CAR-T cells e anticorpi monoclonali bispecifici:

indicazioni e prospettive di impiego in ematologia e reumatologia

Ferrara - 30 Ottobre 2024 Hotel Ferrara

CAR-T cells e anticorpi monoclonali bispecifici: aggiornamenti dalla letteratura ed esperienze in Italia

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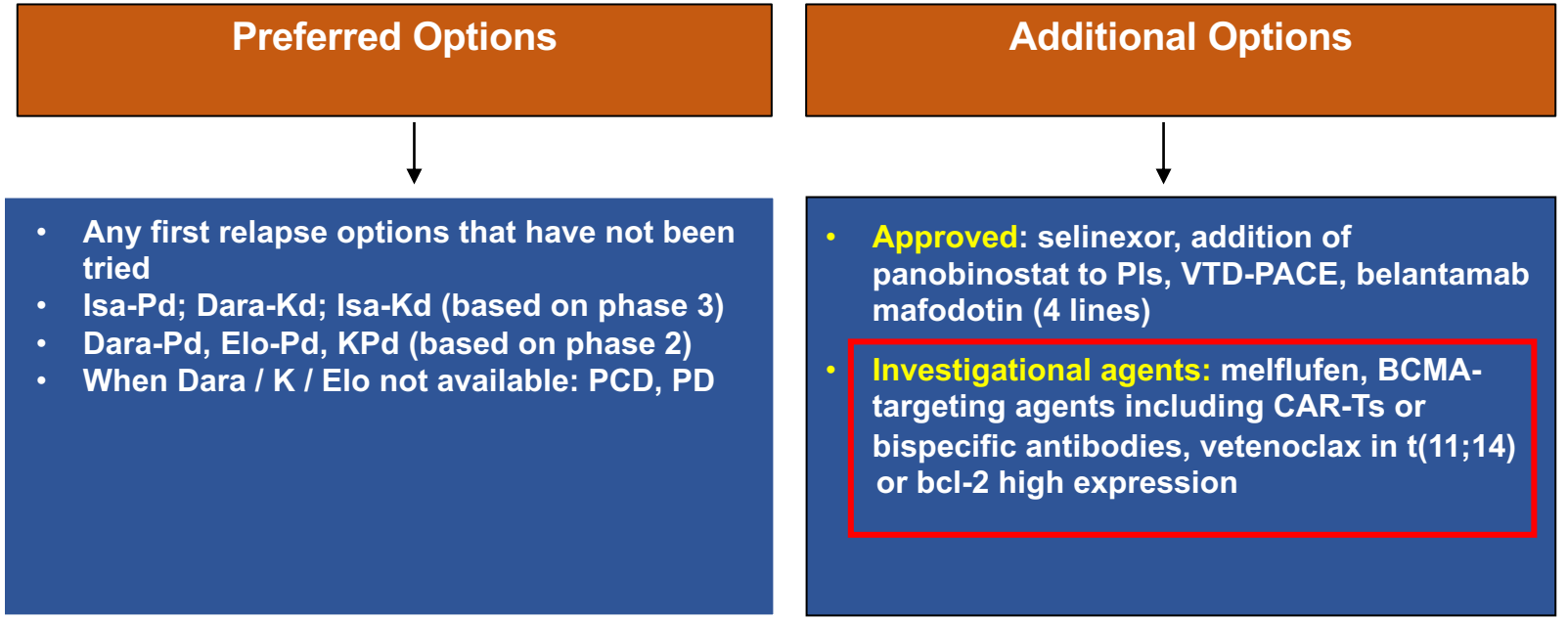
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen						X	X
BMS						X	X
Pfizer						X	X
Amgen						X	X
GSK						X	X
Oncopeptide						X	X
Menarini-Stemline						X	X
Sanofi						X	X

IMWG guidelines 2021: second or higher relapse

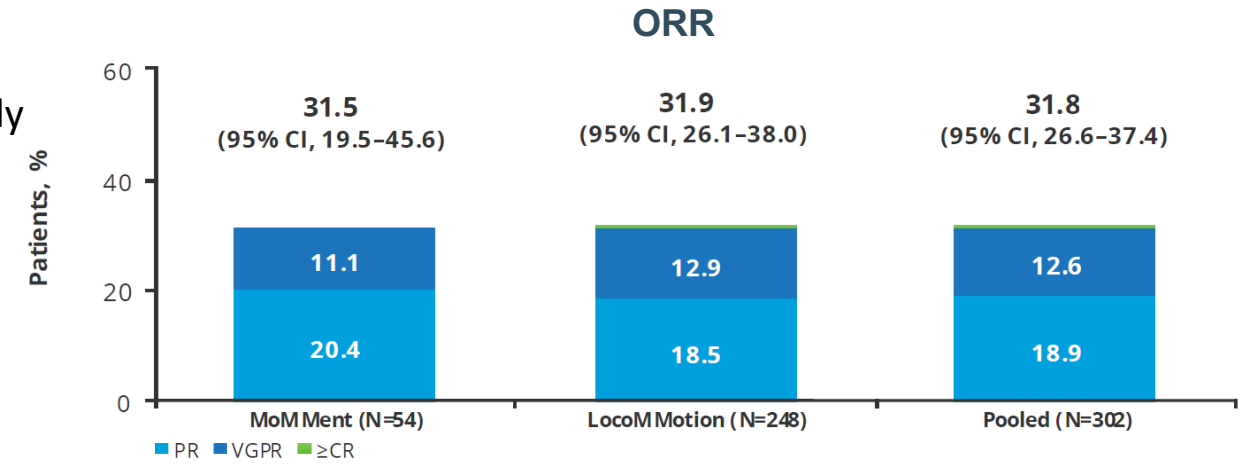


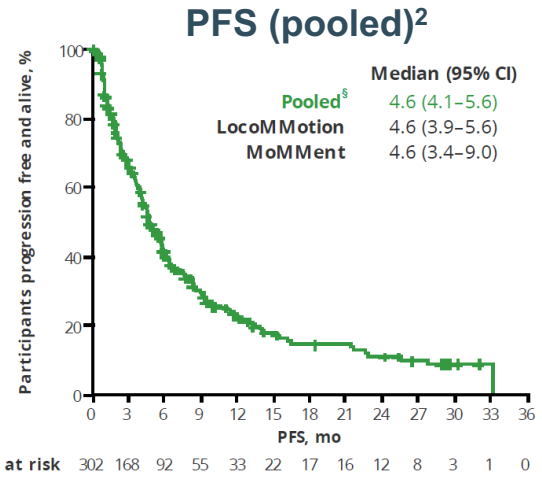
Updated Guidelines eagerly awaited!!

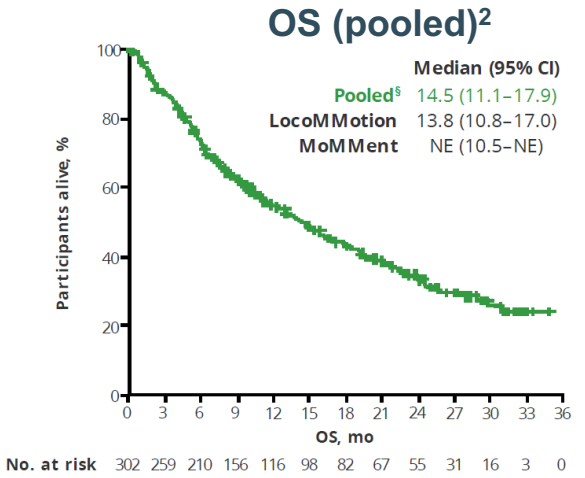
Moreau P et al, Lancet Oncol 2021

Unmet needs in triple-class exposed MM: pooled analysis of LocoMMotion and MoMMent

- LocoMMotion:[1,2]
  - Prospective, non-interventional, multinational study
  - N = 248
  - Follow-up 24 months after LPI
  - Triple class refractory: **73.4%**
  - ≥ 3 prior LOT
  - mPFS: **4.6** months
  - mOS: **13.8** months
- MoMMent:[2]
  - Prospective, non-interventional, multinational study
  - N = 54
  - ≥ 3 prior LOT
  - Follow-up 24 months after LPI
  - Triple class refractory: **74.1%**
  - mPFS: **4.6** months
  - mOS: **NR**







Mateos MV et al, Leukemia 2022
Weisel K et al, IMS 2023

New targets on myeloma cells

BCMA

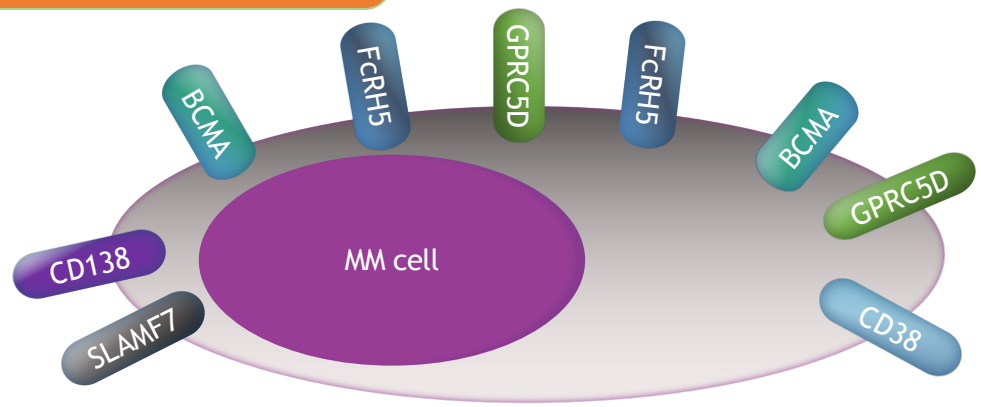
- BCMA is a member of the TNF receptor superfamily
- APRIL and BAFF are known ligands, leading to activation of the NF-κB pathway
- BCMA promotes plasma cell survival, growth, resistance to apoptosis, adhesion, and angiogenesis
- γ-secretase cleaving causes shedding of soluble BCMA
- BCMA is expressed on **malignant PCs, at low levels on normal PCs and mature B lymphocytes** and is absent in non-hematological tissues

FcRH5

- FcRH5 is a surface protein in the Ig superfamily
- It is expressed only in B cells, with increasing expression in **mature B cells and plasma cells**
- FcRH5 is involved in proliferation and isotype expression

GPRC5D

- GPRC5D is a member of the G protein-coupled receptor family with an **unknown function**
- It is highly expressed on **malignant PCs,** as well as hard **keratinized structures** (hair shaft, nail, and central region of the tongue)



Modality of targeting: ADC, Bispecific antibodies, CAR-T cells

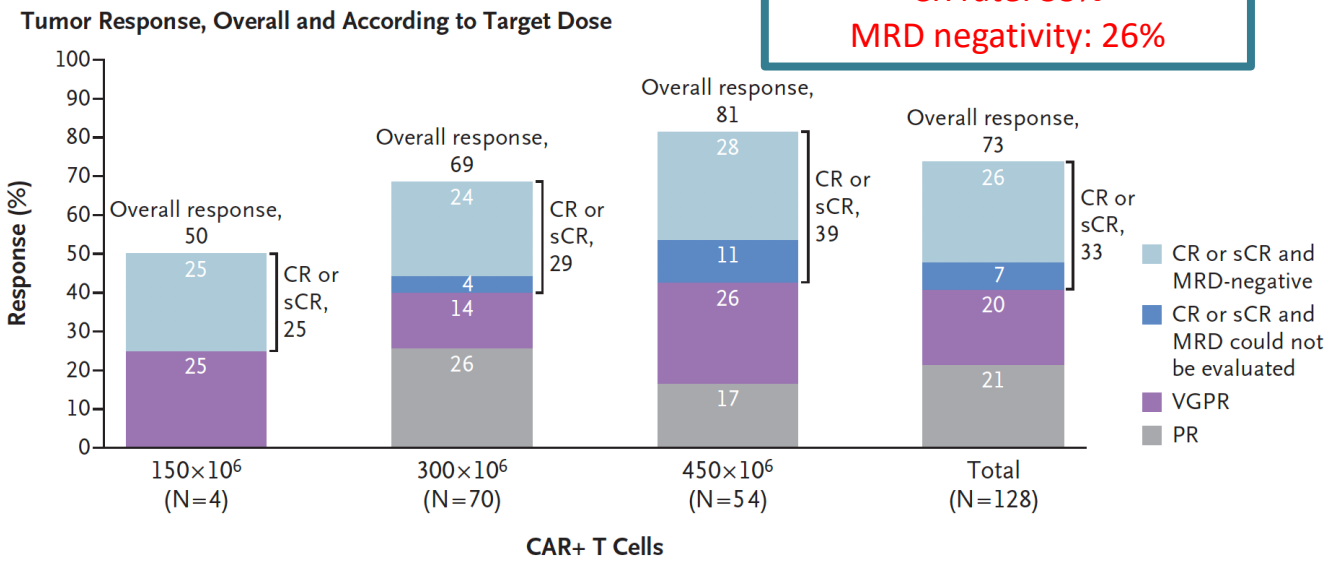
Image adapted from Verkleij CPM, et al. Curr Opin Oncol. 2020;32:664-71 and Bruins WSC, et al. Front Immunol. 2020;11:1155.
APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; CD, cluster of differentiation; FcRH5, Fc receptor-like 5; GPRC5D, G-protein coupled receptor family C group 5 member D; Ig, immunoglobulin; MM, multiple myeloma; NF-κB, nuclear factor Bs; PC, plasma cell; SLAMF7, signaling lymphocytic activation molecule family member 7; TNF, tumor necrosis factor.

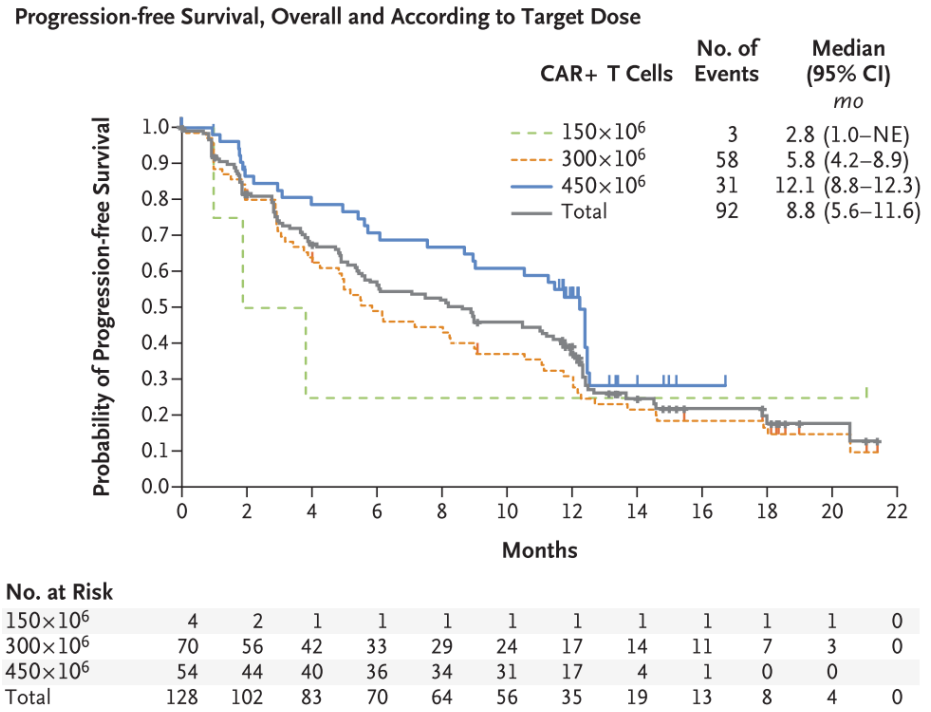
1. Rodríguez-Lobato LG, et al. Front Oncol. 2020;10:1243. 2. Pillarisetti K, et al. Blood Adv. 2020;4:4538–49. 3. Yu B, et al. J Hematol Oncol. 2020;13:125. 4. Verkleij CPM, et al. Blood Adv. 2020;5;2196-215. 5. Smith EL, et al. Sci Transl Med. 2019;11:eaau7746. 6. Li J, et al. Cancer Cell. 2017;31;383-95. 7. Bruins WSC, et al. Front Immunol. 2020;11:1155. 8. Lancman G, et al. Blood Cancer Discov. 2021;2:423-33.

