2024:
È già ora di abbandonare la **chemioterapia** nella **malattia recidivata/refrattaria?**

Napoli, Hotel Paradiso • 29–30 aprile 2024

Anticorpi bispecifici: quali e quando utilizzarli

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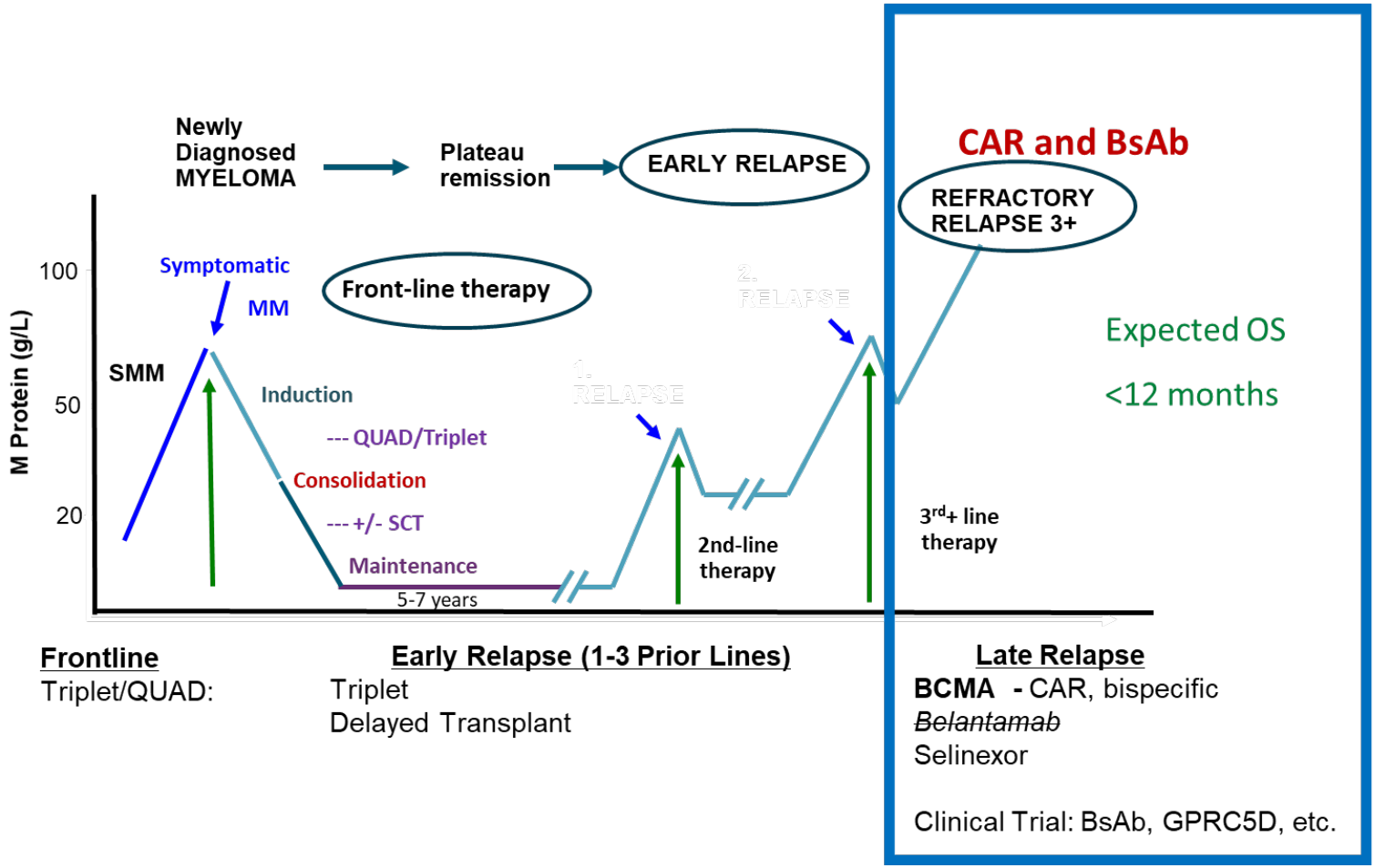
Disclosures of Massimo Offidani

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie					X	x	
Amgen					x	x	
GSK					x	x	
Janssen					x	x	
Menarini					X		
Sanofi	X				x	x	
Takeda					X	X	

Current MM Treatment Paradigm



SMM
Risk assessment

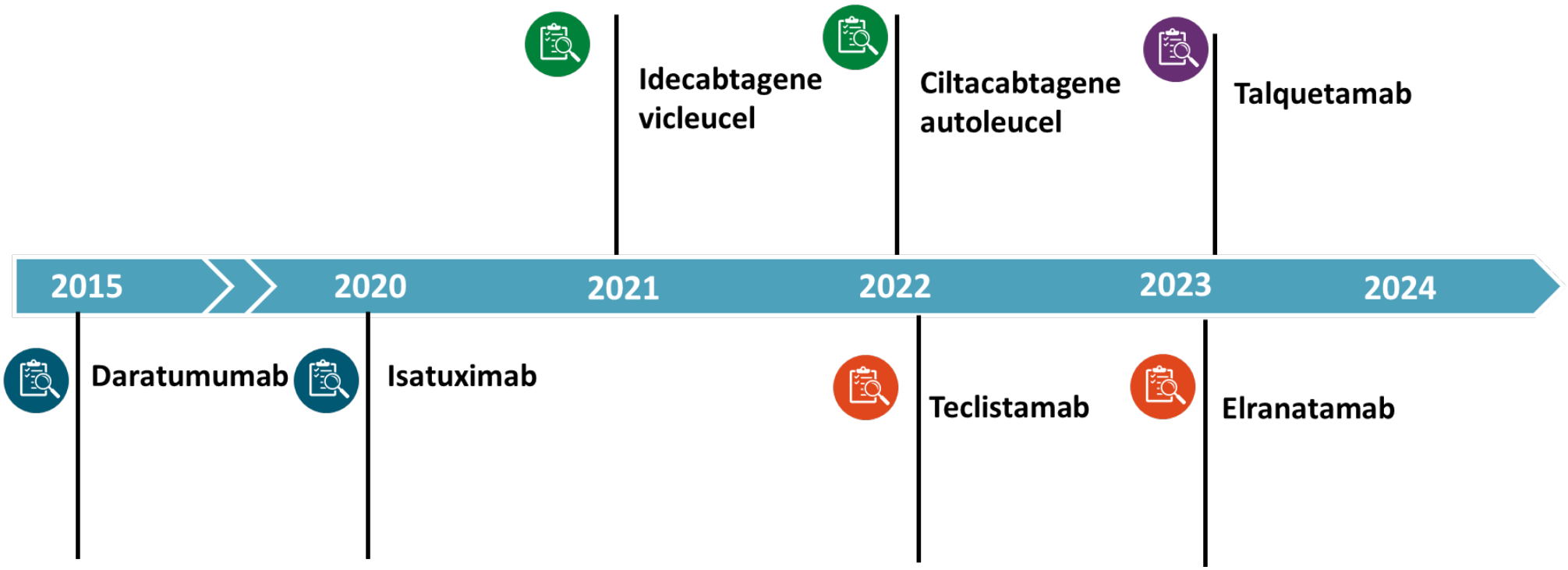
Frontline
Triplet/QUAD:

Early Relapse (1-3 Prior Lines)
Triplet
Delayed Transplant

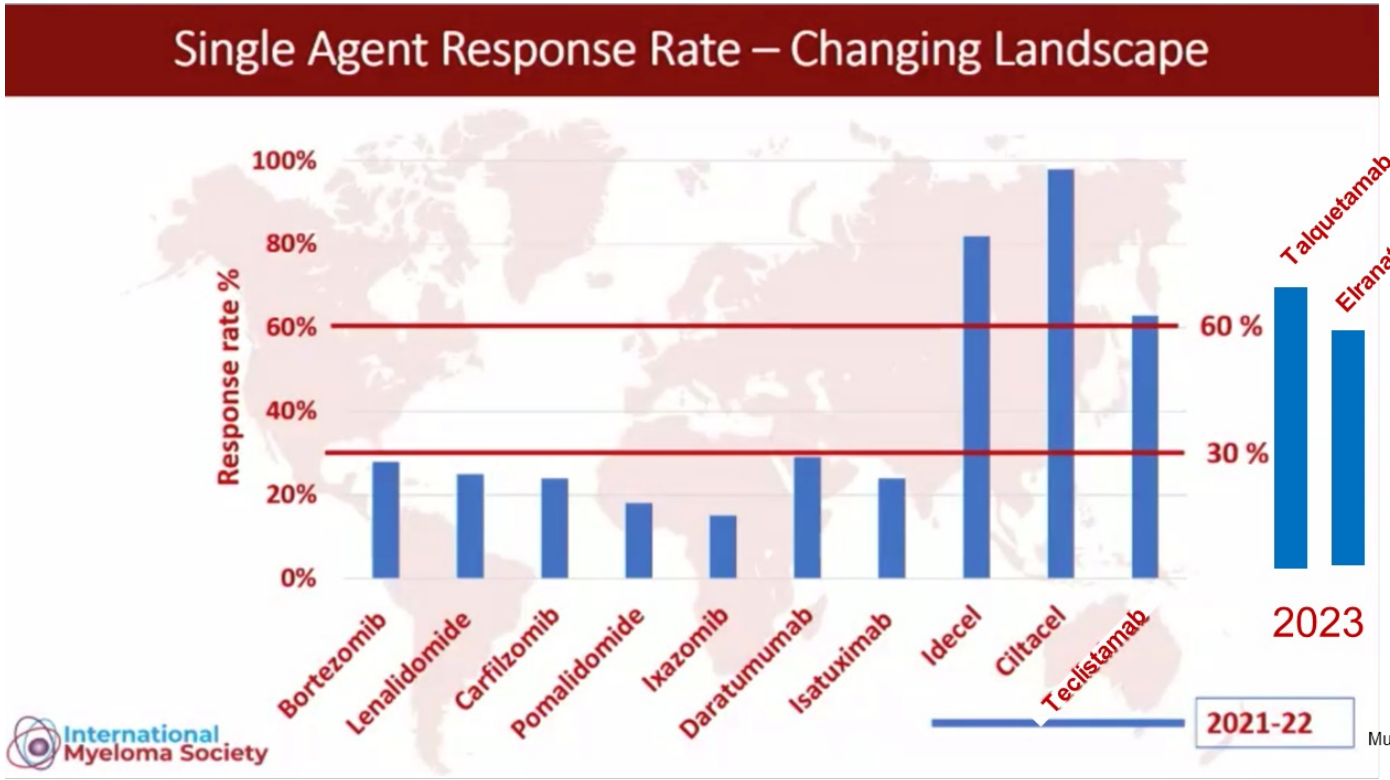
Late Relapse
BCMA - CAR, bispecific
~~*Belantamab*~~
Selinexor

Clinical Trial: BsAb, GPRC5D, etc.

Novel Therapies in Multiple Myeloma



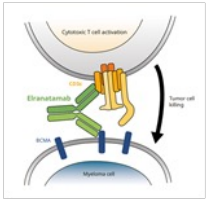
Amazing Success in Immunotherapy for MM

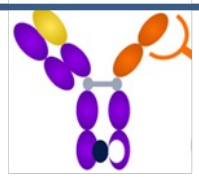


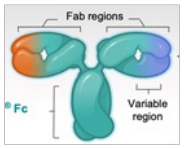
BCMA-targeting bispecific antibodies

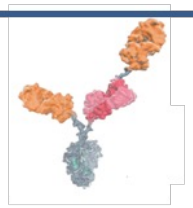
Approved BsAb | IV infusion | 2:1 binding | CD3 low affinity

	Teclistamab MajesTEC-1[1] (n=165)	Elranatamab Magnetismm3[2] (n=123)	ABBV-383B[3] (n=118)	Linvoseltamab LINKER-MM1[4] (n=117)	Alnuctamab[5] CC-93269 (n=68)	REGN5459[6] (n=43)
Phase	I/II	I/II	I	II	I/II	I/II
Target	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3
scFv	Humanized	Humanized	Human	Human	Humanized	Human
Ig	IgG4	IgG2a	IgG4	IgG4	IgG1-based	IgG4
Administration	SC	SC	IV	IV	SC	IV
# prior lines	5 (2-14)	5 (2-12)	5 (1-15)	5 (2-14)	4 (3-11)	5 (2-9)
Age	64 (33-84)	69 (44-89)	68 (35-88)	70 (37-91)	64 (36-79)	67 (26-85)









[1] Nooka et al. ASCO 2022; [2] Bahlis et al. ASH 2022; [3] Voorhees et al. IMS 2022; [4] Hans L. et al. ASCO 2023; [5] Wong et al. ASH 2019; [6] Suvannasankha et al. AACR 2023

Bispecific antibodies redirecting T-cells against myeloma cells[1]

Bispecific antibodies[1,2]

BCMA

Teclistamab
Elranatamab
Linvoseltamab
ABBV-383
Alnuctamab

GPRC5D

Talquetamab
Forimtamig

FcRH5

Cevostamab

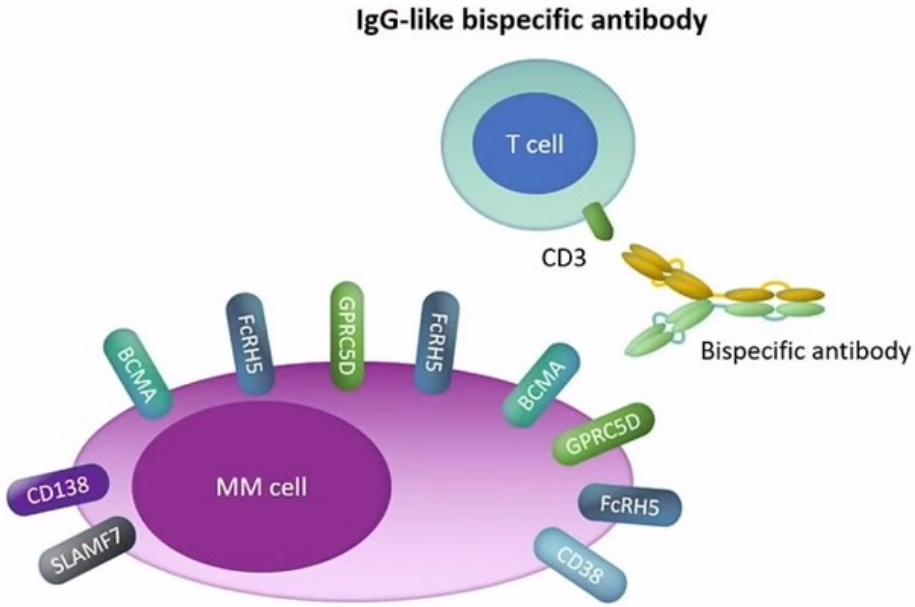


Image adapted from Verkleij CPM, et al. Curr Opin Oncol 2020;32:664–71.[3]

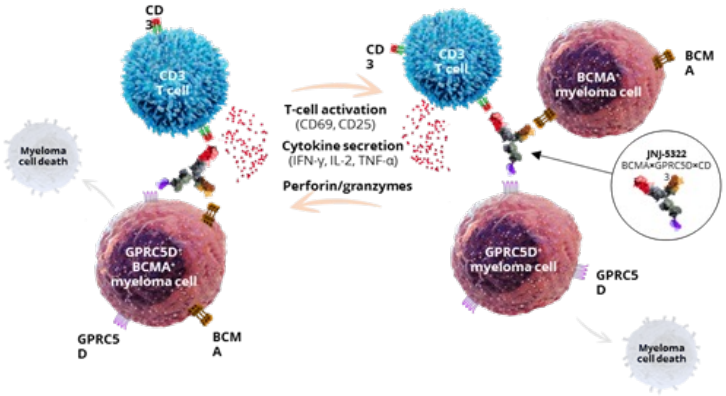
BCMA, B-cell maturation antigen; IgG, immunoglobulin G.

1. Lancman G, et al. Blood Cancer Discov 2021;2:423–433; 2. Tapia-Galisteo A, et al. J Hematol Oncol 2023;16:83; 3. Verkleij CPM, et al. Curr Opin Oncol 2020;32:664–71.

