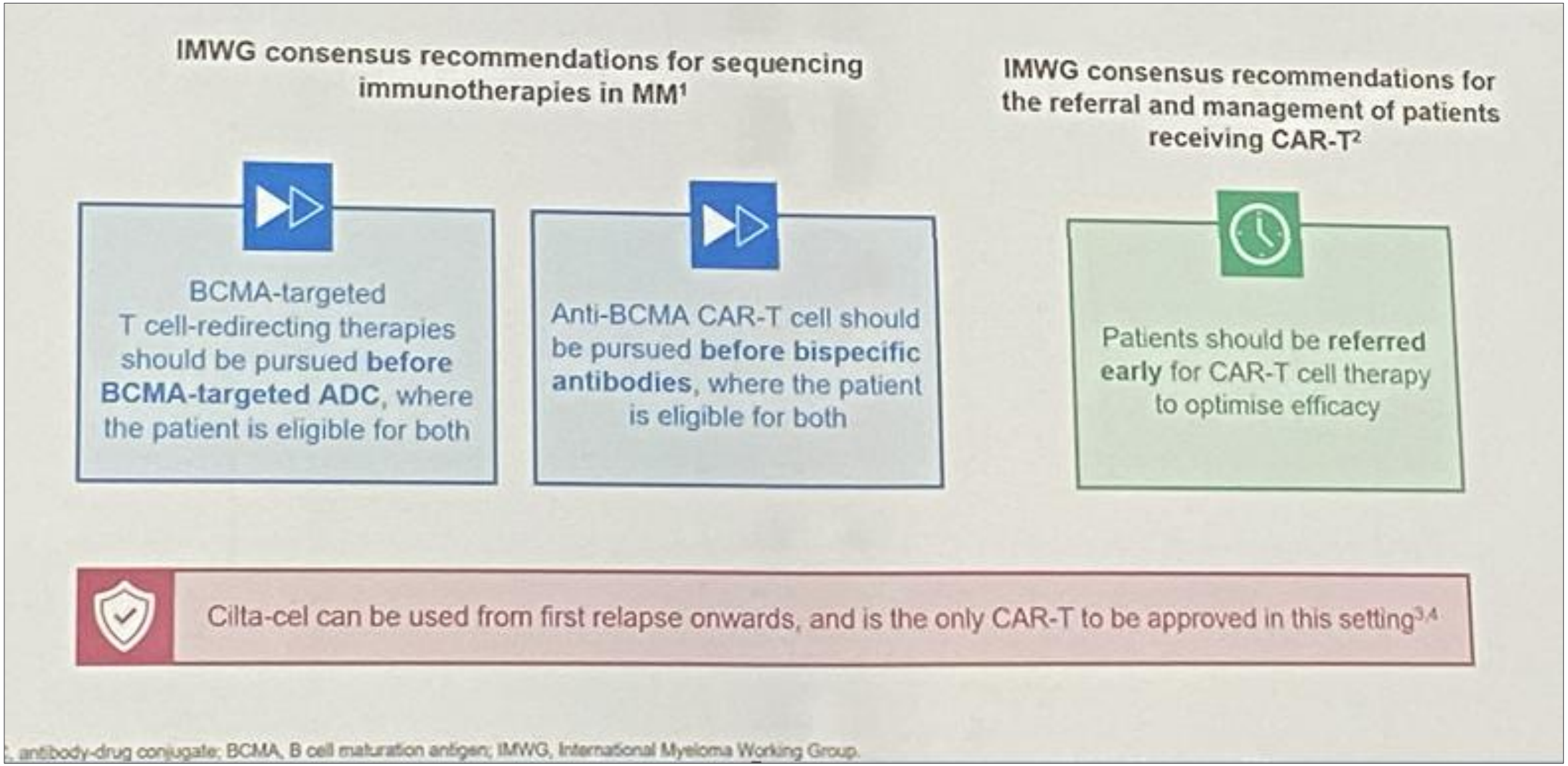


Recommendations about Sequencing of Modern Immunotherapy

- Sequencing of the immunotherapies in patients with RRMM presents challenges; further prospective studies will provide more insights into this important issue.
- Currently available data suggest that CAR T cell therapies might need to be given to eligible patients before BCMA-targeted ADCs or bispecific T cell engagers [panel consensus; III, B].
- Bispecific T cell engagers can be effective immediately after disease progression on CAR T cells, and talquetamab is possibly the agent with better outcomes in this setting [panel consensus; V, C].