Idecabtagene Vicleucel (Ide-cel): FDA/EMA Approved in 2021-AIFA approved June 2024

Baseline Characteristics	N=128
Median age	61 years
Target dose	300-450 million
Median Prior Lines	6
Triple Class Refractory	84%
Penta Refractory	26%
Bridging Therapy	88%

Overall response rate: 73%
CR rate: 33%
MRD negativity: 26%





Survival Outcomes	
Median PFS	8.8 months
Median PFS in CR	20.2 months
Median OS	24.8 months

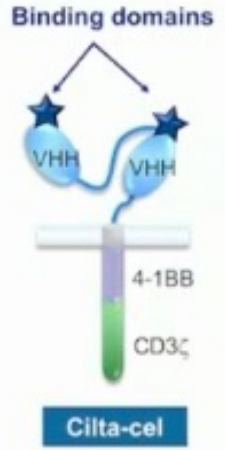
Munshi et al. NEJM 2021;384(8):705-716

Cilta-cel approval: the CARTITUDE-1 trial

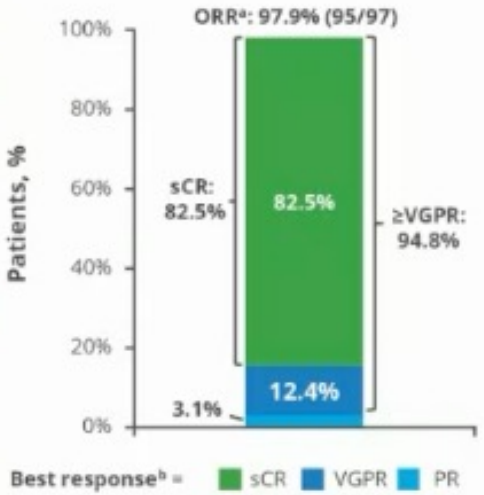
FDA approved in 2022
EMA approved in 2022

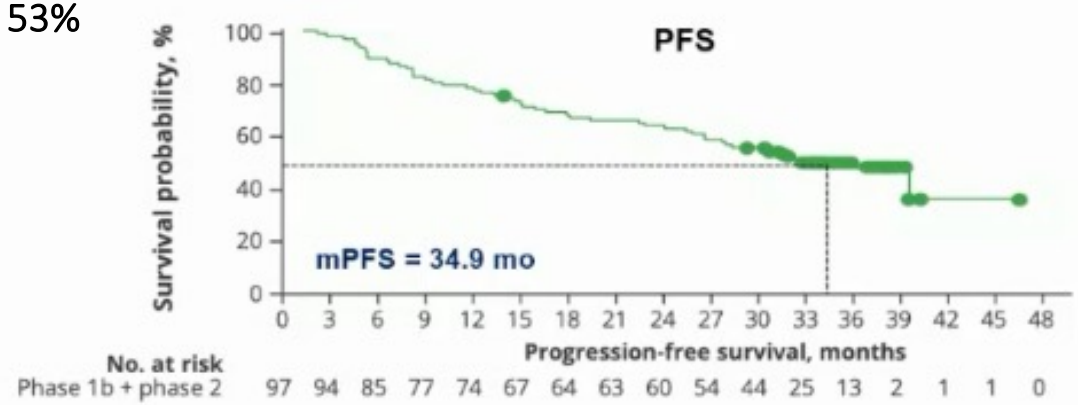
Second generation CAR-T cell, 2 anti-BCMA camelid VHH single domains, 4-1BB costimulatory domain

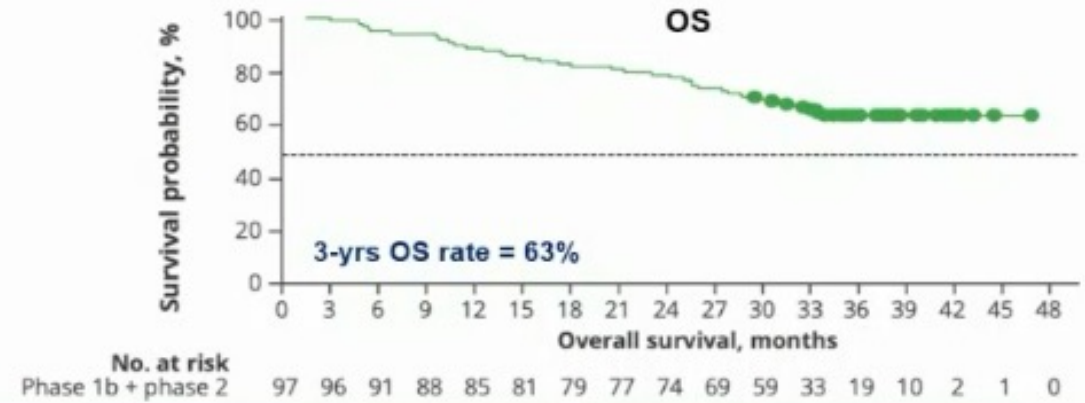
CARTITUDE-1, phase 2 study (N = 97)		
Median prior lines: 6 (3–18)	88% of patients were triple-class refractory	Bridging possible Flu-Cy lymphodepletion



12 mos sustained MRD rate: 53%
PFS @ 30 mos: 75%







AE, n (%)	Cilta-cel-Treated (N=97)	
	Any Grade	Grade ≥3
Hematologic		
Neutropenia	93 (96)	92 (95)
Anemia	79 (81)	66 (68)
Thrombocytopenia	77 (80)	58 (60)
CRS	92 (95)	6 (5)
Neurotoxicity	20 (21)	10 (10)

Berdeja J, et al. *Lancet* 2022;
Lin Y. et al. ASCO 2023

ide-cel (KarMMa) and cilta-cel (CARTITUDE-1): Safety

KarMMa [6-8] n=128	Any grade	Grade 3-4
Neutropenia	**117 (91)**	**114 (89)**
CRS	**107 (84)** **450x10⁶: 96%**	**7 (5)** **450x10⁶: 6%**
Time to onset, median (range) days	1 (1–10)	
Duration, median (range) days	7 (1–63)	
Total CAR T-cell neurotoxicities, n (%)	23 (18)	5 (4)
Infections-pathogen unspecified	90 (70)	34 (27)
Viral infections	22 (23)	7 (7)
Hypogammaglobulinemia	91 (94)	2 (2)

CARTITUDE-1 [1-5] n=97	Any grade	Grade 3-4
Neutropenia	**93 (95.9)**	**92 (94.8)**
CRS	92 (94.8)	5.4%
Time to onset, median (range) days	7 (1–12)	
Duration, median (range) days	4 (1–97)	
Total CAR T-cell neurotoxicities, n (%)	20 (20.6)	10 (10.3)
ICANS, n (%)	16 (16.5)	2 (2.1)
MNT/neurocognitive	5 (5.2)	4 (4.1)
Infections-pathogen unspecified	40 (41)	16 (17)
Viral infections	22 (23)	7 (7)
Hypogammaglobulinemia	91 (94)	2 (2)

6. Munshi et al. ASCO meeting, 2020; May 29-31, 2020. Abs. 8503. 7. San Miguel J et al. Oral presentation EHA 2020, abstract number S209. 8. Munshi N et al, NEJM 2021;384(8):705-716

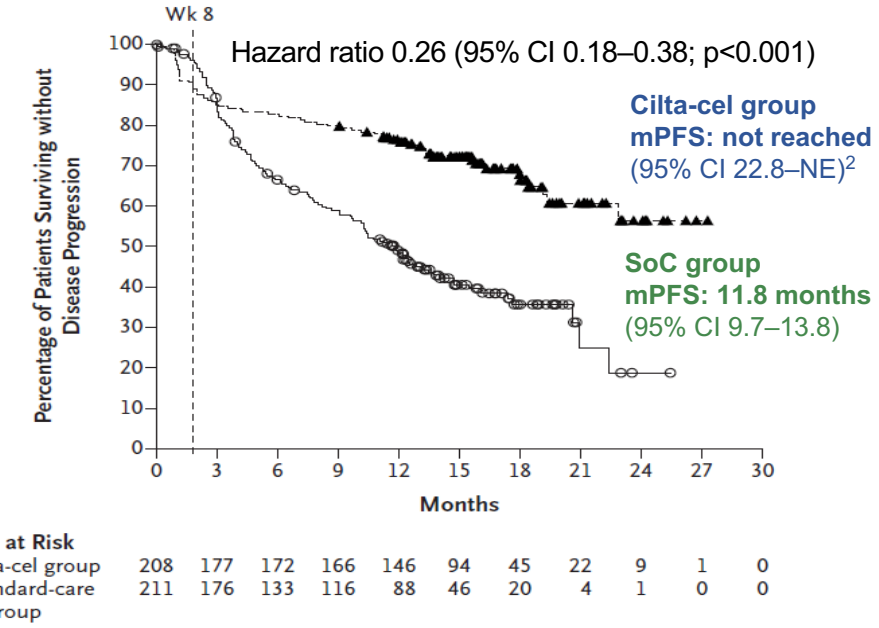
1. Lin Y et al. EHA 2022, Poster P961. 2. Cohen AD et al. *Blood Cancer J*. 2022;12(2):32. doi:10.1038/s41408-022-00629-1 3. Martin T et al. ASH 2021. Oral presentation. Abstract #549. 4. Berdeja JG et al. *Lancet*. 2021;398(10297):314-324. 5. Carvykti. Prescribing information. Janssen Biotech, Inc; 2022.

Targeting BCMA with CAR T-cells in early lines for RRMM

CARTITUDE-4
Cilta-cel vs SOC (PVd/DPd) (FDA/EMA approved)

Median age Cilta-cel arm 61.5 yrs (27-78)
Pts ≥75 years: NA

PFS (primary endpoint)



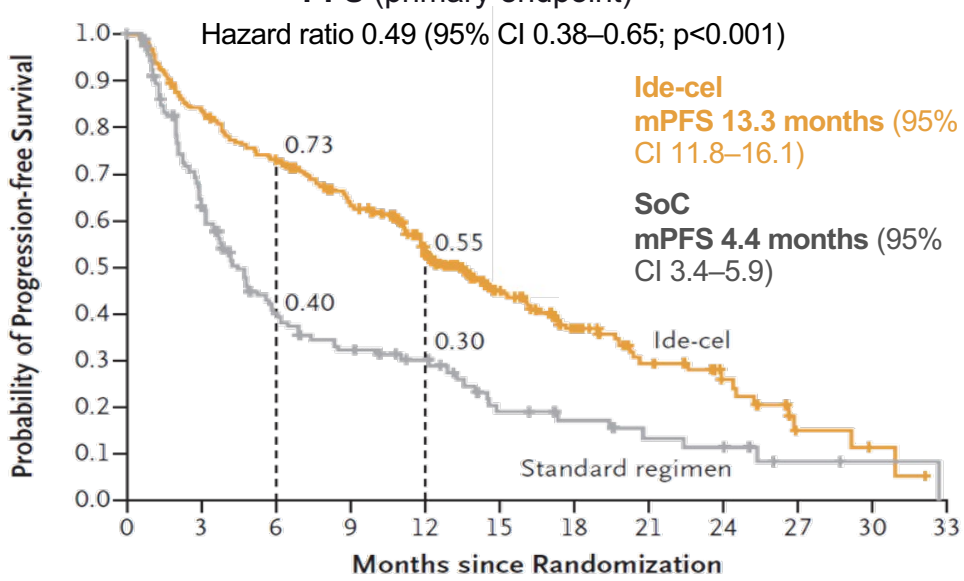
No. at Risk											
Cilta-cel group	208	177	172	166	146	94	45	22	9	1	0
Standard-care group	211	176	133	116	88	46	20	4	1	0	0

HR for PFS in pts 65-75 years: 0.34

KARMMA-3
Ide-cel vs SOC (DPd/DVd/Ird/Epd/Kd) (FDA/EMA approved)

Median age ide-cel arm 63 yrs (30-81)
Pts ≥75 years: 5%

PFS (primary endpoint)



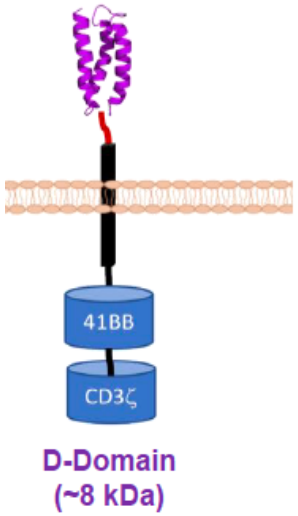
No. at Risk											
Ide-cel	254	206	178	149	110	62	40	22	14	4	2	0
Standard regimen	132	75	42	32	25	13	10	7	6	2	1	0

HR for PFS in pts >75 years: 0.59

BCMA: b-cell maturation antigen; CAR T: chimeric antigen receptor T cell; NA: not available; SOC: standard of care; P: pomalidomide; V: bortezomib; d: dexamethasone; PFS: progressione free survival; HR: hazard ratio;RRMM: relapsed refractory multiple myeloma

P. Rodriguez-Otero et al. NEJM 2023; J. San-Miguel et al. NEJM 2023; M. Mateos et al. ASCO 2024

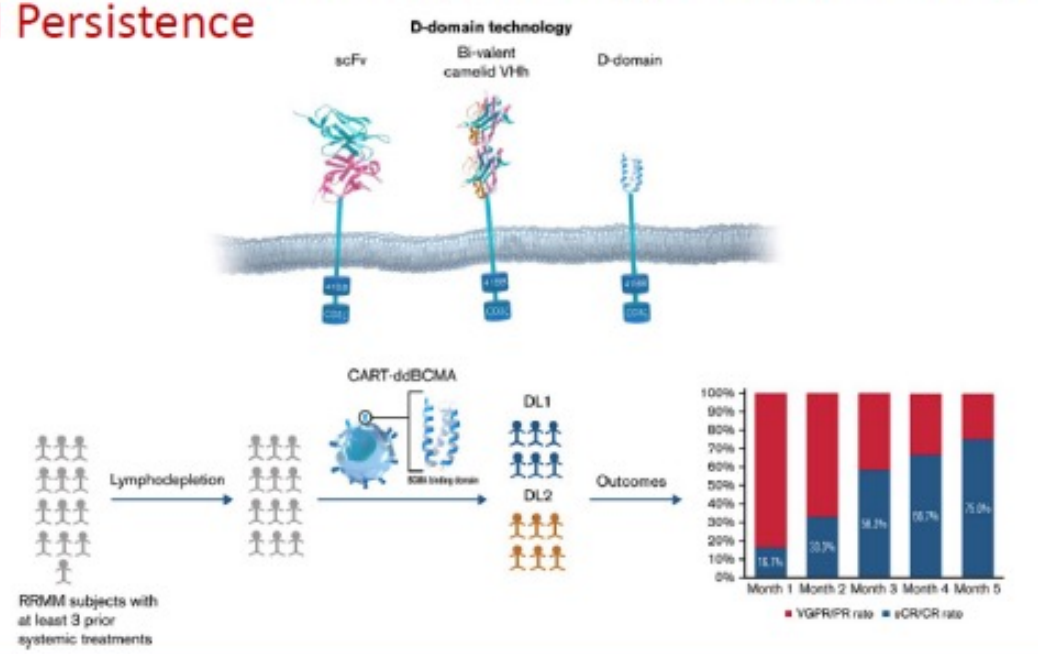
ANITO-CEL: Phase 1/2 Study of CART-ddBCMA for the Treatment of Patients with RRMM:iMMagine-1 study



D-Domain Attributes:
Non-Antibody Derived Synthetic Protein[1,2]

Size	**Small D-Domain construct facilitates high transduction efficiency, CAR positivity, and CAR density on the T-cell surface[2-4]**
Stability	**Rapid D-Domain folding, lack of disulfide bonds, and a hydrophobic core enables stability at and beyond physiologic conditions[5,6]**
Structure	**Due to small size and compact structure, D-Domain CARs have a low risk of tonic signaling[6] and potentially more efficient Multiple Myeloma cell killing**