JNJ-79635322 Is a Potential First-in-Class Trispecific Antibody Targeting BCMA, GPRC5D, and CD3

- Dual antigen targeting may enhance tumor response by circumventing tumor heterogeneity and antigen loss and improving potency due to antigen binding avidity

- JNJ-79635322 (JNJ-5322) is an IgG1 trispecific antibody that binds to CD3 on T cells and BCMA and GPRC5D on MM cells

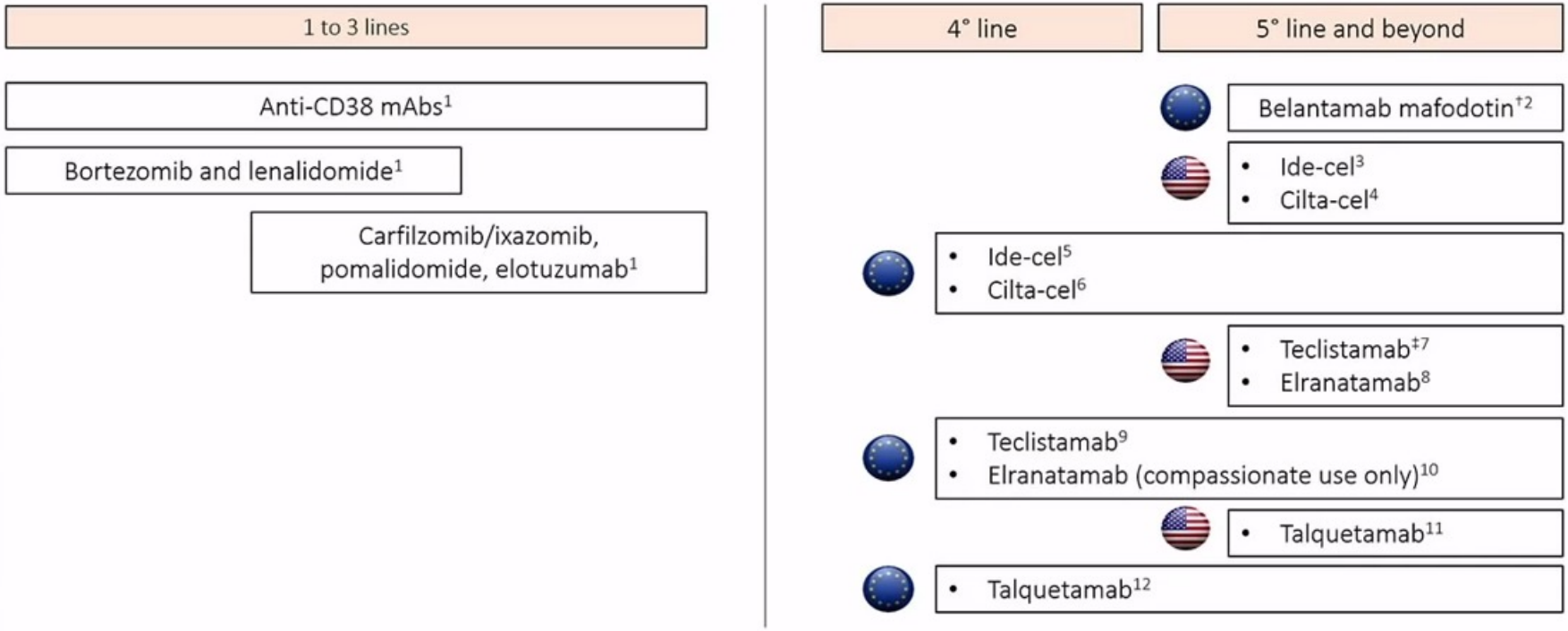


- In vitro, JNJ-5322 induced potent and dose-dependent cytotoxicity with concomitant T-cell activation only in myeloma cell lines that expressed one or both target proteins (BCMA, GPRC5D)
- JNJ-5322 also induced CD138^{+} plasma cell depletion when tested using patient-derived myeloma bone marrow mononuclear cells in a co-culture assay
- In vivo, JNJ-5322 induced potent antitumor activity in models that expressed one or both target proteins

A phase 1 dose-escalating study of JNJ-5322 in patients with RRMM is ongoing (NCT05652335)

Pillarisetti K et al. ASH 2023

Treatment approach to triple-class exposed MM in the "T-cell redirecting" era*



*Please note that not all treatments shown on this slide are currently approved in this setting for the allocated geographical region; †The EMA's human medicine committee recommended to not renew Blenrep's conditional marketing authorization in September 2023[13]; ‡In the US, patients receiving teclistamab should be hospitalised for 48 hours after administration of all doses within the dosing schedule.[7]

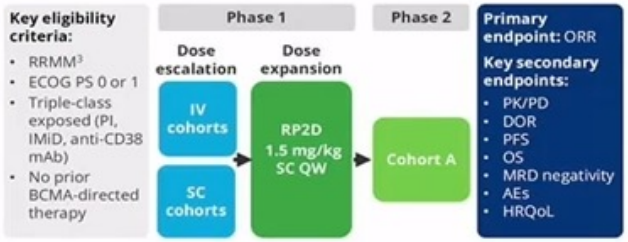
BCMA, B-cell maturation antigen.

1. Dimopoulos MA, et al. Ann Oncol 2021;32:309–322; 2. Blenrep EU SmPC, June 2023; 3 Abecma US PI, March 2021; 4. CARVYKTI US PI, February 2023; 5. Abecma EU SmPC, October 2021; 6. CARVYKTI EU SmPC, July 2023; 7. TECVAYLI US PI, November 2022; 8. ELREXFIO US PI, August 2023; 9. TECVAYLI EU SmPC, August 2023; 10. Pfizer filing acceptance press release. Available at: https://www.pfizer.com/news/press-release/press-release-detail/pfizers-elranatamab-receives-fda-and-ema-filing-acceptance (last accessed August 2023); 11. TALVEY US PI, August 2023; 12. TALVEY EU SmPC, September 2023; 13. Press release. Available at: https://www.ema.europa.eu/en/news/ema-recommends-non-renewal-authorisation-multiple-myeloma-medicine-blenrep (last accessed September 2023).

BCMA × CD3 T-Cell bispecific antibody: Teclistamab

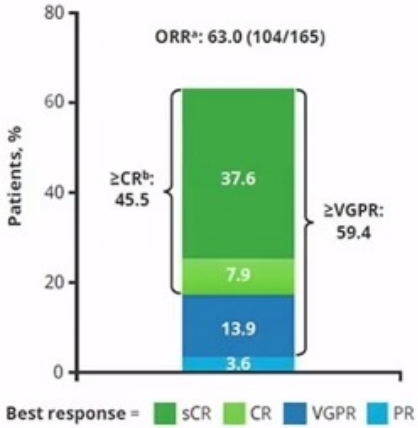
MajesTEC-1, Phase Ib/II study[1]

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]

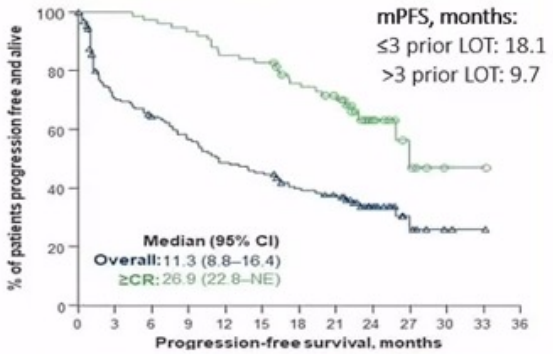
Response rates[1]



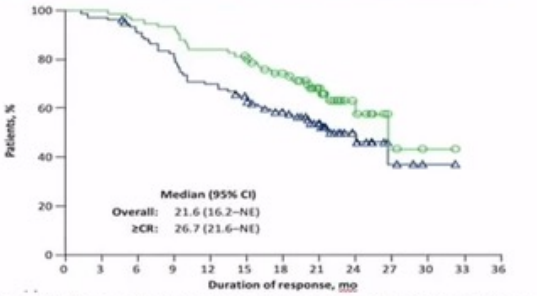
Median time to first response: 1.2 months[1]
Median time to ≥CR: 4.6 months[1]

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

Progression-free survival[1]



Duration of response[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)

*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; ‡ORR assessed by independent review committee; §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).

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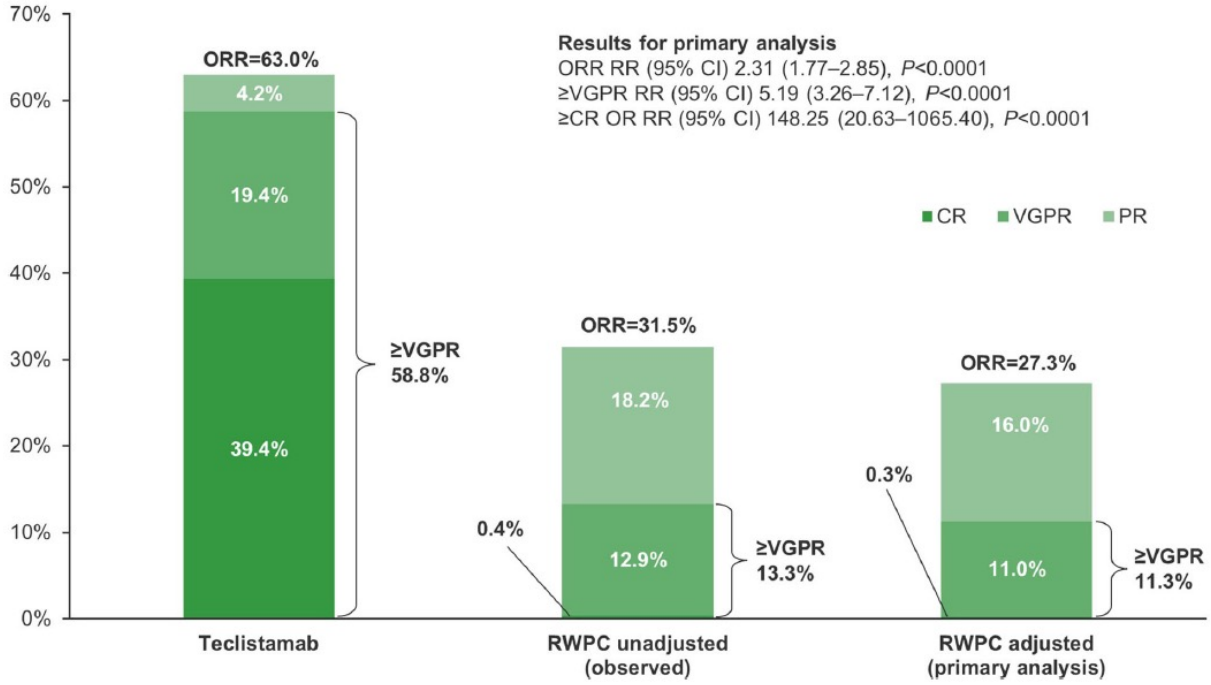
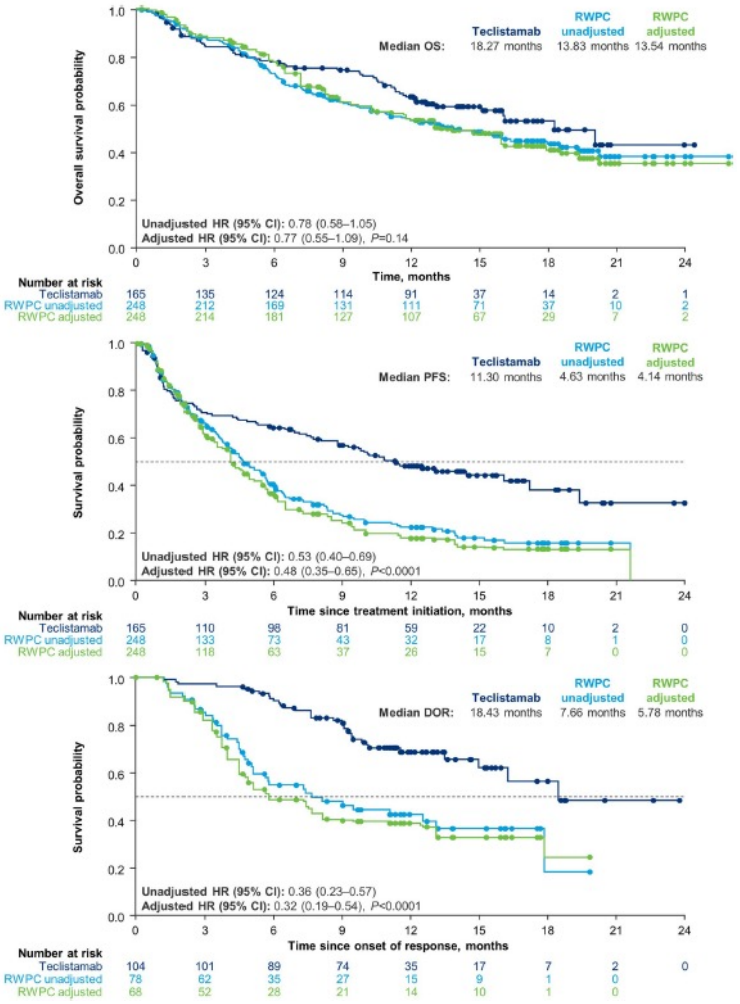
Comparative Efficacy of Teclistamab Versus Current Treatments in Real-World Clinical Practice in the Prospective LocoMMotion Study in Patients with Triple-Class-Exposed Relapsed and/or Refractory Multiple Myeloma

Philippe Moreau · Niels W. C. J. van de Donk · Michel Delforge · Hermann Einsele · Valerio De Stefano · Aurore Perrot · Britta Besemer · Charlotte Pawlyn · Lionel Karlin · Salomon Manier · Xavier Leleu · Katja Weisel · Francesca Ghilotti · Joris Diels · Ahmed Elsada · Raul Morano · Vadim Strulev · Lixia Pei · Rachel Kobos · Jennifer Smit · Mary Slavcev · Maria-Victoria Mateos

Adv Ther (2023)



Results for primary analysis
ORR RR (95% CI) 2.31 (1.77–2.85), *P*<0.0001
≥VGPR RR (95% CI) 5.19 (3.26–7.12), *P*<0.0001
≥CR OR RR (95% CI) 148.25 (20.63–1065.40), *P*<0.0001

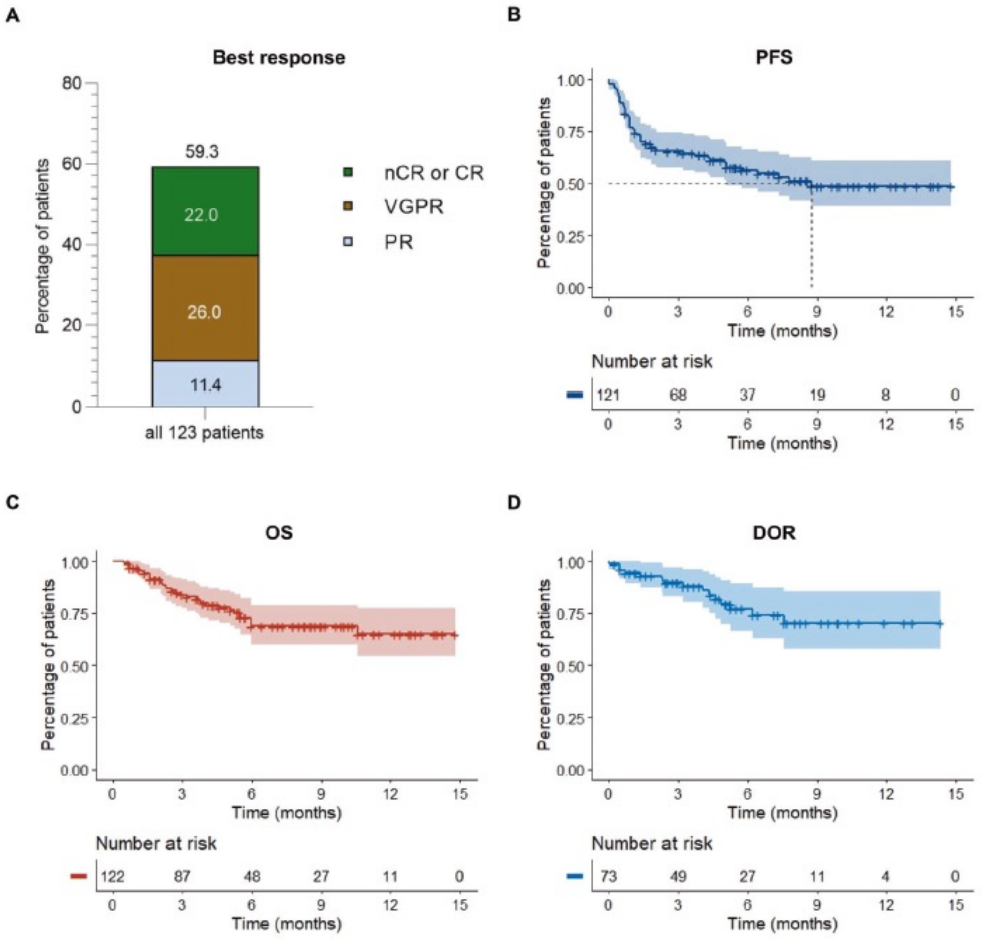


2024: È già ora di abbandonare la **chemioterapia** nella **malattia recidivata/refrattaria?**

Table 1. Patient characteristics at baseline in comparison to MAJESTEC-1.

Characteristic	MAJESTEC-1	Real-world
Median age (range) - yr	64.0 (33.0–84.0)	67.0 (35.0–87.0)
Gender: male/female - %	58.2/41.8	56.9/43.1
Median time since diagnosis - yr (range)	6.0 (0.8–22.7)	6.5 (0.5–18.7)
Median no. of lines of previous therapy (range)	5 (2–14)	6 (3–14)
Extramedullary disease - no./ total no. (%)	28/165 (17.0)	43/119 (36.1)
≥60% plasma cells in bone marrow no./total no. (%)	18/160 (11.2)	21/59 (35.6)
ISS no./total no. (%)		
I	85/162 (52.5)	25/92 (27.1)
II	57/162 (35.2)	35/92 (38.0)
III	20/162 (12.3)	31/92 (33.7)
High risk cytogenetic profile no./total no. (%)	38/148 (25.7)	39/106 (36.8)
Refractory status no./total no. (%)		
triple-class	128/162 (77.6)	113/123 (92.6)
penta-drug	50/162 (30.3	74/123 (60.2)

Riedhammer et al, Leukemia 2024



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Patients Characteristics	N = 106	MTec-1 (N=165)
Age, years, median (range)	66.5 (35–87)	64 (33-84)
Age >70 years, n (%)	34 (32)	
Median time since diagnosis, years (range)	5.5 (0.5-20)	6.0 (0.8-22.7)
Number of prior lines of therapy (median, range)	6 (4–17)	5 (2-14)
>4 prior LOT, n (%)	80 (75)	
Non-Hispanic White, n (%) Non-Hispanic Black, n (%)	72 (68) 28 (26)	134 (81) 21 (13)
R-ISS stage III, n (%)	25/80 (31)	20/162 (12)
ECOG Performance Status ≥2, n (%)	35 (33)	–
High-risk cytogenetics, n (%)	56/95 (59)	38/148 (26)
Extramedullary disease (EMD), n (%)	45 (42)	28 (17)
Refractory status: **• Triple Refractory, n (%)** **• Penta refractory, n (%)**	97 (92) 68 (64)	128 (78) 50 (30)
Prior BCMA-directed Therapy	56 (53)	–
Prior autologous stem cell transplant, n (%)	61 (58)	135 (82)
Prior allogeneic stem cell transplant, n (%)	3 (3)	

High risk cytogenetics: dele17p, t(4,14), t(14,16) and/or amp/gain 1q on FISH
EMD: defined as bone-independent (only) tumors

Results: Response to Teclistamab

Response (Full Cohort) N (%)	RWE cohort N=104	MajesTec-1 N=165
Overall response rate	**70 (66)**	**104 (63)**
Complete response or better	**31 (29)**	**65 (39.4)**
Very good partial response	18 (17)	32 (19.4)
Partial response	21 (20)	7 (4.2)
Minimal response	0	2 (1.2)
Stable disease	10 (9.5)	27 (16.4)
Progressive disease	**26 (24.5)**	**24 (14.5)**
Not evaluable	0	8 (4.8)

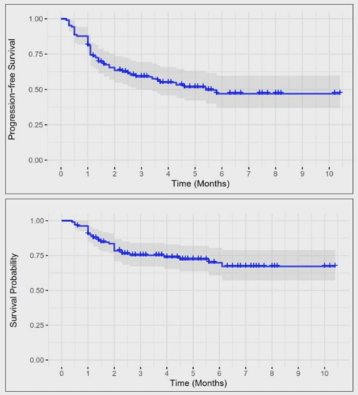
Subgroups of Interest	ORR, N (%)
Age>70 (n=34)	24 (71)
Non-Hispanic Black (n=28)	20 (71)
Pts ineligible for MajestEC-1 trial (n=88)	53 (60)
High-risk cytogenetics (n=56)	35 (63)
Triple Refractory (n=97)	62 (64)
Penta refractory (n=68)	46 (68)
Prior BCMA therapy	33 (59)
R-ISS III (n=25)	13 (52)
EMD (n=45)	21 (47)
Four or less prior LOT (n=26)	21 (81)
>4 lines of prior therapy (n=80)	49 (61)

Results: Survival Outcomes

- After a median follow up of 3.8 months, a total of 46 patients progressed while on teclistamab.
- The median PFS for the entire cohort was **5.4 months** (95% CI, 3.4 months – not reached).
- At data cut off, a total of 29 patients had died; most (86%) from disease progression.