Dimopoulos MA, Terpos E, et al. Nat Rev Clin Oncol 2025; in press

Sequencing


IMWG consensus recommendations for sequencing immunotherapies in MM[1]
BCMA-targeted T cell-redirecting therapies should be pursued **before BCMA-targeted ADC**, where the patient is eligible for both
Anti-BCMA CAR-T cell should be pursued **before bispecific antibodies**, where the patient is eligible for both
IMWG consensus recommendations for the referral and management of patients receiving CAR-T[2]
Patients should be **referred early** for CAR-T cell therapy to optimise efficacy
Cilta-cel can be used from first relapse onwards, and is the only CAR-T to be approved in this setting[3,4]
, antibody-drug conjugate; BCMA, B cell maturation antigen; IMWG, International Myeloma Working Group.

NEWS – JNJ-5322 Trispecific

First-in-Human Study of JNJ-79635322 (JNJ-5322), a Novel, Next-Generation Trispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma: Initial Phase 1 Results

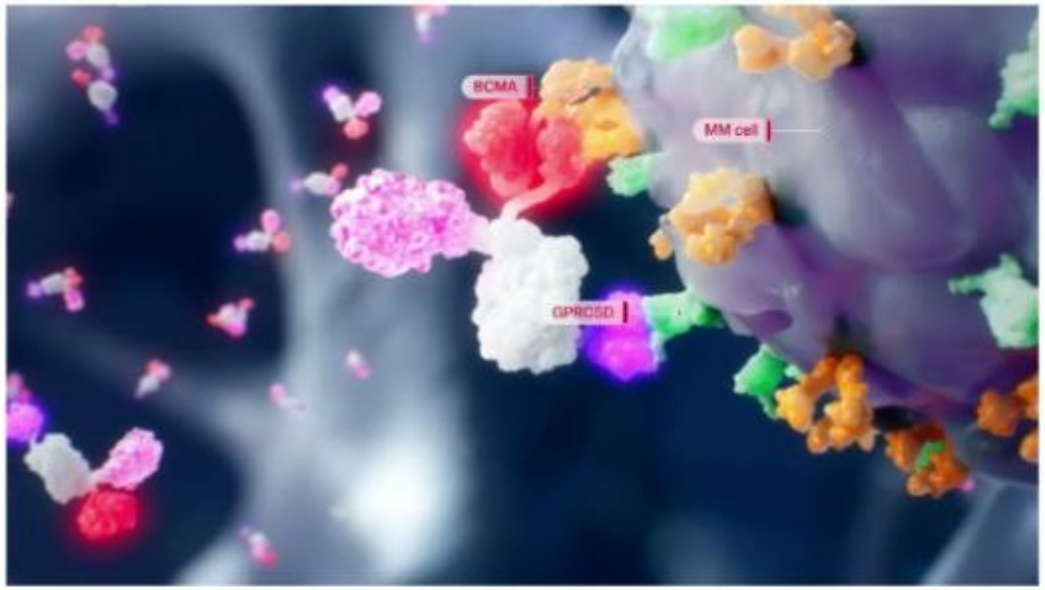
Rakesh Popat,[1] Cyrille Touzeau,[2] Aurore Perrot,[3] Sébastien Anguille,[4] Albert Oriol,[5] Nicolas Kint,[6] Jo Caers,[7] Monique C. Minnema,[8] Martin Kaiser,[9] Hans Lee,[10] Alfred Garfall,[11] Jeffrey Matous,[12] Larysa Sanchez,[13] Azra Borogovac,[14] Lionel Karlin,[15] Laura Rosinol,[16] Wilfried Roeloffzen,[17] Saad Usmani,[18] Cindy Varga,[19] Darren Pan,[20] Tadao Ishida,[21] Pansy Minnick,[22] M. Damiette Smit,[23] Nikki Daskalakis,[22] Thomas Prior,[22] Maria Krevvata,[22] Ashley Nguyen,[22] Brandi Hilder,[22] Daniel Jonathan,[22] Joseph Weidman,[22] Sangmin Lee,[22] Maria-Victoria Mateos,[24] Paula Rodriguez-Otero,[25] Gala Vega,[26] Niels WCJ van de Donk[27]