- **Reduced Immunogenicity,** Enhance Activity and Persistence



Anito-cel utilizes a novel, synthetic, compact and stable **D-Domain binder**

D-Domain facilitates high CAR surface expression, low risk of tonic signaling

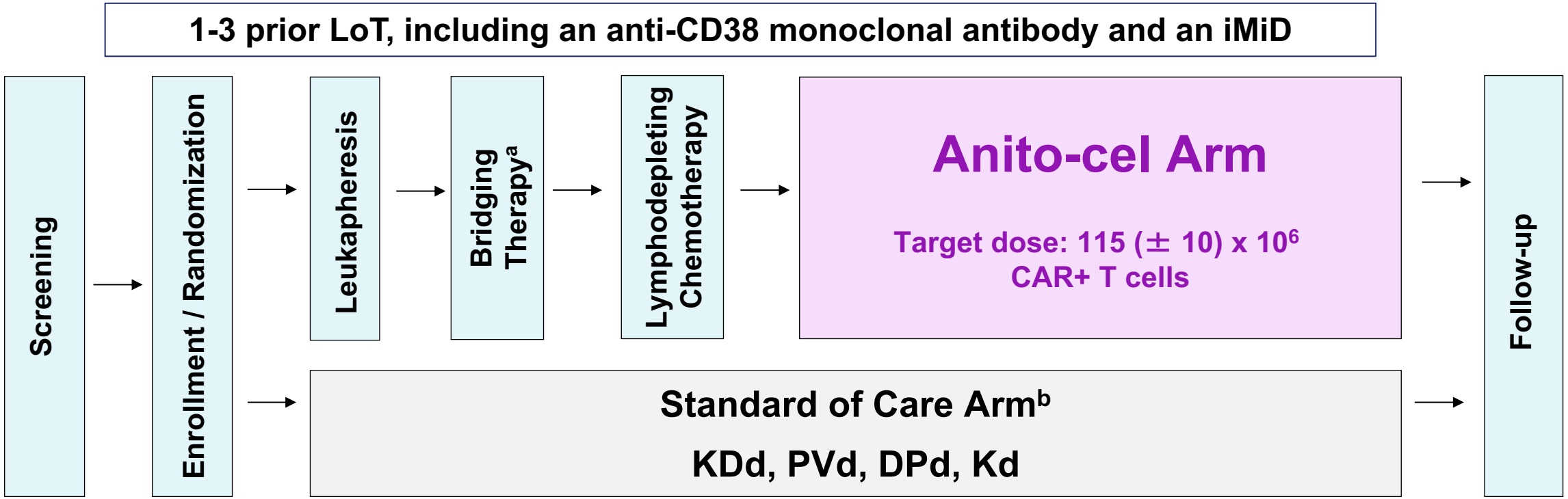
Recommended Phase 2 Dose selected as 115±10 million CAR+ T cells

- 38 RRMM patients all of them TCR received two dose levels of Anito-cel
- Median number of prior lines: 5
- EMD: 34%; ISS III: 18%; High tumor burden: 24%
- 68% of patients received bridging therapy

Frigault M, et al. ASH 2023 (Abstract No. 1023 – oral presentation)

iMMagine-3 Design, Global Phase 3 Study (Kite-Gilead)

PB2724: Martin T, Raje N, San Miguel J, Patel K, Mcloughlin L, Lui C, Jackson C, Heery C, van de Donk N, Berdeja J, Mateos M-V



STUDY DESIGN

- 1:1 Randomization
- n = Approximately 450, ~130 sites globally

STUDY ENDPOINTS

- Primary Endpoint: PFS
- Key Secondary Endpoints: CR rate, MRD, OS, safety

[a] Optional Bridging therapy will be the SOC regimen selected prior to randomization
[b] Cycles will continue until unacceptable toxicity, progression as per IMWG criteria, or patient withdrawal of consent

Ide-cel in MM: Real world (CIBMTR registry) vs. Trial Data

	CIBMTR (N=821)	KarMMa (N=128)
Median age, years	66 years (29-90)	61 years (33-78)
Age ≥ 70 years	251 (31%)	-
Race, Black	120 (15%)	-
Ethnicity, Hispanic	55 (7%)	-
ECOG PS 0/1	728 (89%)	126 (98%)
ISS stage III	68/420 (16%)	R-ISS III: 16%
High-risk cytogenetics	196/727 (27%)	45 (35%)
Extramedullary disease	85/488 (17%)	50 (39%)
Plasma cell leukemia	13 (1.6%)	0%

	CIBMTR (N=821)	KarMMa (N=128)
Prior lines of therapy	7 (4-21)	6 (3-16)
Triple class exposed	776 (97%)	Refractory: 84%
Penta class exposed	490 (60%)	Refractory: 26%
Prior BCMA Therapy • Prior ADC • Prior CAR-T • Prior bispecific	150 (18%) • 16 (14%) • 36 (4%) • 3 (0.4%)	0%
Bridging therapy	442/799 (54%)	112 (88%)
Lymphodepletion Flu/Cy	741 (90%)	128 (100%)

High-risk cytogenetics include del17p, t(4;14) and t(14;16)

- Real world data: Most patients would not have met trial eligibility criteria (> 70%) for comorbidities/other reasons

1. Sidana et al. ASH 2023. 2 Hansen et al. JCO 2023; 3. Munshi et al. NEJM 2021;384(8):705-716.

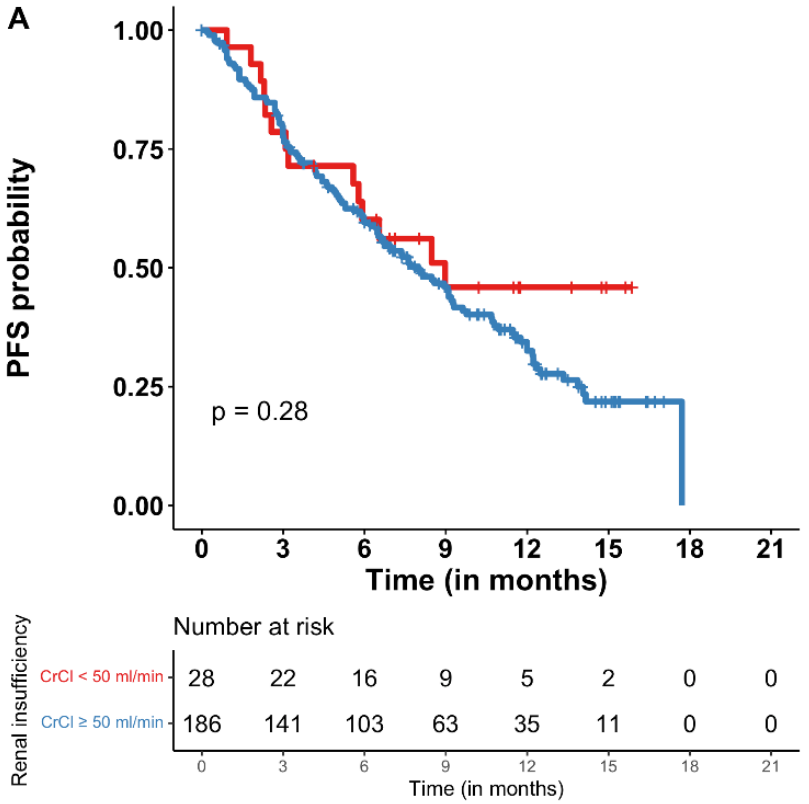
Ide-cel in MM: Real world (CIBMTR registry) vs. Trial Data

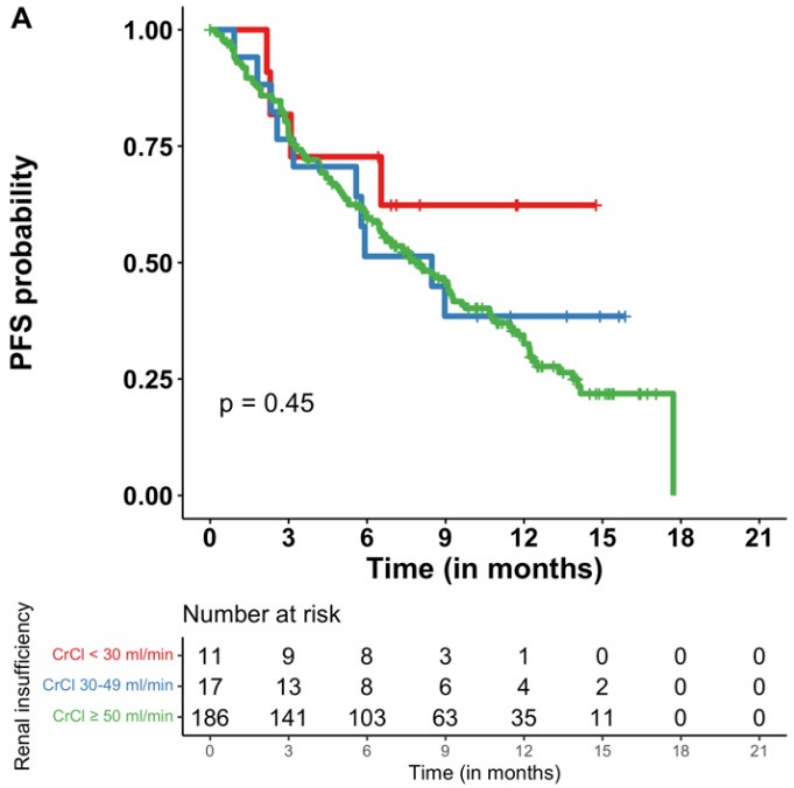
	CIBMTR[1] N=821	US RWE[2] N=159	KarMMa[3] N=128
CRS - Any grade Grade 3 or higher	80% 3%	82% 3%	84% 5%
ICANS– Any grade Grade 3 or higher	28% 5%	18% 6%	18% 3%
Overall response rate	73%	84%	73%
Very good partial response rate	56%	62%	52%
Complete response rate	25%	42%	33%
Progression free survival, median	9.0 months	8.5 months	8.8 months
Median follow-up	11.6 months	6.1 months	13.3 months

1. Sidana et al. ASH 2023. 2 Hansen et al. JCO 2023; 3. Munshi et al. NEJM 2021;384(8):705-716.

Ide-cel in Patients with Renal Impairment

- Renal Impairment: eGFR < 50 ml/min
- Severe renal impairment: < 30 ml/min or dialysis:
- CRS, neurotoxicity and non-relapse mortality comparable
- Longer hospital stay
- Short-term high-grade cytopenias at day 30.
- Similar response rates and PFS.



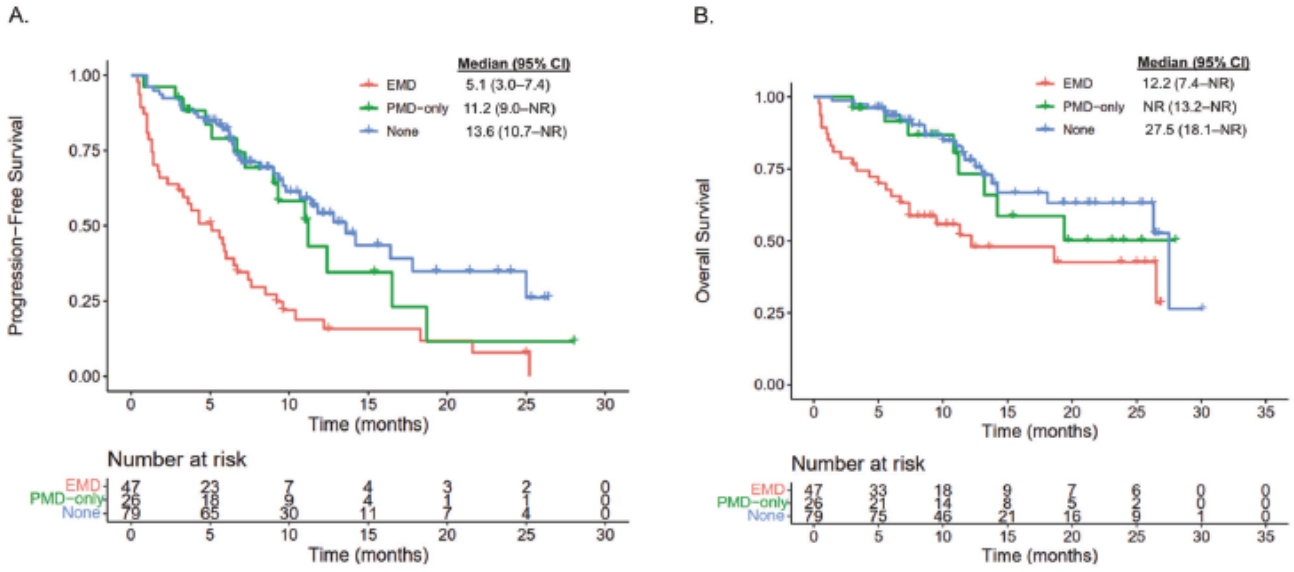


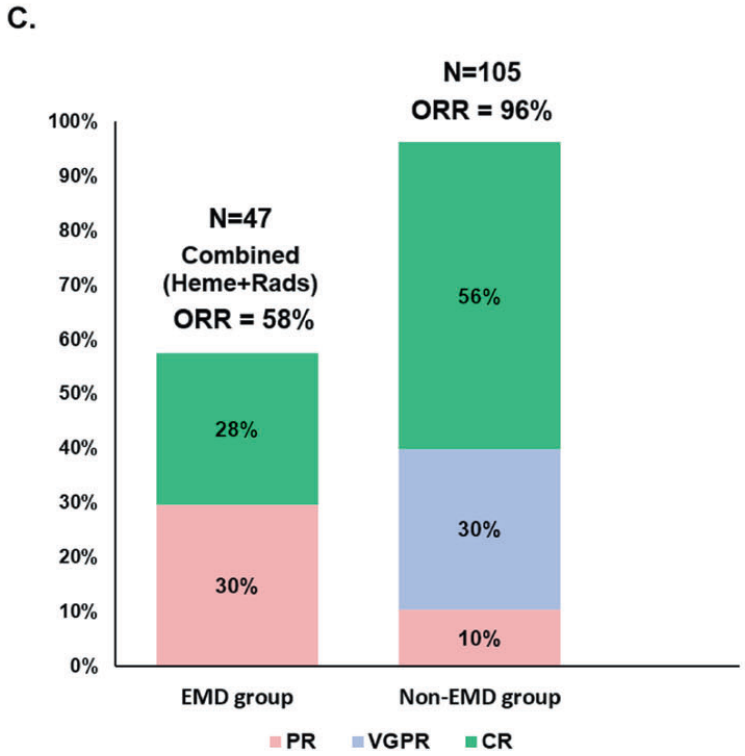
Sidana et al. Haematologica, 2024. 109(3): p. 777-786.

Patients with EMD are still an unmet clinical need with CART therapy

High incidence of EMD and “skeletal escape” in the setting of late relapse

- Real life analysis on 132 pts treated with ide-cel and cilta-cel as per SOC
- 48% (64 pts) previous/current EMD prior to CART; pair matched with rest of population
- No difference in toxicities (CRS, ICANS, infections)
- No difference in response rate/CR rate
- **Significantly shorter PFS and OS** (p = 0.02 and 0.03, respectively)

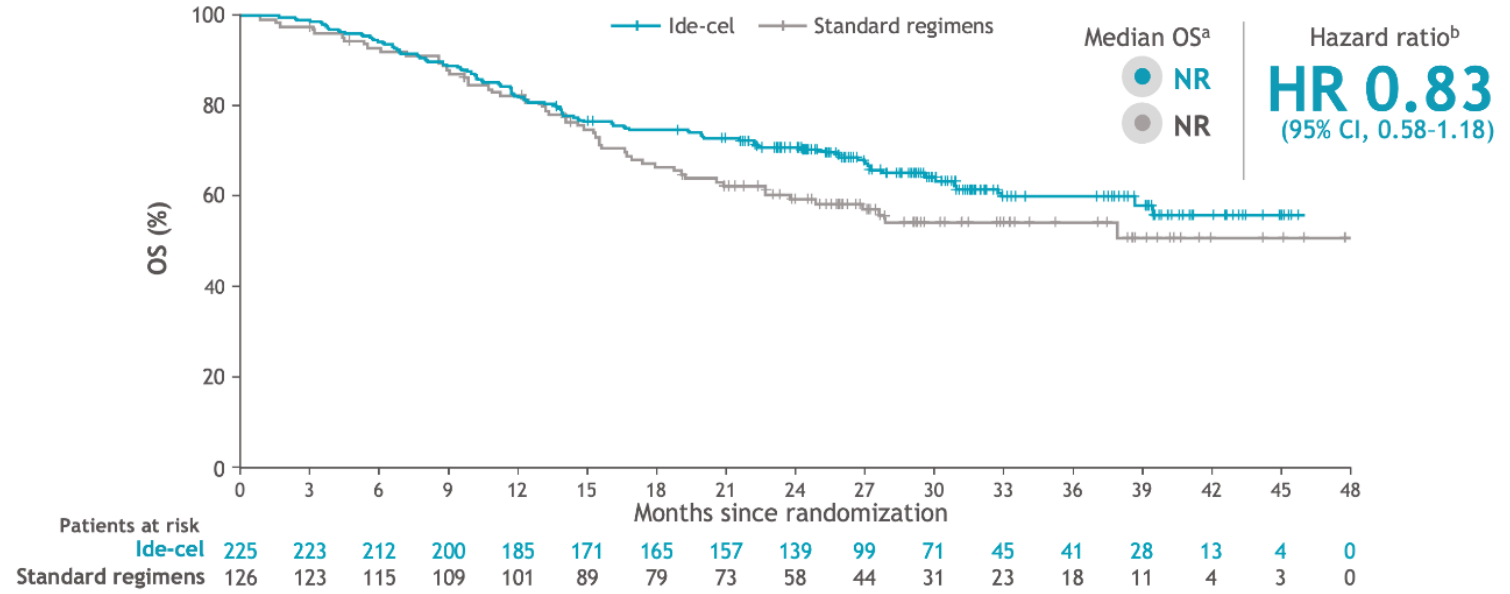




Dima D, et al BCJ 2024

Lessons from KARMMA-3 trial: patients should “make it” to CART

Trend of OS benefit with ide-cel among treated patients



- This is an exploratory analysis of the treated population without adjusting for crossover