Cause of Death	Total deaths = 29
MM progression while on Teclistamab	21
Severe infection while on Teclistamab	3
Later MM progression while on next line of therapy	4
Myocardial infarction while on next line of therapy	1

- The median OS was **not reached**
- The **6-month** and **10-month OS** rates were **70%** (95% CI, 61-80%) and **67%** (95% CI, 57-79%), respectively.

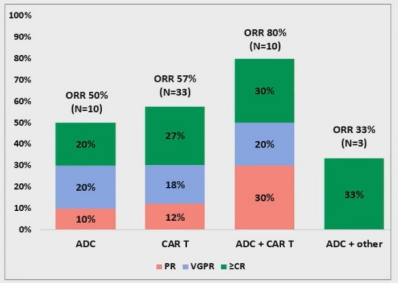


American Society of Hematology

Results: Response Rates to Teclistamab by Specific Type of prior BCMA-directed Therapy

Total Patients	N=56
Type of Prior BCMA-DT	
1. CAR T-cell Therapy	N=42
Idecabtagene Vicleucel	38
Ciltacabtagene Autoleucel	2
· CC-986354	1
· Allogeneic	1
2. Antibody-Drug Conjugate (ADC)	N=24
Belantamab mafodotin (BM)	23
CC-99712	1
3. Other Investigational Agents	
SEA-BCMA monoclonal Ab	2
Tri-specific Ab HPN217	2
No. of prior BCMA-DT	
1	43
2	12
3	1
≥2 prior BCMA-DT	
Idecabtagene Vicleucel + ADC	10
BM + SEA-BCMA MAb	1
BM + HPN217	1
BM + SEA-BCMA MAb + HPN217	1

Abbreviations: Ab=antibody



- Pts who responded to TEC had a numerically longer amount of time from their last BCMA-DT to TEC initiation (339 vs 205 days; **p=0.072**), c/t non-resp, however this did not reach SS.
- Pts who started TEC within 3 mo from their last BCMA-DT had a numerically lower ORR (42.9% vs 64.3%; p=0.27) and ≥VGPR (35.7% vs 47.6%; p=0.64) c/t the pts initiating TEC >3 mo after their last BCMA-DT, but this did not reach SS.
- Similarly, pts who started TEC within 6 mo from their last BCMA-DT had a numerically lower ORR (47.4% vs 64.9%; p=0.33) and ≥VGPR (36.8% vs 48.6%; p=0.57) c/t those initiating TEC >6 mo after the last BCMA-DT.

American Society of Hematology

 Dima et al, ASH 2023; Transplant Cell Ther 2024

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BCMA × CD3 T-cell bispecific antibody: Elranatamab

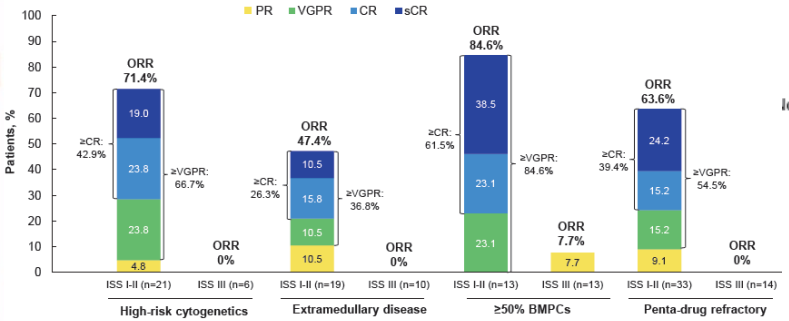
MagnetisMM-3 study, cohort A: BCMA-naïve patients[1]

Elranatamab dosing schedule[1]

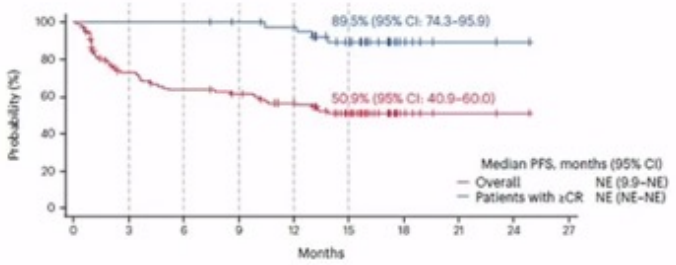
QW cycles 1–6; Q2W cycles 7+ for patients with ≥PR

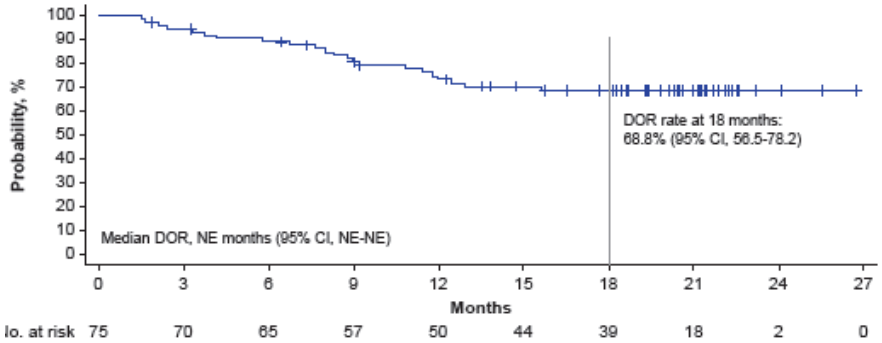
Baseline characteristics, Cohort A (N=123)[1]

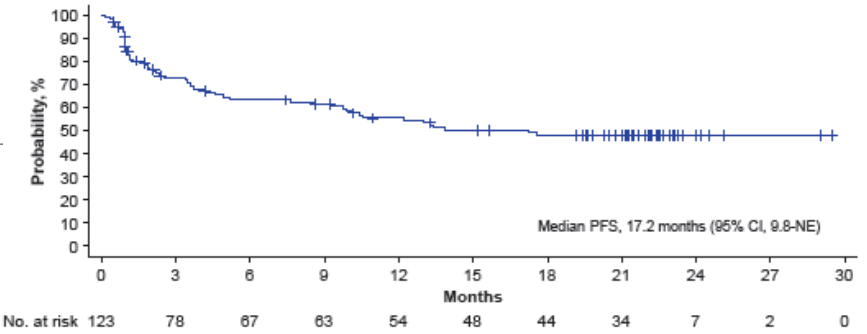
Extramedullary disease by BICR,† n (%)	39 (31.7)
Bone marrow plasma cells, n (%)	
<50%	89 (72.4)
≥50%	26 (21.1)
Missing	8 (6.5)
Prior lines of therapy, median (range)	5 (2–22)
Prior stem cell transplant, n (%)	87 (70.7)
Exposure status, n (%)	
Triple-class	123 (100.0)
Penta-drug	87 (70.7)
Exposure status,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

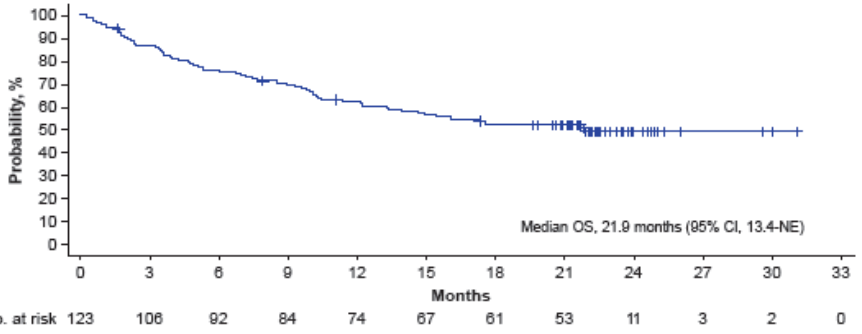


Progression-free survival[1]









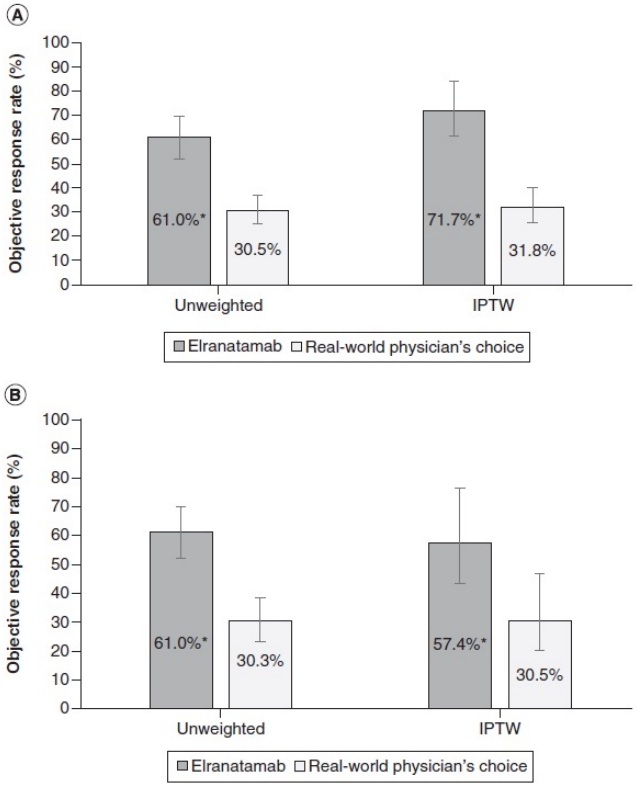
Napoli, Hotel Paradiso • 29–30 aprile 2024

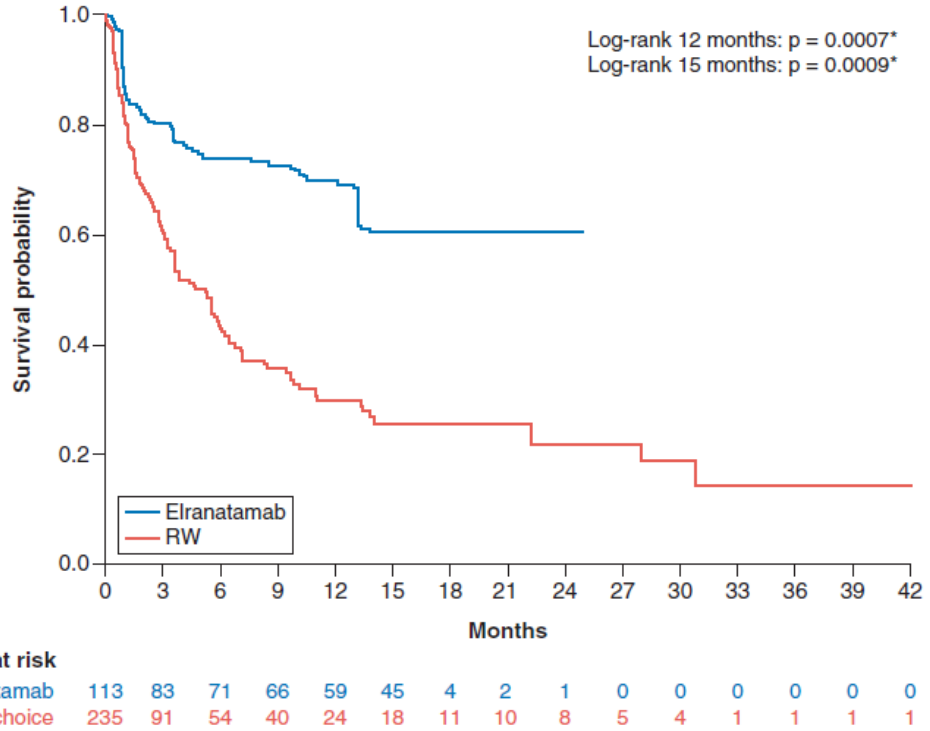
2024: È già ora di abbandonare la **chemioterapia** nella **malattia recidivata/refrattaria?**

Elranatamab efficacy in MagnetisMM-3 compared with real-world control arms in triple-class refractory multiple myeloma

Luciano J Costa[1], Thomas W LeBlanc[2], Hans Tesch[3], Pieter Sonneveld[4], Ryan P Kyle[5], Liliya Sinyavskaya[5], Patrick Hlavacek[6], Aster Meche[6], Jinma Ren[7], Alex Schepart[6], Didem Aydin[6], Guido Nador[8] & Marco daCosta DiBonaventura*,[6]

Future ONCOLOGY
28 February 2024





Napoli, Hotel Paradiso • 29–30 aprile 2024

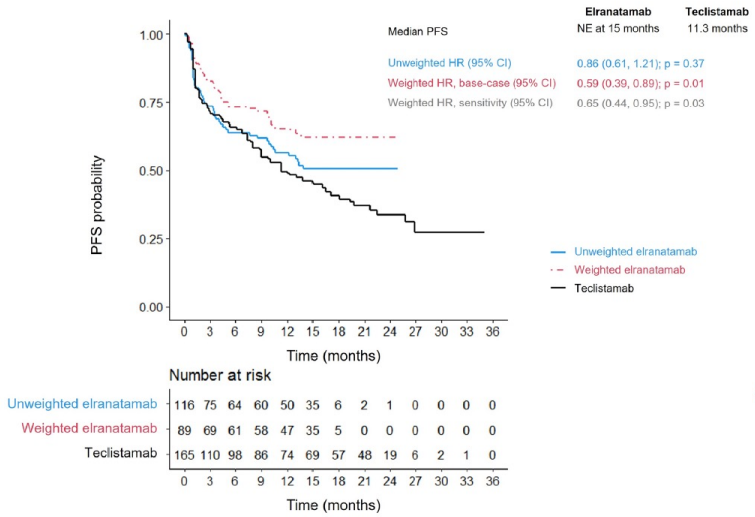
2024: È già ora di abbandonare la chemioterapia nella malattia recidivata/refrattaria?

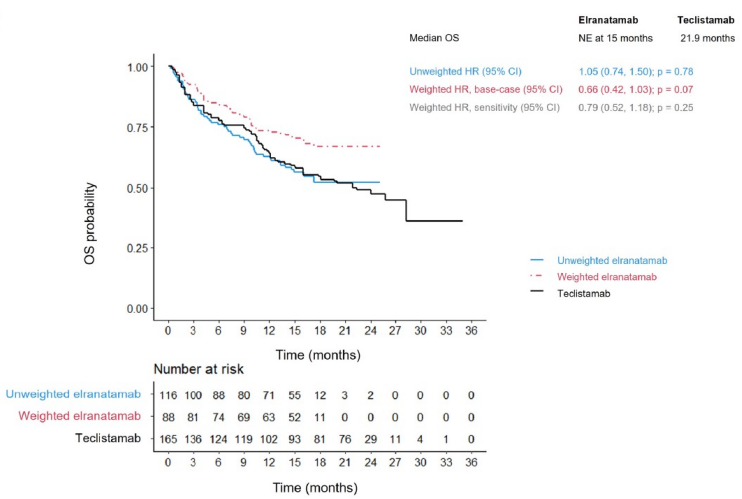
A matching-adjusted indirect comparison of the efficacy of elranatamab versus teclistamab in patients with triple-class exposed/refractory multiple myeloma

Leukemia & Lymphoma 2024

Isha Mol[a], Yannan Hu[a], Thomas W. LeBlanc[b], Joseph C. Cappelleri[c], Haitao Chu[d], Guido Nador[e], Didem Aydin[f], Alex Schepart[d] and Patrick Hlavacek[d]

	MagnestisMM-3 (cohort A; *n* = 116)	Majestec-1 (*n* = 165)
Age, median, years	68	64
≥75 years	18%	15%
Sex, male	55%	58%
Median time since diagnosis, years	6.2	6.0
High-risk cytogenetics	27%	23%
ISS risk stage		
Stage I	30%	52%
Stage II	37%	35%
Stage III	20%	12%
ECOG status		
0	39%	33%
1	61%	67%
Extramedullary disease	28%	17%
Number of prior lines, median	5	5
>3 lines of therapy	79%	74%
Refractory/exposure status		
Triple-class refractory[a]	97%	78%
Penta-drug refractory	41%	30%
Penta-drug exposed	71%	70%





GPRC5D × CD3 T-cell bispecific antibody: Talquetamab

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

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

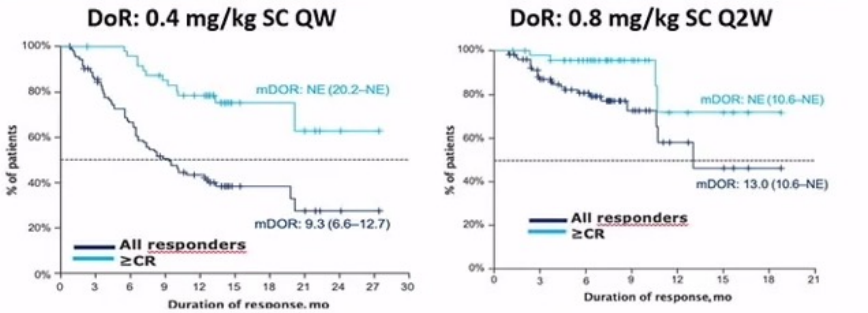
(n=145; n=36 Phase I and n=199 Phase II)

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

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)

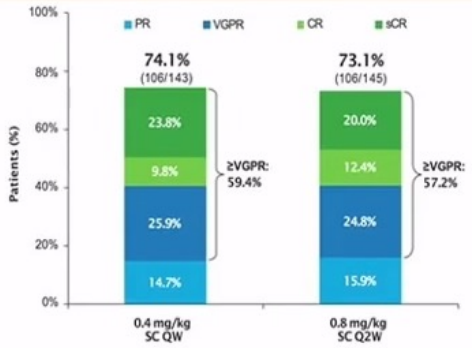
Duration of response[3]



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

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

Response rates[2]



Safety[2]

Selected AEs, n (%)	0.4 mg/kg SC QW (n=143)		0.8 mg/kg SC Q2W[a] (n=145)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
CRS	113 (79.0)	3 (2.1)	108 (74.5)	1 (0.7)
ICANS	NR (10.7)	2 (2)	NR (11.0)	2 (2)
Skin-related AEs	80 (55.9)	0	106 (73.1)	1 (0.7)
Nail-related AEs	78 (54.5)	0	78 (53.8)	0
Dysgeusia	103 (72.0)	NA	103 (71.0)	NA
Weight decreased	59 (41.3)	3 (2.1)	60 (41.4)	8 (5.5)
Infections	84 (58.7)	28 (19.6)	96 (66.2)	21 (14.5)

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).