[1]Clinical Research Facility, National Institute for Health Research University College London Hospitals NHS Foundation Trust, London, UK; [2]Centre Hospitalier Universitaire de Nantes, Nantes, France; [3]CHU de Toulouse, Institut Universitaire du Cancer de Toulouse-Oncopole, Université de Toulouse, Université Paul Sabatier, Service d'Hématologie, Toulouse, France; [4]Division of Hematology and Center for Cell Therapy and Regenerative Medicine, Antwerp University Hospital, University of Antwerp, Antwerp, Belgium; [5]Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Badalona, Spain; [6]Department of Hematology, Ghent University Hospital, Ghent, Belgium; [7]Department of Hematology, CHU de Liège, Liège, Belgium; [8]University Medical Center Utrecht, Utrecht, Netherlands; [9]The Royal Marsden, NHS Trust, London, UK; [10]University of Texas, MD Anderson Cancer Center, Houston, Tx, USA; [11]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA; [12]Colorado Blood Cancer Institute, Sarah Cannon Research Institute, Denver, CO, USA; [13]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [14]City of Hope National Medical Center, Duarte, CA, USA; [15]Service d'Hématologie Clinique, Centre Hospitalier Lyon Sud, Pierre-Bénite, France; [16]Department of Hematology, Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona, Spain; [17]University Medical Center Groningen, Groningen, Netherlands; [18]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [19]Department of Hematology, Levine Cancer Institute Atrium Health, Charlotte, NC, USA; [20]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [21]Department of Hematology, Japanese Red Cross Medical Center, Tokyo, Japan; [22]Johnson & Johnson, Spring House, PA, USA; [23]Enliven Therapeutics, Boulder, CO, USA; [24]University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Salamanca, Spain; [25]Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA, Pamplona, Spain; [26]Division of Hematology, START Madrid-FJD, Hospital Fundación Jiménez Díaz, Madrid, Spain; [27]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Presented by R Popat at the European Hematology Association (EHA) 2025 Hybrid Congress; June 12–15, 2025; Milan, Italy

Novel Binding Domaines of CD3, BCMA, GPRC5D

Molecule	Implications
Dual-Targeted Molecule to Bind Both BCMA and GPRC5D	• Enhanced myeloma cell targeting due to **"double lock-down"** effect of binding 2 myeloma antigens • **More comprehensive targeting of myeloma cells** ◦ BCMA-/GPRC5D+, BCMA+/GPRC5D-, and dual BCMA+/GPRC5D+ • **Prevention of antigen escape** • **Potential to improve GPRC5D-related safety profile** • **Manageable CRS profile with only 1 step-up dose needed**
Novel CD3, BCMA, and GPRC5D Binding Domains	



CRS, cytokine release syndrome.

3

Presented by R Popat at the European Hematology Association (EHA) 2025 Hybrid Congress; June 12–15, 2025; Milan, Italy

JNJ-5322 Trispecific

Characteristic	RP2D (n=36)	All doses (N=147)
Median follow-up, months (range)	11.6 (0.4–18.6)	9.3 (0.3–25.8)
Median age, years (range)	67.5 (43–87)	64.0 (39–87)
Male, n (%)	22 (61.1)	87 (59.2)
Race, n (%)		
White	28 (77.8)	110 (74.8)
Black/African American	1 (2.8)	13 (8.8)
Asian	1 (2.8)	7 (4.8)
Multiple	2 (5.6)	2 (1.4)
Unknown/not reported	4 (11.1)	15 (10.2)
Extramedullary plasmacytomas ≥1,[a] n (%)	3 (8.3)	16 (10.9)
High-risk cytogenetics,[b] n (%)	9 (27.3)	39 (31.2)
ISS stage,[c] n (%)		
I	19 (52.8)	77 (53.1)
II	12 (33.3)	50 (34.5)
III	5 (13.9)	18 (12.4)
Years since diagnosis,[d] median (range)	7.0 (0.9–18.7)	6.9 (0.7–31.9)