KarMMa-3 allowed cross-over which confounds OS interpretation; 56% patients crossed over in SOC arm

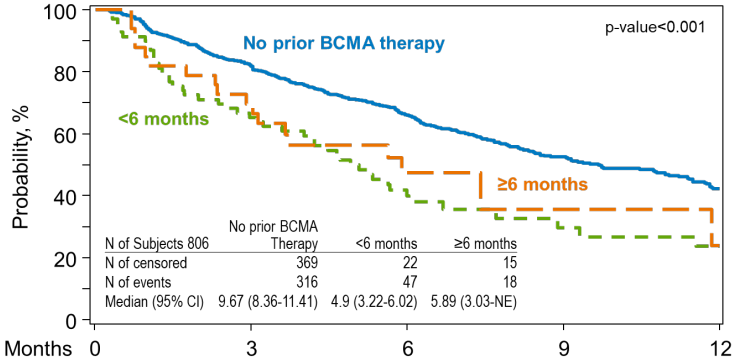
Pre-specified analysis adjusted for cross-over showed improved OS with ide-cel vs SOC

Early deaths in ide-cel in patients who did not receive ide-cel- highlights need for effective bridging

Rodriguez Otero et al. ASH 2023 Abstract #1028

Prior BCMA therapy and timing and Ide-cel

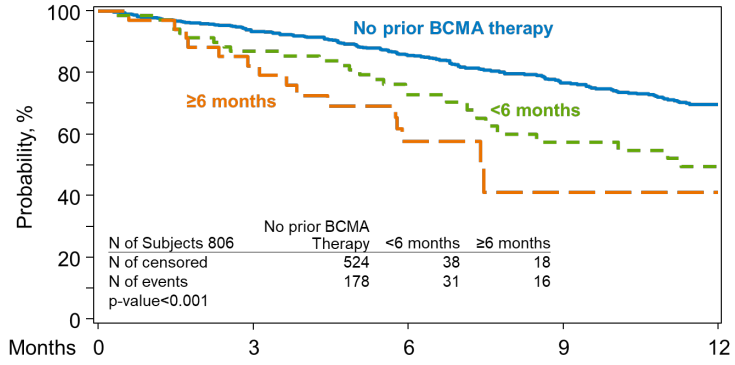
Progression-free Survival



N at Risk

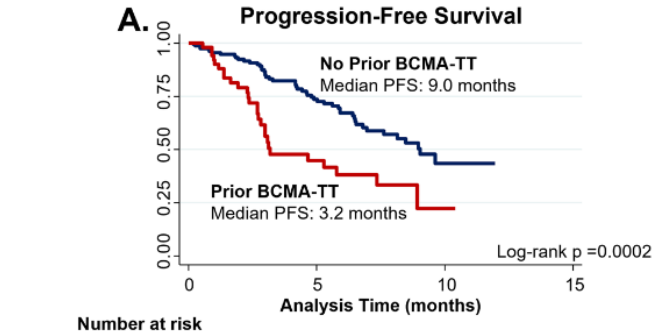
No prior BCMA therapy	685	549	335	186	135
<6 months	69	45	21	10	8
≥6 months	33	22	10	3	2

Overall Survival



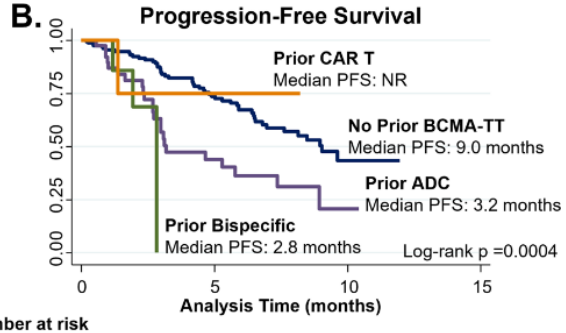
N at Risk

No prior BCMA therapy	702	642	451	281	234
<6 months	69	60	41	22	19
≥6 months	34	27	13	5	5



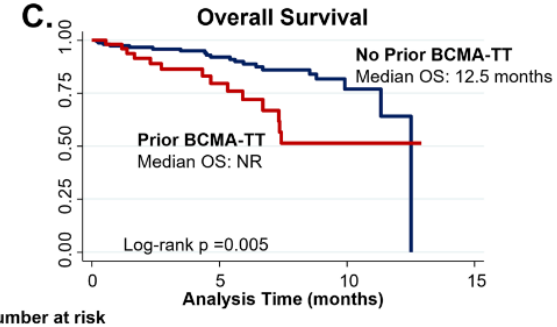
Number at risk

No Prior BCMA-TT	153	73	7	0
Prior BCMA-TT	50	14	1	0



Number at risk

No Prior BCMA-TT	153	73	7	0
Prior ADC	38	12	1	0
Prior Bispecific	7	0	0	0
Prior CAR T	5	2	0	0



Number at risk

No Prior BCMA-TT	153	92	15	0
Prior BCMA-TT	50	22	3	0

Prior bispecific Ab: Worst survival outcomes with ide-cel, with mPFS of ~ 3 mos

Ferreri et al. Blood Cancer Journal 2023. US MM Consortium Data

1. Sidana et al. ASH 2023. 2 Hansen et al. JCO 2023; 3. Munshi et al. NEJM 2021;384(8):705-716.

Cilta-cel in MM: Real world (US MM CART consortium) vs. Trial Data

	RWE Cilta-cel (N=236)	CARTITUDE-1 (N=97)[1]
Age, median (range)	64 y (30-84)	61 y (56-68)
Age ≥ 70 years	62 (26%)	-
Race: Black	26 (11%)	17 (18%)
Ethnicity: Hispanic	19 (8%)	6 (6%)
ECOG PS, 0-1	183 (89%)	93 (96%)
High-risk cytogenetics*	81 (39%)	23 (24%)
R-ISS stage III	30 (19%)	ISS-3:14 (14%)
Extramedullary Disease**	60 (26%)	13 (13%)
BM Plasma cells ≥ 50%	35 (18%)	≥ 60%= 21 (22%)
H/o plasma Cell Leukemia	13 (6%)	0
H/o AL amyloidosis	8 (3%)	0

*High-risk cytogenetics: Del 17p, t(14;16), t(4;14)
**EMD included patients with plasmacytomas non-contiguous from bone lesions

	RWE Cilta-cel (N=236)	CARTITUDE-1 (N=97)[1]
Prior Lines of Therapy	6 (2-18)	6 (4-8)
Prior Auto SCT	200 (85%)	87 (90%)
Triple Class Refractory	163 (69%)	85 (88%)
Penta Drug refractory	70 (30%)	41 (42%)
Prior BCMA Therapy	33 (14%)	0%

56% of real-world patients would have been ineligible for CARTITUDE-1

- Cytopenias (17%)
- Organ function (12%)
- Performance Status (12%)
- Prior BCMA therapy (12%)
- PCL/Amyloid/POEMS (12%)
- CNS pathology (6%)

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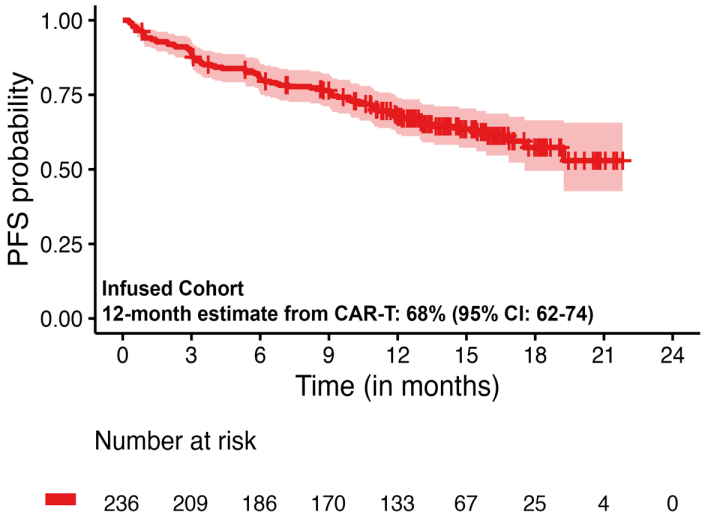
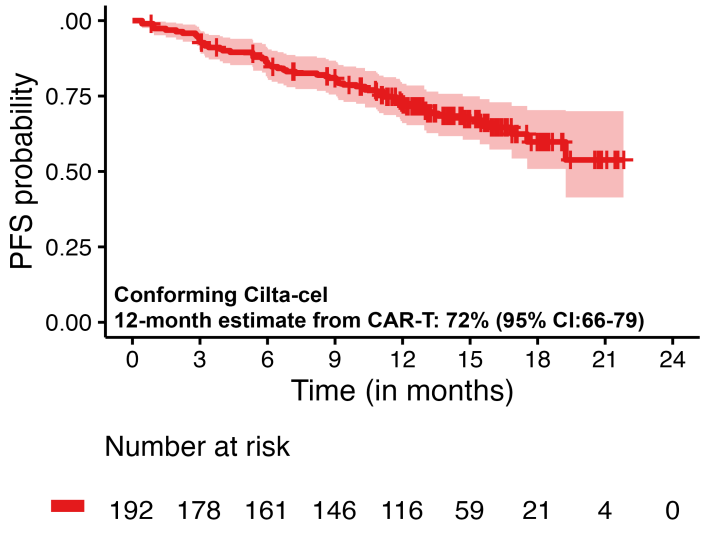
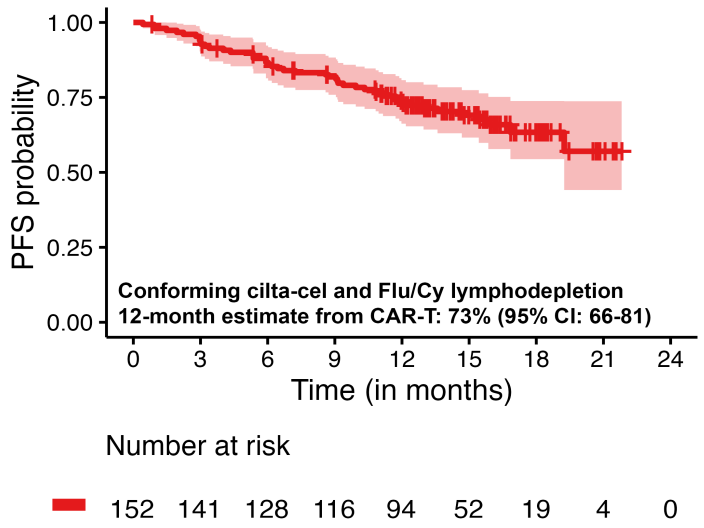
Progression Free Survival







Median follow-up: 13 months from CAR-T infusion

	Infused cohort N=236	Conforming cilta-cel N=192	Conforming + Flu/Cy LD N=152	CARTITUDE-1 [1-3] N=97
PFS: 12-month estimate (95% CI)	68% (62-74)	72% (66-99)	73% (66-81)	12m : 77%[1] Median: 34.9 m

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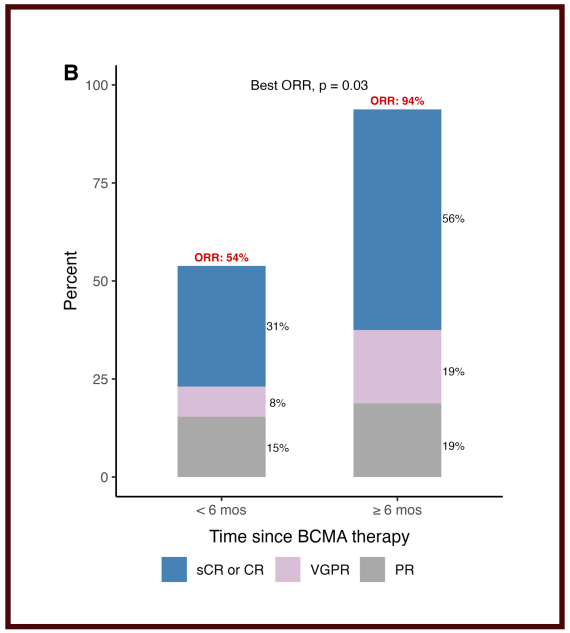
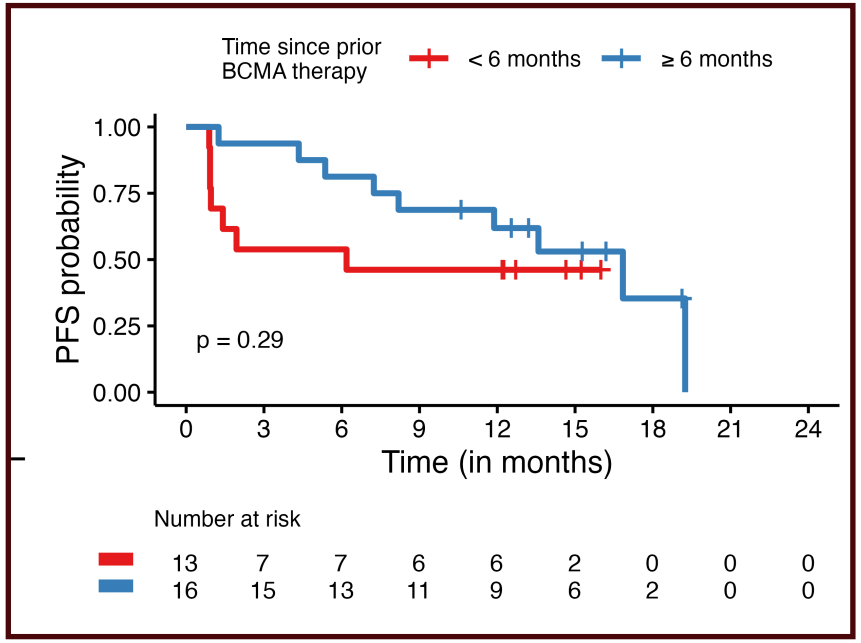
1.. Berdeja et al. Lancet 398:314-324, 2021; 2. Martin et al. J Clin Oncol 41:1265-1274, 2023. 3. Lin et al ASCO 2023

Cilta-cel after Prior BCMA Therapy: Timing Matters!