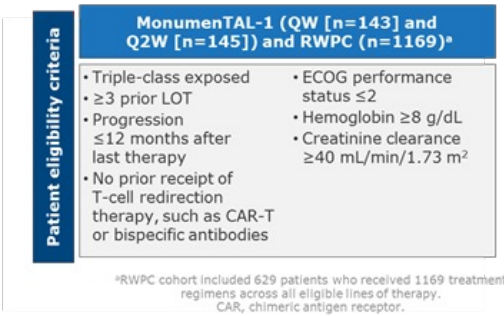
Talquetamab vs Real-World Physician's Choice of Therapy: Comparative Efficacy in Patients With TCE RRMM

Data sources

- Individual patient-level data from MonumenTAL-1 were included for pts who received sc talquetamab 0.4 mg/kg QW or 0.8 mg/kg Q2W by a data cut-off of January 2023
- An external control group was created from eligible pts in the Flatiron database who met MonumenTAL-1 eligibility criteria by a data cut-off of July 2022

Outcome/analysis	Talquetamab QW vs RWPC			Talquetamab Q2W vs RWPC		
	Median, mo	HR (95% CI)	*P* value	Median, mo	HR (95% CI)	*P* value
PFS						
Primary analysis	7.5 vs 4.0	0.55 (0.44–0.69)	<0.0001	14.2 vs 4.0	0.40 (0.31–0.53)	<0.0001
Fully adjusted model	7.5 vs 4.2	0.56 (0.45–0.71)	<0.0001	14.2 vs 4.0	0.41 (0.31–0.54)	<0.0001
TTNT						
Primary analysis	9.1 vs 5.1	0.59 (0.47–0.74)	<0.0001	13.3 vs 5.1	0.45 (0.35–0.59)	<0.0001
Fully adjusted model	9.1 vs 5.1	0.60 (0.48–0.77)	<0.0001	13.3 vs 5.0	0.46 (0.36–0.61)	<0.0001
OS						
Primary analysis	NR vs 16.5	0.56 (0.40–0.78)	0.0007	NR vs 15.9	0.48 (0.33–0.70)	0.0002
Fully adjusted model	NR vs 16.8	0.58 (0.41–0.83)	0.0029	NR vs 17.5	0.50 (0.34–0.75)	0.0008

FIGURE 1: Key patient eligibility criteria



[a]RWPC cohort included 629 patients who received 1169 treatment regimens across all eligible lines of therapy.
CAR, chimeric antigen receptor.

TABLE 1: Treatment regimens in the RWPC cohort[a]

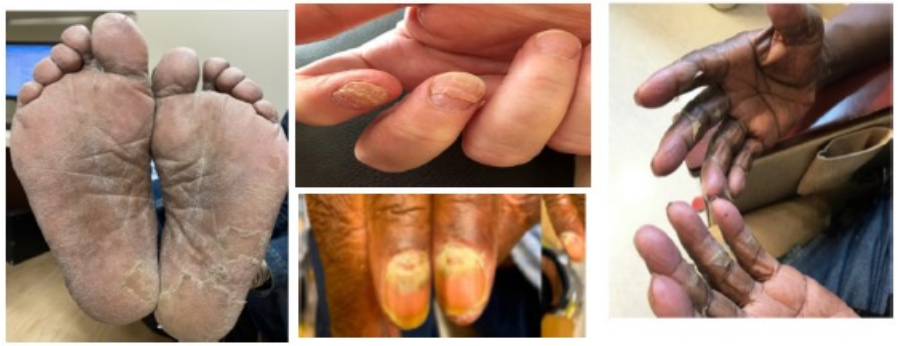
Treatment regimen	Frequency, n (%)[b] (n=1169)
Pomalidomide, elotuzumab, dexamethasone	56 (4.8)
Pomalidomide, daratumumab, dexamethasone	46 (3.9)
Clinical study drug	43 (3.7)
Carfilzomib, dexamethasone	42 (3.6)
Carfilzomib, cyclophosphamide, dexamethasone	36 (3.1)
Carfilzomib, dexamethasone, pomalidomide	32 (2.7)
Belantamab mafodotin-blmf	23 (2.0)
Bortezomib, selinexor, dexamethasone	23 (2.0)
Elotuzumab, lenalidomide, dexamethasone	22 (1.9)
Daratumumab, dexamethasone	21 (1.8)
Selinexor, dexamethasone	21 (1.8)
Daratumumab, dexamethasone, lenalidomide	19 (1.6)
Pomalidomide, dexamethasone	19 (1.6)
Bortezomib, daratumumab, dexamethasone	18 (1.5)
Clinical study drug, dexamethasone	18 (1.5)
Daratumumab/hyaluronidase-fihj, dexamethasone, pomalidomide	16 (1.4)

[a]Only treatment combinations used in ≥16 patients are presented.
[b]Percentages are calculated with the number of treatment regimens received by the 629 patients in the RWPC cohort set as the denominator (n=1169).

Ye JC, et al. IMS 2023. Poster P-328

MonumenTAL-1: Toxicity Data

- In QW, Q2W, and prior TCR cohorts, respectively
  - ICANS occurred in 10.7%, 11.0%, and 2.9%
  - AEs led to dose reductions in 14.7%, 8.3%, and 9.8%
  - AEs led to discontinuation in 4.9%, 8.3%, and 7.8%
- Across all 3 cohorts
  - Dysgeusia and skin- and nail-related AEs were mostly grade 1/2
  - 5 patients discontinued due to skin-related AEs (n=3) or dysgeusia (n=2)
  - No patients discontinued due to nail-related AEs



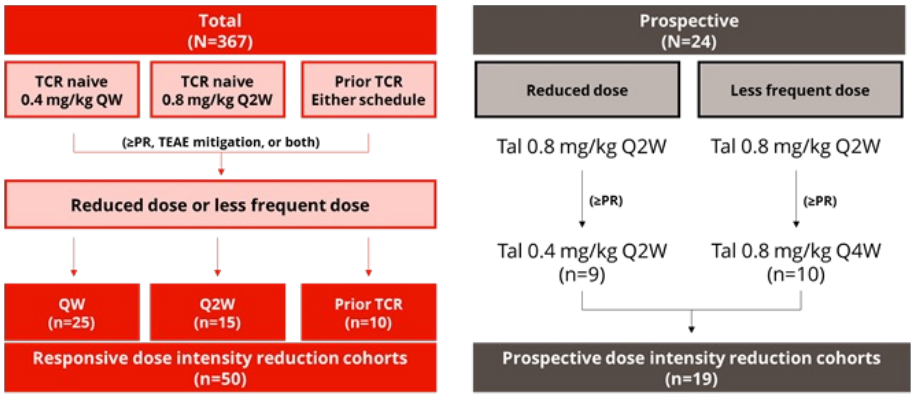
AEs (≥30% in any cohort), n (%)	0.4 mg/kg SC QW (n=143)		0.8 mg/kg SC Q2W (n=145)		Prior TCR (n=51)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Nonhematologic AEs						
CRS	113 (79.0)	3 (2.1)	108 (74.5)	1 (0.7)	39 (76.5)	1 (2.0)
Dysgeusia	103 (72.0)	NA	103 (71.0)	NA	39 (76.5)	NA
Infections	84 (58.7)	28 (19.6)	96 (66.2)	21 (14.5)	37 (72.5)	14 (27.5)
Skin related	80 (55.9)	0	106 (73.1)	1 (0.7)	35 (68.6)	0
Nail related	78 (54.5)	0	78 (53.8)	0	32 (62.7)	0
Weight decreased	59 (41.3)	3 (2.1)	60 (41.4)	8 (5.5)	15 (29.4)	0
Rash related	57 (39.9)	2 (1.4)	43 (29.7)	8 (5.5)	18 (35.3)	2 (3.9)
Pyrexia	56 (39.2)	4 (2.8)	40 (27.6)	2 (1.4)	16 (31.4)	0
Dry mouth	38 (26.6)	0	58 (40.0)	0	26 (51.0)	0
Fatigue	35 (24.5)	5 (3.5)	40 (27.6)	1 (0.7)	23 (45.1)	1 (2.0)

- Dysgeusia and dry mouth managed with mouth washes, saliva stimulants, or dose modifications
- Rashes managed with topical or oral steroids
- Most grade 3/4 AEs hematologic (60%); generally confined to cycle 1/2

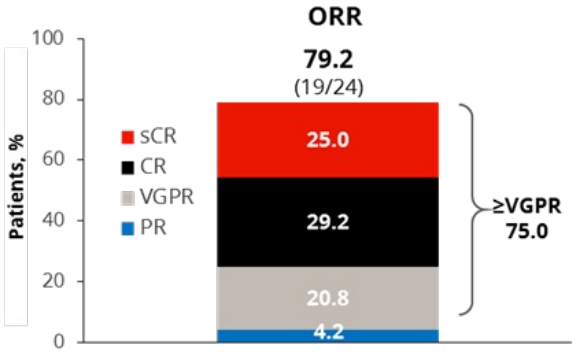
NA = not applicable.

Touzeau C, et al. Presented at: EHA 2023 Congress; June 8-11, 2023; Frankfurt, Germany. Abstract S191. Narayan N, et al. *JAAD Case Rep*. 2023;31:66-68.

MonumentTAL-1: Efficacy and Safety of Less Frequent/Lower Intensity Dosing of Talquetamab

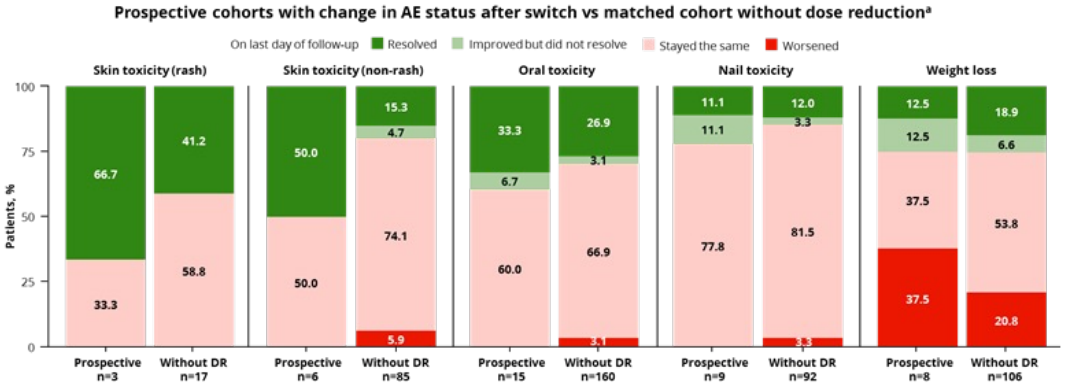


Patients with dose reductions had to be in response (n=19); dose reduction occurred at a median of 3.1 mo (range, 2.3–4.2) relative to treatment start



	Prospective (n=19)
Median follow-up, mo (range)[a]	13.2 (4.0+–16.1)
Median PFS, mo (95% CI)[a]	13.2 (8.8–NE)
12-mo PFS rate, % (95% CI)[a]	50.1 (27.9–68.7)
Median DOR, mo (95% CI)	NE (8.3–NE)

- In the 0.8 mg/kg Q2W registrational cohort (n=145)[1,b]
  - ORR: 71.7%
  - Median PFS: 14.2 mo (95% CI, 9.6–NE)
    - 12-mo PFS rate: 54.4%
  - Median DOR: NE (95% CI, 13.0–NE)



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

Chari A, et al. ASH 2023

BCMA-targeting BsAbs: summary of efficacy

Bispecific Antibody	Teclistamab	Elranatamab	Linvoseltamab (REGN5458)	ABBV-383	Alnuctamab (BMS-93269)
Structure/Function	Humanized antibody	Humanized antibody	Veloci-Bi® platform **fully human antibody**	Low CD3 affinity **fully human antibody**	Humanized antibody **Bivalent binding**
Treatment	Weekly SC	Weekly SC	Weekly IV	**IV q3w**	**Qwk -> Q4wk SC**
Patients	n= 165	n= 123	n= 252	n= 174	n= 68
Median prior lines	5	5	5	5	4
Triple-class refractory	**78%**	**97%**	**81%**	**80%**	**63%**
ORR at RP2d	**63%**	**61%**	**64%**	**58-61%**	**65%**
RP2D	1.5 mg/kg SC	76 mg SQ	200 mg IV	40 to 60 mg IV	30 mg SQ
(n)	(n=165)	(n=123)	(n=58)	(n=52; n=59)	(n=26)
PFS	11.3 mos (8.8-17.1)	NE @ 12 mos; 51% @ 15 mos	NR	13.7 or 11.2 mos	NR
DOR	18.4 mos (14.9-NE)	NE @12 mos	89% @ 6 mos	NE	NE
Median f/u	14.1 mos	10.4 mos	3.2 mos	6.8	4.6 mos

Most BCMA×CD3 bispecific antibodies have been evaluated in TCR MM patients.
ORR ranges from 50–71% and covers the unmet need. PFS is approx 1 year for most bsAbs

Moreau P et al. *N Engl J Med*. 2022;387(6):495-505. Bahlis NJ et al. 2022 ASH. Abstract 97. Bumma N et al. 2022 ASH. Abstract 1936. Voorhees PM et al. 2022 ASH. Abstract 1919. Wong SW et al. 2022 ASH. Abstract 162. Abdallah AO et al. 2022 ASH. Abstract 3240. D'Souza A et al. *J Clin Oncol*. 2022;40(31):3576-3586.

Non-BCMA Bispecific Antibodies

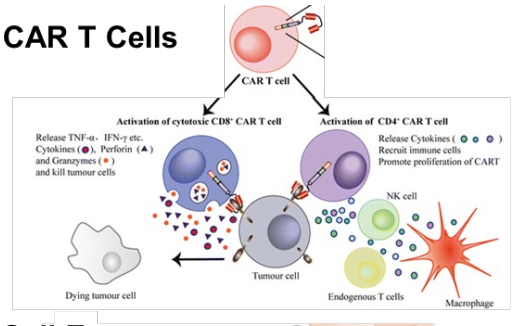
	Anti-GPRC5d Talquetamab			Anti-GPRC5D Forimtamig		Anti-FCRH5 Cevostamab
Patients (n)	143 T-cell redirecting therapy naïve (ADC allowed)	145 T-cell redirecting therapy naïve (ADC allowed)	51 Prior anti-BCMA TT (CARs/BsAb) allowed	51 Prior anti-BCMA TT (CARs/BsAb) allowed	57 Prior anti-BCMA TT (CARs/BsAb) allowed	161
Dosing schedule	405 µg/Kg SC QW	800 µg/Kg SC Q2W	5-1600 µg/Kg SC	18-10000µg/Kg IV Q2-3W	1200-7200 µg/Kg IV Q2-3W	20-198 mg IV Q3W
Prior LoT	5	5	6	5	4	6
TCR/Penta-ref (%)	74/29	69/23	84/41	62/36	72/42	85/68
ORR/≥CR (%) ORR prior BCMA (%)	74.1/33.6	71.7/38.7	64.7/35.3 75% prior CAR-T 44.4% prior BsAbs	71/35 50	64/25 55	56.7/8.9
PFS DoR OS	7.5 79% at 12m (≥CR) 76% at 12m	14.2 90% at 12m (≥CR) 76% at 12m	5.1 63% at 12m (≥CR) 80% at 12m	NR	NR	NR 11.5 m NR
Toxicity	CRS overall is reported in 74-80% of patients and no more than 3% G3-4 Infections overall are reported in 46-73% of patients and nearly 20% G3-4 Dysgeusia is reported in 70-75% of patients Skin/Nails toxicity reported in 56-70% of the patients					

Schinke et al- ASCO 2023; Chari et al. NEJM 2023; Carlo-Stella et al. ASH 2022; Trudel et a ASH2021; Harrison et al. IMS 2023

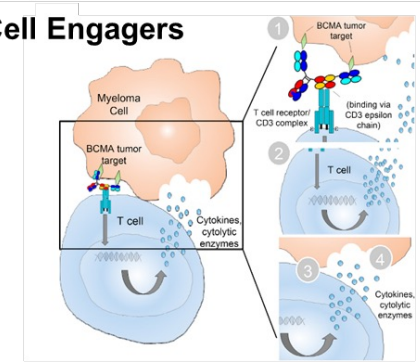
T-cell redirecting therapies related toxicities

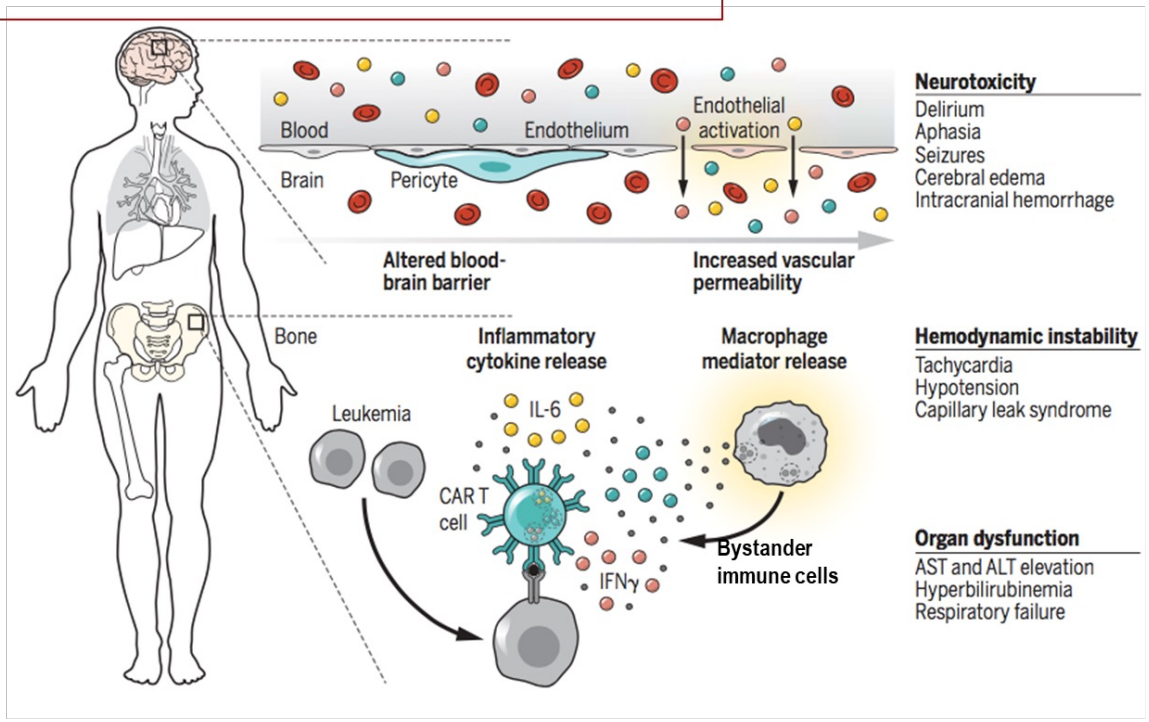
- **ACUTE:** CRS, ICANS and HLH: class-toxicity events
- **LONG LASTING/LATE-ONSET:** Cytopenia, hypogammaglobulinemia, infections, SPM
- **TARGET SPECIFIC**

