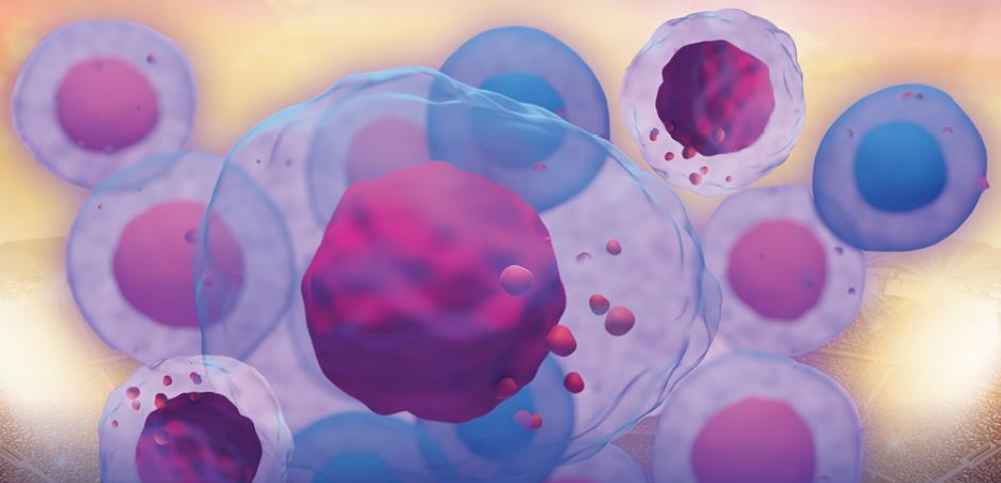
Clinical OLYMPICS℠

EXPLOITING BCMA IN THE TREATMENT OF MULTIPLE MYELOMA:

How Could Bispecific Antibodies and T-Cell Engagement Impact Relapsed/Refractory Disease?



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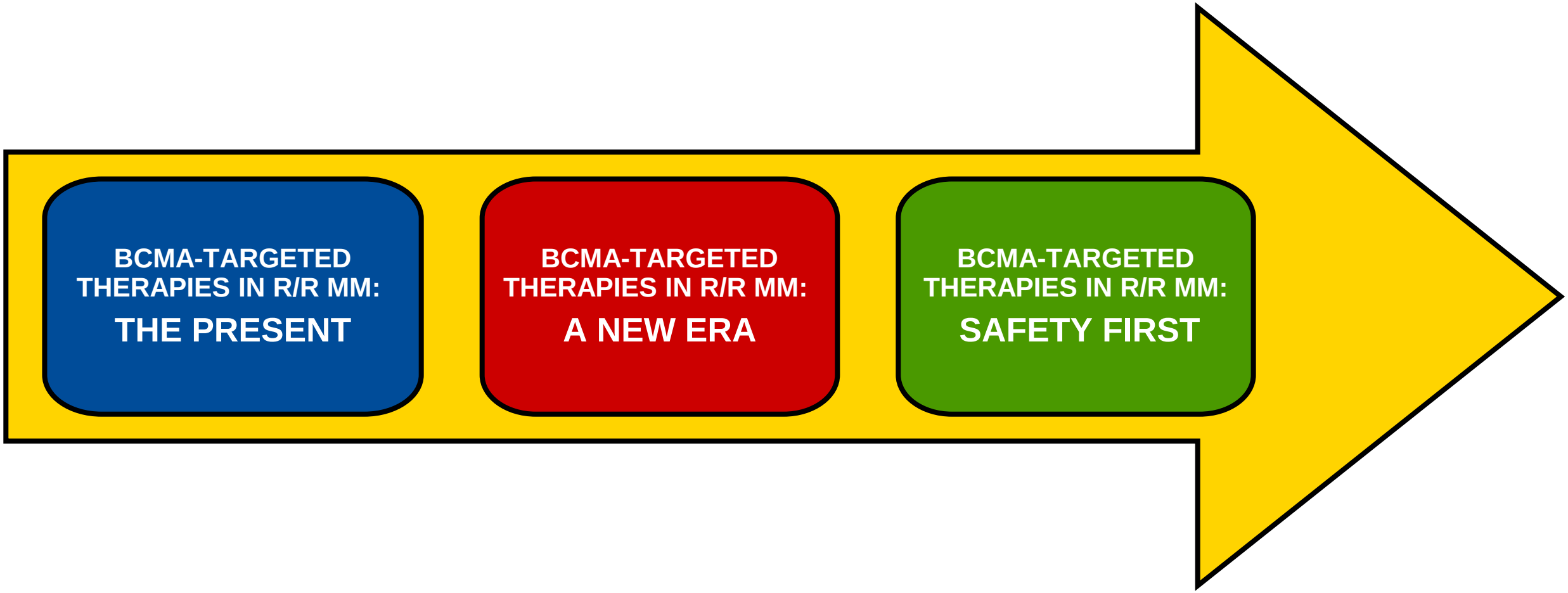
Program Overview