Time from last BCMA Therapy Exposure	N=29/33
Median time	7.1 months
≥6 months	16 (55%)
< 6 months	13 (45%)
Unknown	4





Patients with last BCMA targeted therapy < 6 months prior to cilta-cel had lower response rates and numerically lower PFS

Efficacy Measure	Last BCMA exposure < 6 months vs. ≥6 months
Overall response Rate	54% vs 94%, p=0.03
Complete Response Rate	31% vs. 56% p=0.2
Median PFS	6.2 vs 16.8 months, p=0.29

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Safety of SOC Cilta-cel: CRS/ICANs and other neurotoxicities

	Real-world N=236	CARTITUDE-1 [1-2] N=97
CRS - Any grade	177 (75%)	95%
Grade ≥ 3	12 (5%)	4%
Median time to onset of CRS	7 days (0-14)	
ICANS – Any grade	32 (14%)	17%
Grade ≥ 3	9 (4%)	2%
Delayed neurotoxicity	24 (10%)	12%
Parkinsonism	5 (2%)	6%
Cranial nerve palsy	11 (5%)	-
Others	8	
IEC-HS/HLH	5 (2%)	~1%
Severe infections	49 (21%)	20%

Other delayed NT: Diplopia in 4, posterior reversible encephalopathy syndrome (PRES) in 2, dysautonomia in 1 patient, and polyneuropathy in 1 patient

Multivariable Analysis:

- **Grade ≥ 2 CRS**: poor performance status and high baseline ferritin increased risk
- **ICANS**: poor performance status and penta-refractory status increased risk

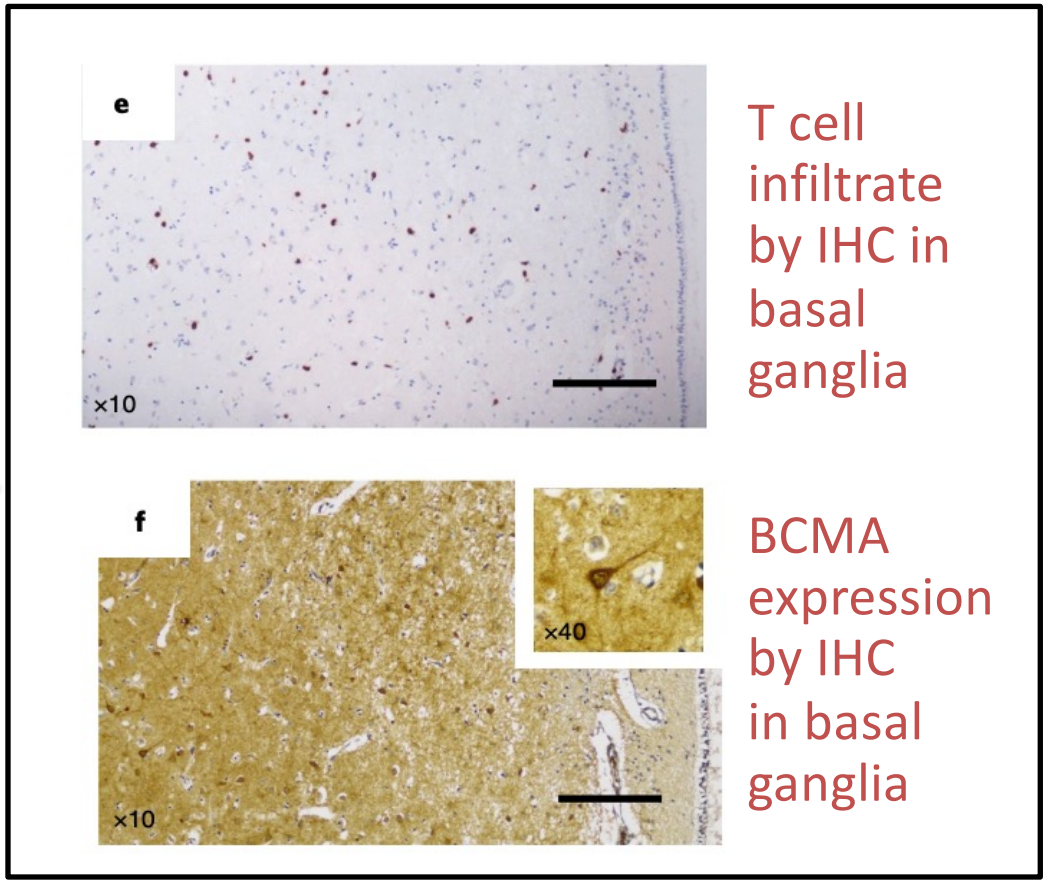
Sidana S et al, IMS 2024

1. Berdeja et al. Lancet 398:314-324, 2021; 2. Martin et al. J Clin Oncol 41:1265-1274, 2023.

Parkinsonism with Cilta-Cel

- Risk Factors: High-tumor burden, CRS/ICANS, high CAR-T expansion
- Mechanism: potential on-target, off-tumor effect

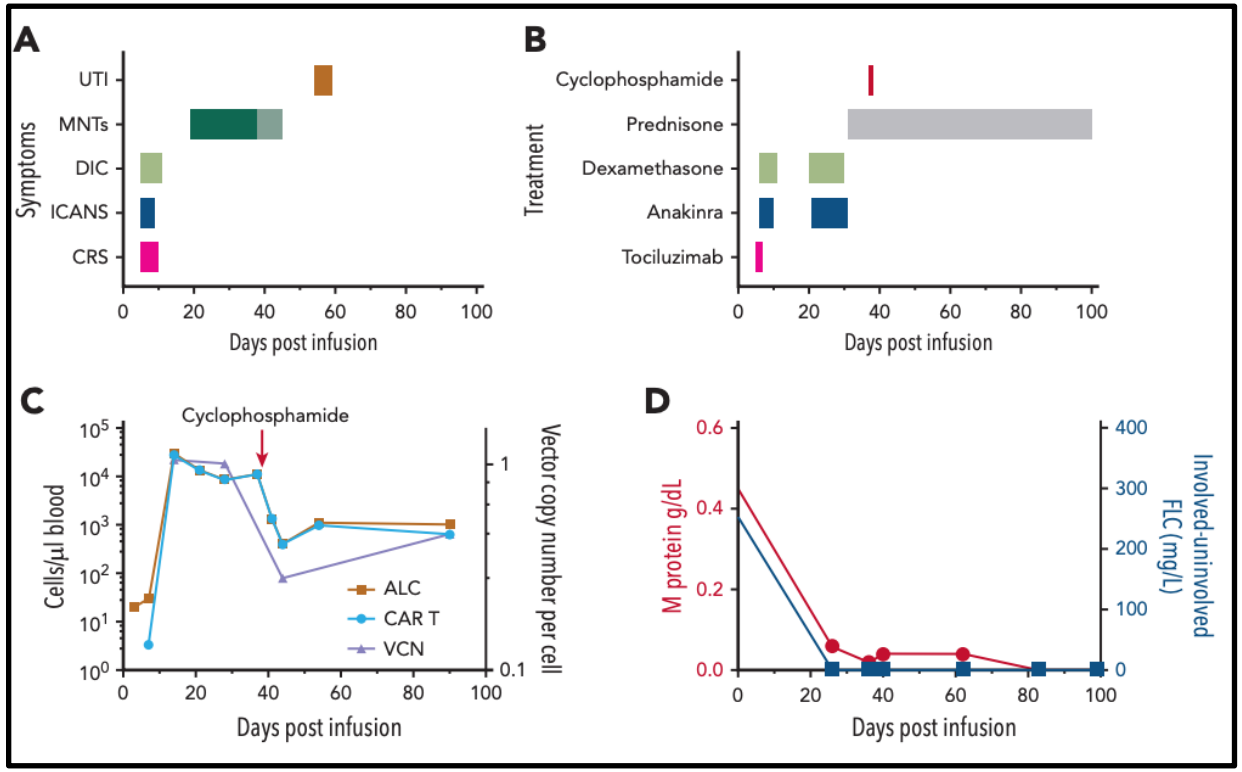
- Parkinsonism 3 months after cilta-cel
- CAR-T persistence in blood and CSF
- Lymphocytic infiltrate in basal ganglia on autopsy
- BCMA expression on neurons and astrocytes in the patient's basal ganglia.



1. Van Oekelen O et al. *Nature medicine.* 2021;27(12):2099-2103. 2. Cohen et al. Blood Cancer Journal 12:32, 2022

Management of Parkinsonism

- Levodopa/carbidopa and other typical Parkinson's directed therapies are ineffective
- Some evidence suggests that decreasing CAR-T expansion with chemotherapy and steroids may be effective



Graham et al. Blood 142:1248-1252, 2023

Cranial Nerve Palsies (CNP) with Cilta-cel

	Cilta-cel RWE[1]	All CARTITUDE trials[2]
Incidence	6% (n=9)	6% (n=21)
Nerves involved	All: VII nerve	All: VII nerve Additional CN in n=3
Median time to onset	21 days	22 days
Treatment	Steroids in 7 of 9	Steroids in 19 of 21
Resolution	4 of 9	19 of 21

Risk Factors: High CAR-T expansion;
CRS/ICANS were not risk factors

Management Recommendations

- Strongly consider brain imaging (MRI) to rule out other causes
- Consider CSF analysis on case-by-case basis
- Treatment: Low dose steroids – taper over days

1. Sidana, Patel et al IMS 2023 presentation (Athens). 2. Van den Donk et al. ASH 2023 Poster #3501. Blood 142:3501, 2023.

Safety of SOC Cilta-cel: SPMs

	Real-world N=236
Non-relapse mortality (NRM)	**23 (10%)**
• Infections	12
• CRS	3
• CRS and infection	1
• Delayed neurotoxicity	3
• IEC-HS	2
• ICANS	1
• SPM	1
SPMs	**20 (8.5%)**
Excl. non-melanoma skin cancer	13 (5.5%)
Myeloid neoplasm/acute leukemia	3 (1.3%)
T cell lymphoma	1

SPMs in CARTITUDE-1:

- At **1-year** median follow-up, SPM rate was **7%** including 5 cases of MDS and 2 of acute leukemia[1]
- At **2-year** median follow-up, SPM rate was **16.5%** including 8% myeloid neoplasms and acute leukemia[2]

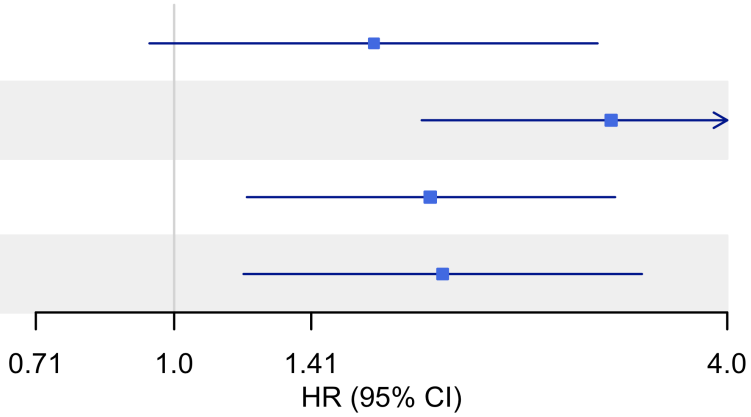
Sidana S et al, IMS 2024

1. Berdeja et al. Lancet 398:314-324, 2021; 2. Martin et al. J Clin Oncol 41:1265-1274, 2023.

Multivariable Analysis: PFS and OS

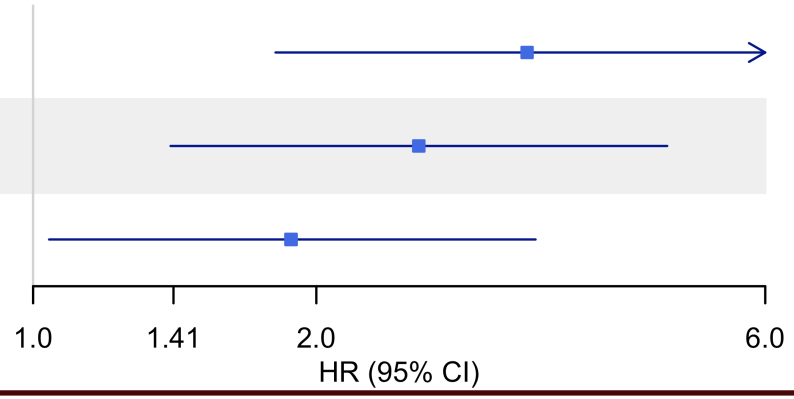
PFS

Variable	HR (95% CI)	P-value
Prior BCMA-TT (Yes vs. No)	1.65 (0.94, 2.89)	0.08
Ferritin (≥ 400 vs. < 400 ng/mL)	2.99 (1.86, 4.80)	<0.001
High-risk cytogenetics (Yes vs. No)	1.90 (1.20, 3.02)	0.006
Extramedullary disease (Yes vs. No)	1.96 (1.19, 3.23)	0.009



OS

Variable	HR (95% CI)	P-value
Ferritin (≥ 400 vs. < 400 ng/mL)	3.35 (1.81, 6.19)	<0.001
High-risk cytogenetics (Yes vs. No)	2.57 (1.40, 4.72)	0.005
Extramedullary disease (Yes vs. No)	1.88 (1.04, 3.42)	0.04



Cox Proportional Hazards model using a stepwise variable selection approach.

Sidana S et al, IMS 2024

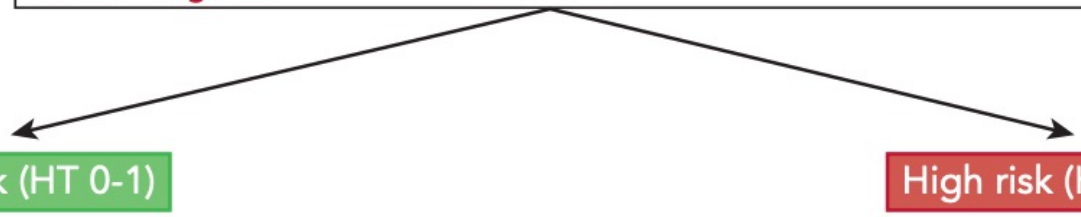
ICAHT risk evaluation: CAR-HEMATOTOX

Prior to lymphodepleting chemotherapy (day -5)

→ Determine patient-individual risk of heme-tox and infections using the **CAR-HEMATOTOX score**

- Leniency time period for lab values: 3 days

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			



Risk profile

	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%

Stanford MEDICINE

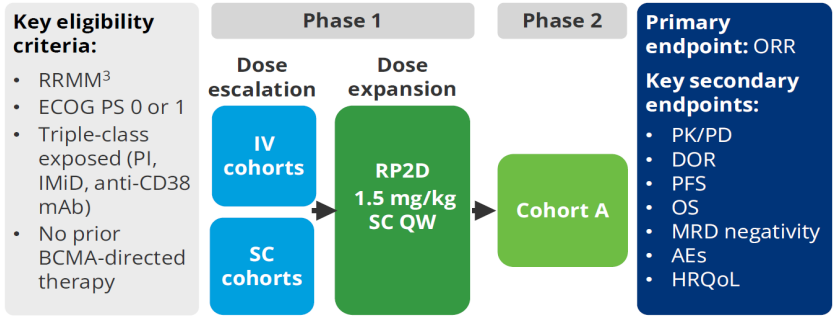
Rejeski K. Blood (2023) 142 (10): 865–877.

BCMA × CD3 T-Cell bispecific antibody: Teclistamab

MajesTEC-1, Phase Ib/II study[1]

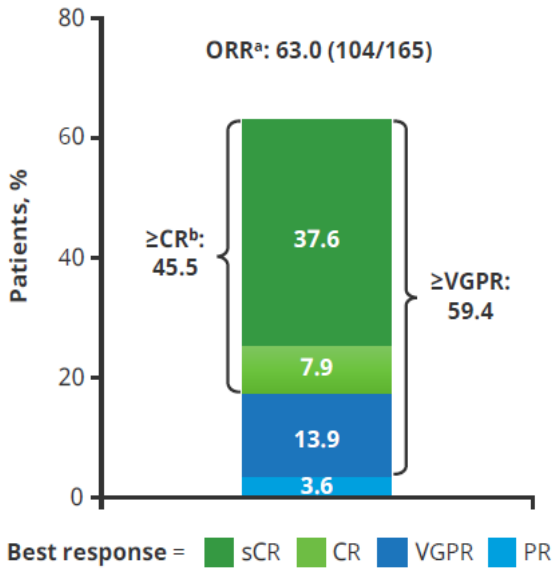
FDA/EMA/AIFA approved

Trial design and dosing schedule[1]



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]

Response rates[1]

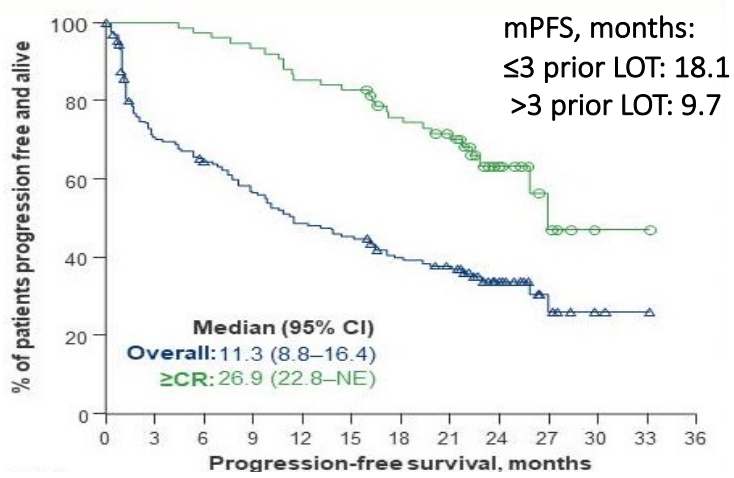


Median time to first response: 1.2 months[1]

Median time to ≥CR: 4.6 months[1]

MRD-negativity rate (10^{-5}): 27%[1]

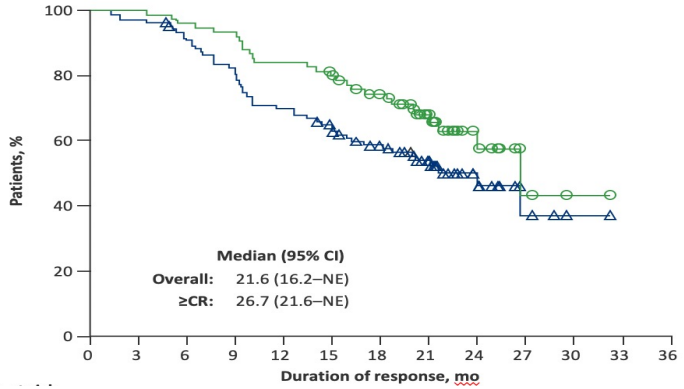
Progression-free survival[1]



Baseline characteristics, N=165[1]

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)

Duration of response[1]



*Patients could further switch to monthly dosing if they demonstrated continued response on the Q2W schedule; †Includes patients who had ≥1 soft tissue plasmacytoma not associated with bone; [a]ORR assessed by independent review committee; [b]For the Phase II efficacy population (patients enrolled in cohort A on or before March 18, 2021), ≥CR rate was 46.4% (51/110).