Characteristic	RP2D (n=36)	All doses (N=147)
Median prior LOT, n (range)	4.0 (2–11)	4.0 (1–11)
Exposure status, n (%)		
Triple-class[e]	36 (100.0)	147 (100.0)
Penta-drug[f]	15 (41.7)	72 (49.0)
BCMA/GPRC5D exposed	9 (25.0)	29 (19.7)
Prior BCMA	8 (22.2)	26 (17.7)
Prior GPRC5D	1 (2.8)	5 (3.4)
BCMA/GPRC5D naive	27 (75.0)	118 (80.3)
Antibody-drug conjugate	2 (5.6)	7 (4.8)
CAR-T therapy	4 (11.1)	12 (8.2)
Bispecific antibody	6 (16.7)	16 (10.9)
Refractory status, n (%)		
PI	19 (52.8)	86 (58.5)
IMiD	36 (100.0)	136 (92.5)
Anti-CD38	36 (100.0)	138 (93.9)
Triple-class[e]	19 (52.8)	79 (53.7)
Penta-drug[f]	2 (5.6)	10 (6.8)
To last LOT	34 (94.4)	132 (89.8)

Data cut-off date: April 15, 2025. RP2D selected as 100 mg Q4W with one 5 mg SUD.
[a]≥1 nonradiated, bone-independent lesion ≥2 cm. Patients with paraskeletal plasmacytomas were permitted but not counted as EMD. [b]FISH or karyotype testing in n=33 (RP2D) and n=125 (total). Defined as del(17p), t(4;14), or t(14;16). [c]In n=145 (total). [d]In n=35 (RP2D) and n=144 (total). [e]≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb. [f]≥2 PIs, ≥2 IMiDs, and ≥1 anti-CD38 mAb.

5

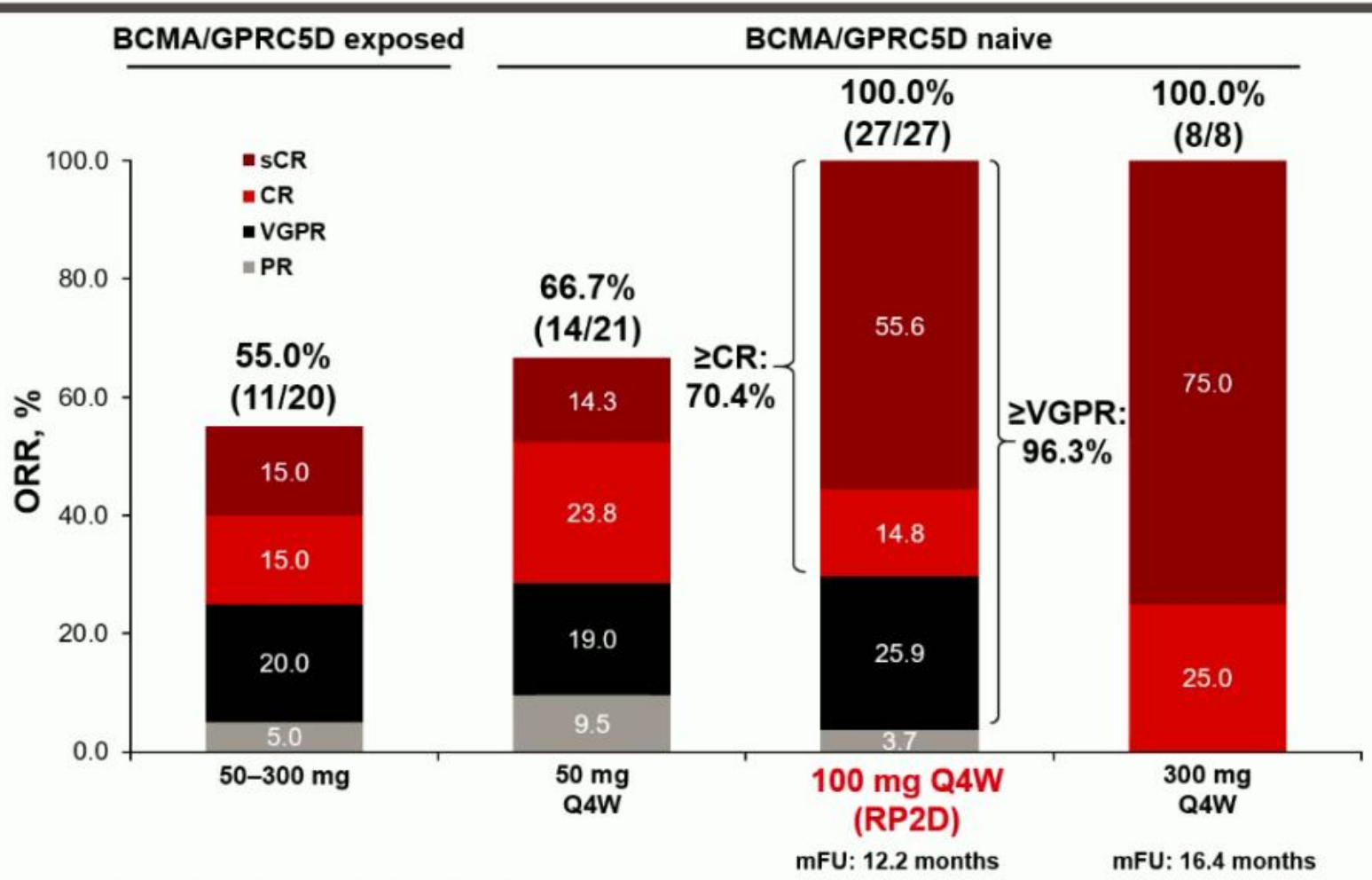
Presented by R Popat at the European Hematology Association (EHA) 2025 Hybrid Congress; June 12–15, 2025; Milan, Italy.