CAR T Cells



T-Cell Engagers





CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector-cell associated neurotoxicity syndrome

June C et al. Science 2018;359:1361-1365

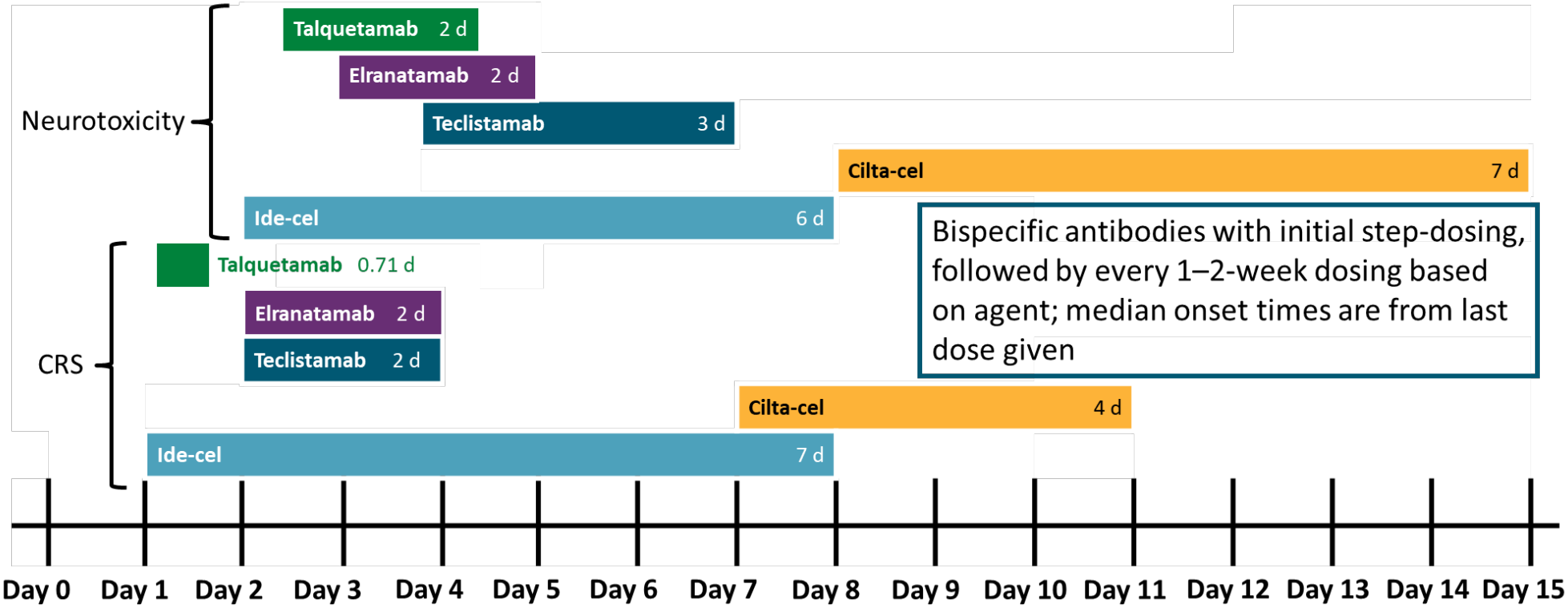
BCMA-bispecific mAbs: summary of Safety profile

	Alnuctamab	Teclistamab	Elranatamab	Linvoseltamab	ABVV-3883
CRS (G 3-4)	50% (0%)	71.5% (0.6%)	56.3% (0%)	44% (0%)	60% (1%)
Median onset	3	2(1-6)	2	11 hours	1(1-2)
Duration	2	2(1-9)	2	15 hours	1(1-8)
Tocilizumab	56%	36.4%	40%	18%	NR
NTS	15%	14.5%	NR	NR	NR
ICANS	3% (G1)	3%	4%	5.6%	3%
Grade 3-4	0	0	0	1.2%	0.5%
Median onset	NR	3 days	2.5 days	NR	NR
Duration	3 and 5 days	7 days	2 days	NR	NR
Treatment required	NR	8.5%	3%	NR	NR
Cytopenias Grade 3-4					
Neutropenia	32%	64%	48%	22%	26%
Anemia	25%	37%	36%	23%	18%
Thrombopenia	9%	21%	22%	13%	11%
Infections	34%	76%	66%	54%	NR
Grade 3-4	9%	44%	35%	29%	22%

Hypogammaglobulinemia as AEs observed in most patients treated with BCMA-CD3 mABs along the therapy

1. Wong ASH 2022 Abstract 162; 2.Moreau et al.. NEJM 2022; 3. Bahlis N et al. ASH 2022: Abstr 158; 4. Bumma et al. ASH 2022; Abstract 4555; 5. Voorhes et al. ASH 2022;Absttract 1919

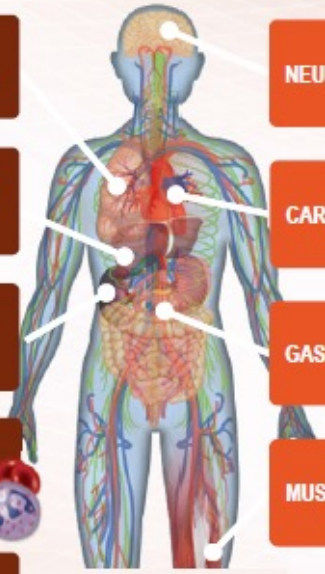
CRS and Neurotoxicity: Median Time to Onset and Duration by CAR T-Cell or Bispecific Antibody Product



Ciltacabtagene autoleucel PI. Elranatamab PI. Idecabtagene vicleucel PI. Talquetamab PI. Teclistamab PI.

CRS Severity Is Typically Mild: Early Recognition and Treatment Is Key

RESPIRATORY	• Difficulty breathing • Shortness of breath
HEPATIC	• Altered liver function tests in the blood
RENAL	• ↑ Serum creatinine • Renal insufficiency
HEMATOLOGIC	• Anemia • Thrombocytopenia • Neutropenia
CONSTITUTIONAL	• Fever • Fatigue • Headache
NEUROLOGIC	• Tremors • Altered wakefulness • Difficulty speaking
CARDIOVASCULAR	• Rapid heart rate • Low blood pressure • Arrhythmias
GASTROINTESTINAL	• Nausea • Vomiting • Diarrhea
MUSCULOSKELETAL	• Weakness



Mitigation and monitoring for CRS

- Step-up dosing with hospitalization for monitoring
- Frequent vital signs
- Rule out infection
- Laboratory monitoring
- Early intervention with tocilizumab

ALP, alkaline phosphatase; CPK, creatine phosphokinase; CRP, C-reactive protein; CRS, cytokine release syndrome; LDH, lactate dehydrogenase; O_2, oxygen; TLS, tumor lysis syndrome.

Oluwole OO, Davila ML. *J Leukoc Biol*. 2016;100:1265. June CH, et al. *Science*. 2018;359:1361. Brudno JN, Kochenderfer JN. *Blood*. 2016;127(26):3321. Brudno JN, Kochenderfer JN. *Blood Rev*. 2019:34:45. Shimabukuro-Vornhagen, et al. *J Immunother Cancer*. 2018;6:56. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625.

Prophylactic tocilizumab

Teclistamab

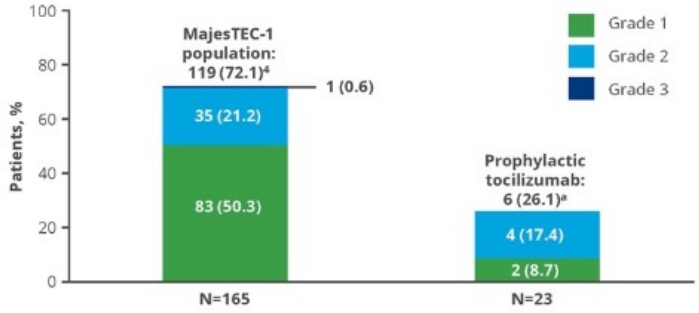
RESULTS

- 23 patients with a median of 4 (range, 2–9) prior lines of therapy received prophylactic tocilizumab prior to teclistamab (median follow-up, 2.6 months [range, 0.1–7.0])

CRS incidence and severity with prophylactic tocilizumab

- Prophylactic tocilizumab reduced CRS incidence to 26.1% (6/23) (**Figure 2**)
  - Grade 1 (n=2), grade 2 (n=4); no grade ≥3

FIGURE 2: CRS incidence and severity

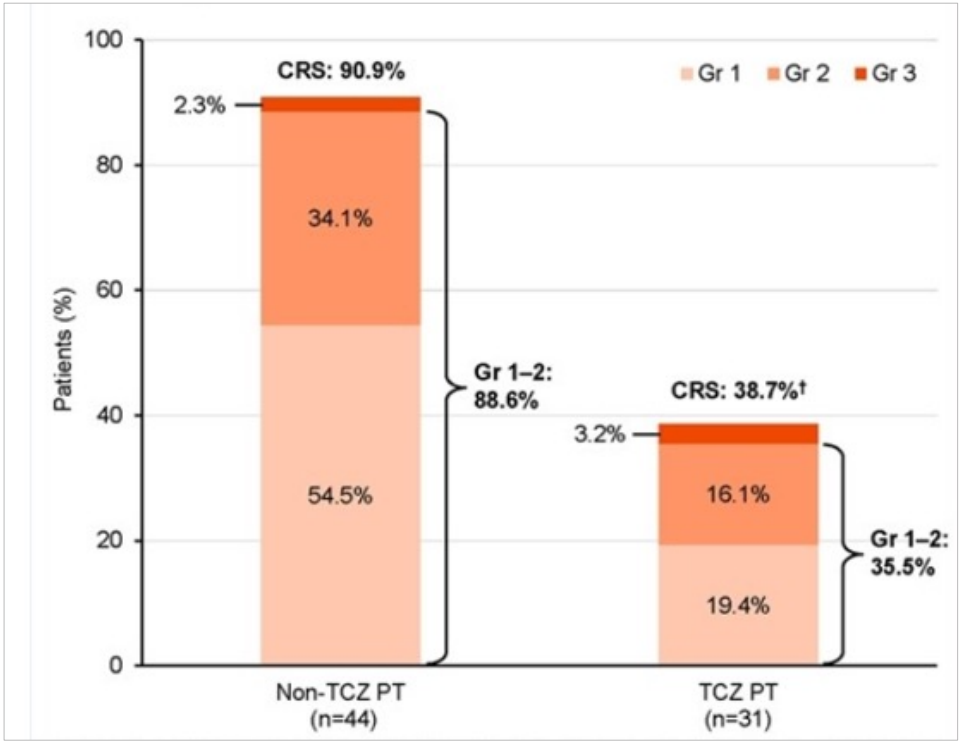


N indicates number of patients. Grade indicates maximum toxicity grade of CRS. [a]As of April 28, 2023.

- 3 patients had subsequent CRS events (**Table 1**). All CRS occurred during teclistamab step-up dosing or cycle 1, except 1 recurrent event in cycle 2

Marin et al, ASH 2023

Cevostamab



Mateos et al, EHA 2023

BCMA-Targeted Therapies Are Associated With an Increased Risk of Infections

A pooled analysis of 1,185 RRMM patients in 11 different clinical trials treated with single agent bispecific antibodies (with no prior use of different bispecifics)

Majority of patients (72%) treated with BCMA-targeted bispecific antibodies

	Patients (%)	
Adverse event	**All grades**	**Grade 3/4**
Neutropenia	38.6	34.8
Infections	50	24.5
CRS	59.6	NR
Pneumonia	NR	10
COVID-19	NR	11.4

Hypogammaglobulinemia occurred in 75.3% of patients with intravenous immunoglobulin used in 48%.

Death was reported in 110 patients of which 28 (25.5%) were reported to be secondary to infections.

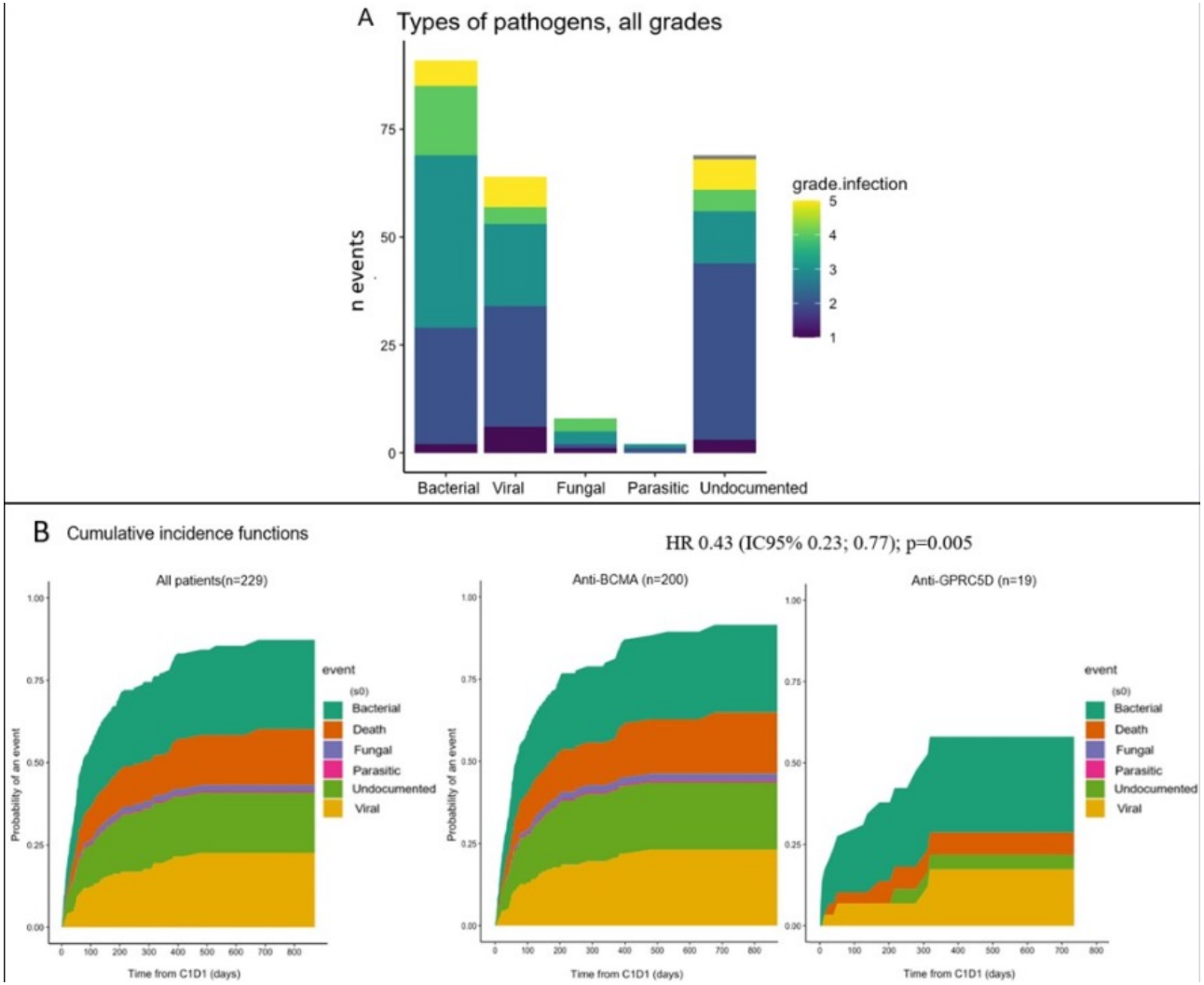
Certain precautions should be used when using BsAbs to mitigate the risk and/or identify and treat infections promptly.

NR, not reported.

Lancman G et al. *Blood Adv.* March 1, 2023 [Online ahead of print].