AE, adverse event; BCMA, B-cell maturation antigen; CI, confidence interval; CR, complete response; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQoL, heatlh-related quality of life; IMiD, immunomodulatory agent; IV, intravenous; LOT, line of therapy; (m)PFS, (median) progression-free survival; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PI, proteasome inhiitor; PK, pharmacokinetic; PR, partial response; PS, performance status; Q2W, every 2 weeks; QW, weekly; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; sCR, stringent complete response; VGPR, very good partial response.

1. Van de Donk NWCJ, et al. ASCO 2023 (Abstract No. 8011 – presentation); 2. Press release, August 2023. Available at: https://www.jnj.com/european-commission-approves-reduced-dosing-frequency-for-janssens-bispecific-antibody-tecvayli-teclistamab#:~:text=BEERSE%2C%20Belgium%2C%2018%20August%202023,kg%20every%20two%20weeks%20in (last accessed September 2023).

BCMA × CD3 T-cell bispecific antibody: Elranatamab

MagnetisMM-3 study, cohort A: BCMA-naïve patients[1]

FDA/EMA approved, CNN in Italy

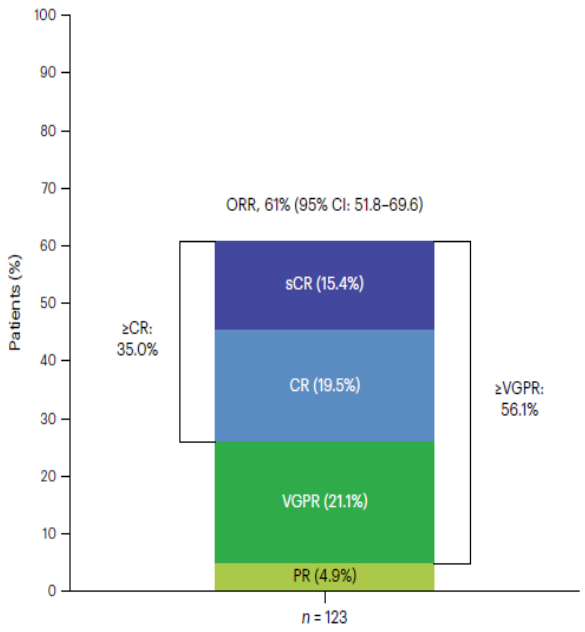
Elranatamab dosing schedule[1]

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

Baseline characteristics, Cohort A (N=123)[1]

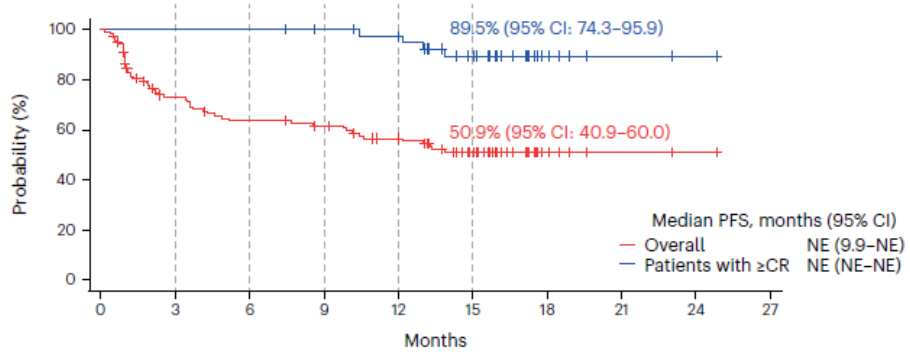
Extramedullary disease by BICR,[†] n (%)	39 (31.7)
Bone marrow plasma cells, n (%)	
<50%	89 (72.4)
≥50%	26 (21.1)
Missing	8 (6.5)
Prior lines of therapy, median (range)	5 (2–22)
Prior stem cell transplant, n (%)	87 (70.7)
Exposure status, n (%)	
Triple-class	123 (100.0)
Penta-drug	87 (70.7)
Exposure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

Response rates[1]

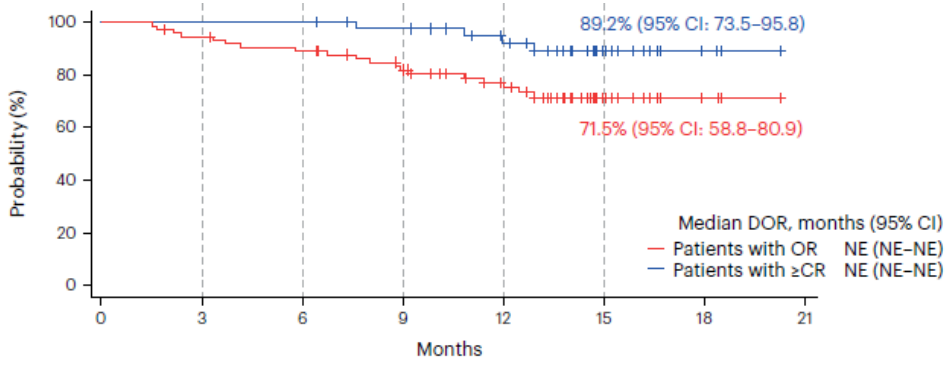


Median time to first response: 1.2 months[1]
Median time to ≥CR: 6.1 months[1]

Progression-free survival[1]



Duration of response[1]



[d]Extramedullary disease was defined as presence of any plasmacytoma (extramedullary and/or paramedullary) with a soft-tissue component.

BCMA, B-cell maturation antigen; BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; NE, not evaluable; NR, not reported; ORR, overall response rate; PFS, progression-free survival; PR, partial response; Q2W, every 2 weeks; QW, weekly; VGPR, very good partial response.

1. Lesokhin AM, et al. Nat Med 2023; doi: 10.1038/s41591-023-02528-9. Online ahead of print.

CRS management with bispecifics

- Highly predictible
  - Median time 2 days after subcutaneous dosis
  - Median time hours - 1 day after IV
- Mostly low grade
  - Grade 3 in less tan 2% of patients throughout the different programs
  - Split between grade 1/grade 2
- Occurs after first or second step-up doses
- Median time to recovery 1-2 days (short-live)
- Mitigation strategies
  - Premedication
  - **Prophylactic Tocilizumab (dutch experience and others: CRS from 70% to 26%)**
  - **Prophylactic dexamethasone (Italian, german, French experience)**
- **Biomarkers are lacking although higher risk in patients with high-tumor burden**
- Other supportive care measures should be considered and infection complications should be rule out. **Consider starting antibiotic therapy in patients with neutropenia, concomitant infection, or other predisposing risk factors for infection**

Infectious complications of bispecific antibodies

Majestec-1: Teclistamab

Median F.up 14.1 m

Clinically relevant infections,[a] 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 infection	48 (29.1)	35 (21.2)	18 (10.9)
Key viral infections[b]	20 (12.1)	7 (4.2)	1 (0.6)
GI infections	15 (9.1)	2 (2.1)	0
Fungal infections[c]	9 (5.5)	0	0
PJP	7 (4.2)	7 (4.2)	0
HBV reactivation	1 (0.6)	1 (0.6)	0

- Dose reductions: 0.6%
- Discontinuation: < 5%

Magnetismm-3: Elranatamab

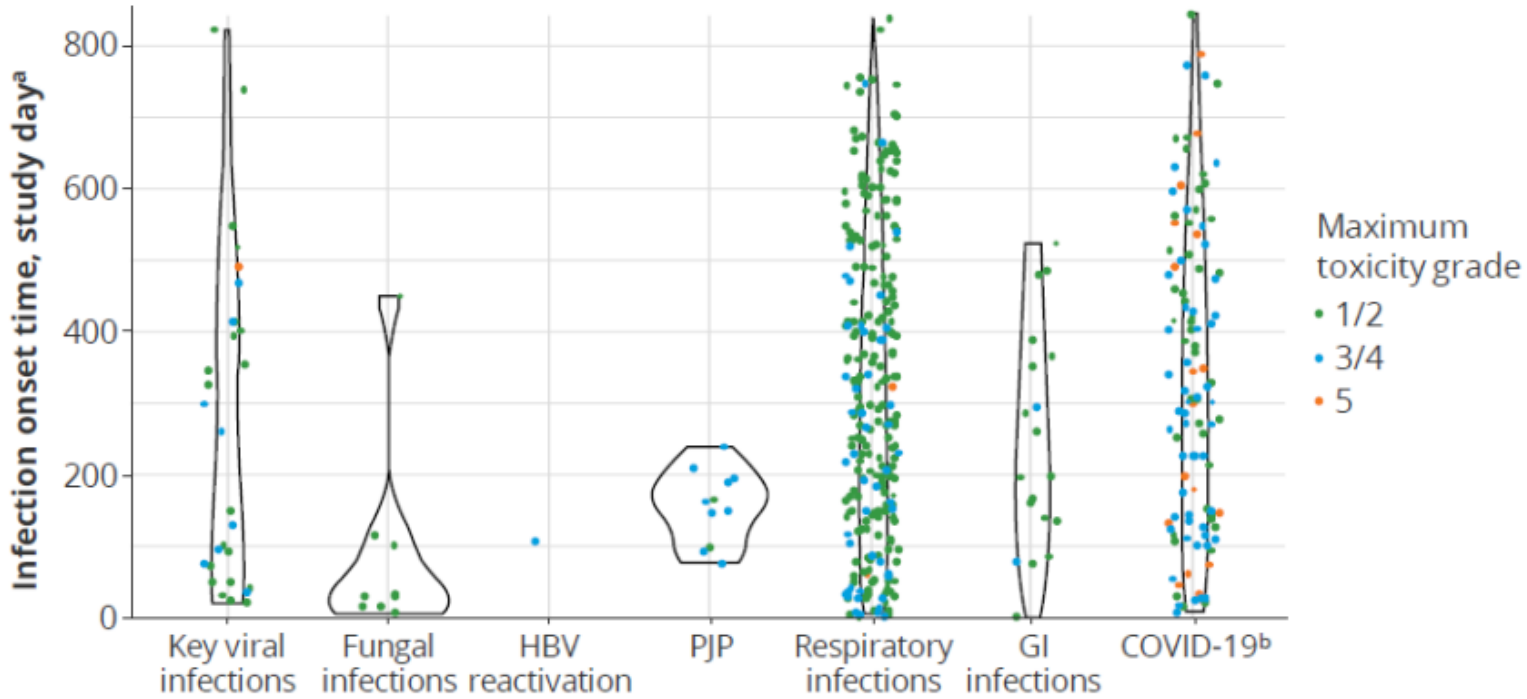
TEAEs of special interest, n (%)[a]	Any grade	Grade 3/4
ICANS	6 (4.9)	0
Infections[b]	86 (69.9)	58 (47.2)

[a] TEAEs according to the Medical Dictionary for Regulatory Activities v26.0 and Common Terminology Criteria for Adverse Events v5. Any-grade TEAE reported in ≥25% of patients; Grade 3/4 TEAE reported in ≥10% of patients; severity of CRS and ICANS was assessed according to the American Society for Transplantation and Cellular Therapy criteria; [b] Infections include preferred terms in the system organ class of infections and infestations
CRS=cytokine release syndrome; ICANS=immune effector cell–associated neurotoxicity syndrome; TEAE=treatment-emergent adverse event

Van De Donk N et al, ASCO 2023, oral presentation
Garfall A et al. Poster presentation, ASCO 2024. #7540; JCO Volume 42, Number 16_suppl June 2024

Timing and maximun toxicity grade of clinically relevant infections during Teclistamab therapy was variable

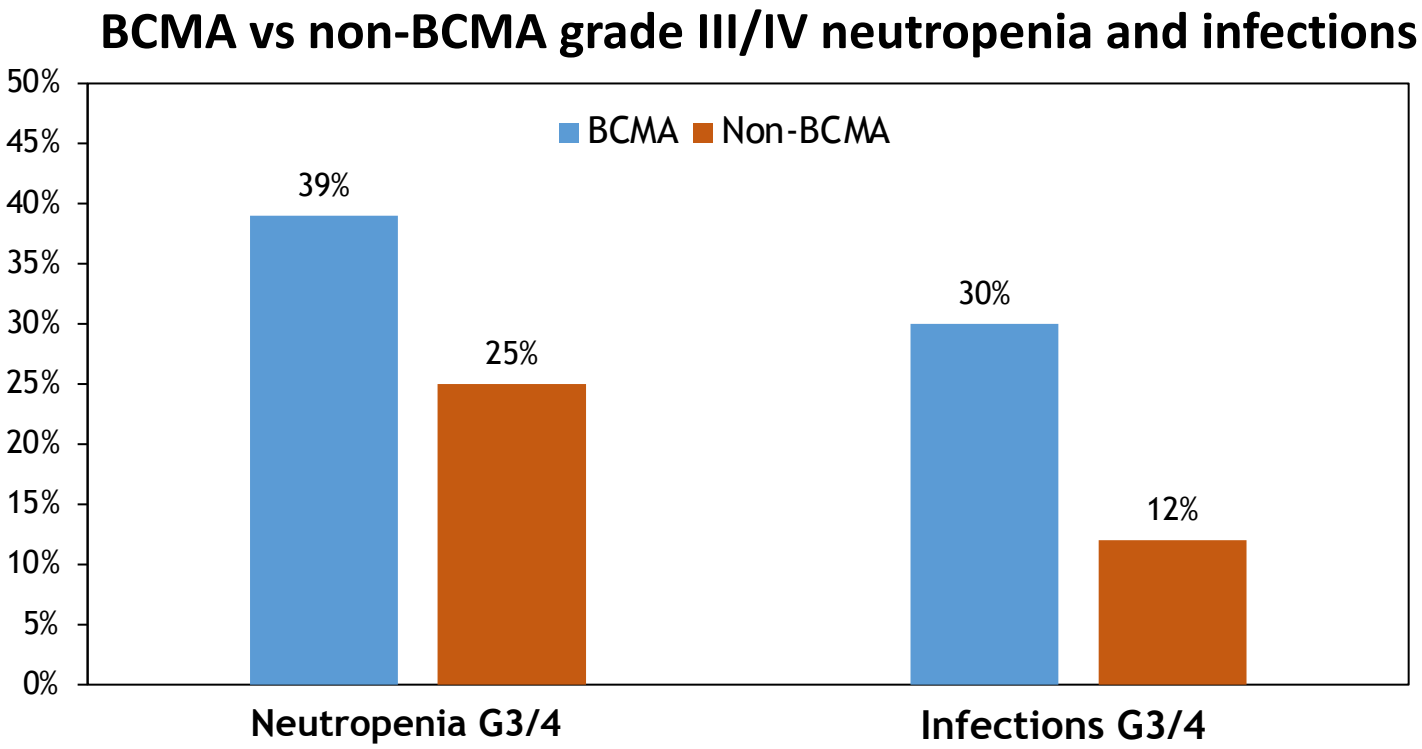
- Respiratory infections occurred throughout the study (mostly grade 1/2)
- COVID-19 infections of all grades were observed throughout the study
- Most viral infections occurred during the first 12 months
- GI infections were seen throughout the study
- Most fungal and PJP infections were observed early