Adverse events

Most common TEAEs,[a] n (%)	RP2D (n=36)		All doses (N=147)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic TEAEs (≥10% of total)				
Neutropenia	15 (41.7)	11 (30.6)	72 (49.0)	61 (41.5)
Lymphopenia	16 (44.4)	15 (41.7)	55 (37.4)	52 (35.4)
Anemia	6 (16.7)	3 (8.3)	37 (25.2)	22 (15.0)
Thrombocytopenia	8 (22.2)	3 (8.3)	27 (18.4)	12 (8.2)
Leukopenia	5 (13.9)	3 (8.3)	19 (12.9)	11 (7.5)
Nonhematologic TEAEs (≥30% of total)				
Infections	29 (80.6)	12 (33.3)	111 (75.5)	42 (28.6)
Taste-related[b]	21 (58.3)	NA	85 (57.8)	NA
CRS	19 (52.8)	0	83 (56.5)	0
Nail-related[c]	22 (61.1)	0	81 (55.1)	0
Skin (non-rash)[d]	23 (63.9)	0	73 (49.7)	1 (0.7)
Hypogammaglobulinemia[e]	10 (27.8)	1 (2.8)	53 (36.1)	4 (2.7)
Diarrhea	11 (30.6)	1 (2.8)	49 (33.3)	5 (3.4)
Fatigue	13 (36.1)	3 (8.3)	48 (32.7)	4 (2.7)

Parameter	100 mg without prophylactic tocilizumab (n=26)	100 mg with prophylactic tocilizumab (n=20)
Patients with CRS,[a] n (%)	18 (69.2)	4 (20.0)
Grade 1	14 (53.8)	4 (20.0)
Grade 2	4 (15.4)	0
Grade 3	0	0
Onset of CRS,[b] days, median (range)	2 (1-4)	1 (1-2)

ORR



At the RP2D in patients naive to BCMA/GPRC5D (n=27)

Median follow-up, months (range)	12.2 (7.4–18.6)
Median time to first response, months (range)	1.2 (0.3–5.2)
Median time to best response, months (range)	5.9 (0.3–11.1)

Data cut-off date: April 15, 2025. RP2D selected as 100 mg Q4W with one 5 mg SUD.