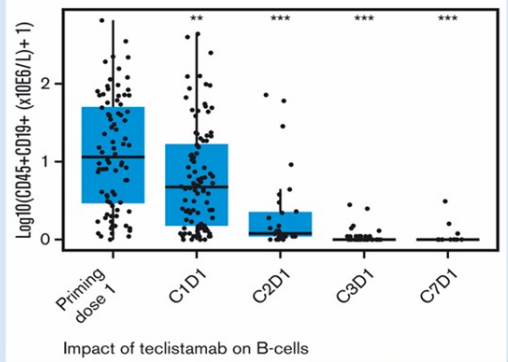
Cumulative Incidence and Characteristics of Infections Requiring Treatment, Delay in Treatment Administration or Hospitalisation in Patients with Relapsed or Refractory Multiple Myeloma Treated with Anti BCMA or Anti GPRC5D Bispecific Antibodies

Cellerin E et al ASH 2023



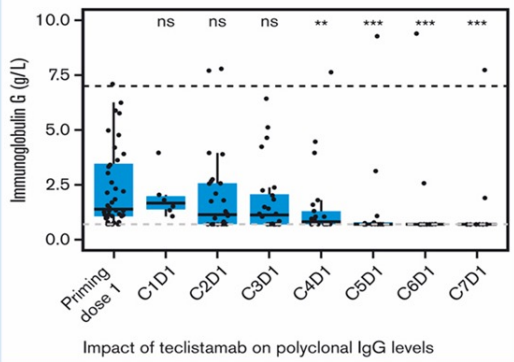
Teclistamab impairs humoral immunity in patients with heavily pretreated myeloma: importance of immunoglobulin supplementation

Teclistamab depletes peripheral blood B cells and eliminates normal plasma cells

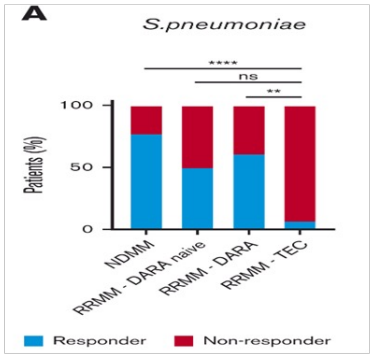


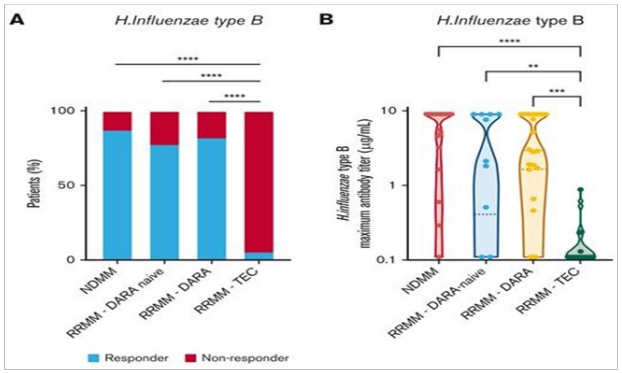
Impact of teclistamab on B-cells

Teclistamab treatment results in reduced levels of polyclonal immunoglobulins and impaired vaccination responses

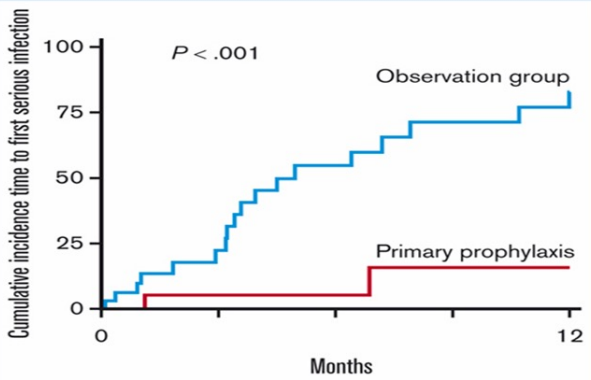


Impact of teclistamab on polyclonal IgG levels





The negative impact of teclistamab on humoral immunity can be partly reversed by IVIG supplementation



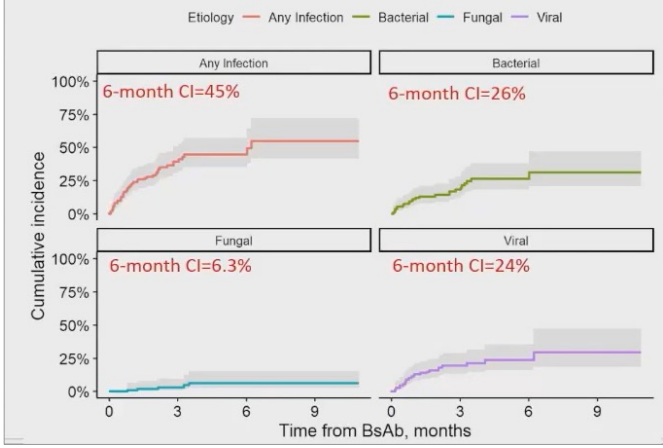
Impact of IVIG supplementation on risk of serious infections

Kristine A Frerichs et al. Blood Adv 2024 Jan

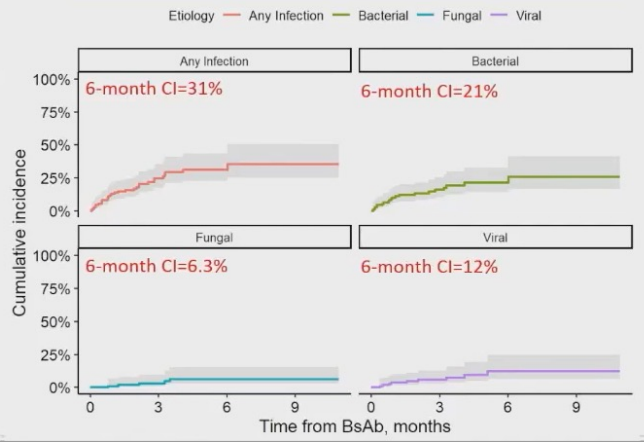
Cumulative Incidence (CI) Of Infections Remains High

A total of 78 infections were diagnosed in 44 patients
Median time to first infectious event was 60 (range 23-99) days from therapy
Most common etiology was bacterial (48%; 36), followed by viral (n=34; 45%) and fungal (n=5; 6.7%)

6-month CI of all grades of infection 45%

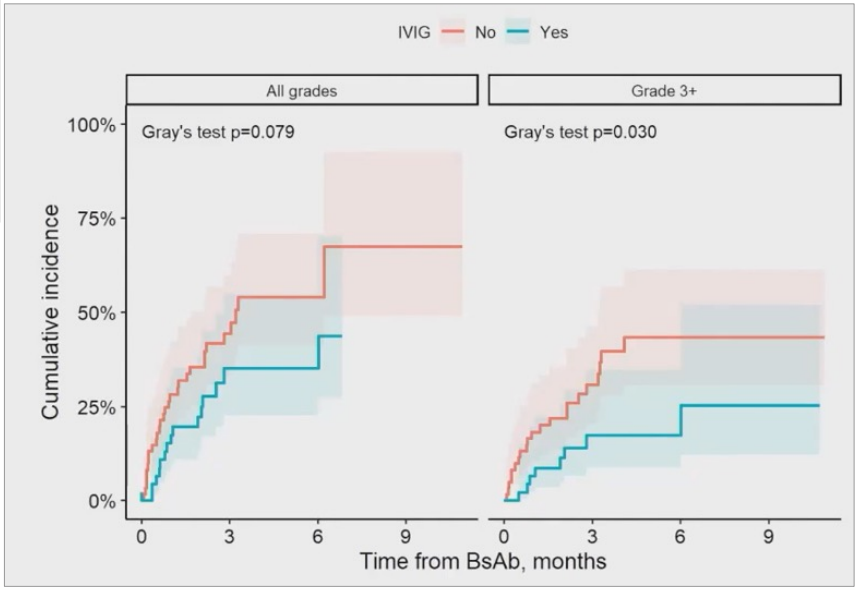


6-month CI of ≥ grade 3 infections 31%



Mohan et al, ASH 2023

Effects of IVIG prophylaxis on infections



Infection Prophylaxis and Vaccinations

Toxicity	Ide-cel	Cilta-cel	Teclistamab	Elranatamab	Talquetamab
Infections (bacterial, viral, fungal), %	69	58	80	70	62
Hypogammaglobulinemia, %	21	12	21	13	NR
Grade ≥3 neutropenia, %	89	95	64	49	35

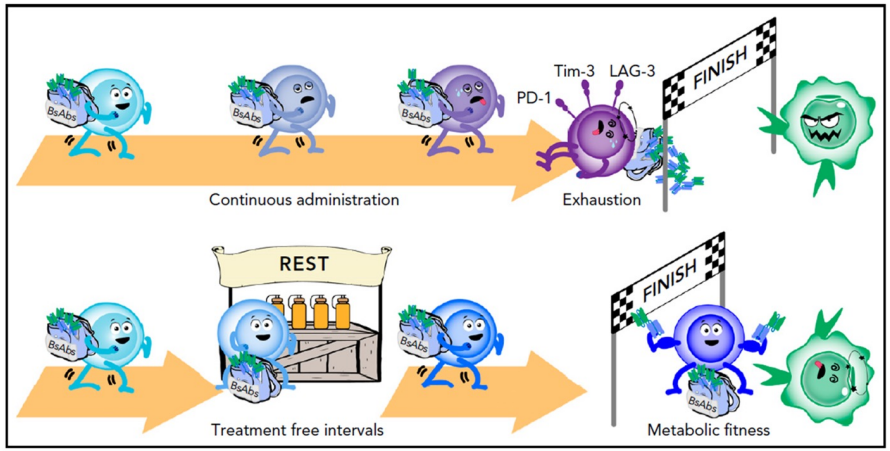
- Complete outstanding vaccinations at least 2 wk prior to starting CAR T-cell therapies or bispecific antibodies (eg, influenza, pneumococcal, COVID-19)
- Delay postinfusion vaccinations for at least 3-6 mo (1 yr for live)
- Consider checking antibody titers

Antibacterial Prophylaxis	Antiviral Prophylaxis	Antifungal Prophylaxis
Recommend for patients with high risk of infection	HSV/VZV prophylaxis in all patients	▪ PJP prophylaxis recommended ▪ Other antifungal prophylaxis recommended for patients with high risk of fungal infection

Ciltacabtagene autoleucel PI. Idecabtagene vicleucel PI. Teclistamab PI. Elranatamab PI. Talquetamab PI. Munshi. NEJM. 2021;384:705. Berdeja. Lancet. 2021;398:10297. Hill. Blood. 2020;136:925. Lesokhin. Nat Med. 2023; 29:2259. Ludwig. Lancet Oncol. 2023;24:e255. Moreau. NEJM. 2022;387:495. Raje. Blood Ca J. 2023;13:116.

2024: È già ora di abbandonare la **chemioterapia** nella **malattia recidivata/refrattaria?**

Bispecifics need
a mindful pause



Efficacy Can Be Maintained With Less Intensive Dosing

majesTEC-1:
Efficacy maintained in patients who switched to biweekly dosing: 42/63 patients who switched to reduced dosing maintained response[1]

MagnetisMM-3:
Efficacy maintained in patients who switched to biweekly dosing: 80.6% of patients maintained or improved their response following dose switch[2]

Management of Infections With BCMA Bispecific Abs
Faculty Experience (cont)

Less intensive dosing

Using IVIG

Prophylactic antimycotics in patients who are neutropenic

1. Usmani SZ, et al. J Clin Oncol. 2023;41(Suppl 16):8034; 2. Mohty M, et al. J Clin Oncol. 2023;41(Suppl 16):8039.

Open questions:

- What are the “ideal” patient?
- What are the mechanisms of resistance?
- What is the optimal sequencing?
- What is the optimal timing?
- What are the optimal combinations?

Similarities and Differences Between CAR T-Cell Therapy and Bispecific Antibodies

	CAR T-cell therapy	Bispecific antibody
Approved product	Abecma, Carvykti	Tecvayli
Efficacy	++++	+++
How given	One-and-done	IV or SC, weekly to every 3 weeks until progression
Where given	Academic medical centers	Academic medical centers
Notable adverse events	CRS and neurotoxicity	CRS and neurotoxicity
Cytokine release syndrome	+++	++
Neurotoxicity	++	+
Availability	Wait time for manufacturing	Off-the-shelf, close monitoring for CRS and neurotoxicity

BCMA Therapeutics: Advantages/Disadvantages

	CAR T cells	Bispecific antibodies
Advantages	Personalized	Off the shelf
	Targeted immunocytotoxicity	Targeted immunocytotoxicity
	Single infusion (one and done)	No lymphodepletion Minimal steroids
	Potentially persistent	
Disadvantages	FACT-accredited center required (hospitalization likely required)	Initial hospitalization required
	CRS and neurotoxicity; requires ICU and neurology services	CRS and neurotoxicity possible
	Dependent on T-cell health (manufacturing failures)	Dependent on T-cell health (T-cell exhaustion)
	Requires significant social support; caregiver required	Requires treatment until disease progression
	$$$$	$$$

2024: È già ora di abbandonare la **chemioterapia** nella **malattia recidivata/refrattaria?**

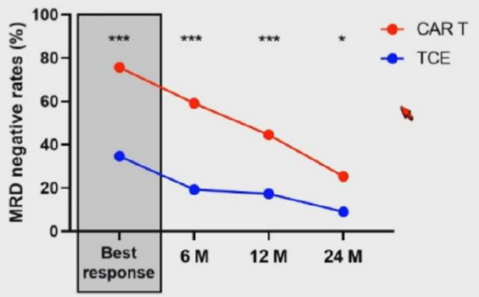
American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Clinical Significance of Measurable Residual Disease (MRD) in Relapse/Refractory Multiple Myeloma (RRMM) Patients Treated with Chimeric Antigen Receptor (CAR) T Cells and T-cell Engagers (TCE)

Aintzane Zabaleta*, Noemí Puig*, María-Teresa Cedena*, José. J Perez, Cristina Moreno, Luis-Esteban Tamariz-Amador, Paula Rodríguez-Otero, Veronica Gonzalez-Calle, Lucía López-Corral, Beatriz Rey-Búa, Borja Puertas, Fátima Mirás, José María Sánchez-Pina, Nieves López-Muñoz, Joaquín Martínez-Lopez, María-Victoria Mateos, Jesús F. San Miguel, Bruno Paiva

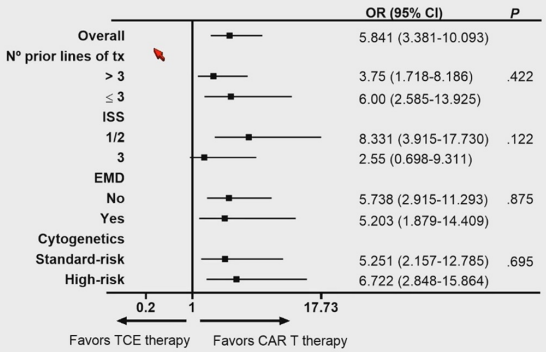
Higher and durable MRD negative rates with CAR T therapy

Best response and longitudinal rates in the ITT population



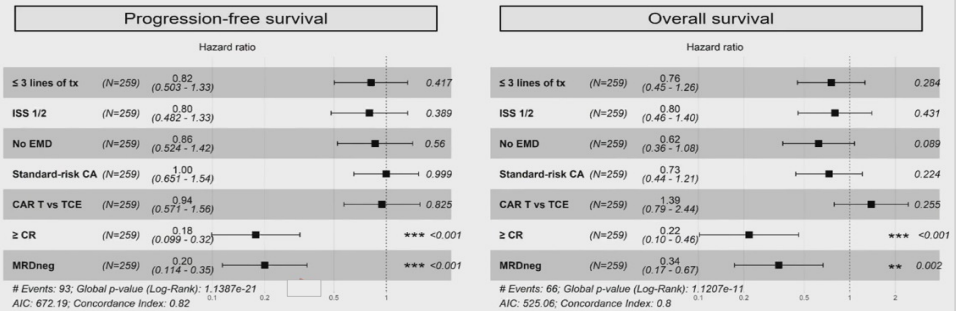
Higher and durable MRD negative rates with CAR T therapy

Subgroup analysis according to risk factors



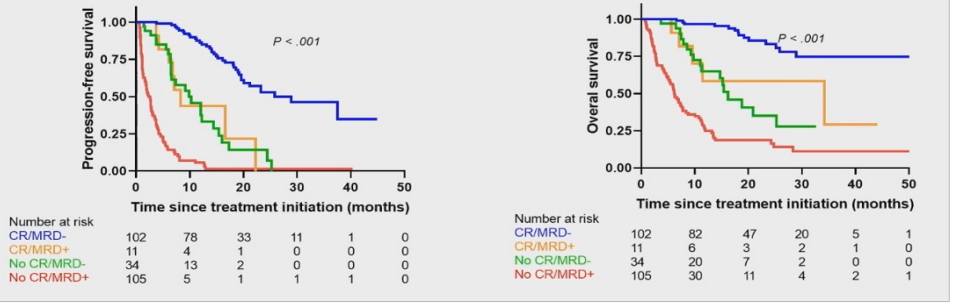
CR and MRD status are the most relevant prognostic factors

Multivariate analysis



CR and MRD status are the most relevant prognostic factors

Prolonged survival in patients achieving CR and undetectable MRD

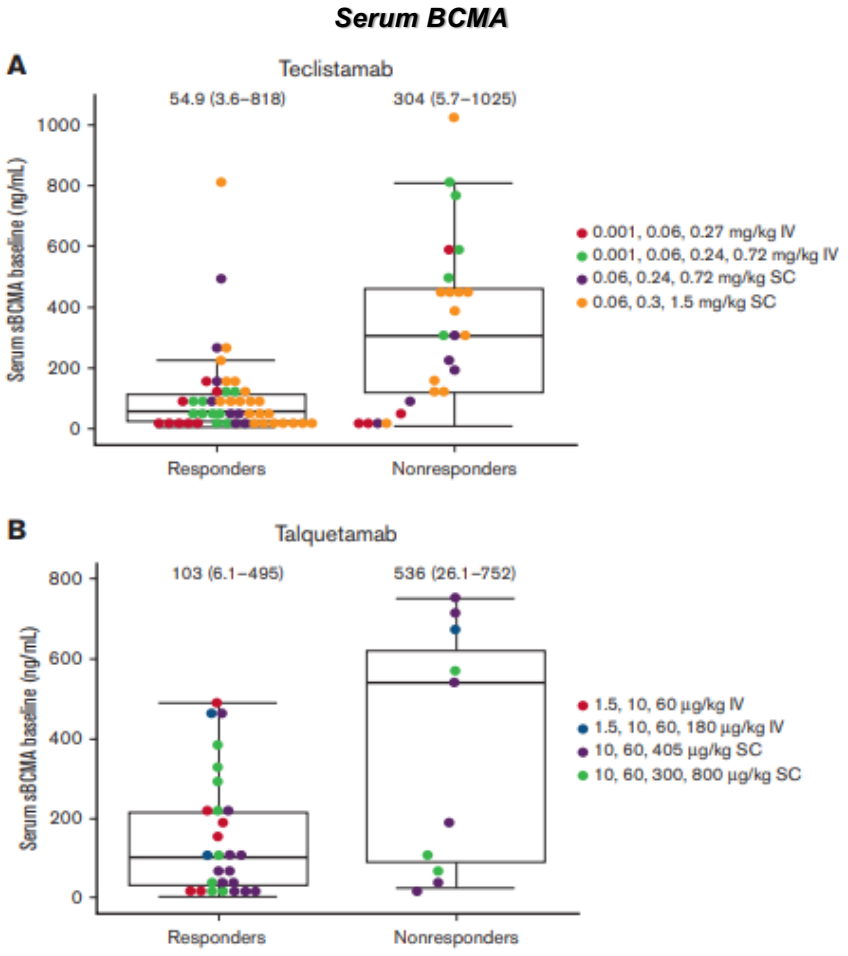


Napoli, Hotel Paradiso • 29–30 aprile 2024

Clinical characteristics associated with primary resistance to BsAbs

~ 30% of myeloma patients do not respond to BsAbs:

- High disease burden:
  - →Increased bone marrow plasma cells
  - →ISS stage III
- Extramedullary disease (EMD)
- High risk cytogenetics ?
- Prior treatment with bispecific antibodies?