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

Van De Donk N et al, IMS 2023. Oral presentation

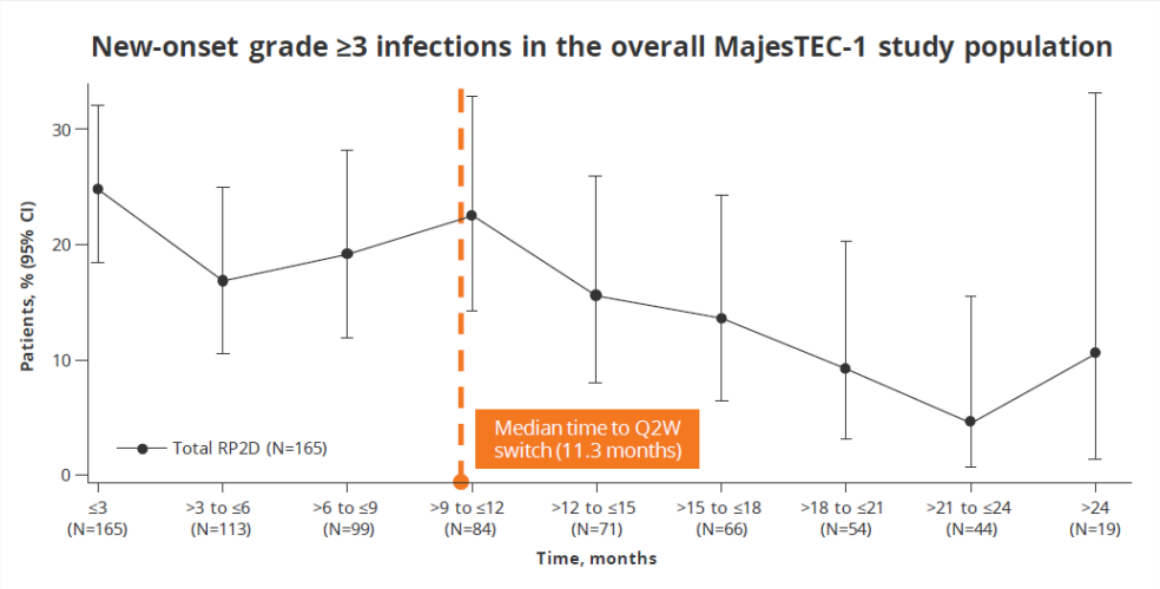
Infectious complications of bispecific antibodies

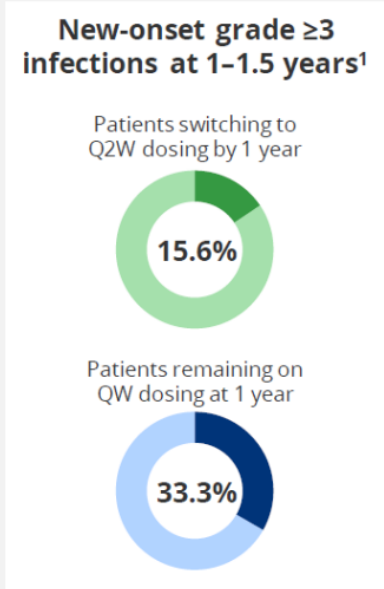


- Pooled analysis of 1185 patients treated for the first time with bispecific Abs within 11 trials (71% anti-BCMA)
- Median follow-up 6 months

Mazahreh F et al. Blood Adv 2022;doi:bloodadvances.2022009435

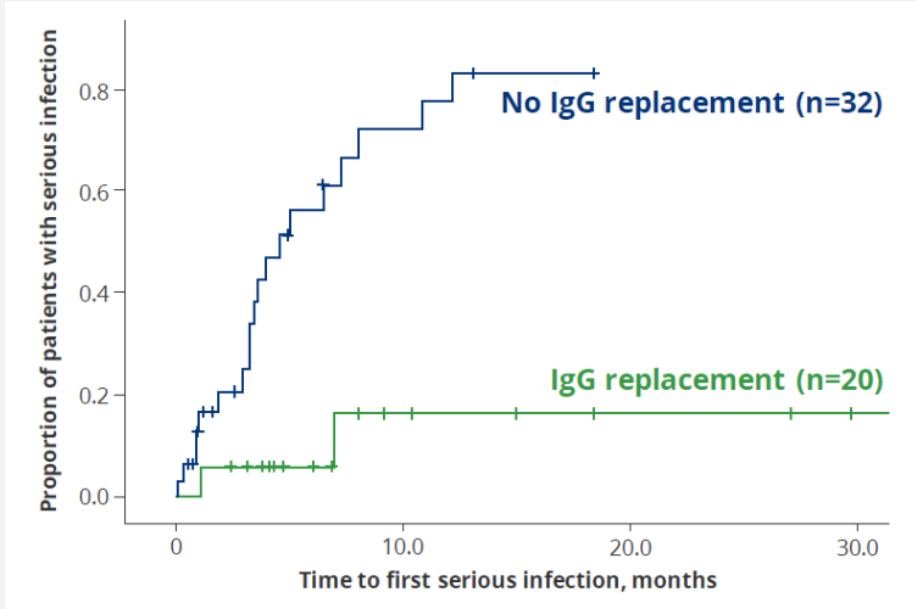
Infections mitigation strategies with Teclistamab





New onset grade ≥ 3 infections decreased over time with lower incidence in patients **switching to Q2W/Q4w schedule**

- 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 replacement significantly reduced the risk of new grade ≥ 3 infections

Van De Donk N et al, IMS 2023. Oral presentation

BCMA-targeting BsAbs are also being investigated in earlier lines: Phase III studies

Study	Treatment line	Treatment arms
MajesTEC-3[1]	1-3 prior LOT	Teclistamab + Dara, Dara-Pd or Dara-Vd (comparator)
MajesTEC-4[2]	TE NDMM	Teclistamab + R, Teclistamab, R (comparator)
MajesTEC-7[3]	TIE* NDMM	Teclistamab + Dara-R, talquetamab + Dara-R, Dara-Rd (comparator)
MajesTEC-9[4]	1-3 prior LOT	Teclistamab, PVd or Kd (comparator)
MagnetisMM-5[5]	>1 prior LOT	Part 2: Elranatamab, elranatamab + Dara, Dara-Pd (comparator)
MagnetisMM-6[6]	TIE NDMM	Part 2: Elranatamab + Dara-R, Dara-Rd (comparator)
MagnetisMM-7[7]	TE NDMM	Elranatamab, lenalidomide (comparator)
MagnetisMM-32[8]	1-4 prior LOT	Elranatamab, Elo-Pd or PVd or Kd (comparator)
MonumenTAL-6[9]	1-4 prior LOT	Talquetamab + pomalidomide, talquetamab + teclistamab, elotuzumab + Pd or PVd (comparator)

Daratumumab depletion of CD38-expressing Tregs may potentiate teclistamab/talquetamab-mediated killing of myeloma cells

*Not eligible or not intended for transplant. ASCT, autologous stem cell transplantation; Dara, daratumumab; DRd, daratumumab-lenalidomide-dexamethasone; DPd, daratumumab-pomalidomide-dexamethasone; DVd, daratumumab-bortezomib-dexamethasone; EPd, elotuzumab-pomalidomide-dexamethasone; IMiD, immunomodulatory drug; Kd, carfilzomib-dexamethasone; LOT, lines of therapy; PVd, pomalidomide-bortezomib-dexamethasone; RRMM, relapsed/refractory multiple myeloma; SVd, selinexor-bortezomib-dexamethasone. 1. NCT05083169; 2. NCT05243797; 3. NCT05552222; 4. NCT05572515; 5. NCT05020236; 6. NCT05623020; 7. NCT05317416; 8. NCT06152575; 9. NCT06208150. All clinical trial pages accessed at: https://clinicaltrials.gov/ (last accessed June 2024).

GPRC5D × CD3 T-cell bispecific antibody: Talquetamab

MonumenTAL-1, Phase I/II study[1-3]

FDA/EMA approved

Trial design[2]

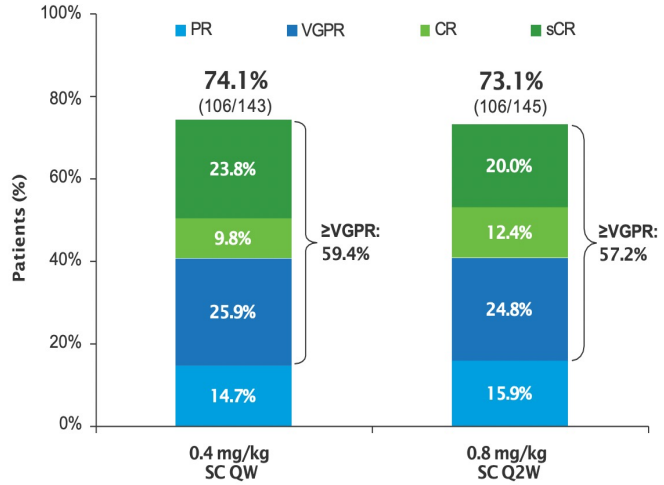
RP2D 0.4 mg/kg QW SC
- Prior BCMA-targeting ADC treatment allowed
- Prior T-cell redirecting therapy-naïve
  (n=143; n=21 Phase I and n=122 Phase II)

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)

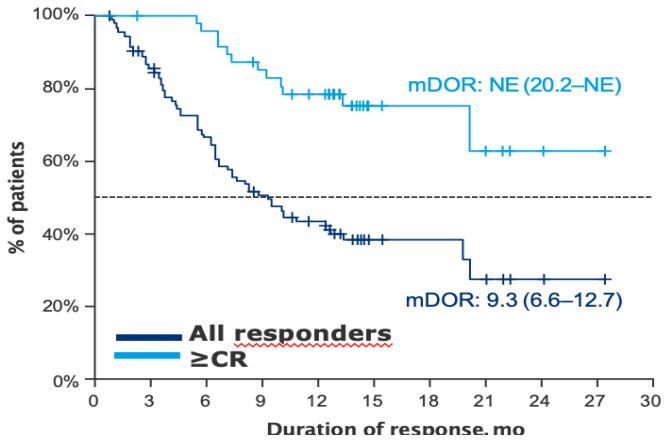
100% triple-class exposed
69–74% triple-class refractory

Response rates[2]



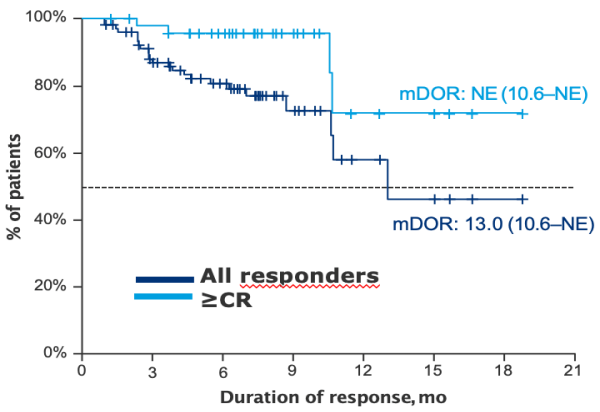
Duration of response[3]

DoR: 0.4 mg/kg SC QW



Overall mPFS: 7.5 months (95% CI, 5.7–9.4)

DoR: 0.8 mg/kg SC Q2W



Overall mPFS: 11.9 months (95% CI, 8.4–NE)

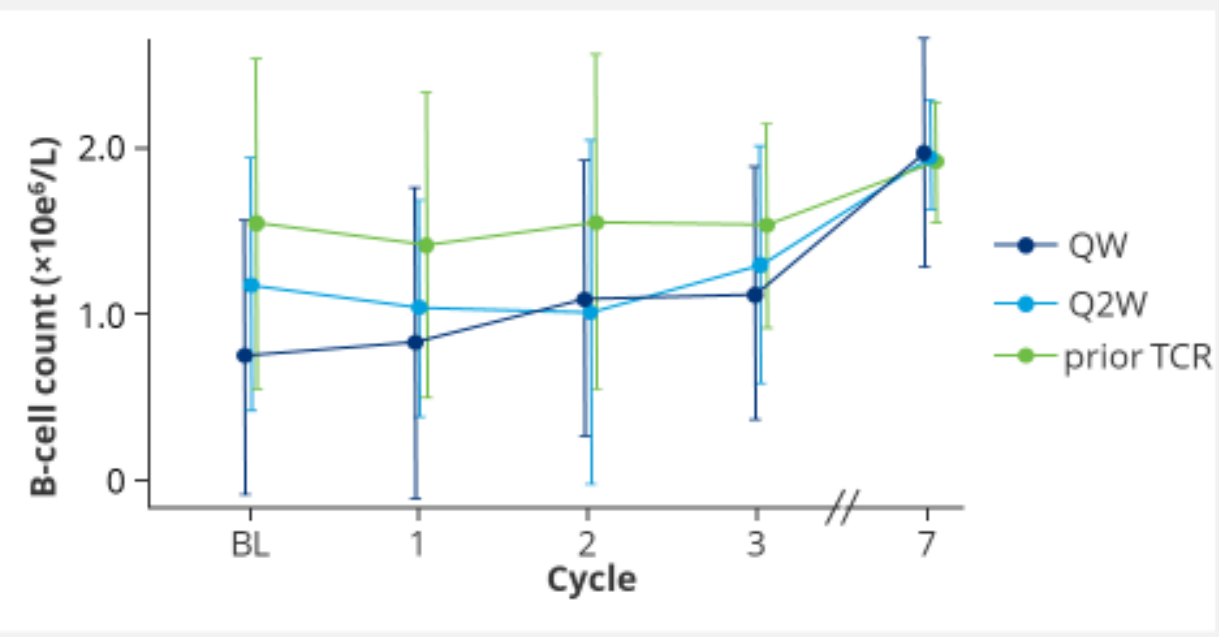
The most relevant information is that BsAbs targeting antigens different than BCMA are being evaluated and proved equally effective in patients previously exposed to BCMA-TT and the information for the sequencing is relevant

AE, adverse event; BCMA, B-cell maturation antigen; CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; ICANS, immune cell effector cell-associated neurotoxicity syndrome; mPFS, median progression-free survival; PR, partial response; NA, not applicable; NR, not reported; Q2W, every 2 weeks; QW, weekly; RP2D, recommended Phase II dose; SC, subcutaneous; sCR, stringent complete response; VGPR, very good partial response.

1. Chari A, et al. N Engl J Med 2022;387:2232-2244; 2. Schinke CD, et al. ASCO 2023 (Abstract No. 8036 – oral presentation); 3. Chari A, et al. ASH 2022 (Abstract No. 157 – presentation).