Presented by R Popat at the European Hematology Association (EHA) 2025 Hybrid Congress; June 12–15, 2025; Milan, Italy

11

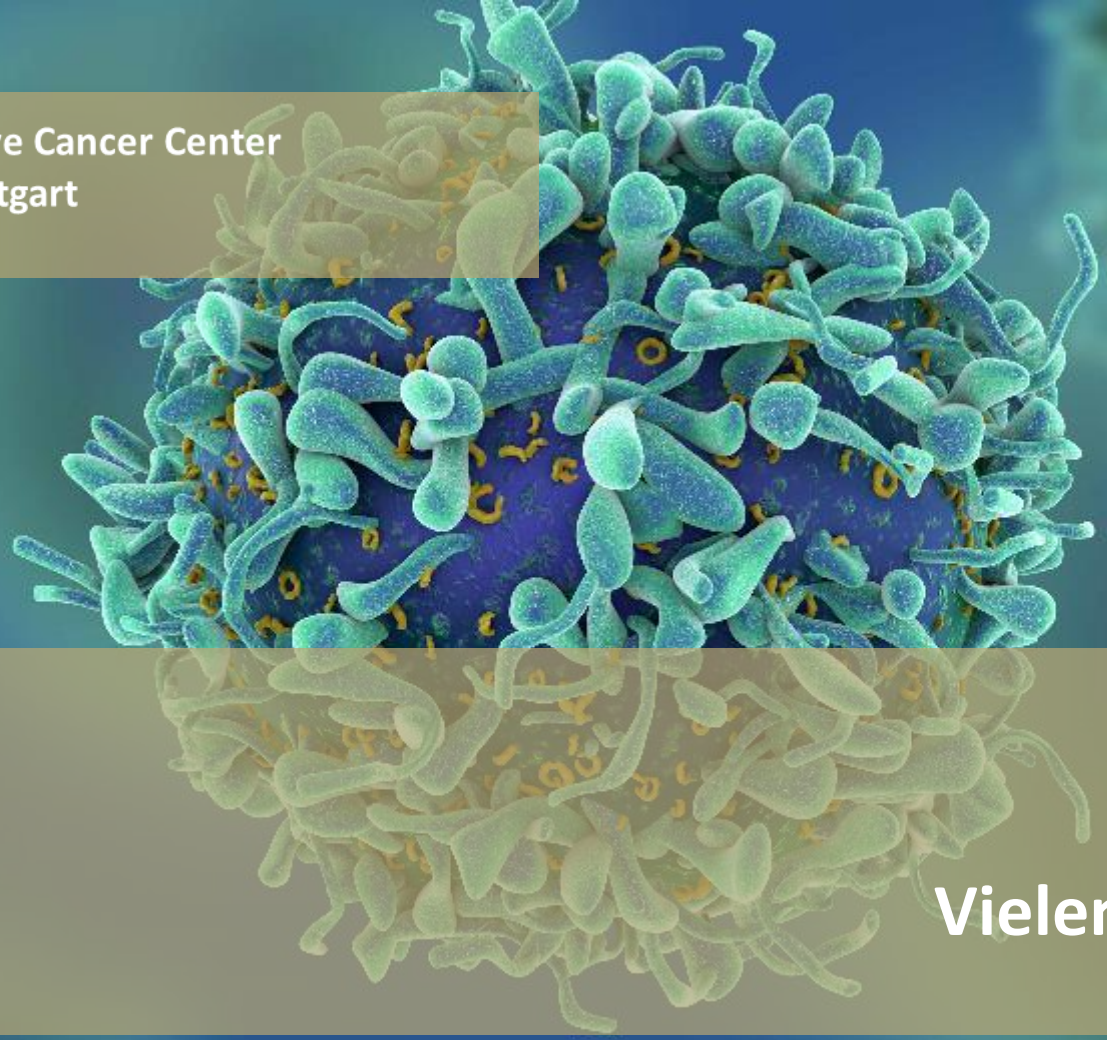
JNJ-5322 – paradigm shift?