Girgis S et al, Blood Adv 2023

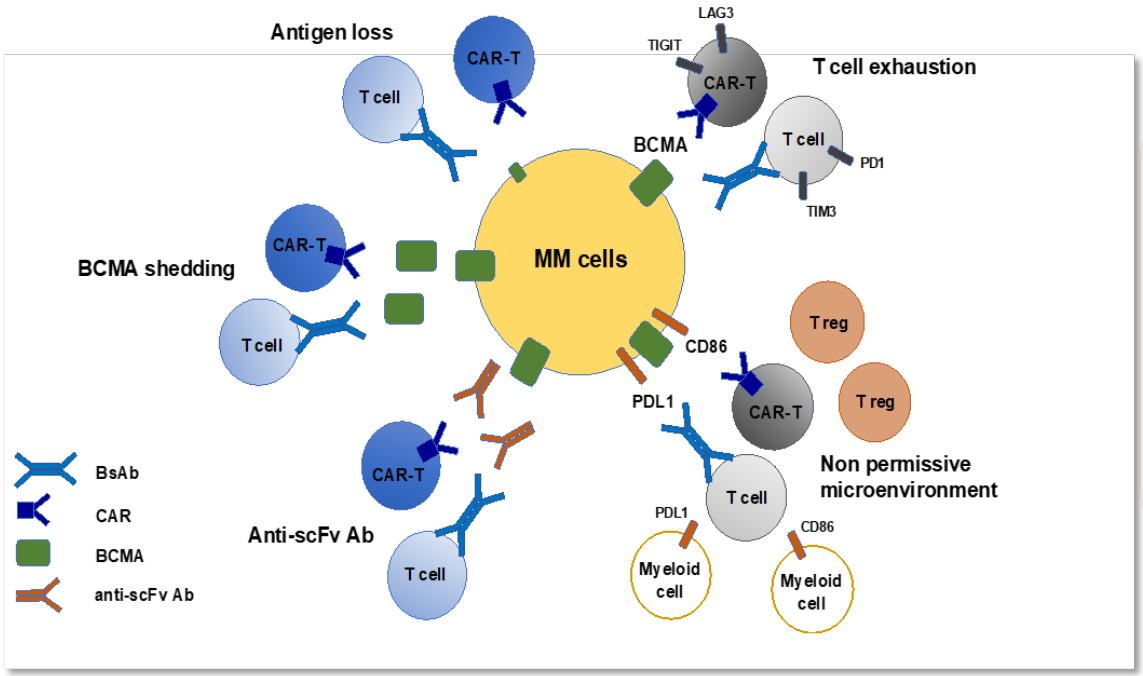
How To Select Patients for CAR T-Cell Therapy vs Bispecific Abs
Faculty Experience

CAR T-cell therapy is preferred if

The patient does not have aggressive disease and can wait for the manufacturing time

A good bridging therapy is available

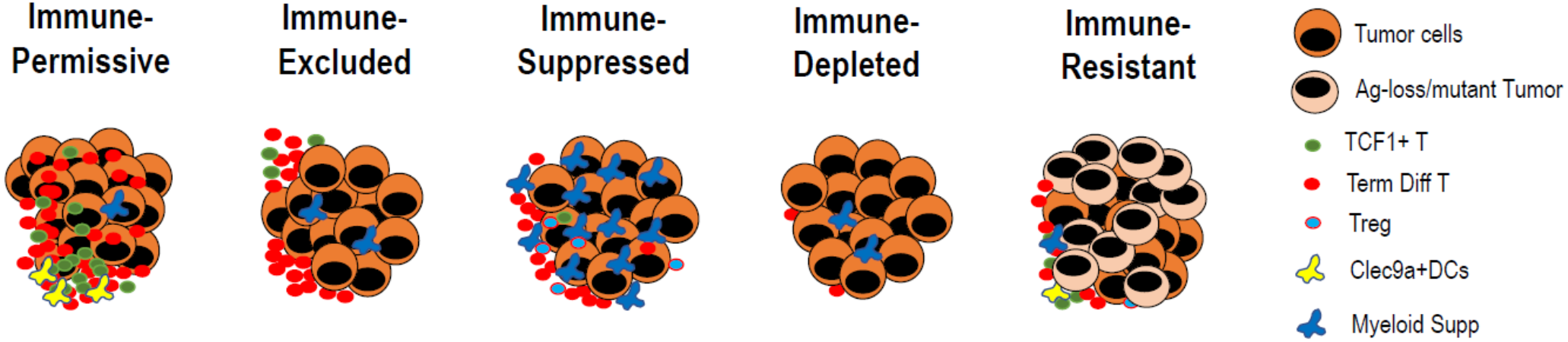
Understanding mechanism of resistance



- Target dependent
  - Antigen loss for BCMA or GPRC5D
  - BCMA shedding
  - Anti-scFv Ab
- T cell dependent
  - T cell exhaustion
  - Non-permissive microenvironment

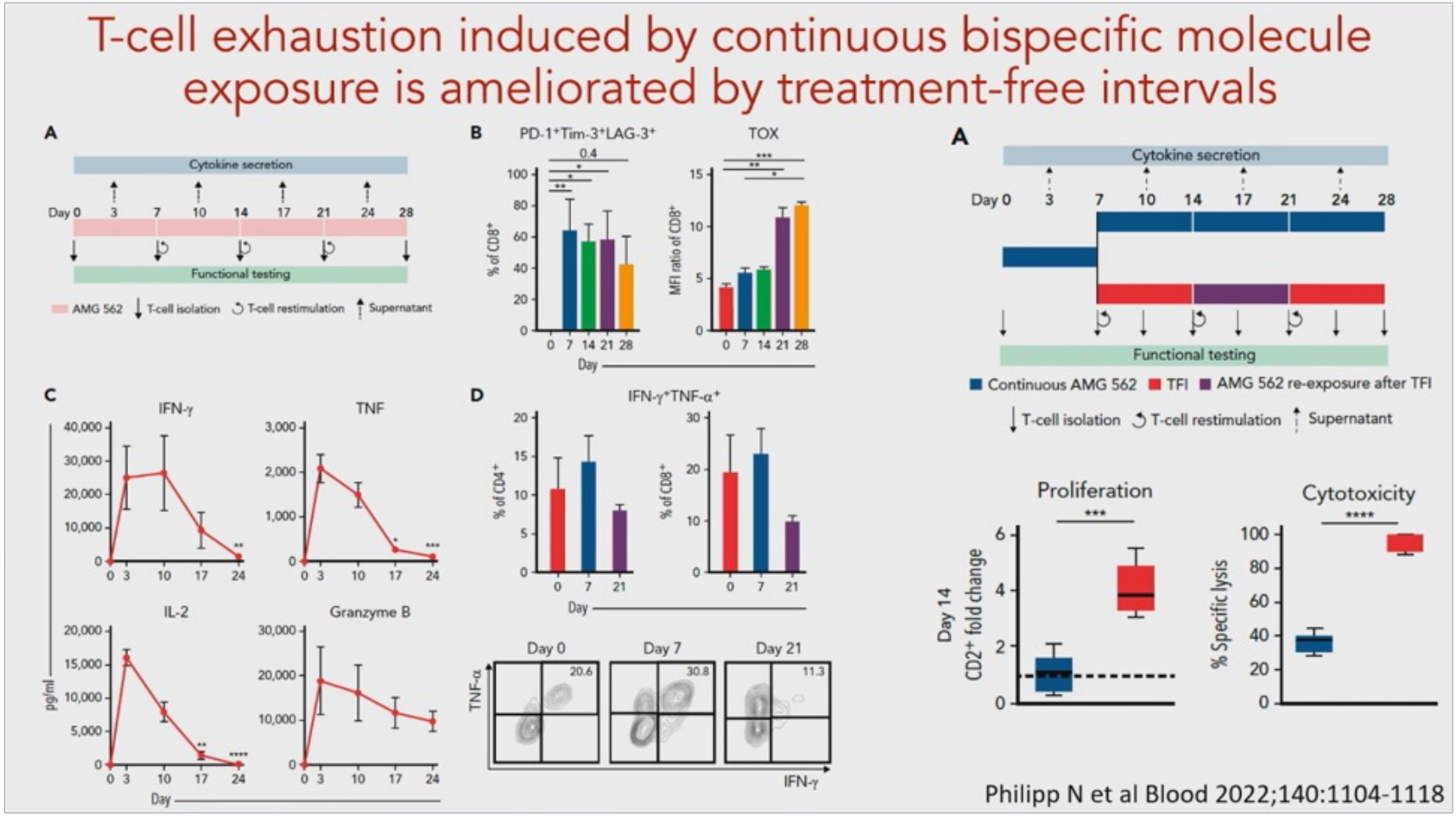
- BCMA seems to remain at the moment of the relapse and it has been reported its loss in 4%
- GPRC5D seems to be not so stable and mutations can occur more frequently
- T cell fitness is relevant for the T cell redirecting therapy

Immune status and selection of patients for immunotherapy in myeloma: a Proposal



Dhodapkar M et al, Blood Adv 2024

2024: È già ora di abbandonare la **chemioterapia** nella **malattia recidivata/refrattaria?**



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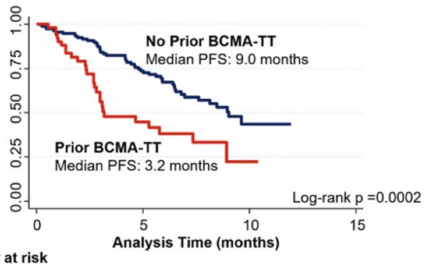
Sequencing Bispecific Abs and CAR T-Cell Therapies

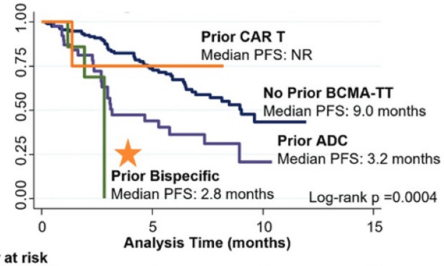
Myeloma CAR T-Cell Consortium data suggest poorest CAR T cell outcome with prior BCMA bispecific Abs

PFS With Ide-Cel (CAR T-Cell Therapy) With or Without Any Prior BCMA-Directed Therapy



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

PFS With Ide-Cel (CAR T-Cell Therapy) With or Without Prior BCMA-Directed Bispecific Ab



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

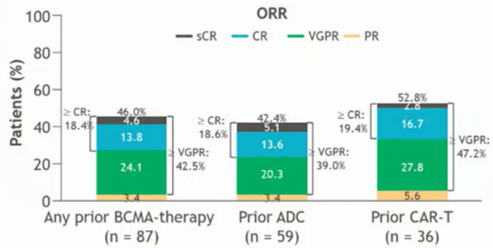
ADC, Ab-drug conjugate; BCMA-TT, BCMA targeted therapy.
Ferreri CJ, et al. Blood Cancer J. 2023;13:117.

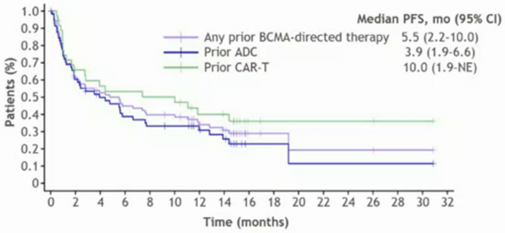
Sequencing and duration of therapy

- Can we treat sequentially with BsAb?
- How do we sequence CAR Ts and BsAbs?
- How long to treat? Continuous vs treatment free intervals?

Sequencing: BCMA-BsAbs after BCMA targeted therapies (pooled analysis of MagnetisMM 1, 2, 3 and 9 studies)

	Any prior BCMA therapy N = 87	Any prior ADC n = 59	Any prior CAR T cell therapy n = 36
Prior BCMA-targeted therapy, n (%)			
ADC	59 (67.8)	59 (100)	8 (22.2)
CAR T cell therapy	36 (41.4)	8 (13.6)	36 (100)
ADC and CAR T cell therapy	8 (9.2)	8 (13.6)	8 (22.2)
Refractory to prior BCMA therapy, n (%)	54 (62.1)	48 (81.4)	13 (36.1)



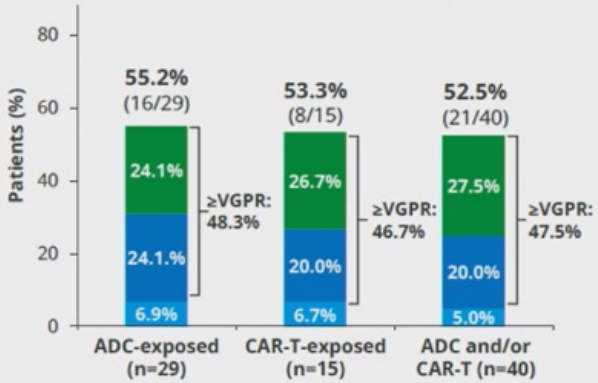


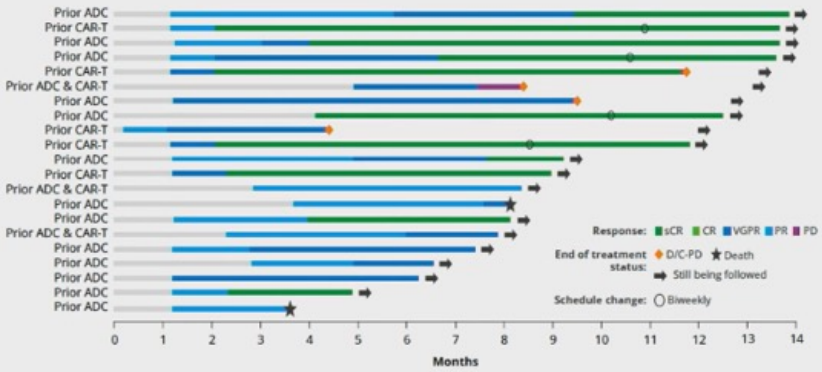
Elranatamab is an investigational agent and has not been approved by any regulatory agency.
IMWG, International Myeloma Working Group; NE, not evaluable.
Nooka AK, et al, Presented at ASCO 2023, abstract 8039. NCT03269136, NCT04798586, NCT04649359, NCT05014412 Available from: https://clinicaltrials.gov, Accessed March 2023.

EHA 2023 - Harnessing the Immune System: New Emerging Data in Multiple Myeloma

Sequencing BsAb post CAR T (CAR → BsAb)

- Teclistamab (MajesTEC-1, cohort C, previously exposed to BCMA-targeted agents): ORR 52.5% and mDOR not reached at median f/up 12 months





- Elranatamab (Magnestis-MM1 trial) : ORR 7/10 (70%) patients previously exposed to anti-BCMA ADC or CART treatments

- Talquetamab with daratumumab (TRIMM-2 trial): ORR 18/25 (72%) response in patients with prior BCMA-targeted treatment (includes prior BCMA BsAb, CART and ADC)

- Cevostamab : ORRs 33.3-50% (based on dose level) post anti-BCMA treatment.

Will Future Combinations With Bispecifics Lead to Overlapping Toxicities?

Combinations With Other MM Therapies for Synergy

Study	Combination
NCT04108195	Talquetamab + Daratumumab
	Teclistamab + Daratumumab
	Talquetamab + Dara/Pom
	Teclistamab + Dara/Pom
MagnetisMM-4	Elranatamab + Len/Dex
MagnetisMM-5	Elranatamab + Dara vs DPd
Linker-MM2	Linvoseltamab + Daratumumab
	Linvoseltamab + Carfilzomib
	Linvoseltamab + Lenalidomide
	Linvoseltamab + Bortezomib

Bispecific Combinations to Reduce Antigen Loss Related to Relapse

Study	Combination
NCT04586426	Talquetamab + Teclistamab
	Talquetamab + Teclistamab + Daratumumab

Combinations to Enhance Target Expression

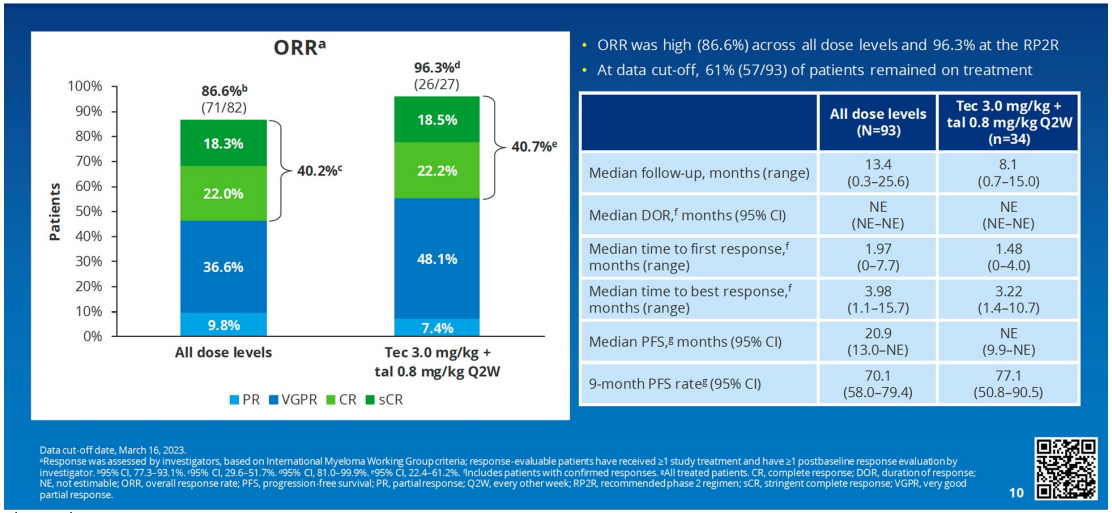
Study	Combination
NCT04722146	Talquetamab + Nirogacestat
MagnetisMM-4	Elranatamab + Nirogacestat

Dara, daratumumab; Dex, dexamethasone; DPd, daratumumab/pomalidomide/dexamethasone; Len, lenalidomide; MM, multiple myeloma; Pom, pomalidomide.

2024: È già ora di abbandonare la **chemioterapia** nella **malattia recidivata/refrattaria?**

RedirecTT-1: Efficacy

TEC + TAL



- ORR was high (86.6%) across all dose levels and 96.3% at the RP2R
- At data cut-off, 61% (57/93) of patients remained on treatment

	All dose levels (N=93)	Tec 3.0 mg/kg + tal 0.8 mg/kg Q2W (n=34)
Median follow-up, months (range)	13.4 (0.3–25.6)	8.1 (0.7–15.0)
Median DOR,[f] months (95% CI)	NE (NE–NE)	NE (NE–NE)
Median time to first response,[f] months (range)	1.97 (0–7.7)	1.48 (0–4.0)
Median time to best response,[f] months (range)	3.98 (1.1–15.7)	3.22 (1.4–10.7)
Median PFS,[g] months (95% CI)	20.9 (13.0–NE)	NE (9.9–NE)
9-month PFS rate[g] (95% CI)	70.1 (58.0–79.4)	77.1 (50.8–90.5)

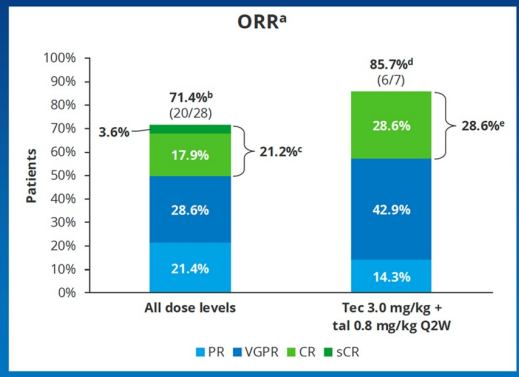
Data cut-off date, March 16, 2023.
[a]Response was assessed by investigators, based on International Myeloma Working Group criteria; response-evaluable patients have received ≥1 study treatment and have ≥1 postbaseline response evaluation by investigator. [b]95% CI, 77.3–93.1%. [c]95% CI, 29.6–51.7%. [d]95% CI, 81.0–99.9%. [e]95% CI, 22.4–61.2%. [f]Includes patients with confirmed responses. [g]All treated patients. CR, complete response; DOR, duration of response; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial response; Q2W, every other week; RP2R, recommended phase 2 regimen; sCR, stringent complete response; VGPR, very good partial response.