Analysis of infections and Parameters of humoral immunity in the MonumenTAL-1 study

CD19+ B-cell levels sowed no reduction over time, with an increasing trend at cycle 7

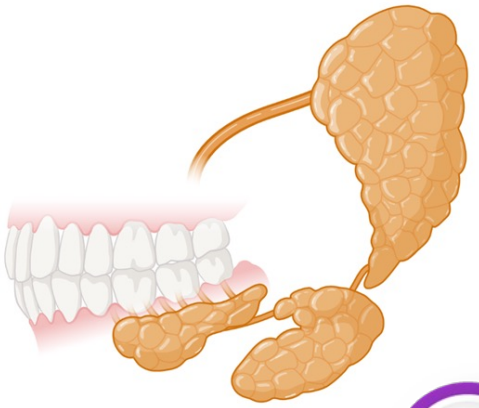


- There was no decrease in polyclonal IgG over time across cohorts
- Note that data were censored for patients with IgG myeloma and after IVIG administration

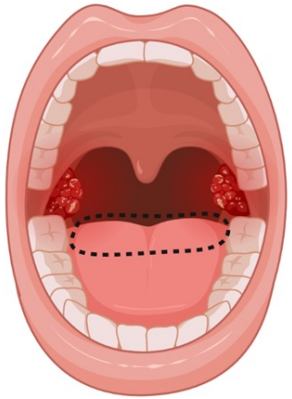
Rodriguez-Otero P et al, ASCO 2023, poster presentation

On-target Off-tumor effects: GPRC5d

Minor salivary glands

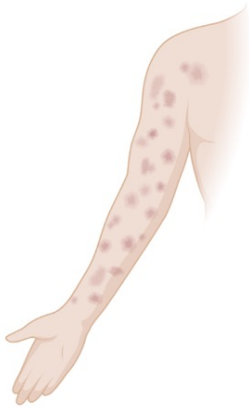


Gustative Papillae



Nails

Skin



- Dysgeusia, ageusia, hypogeusia
- Xerostomia
- Dysphagia
- Weight loss

- Dryness and pruritus
- Palmar/plantar desquamation
- Rash and injection site reactions
- Nail disorders

Specific toxicities in anti-GPRC5D CAR-Ts and BsABs

	BMS-986393 (CC-95266)[1] N = 33		MCARH109[2] N= 17		Talquetamab 405 ng SC weekly[3] N=30		Talquetamab 800 ng SC biweekly[3] N=44	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
CRS	21 (63.6)	2 (6.1)	88%	6%	23 (77)	1 (3)	35 (80)	0
ICANS, n (%)	2 (6.0)	0 (0)	6%	6%	NR	NR	NR	NR
Neutropenia N (%)	22 (66.7)	20 (60.6)	17 (100)	17 (100)	49 (34)	44 (31)	41 (28)	32 (22)
Lymphopenia N (%)	7 (21.2)	6 (18.2)	17 (100)	17 (100)	40 (28)	NR	38 (26)	NR
On-target/off-tumor AEs								
Skin[b]	10 (30.3)	0 (0)	18%	0 (0)	20 (**67**)	0 (0)	31 (**70**)	1 (2)
Dysgeusia/taste disorder	5 (15.2)	0 (0)	12%	0 (0)	19 (**63**)	NR	25 (**57**)	NR
Nails[c]	3 (9.1)	0 (0)	65%	0 (0)	17 (**57**)	0	12 (**27**)	1 (2)
Dysphagia	1 (3.0)	0 (0)	NR	0 (0)	11 (**37**)	0	12 (**27**)	0

1, Bal S et al. – Abs 364 ASH 2022. 2, Mailankody S, et al. N Engl J Med, 2022;387:1196-206. 3, Chari A. et al. N Engl J Med 2022; 387:2232-2244

Best Practices: Skin and nail Toxicities

Dry skin

- Heavy emollients
- Hydration
- Sun protection

Palmar/plantar desquamation

- Triamcinolone + emollients + AmLactin BID

Skin rash/pruritus

- Antihistamines
- Grade 1–2: Topical steroids
- Grade 3: Oral steroid taper + topical steroids

Nail toxicity

Emollients; cuticle/Vitamin E oil

Nail hardeners

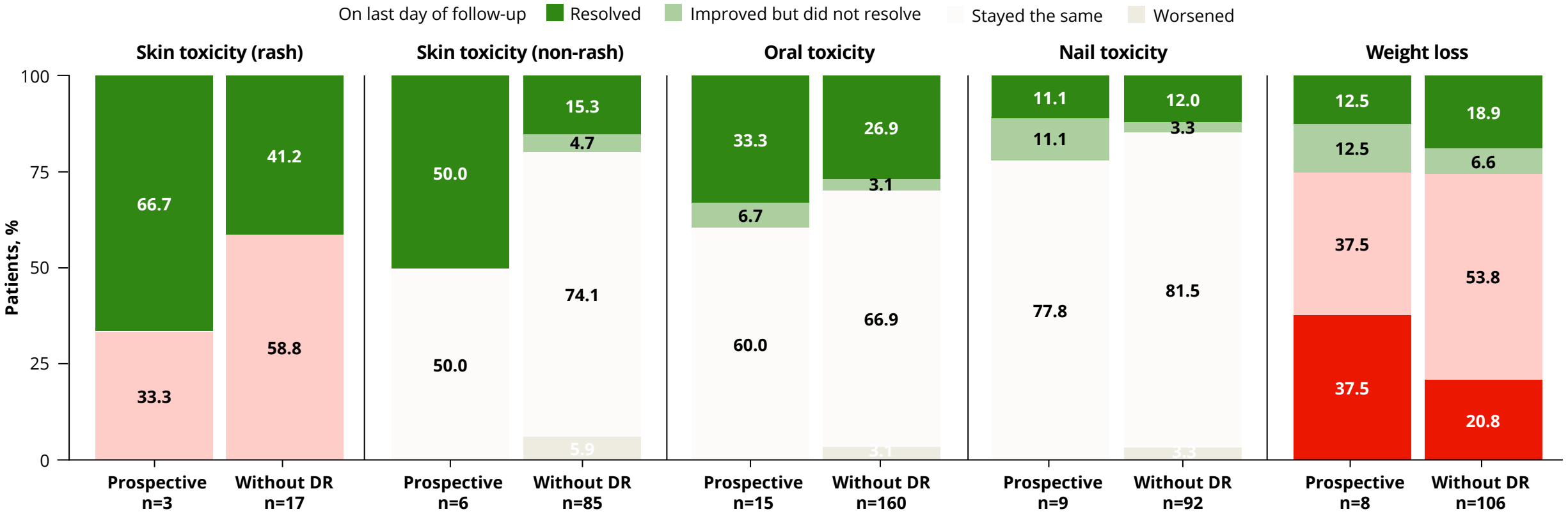
Good hygiene

Courtesy of Samantha Shenoy, presented at Haimatus meeting 2024

MonumenTAL-1: Responsive Dose Intensity Reduction Cohorts

Prospective cohorts with change in AE status after switch vs matched cohort without dose reduction[a]

Disease Response Maintained Even With Dose Reduction



- Trend toward improved resolution of GPRC5D-related AEs, except weight loss

Data cut-off date: October 2, 2023. [a]Patients included had ≥PR before day 200 from the prospective dose modification cohort (n=18) and from the MonumenTAL-1 cohort who did not dose reduce (n=206). Each category shows only patients who had a respective AE on day 100. Color signifies how that respective AE grade changed from day 100 to last day of follow-up (within 30 days of last treatment; capped at 500 days).
AE, adverse event; DR, dose reduction; GPRC5D, G protein–coupled receptor family C group 5 member D; PR, partial response.

Chari A et al. Oral presentation, ASH 2023.

GPRC5D-targeting BsAbs are also being investigated in novel combinations, including in earlier lines[1–10]

New combinations

TRIMM-2, Phase Ib[1,2]

Talquetamab + dara ± pom
Tal 0.4 mg/kg QW + dara (n=14)
ORR 71.4%; mPFS NR

Tal 0.8 mg/kg Q2W + dara (n=50)
ORR 84.0%; mPFS 19.4 months

TRIMM-3, Phase Ib[3]

Talquetamab + PD-1 inhibitor
or teclistamab + PD-1 inhibitor

RedirecTT-1, Phase I/II[4,5]

Talquetamab + teclistamab
ORR 96.3% (n=27; RP2R); mPFS 20.9 months (all treated patients)

New combinations in earlier lines

MonumenTAL-2, ≥1 prior LOT, Phase Ib[6,7]

Talquetamab + len ± dara or **talquetamab + pom**
ORR 93.8% (n=16; tal 0.4 mg/kg QW + pom)
ORR 84.2% (n=19; tal 0.8 mg/kg Q2W + pom)

MonumenTAL-3, ≥1 prior LOT, Phase III[8]

Talquetamab + dara ± pom vs dara-Pd

MonumenTAL-6, ≥1 prior LOT, Phase III[9]

Talquetamab + pom or **talquetamab + teclistamab** vs EPd or PVd

MajesTEC-7, NDMM, Phase III[10]

Talquetamab + len + dara or **teclistamab + len + dara** vs Dara-Rd

BsAb, bispecific antibody; d, dexamethasone; dara, daratumumab; E, elotuzumab; GPRC5D, G protein-coupled receptor class C group 5 member D; len/R, lenalidomide; LOT, line(s) of therapy; mPFS, median progression-free survival; NDMM, newly diagnosed multiple myeloma; NR, not reached; PD-1, programmed cell death protein 1; pom/P, pomalidomide; Q2W, every 2 weeks; QW, weekly; RP2R, recommended Phase II regimen; tal, talquetamab; V, bortezomib.

1. NCT04108195. Available at: https://clinicaltrials.gov/study/NCT04108195 (last accessed June 2024); 2. Dholaria B, et al. ASCO 2023 (Abstract No. 8003 – oral presentation); 3. NCT05338775. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT05338775 (last accessed June 2023); 4. NCT04586426. Available at: https://clinicaltrials.gov/study/NCT04586426 (last accessed June 2024); 5. Cohen YC, et al. ASCO 2023 (Abstract No. 8003 – oral presentation); 6. NCT05050097. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT05050097 (last accessed June 2024); 7. Matous J, et al. ASH 2023 (Abstract No. 1014 – oral presentation); 8. NCT05455320. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT05455320 (last accessed June 2024); 9. NCT06208150. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT06208150 (last accessed June 2024); 10. NCT05552222. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT05552222 (last accessed June 2024).

IMWG consensus guidelines

Consensus guidelines and recommendations for the management and response assessment of chimeric antigen receptor T-cell therapy in clinical practice for relapsed and refractory multiple myeloma: a report from the International Myeloma Working Group Immunotherapy Committee

Yi Lin, Lugui Qiu, Saad Usmani, Chng Wee Joo, Luciano Costa, Benjamin Derman, Juan Du, Hermann Einsele, Carlos Fernandez de Larrea, Roman Hajek, P Joy Ho, Efstathios Kastritis, Joaquin Martinez-Lopez, Maria-Victoria Mateos, Joseph Mikhael, Philippe Moreau, Chandramouli Nagarajan, Ajay Nooka, Michael O'Dwyer, Fredrik Schjesvold, Surbhi Sidana, Niels WCJ van de Donk, Katja Weisel, Sonja Zweegman, Noopur Raje, Paula Rodriguez Otero, Larry D Anderson Jr, Shaji Kumar, Tom Martin, on behalf of the International Myeloma Working Group

Policy Review

International Myeloma Working Group immunotherapy committee consensus guidelines and recommendations for optimal use of T-cell-engaging bispecific antibodies in multiple myeloma

*Paula Rodriguez-Otero, Saad Usmani, Adam D Cohen, Niels W C J van de Donk, Xavier Leleu, Jaime Gállego Pérez-Larraya, Salomon Manier, Ajay K Nooka, Maria Victoria Mateos, Hermann Einsele, Monique Minnema, Michele Cavo, Benjamin A Derman, Noemi Puig, Francesca Gay, P Joy Ho, Wee-Joo Chng, Efstathios Kastritis, Gösta Gahrton, Katja Weisel, Chandramouli Nagarajan, Fredik Schjesvold, Joseph Mikhael, Luciano Costa, Noopur S Raje, Elena Zamagni, Roman Hájek, Niels Weinhold, Kwee Yong, Jing Christine Ye, Surbhi Sidhana, Giampaolo Merlini, Tom Martin, Yi Lin, Ajai Chari, Rakesh Popat, Jonathan L Kaufman, on behalf of the International Myeloma Working Group**

Lin Yi et al, Lancet Oncology May 2024.
Rodriguez-Otero P et al, Lancet Oncology May 2024.

How to choose, with the current approval status, among the 2 different immune therapies?

- Real world patients receiving CAR-T have more co-morbidities than patients on trials
- Half to three-fourths of patients treated with SOC ide-cel and cilta-cel would be trial ineligible
- **SOC CAR-T: good safety and efficacy**
- **Need to "make it" to CART**
- **Avoid, within some months from apheresis, lymphodepletion chemo (bendamustine, others) and other BCMA targeted therapy; unclear wash out with bispecifics against other targets**

CARTs

- Young patient or fit elderly patient
- Search for sustained MRD negativity and treatment-free interval
- **Patient without rapidly progressing disease/soft tissue clinically relevant involvement**
- eGFR around 30 ml/min…but this threshold will soon go down with further RWE
- Patients in which **sequencing matters**

Bispecifics

- Search for high quality response/response duration
- **Enaugh fitness to follow anti-infection prophylaxis/treatment, in particular when BCMA is the target**
- Non recurrent pulmonary infections/underlying lung diseases for BCMA as a target
- Patients with rapidly progressing disease/EMD; CNS involvement?
- Space for totally out patient treatment

Zamagni E personal communication

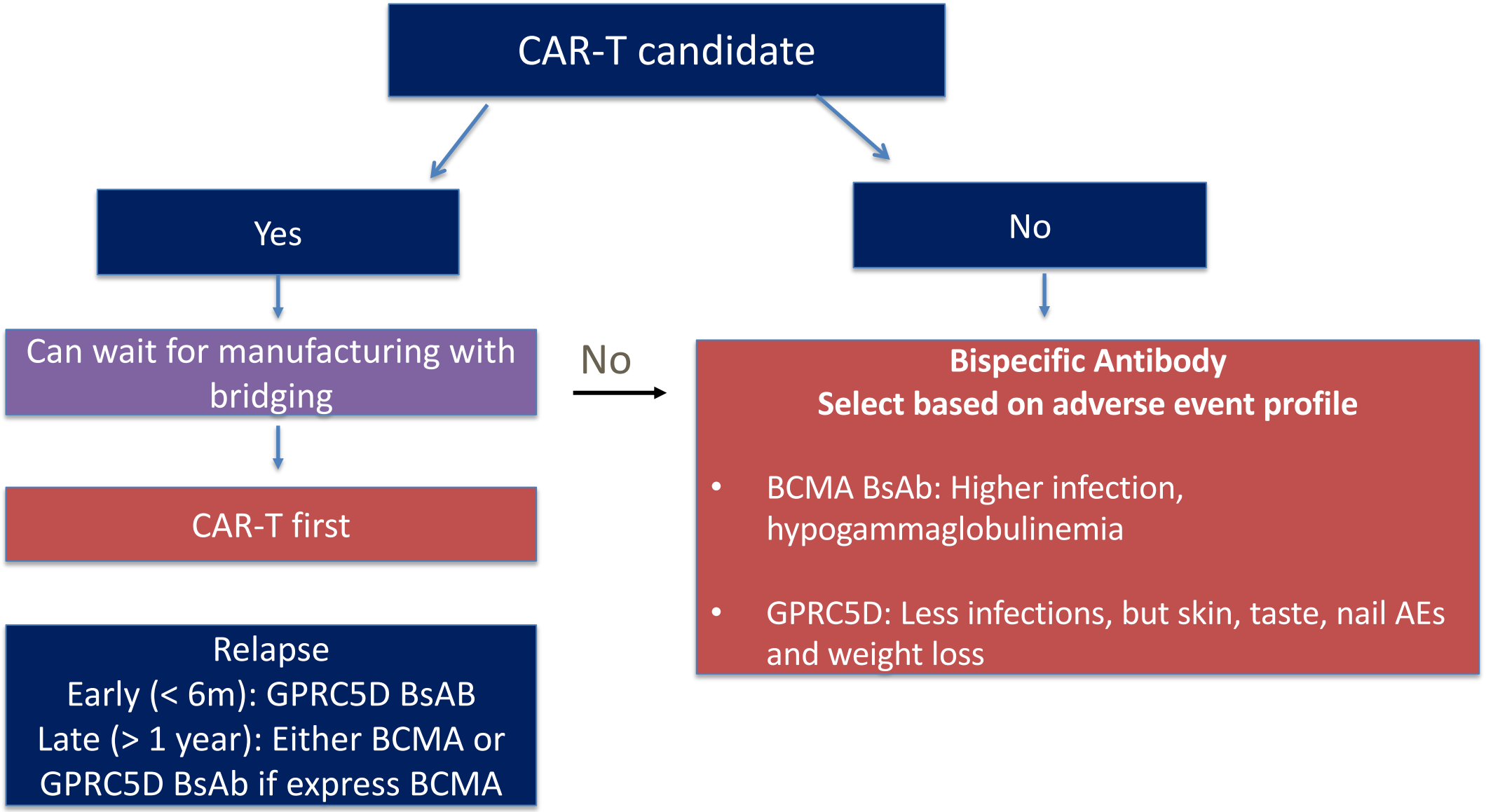
Bispecific Antibodies After BCMA Therapy

Good efficacy after prior CAR-T

	Talquetamab[1]	Elranatamab[2]	Teclistamab[3]
Target	GPRC5D	BCMA	BCMA
N	51	24% of N=55	40
Prior BCMA type	BCMA CAR-T: 36 BsAb:=18	-	ADC:73% CAR-T: 38%
Response prior BCMA	**65%**	**54%**	**53%**
Response based on prior immunotherapy	**Prior CAR-T: 75%** **BsAB: 44%**	**Not reported**	**Prior CAR-T: 53%** **ADC: 55%**

1. Schinke et al ASCO 2023; 2. Raje et al ASH 2022; 3. Touzeau et al ASCO 2022

Possible Sequencing Approach



Conclusions

- Treatment choice at relapse is becoming increasingly difficult due to the utilization of multi-drug regimens upfront.

- Anti-BCMA agents (CAR T-cells and TCE) in early lines will change the SoC for 2x-3x class RR patients; currently are becoming a SOC in later lines and proved safe and effective also in real-life setting. Guidelines for management are available

- Other targets may enlarge treatment opportunities

- Sequencing of different agents is still under investigation despite initial data are becoming available (in particular from US colleagues!)