- **JNJ-5322 100 mg Q4W SC with 1 SUD (2–8 days before first full dose) of 5 mg was selected as the RP2D**
- **JNJ-5322 appeared to have an improved or similar safety profile compared with bispecific antibodies targeting BCMA/GPRC5D**
  - Grade 3/4 infection rate of 28.6% with appropriate infection management
  - Improved oral TEAE profile, with minimal to no weight loss
  - CRS events were low grade with only 1 SUD; prophylactic tocilizumab data support option for outpatient dosing
- **ORR of 100% (≥CR, 70.4%) at the RP2D in patients naive to BCMA/GPRC5D**
  - 12-month PFS of 95.0% at the RP2D in BCMA/GPRC5D-naive patients

JNJ-5322, a BCMA×GPRC5D T-cell engaging trispecific antibody, demonstrated manageable safety and an ORR comparable to CAR-T, with convenient, off-the-shelf, Q4W dosing with 1 SUD to facilitate outpatient dosing

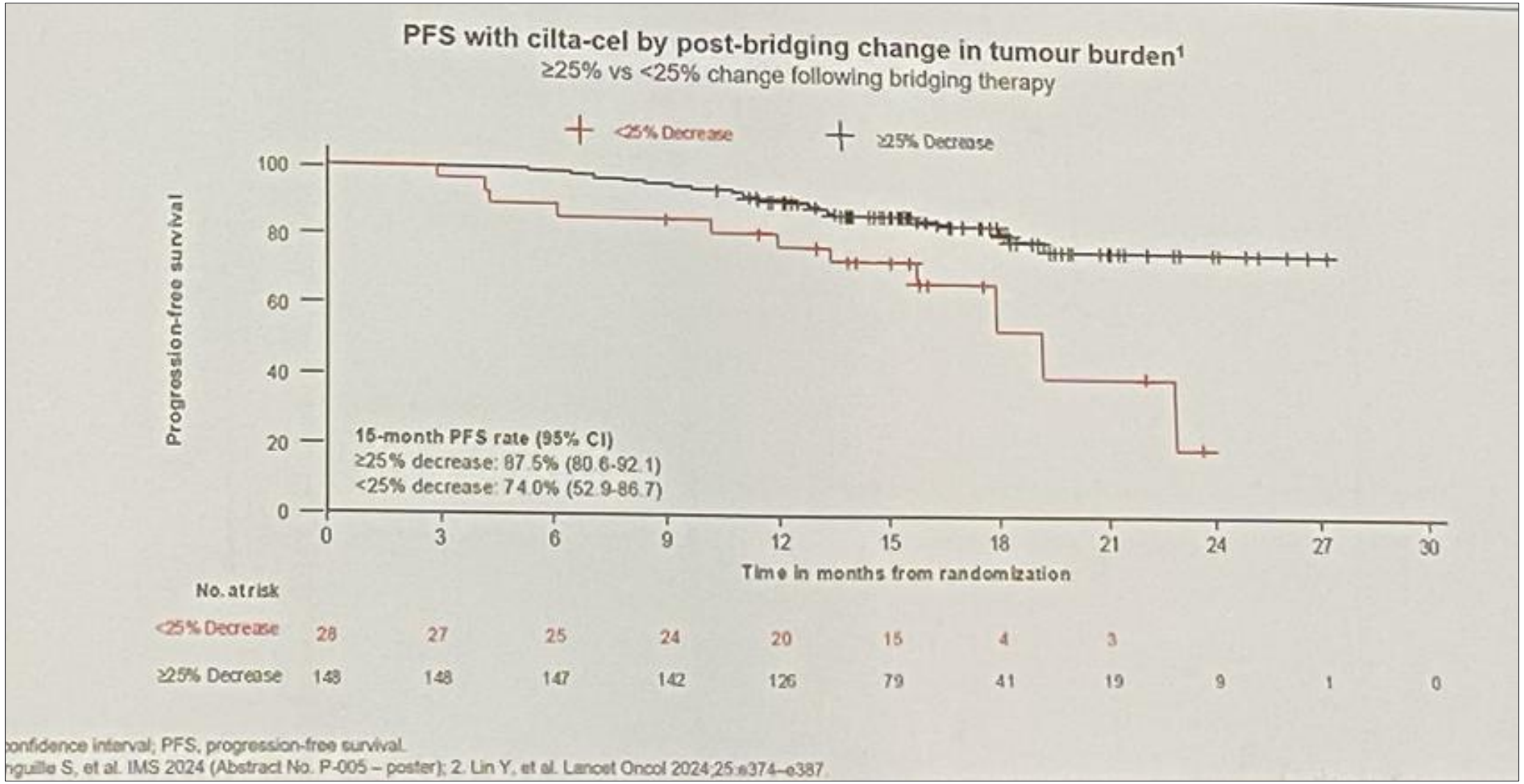
14

Presented by R Popat at the European Hematology Association (EHA) 2025 Hybrid Congress, June 12–15, 2025, Milan, Italy