BCMA-Targeted Therapies in R/R MM: The Present

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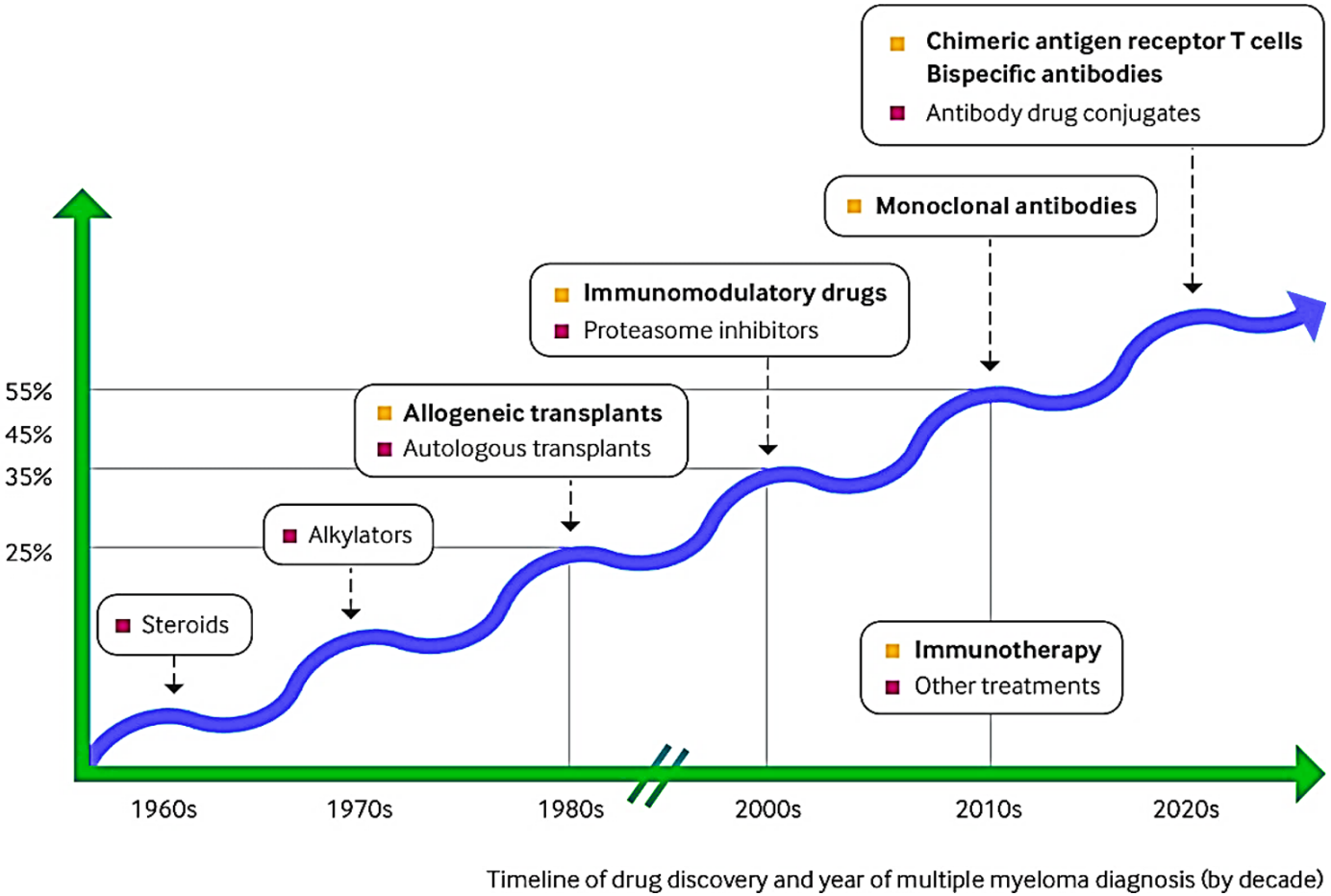
Treatment Overview

Relative Survival at 5 Years (%), Based on Year of Diagnosis



Timeline of drug discovery and year of multiple myeloma diagnosis (by decade)