10

Cohen et al. ASCO 2023

RedirecTT-1: High ORR in Extramedullary Disease

TEC + TAL



- All were soft tissue plasmacytomas
- At the RP2R (n=11):
  - Median follow-up, 7.2 mo (range 0.7–14.2)
  - 85.7% (6/7 evaluable) ORR
  - 28.6% (2/7 evaluable) ≥CR

	All dose levels (N=35)	Tec 3.0 mg/kg + tal 0.8 mg/kg Q2W (N=11)
Median DOR,[f] months (95% CI)	12.9 (4.17–NE)	NE (4.17–NE)
Median PFS,[g] months (95% CI)	6.1 (2.5–9.9)	9.9 (2.4–NE)

Data cut-off date, March 16, 2023.
[a]Response was assessed by investigators, based on International Myeloma Working Group criteria; response-evaluable patients have received ≥1 study treatment and have ≥1 postbaseline response evaluation by investigator. [b]95% CI, 51.3–86.8%. [c]95% CI, 8.3–41.0%. [d]95% CI, 42.1–99.6%. [e]95% CI, 3.7–71.0%. [f]Includes patients with confirmed responses. [g]All treated patients. CR, complete response; DOR, duration of response; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial response; Q2W, every other week; RP2R, recommended phase 2 regimen; sCR, stringent complete response; VGPR, very good partial response.

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TEAE[e] (≥25% overall), n (%)	All dose levels (N=93)		Tec 3.0 mg/kg + tal 0.8 mg/kg Q2W (n=34)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Non-hematologic TEAEs				
CRS	71 (76.3)	3 (3.2)	25 (73.5)	0
Dysgeusia	57 (61.3)	–	16 (47.1)	–
Pyrexia	47 (50.5)	2 (2.2)	13 (38.2)	1 (2.9)
Skin toxicity	50 (53.8)	0	18 (52.9)	0
Nail disorders	43 (46.2)	0	14 (41.2)	0
Diarrhea	38 (40.9)	2 (2.2)	14 (41.2)	1 (2.9)
Cough	36 (38.7)	0	8 (23.5)	0
Dry mouth	35 (37.6)	0	11 (32.4)	0
Rash	32 (34.4)	1 (1.1)	10 (29.4)	1 (2.9)
COVID-19	31 (33.3)	9 (9.7)	14 (41.2)	1 (2.9)
Pneumonia	25 (26.9)	10 (10.8)	4 (11.8)	2 (5.9)
Fatigue	24 (25.8)	7 (7.5)	6 (17.6)	2 (5.9)

- AE profile was consistent with both monotherapy profiles
- Rates of grade 3-4 non-hematologic TEAEs were low overall, including at the RP2R

The future: Bispecific Combinations

		Teclistamab + Dara + Len[1] MajesTEC-2 (Cohort E, N=32)		Talquetamab + Dara[2] TRIMM-2 (N=65)	Talquetamab + POM[3] MonumenTAL-2 (N=35)		Teclistamab + Talquetamab[4] RedirecTT-1 (N=93)
Attribute	Key Data Element	Teclistamab 0.72 mg/kg, SC n=13	Teclistamab 1.5 mg/kg, SC n=19	Talquetamab 0.8 mg/kg, Q2W n=51	Talquetamab 0.4 mg/kg, QW n=16	Talquetamab 0.8 mg/kg, Q2W n=19	Teclistamab 3.0 mg/kg + Talquetamab 0.8 mg/kg, Q2W (n=34)
Characteristics	**High-Risk**, %	25	46.7	21.2	31.3	21.1	33.3
	Median prior LoT, n (range)	2 (1-3)	2 (1-3)	5 (2-14)	3 (2-12)	3 (2-5)	4 (2-10)
	Prior PI / IMiD / Anti-CD38, %	100 / 100 / 38.5	100 / 100 / 26.3	-/-/90.2	-/-/75.0	-/-/73.7	-/-/-
	Extramedullary Disease, %	7.7	5.3	25.5	12.5	15.8	32.4
	Prior BCMA, %	-	-	52.9	25.1	0	-
	Prior CAR T / ADC / Bispecific, %	-	-	17.6 / 21.6 / 19.6	18.8 / - / 6.3	0 / - / 0	2.9[d]/11.8/0
Efficacy	**Median Follow-Up**, mo (range)	8.4 (1.1-12.9)		15.0 (1.0-23.3)	15.0 (1.2-19.0)	11.1 (1.2-14.8)	8.1 (0.7-15.0)
	ORR, %	100	81	84.0 [42/50] 82.2 [37/45] (prior anti-CD38) 88.9 [8/9] (prior CAR T) 70.0 [7/10] (prior bispecific)	93.8 (all patients) 100 [3/3] (prior CAR T) 50.0 [1/2] (EMD) 80.0 [4/5] (HR cytogenetics)	84.2 (all patients) No prior CAR T 67.0 [2/3] (EMD) 75.0 [3/4] (HR cytogenetics)	96.3
	≥VGPR, %	92	Not mature	74.0	87.5	68.4	88.8
	mDoR, mo	NR	NR	20.3	NR (12.0-NR)	NR (7.4-NR)	NE (NE-NE)
Safety	**CRS**, all gr (gr ≥ 3), %	81.3 (0)		80.4 (0)	74.3 (2.9)		73.5 (0)
	Median onset, d (range)	2 (1-8)		2 (1-4)	-		2 (1-4)
	Median duration, d (range)	2 (1-22)[a]		2 (1-9)	-		2 (1-4)
	ICANS NT, all gr (gr ≥ 3), %	Not reported		-[b]	9.0 (0)		3 (0)
	Non-ICANS NT, all gr (gr ≥ 3), %	-		-	-		-
	Weight decreased, all gr (gr ≥ 3), %	-		27.5 (0)	-		-
	Infections, all gr (gr ≥ 3), %	75 (28.1)		72.5 (25.5)	80.0 (22.9)		79.4 (38.2)
	Neutropenia, all gr (gr ≥ 3), %	84.4 (78.1)		39.2 (27.5)	62.9 (54.3)		55.9 (44.1)
	Dysgeusia, all gr (gr ≥ 3), %	-		-[c]	85.7 (0)		47.1[e] (-)
	Nail and skin disorders, all gr (gr ≥ 3), %	-		Nail: 68.6 (2.0) Skin: 84.3 (7.8)	Nail: 68.6 (0) Skin: 74.3 (5.7)		Nail: 41.2 (0) Skin: 52.9 (0)

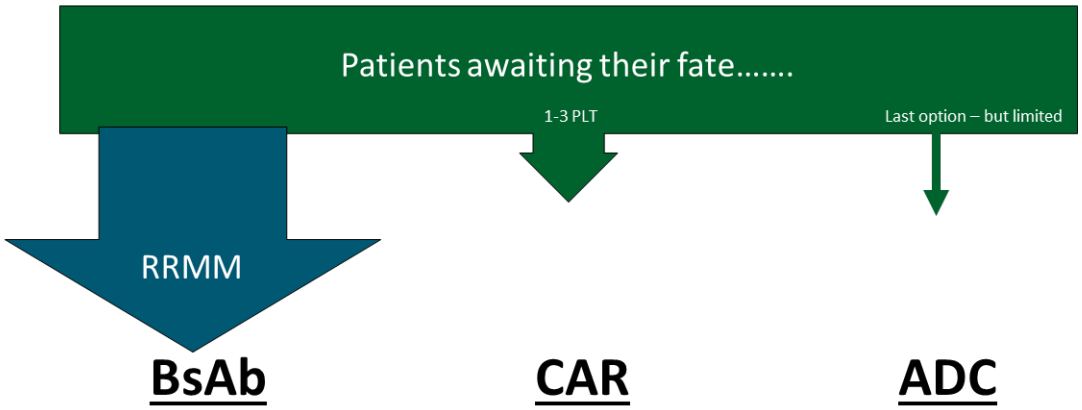
[a]The median duration range was confounded by ongoing infection. [b]ICANS in 4.6% of patients (QW and Q2W). [c]76.9% had dysgeusia (QW and Q2W). [d]Includes ide-cel. [e]**Includes ageusia, dysgeusia, hypogeusia, and taste disorder. NE, not estimable.** NR, not reached.

1. Searle et al. ASH 2022. Abstract 160. 2. Dholaria et al. ASCO 2023. Abstract 8003. 3. Matous et al. ASH 2023. Abstract 1014. 4. Cohen et al. ASCO 2023. Abstract 8002.

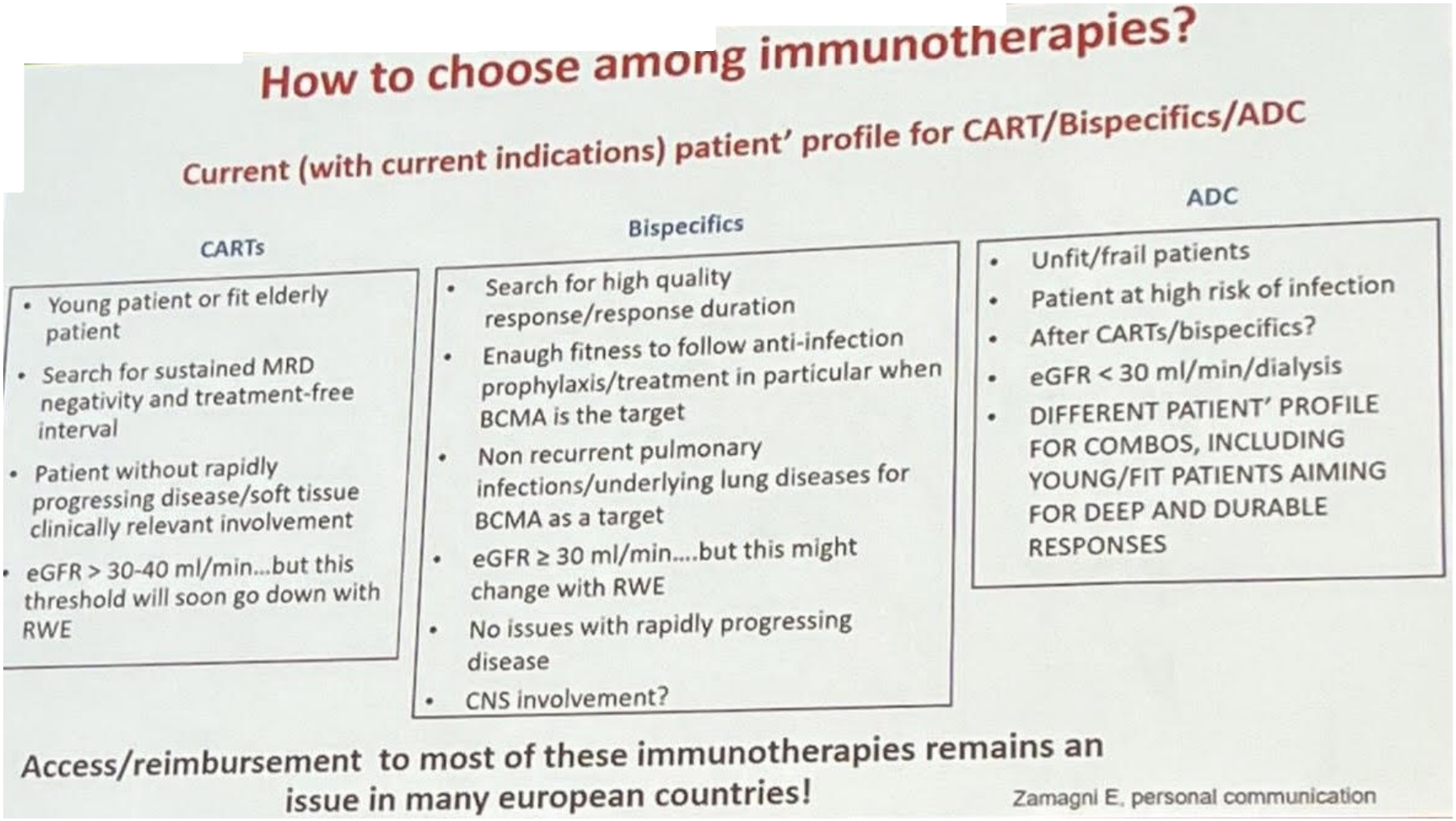
Ongoing phase 3 studies with anti-BCMA bispecific antibodies as treatment of RRMM at early relapse or NDMM

Study	Regimen	Condition
MajesTEC-3 NCT05083169	Tec-Dara vs DaraPd or DaraVd (on held)	RRMM 1-3 prior LOT (including len and PI)
MajesTEC-9 NCT05572515	Tec vs PVd or Kd (open for enrollment)	RRMM 1-3 prior LOT (including len and antiCD38 mAb)
MagnetisMM-5 NCT05020236	Elranatamab vs Elra-Dara vs DaraPd (fully enrolled)	RRMM ≥ 1 prior LOT (including len and PI)
MajesTEC-7 NCT05552222	Tec-Dara-Len vs DaraRd (open) Tal-Dara-Len vs DaraRd	NDMM ineligible or not intended for ASCT
MagnetisMM-6 NCT05623020	Elra-Dara-Len vs DaraRd (open)	NDMM not candidates for ASCT
MajesTEC-4 NCT05243797	Tec-Len vs Len vs Tec (safety-run-in analysis)	NDMM maintenance following ASCT
MagnetisMM-7 NCT05317416	Elranatamab vs Len (open)	NDMM maintenance following ASCT

Real World in 2023 – Bispecifics being used most



- Availability of BsAb and financial concerns will drive practice patterns
- Real-world experience will drive success
- Line of therapy will also guide choice => favor CAR 1-2 then BsAb maint/2-4

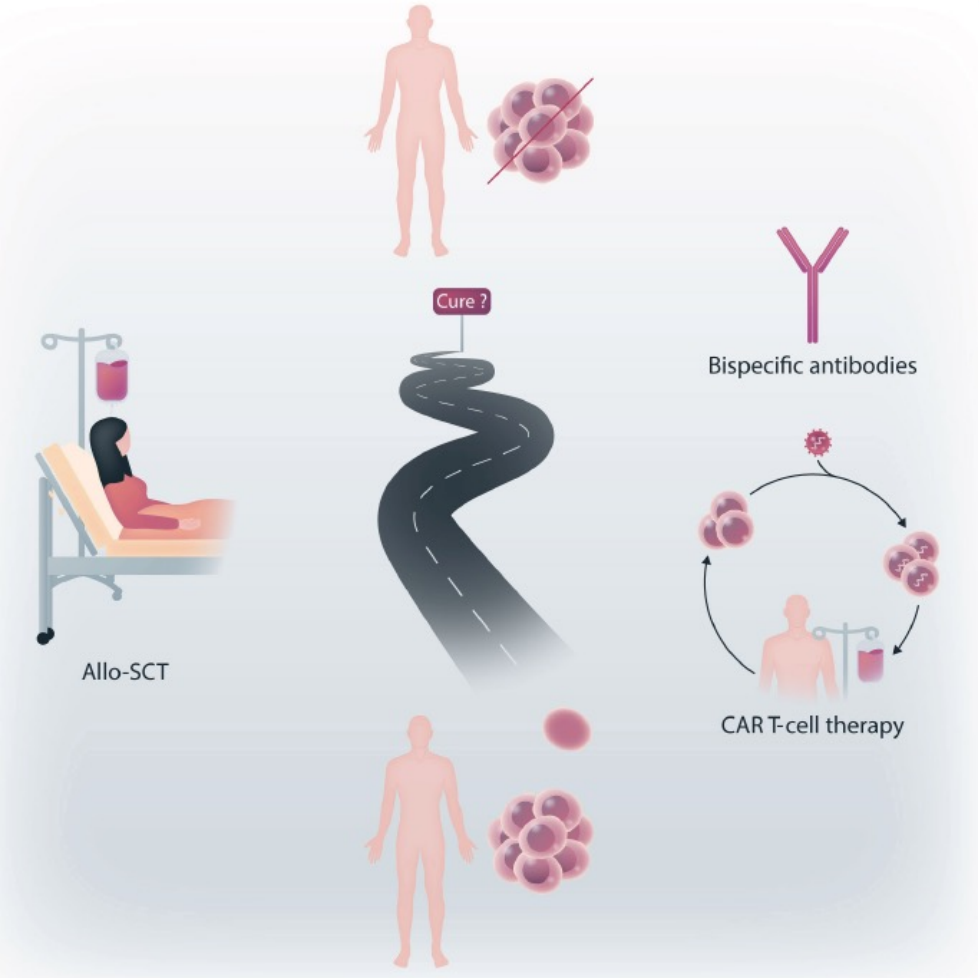

How to choose among immunotherapies?
Current (with current indications) patient' profile for CART/Bispecifics/ADC
CARTs
• Young patient or fit elderly patient
• Search for sustained MRD negativity and treatment-free interval
• Patient without rapidly progressing disease/soft tissue clinically relevant involvement
• eGFR > 30-40 ml/min...but this threshold will soon go down with RWE
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
• eGFR ≥ 30 ml/min....but this might change with RWE
• No issues with rapidly progressing disease
• CNS involvement?
ADC
• Unfit/frail patients
• Patient at high risk of infection
• After CARTs/bispecifics?
• eGFR < 30 ml/min/dialysis
• DIFFERENT PATIENT' PROFILE FOR COMBOS, INCLUDING YOUNG/FIT PATIENTS AIMING FOR DEEP AND DURABLE RESPONSES
Access/reimbursement to most of these immunotherapies remains an issue in many european countries!
Zamagni E. personal communication

2024: È già ora di abbandonare la **chemioterapia** nella **malattia recidivata/refrattaria?**

In search for cure of multiple myeloma

Ralph Wäsch and Monika Engelhardt

Haematologica | 109 May 2024



The long way in the search for myeloma cure. The current promising alternatives to allogeneic stem cell transplantation (alloSCT) are chimeric antigen receptor (CAR) T cells and bispecific antibodies, or a combination of these options.

Conclusions: MM can be CURED? CARs and BsAbs) are the way !!!

Future treatment paradigms…….