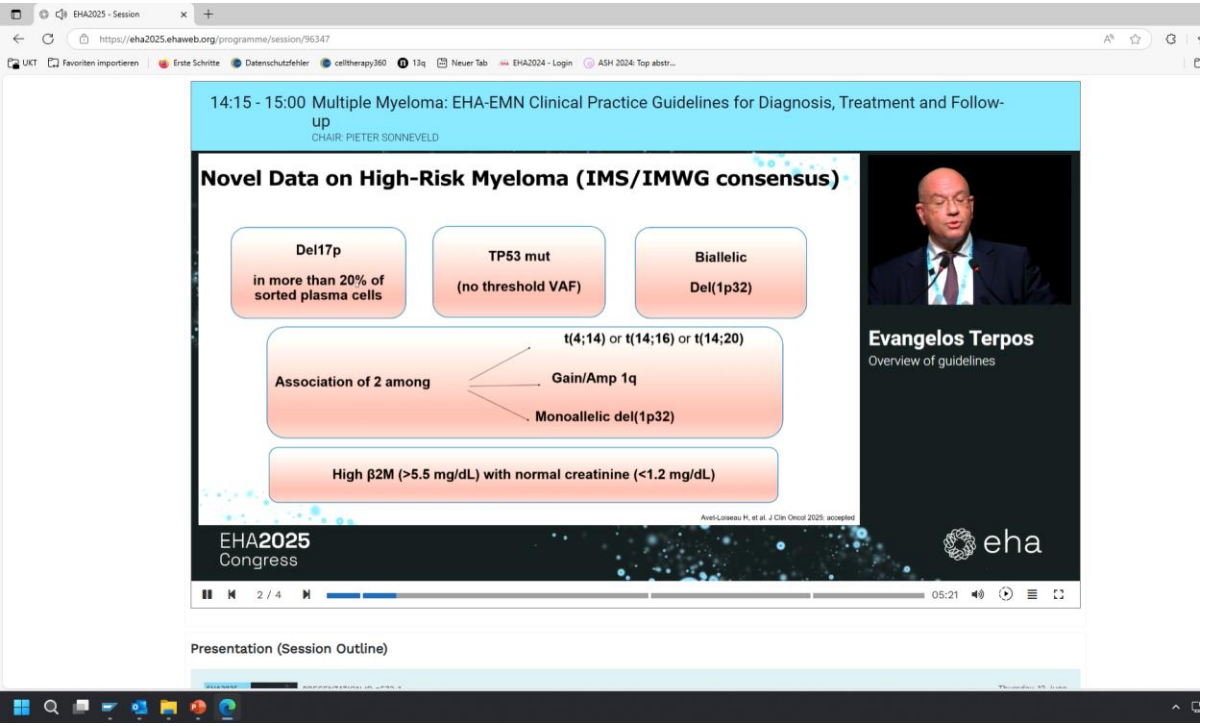


Vielen Dank für Ihre Aufmerksamkeit

Reduction of disease burden



onfidence interval; PFS, progression-free survival.
nguille S, et al. IMS 2024 (Abstract No. P-005 – poster); 2. Lin Y, et al. Lancet Oncol 2024;25:e374–e387.


EHA2025 - Session
https://eha2025.ehaweb.org/programme/session/96347
14:15 - 15:00 Multiple Myeloma: EHA-EMN Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up
CHAIR: PIETER SONNEVELD
Novel Data on High-Risk Myeloma (IMS/IMWG consensus)
Del17p
in more than 20% of sorted plasma cells
TP53 mut
(no threshold VAF)
Biallelic
Del(1p32)
Association of 2 among
t(4;14) or t(14;16) or t(14;20)
Gain/Amp 1q
Monoallelic del(1p32)
High β2M (>5.5 mg/dL) with normal creatinine (<1.2 mg/dL)
Avet-Loiseau H, et al. J Clin Oncol 2025: accepted
Evangelos Terpos
Overview of guidelines
EHA2025
Congress
eha
2 / 4
05:21
Presentation (Session Outline)