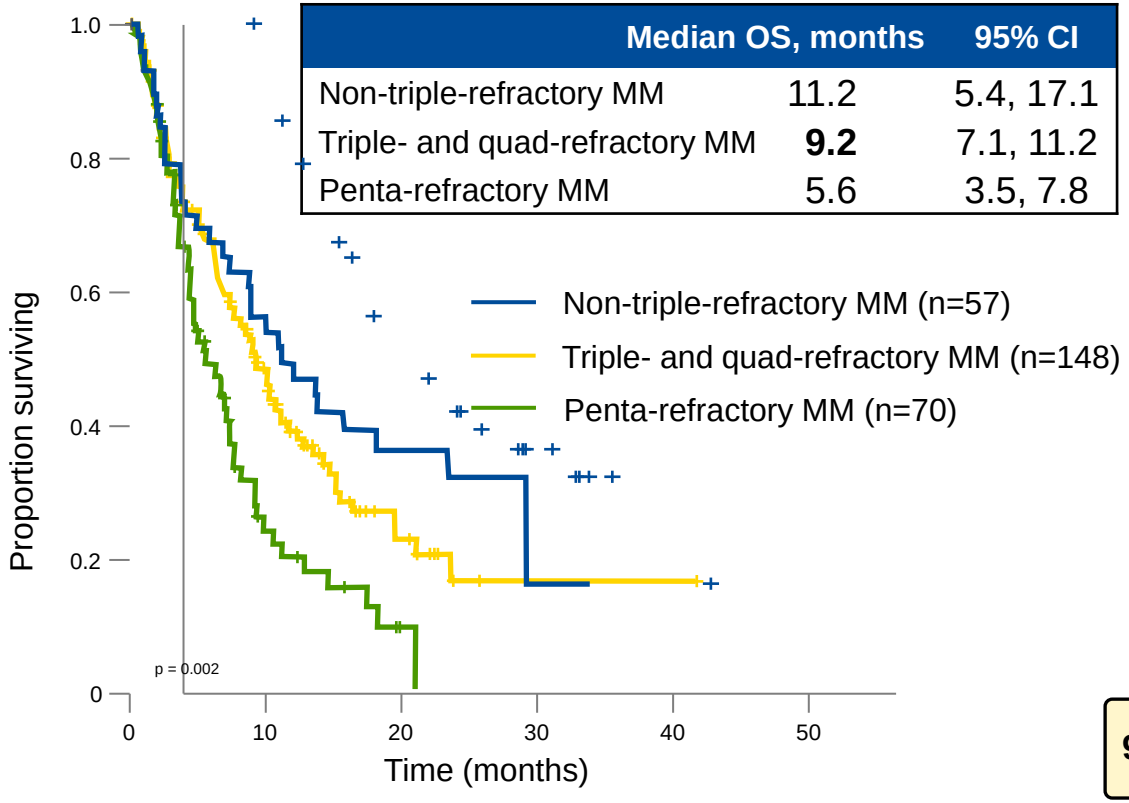
- New treatments have been emerging to cover the complexity of the disease
- Significant improvement in OS

Mateos MV, personal communication. Image reproduced from Shah UA, et al. *BMJ*. 2020;370:m3176. Moreau P, et al. *Ann Oncol.* 2017;28(Suppl 4):iv52-61.

Unmet Medical Need Did Exist

MAMMOTH STUDY (OS; REFRACTORY STATUS)[1]

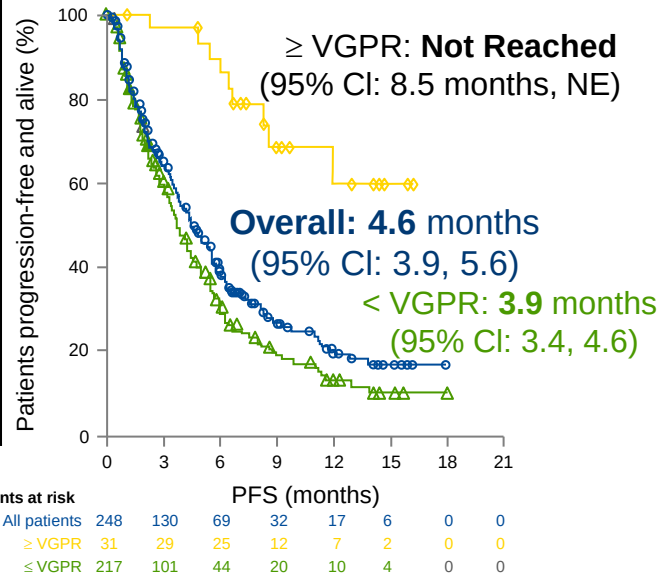
	Median OS, months	95% CI
Non-triple-refractory MM	11.2	5.4, 17.1
Triple- and quad-refractory MM	**9.2**	7.1, 11.2
Penta-refractory MM	5.6	3.5, 7.8



LOCOMMOTION STUDY (PFS; VGPR STATUS)[2,3]

	n=248
ORR, %	**29.8**
Best response, %	
sCR	0
CR	0.4
VGPR	12.1
PR	17.3
Minimal response	5.2
Stable disease	31.0
PD	18.5
NE	15.3
Median DOR (95% CI)	7.4 (4.7,12.5)

MEDIAN PFS BY VGPR STATUS



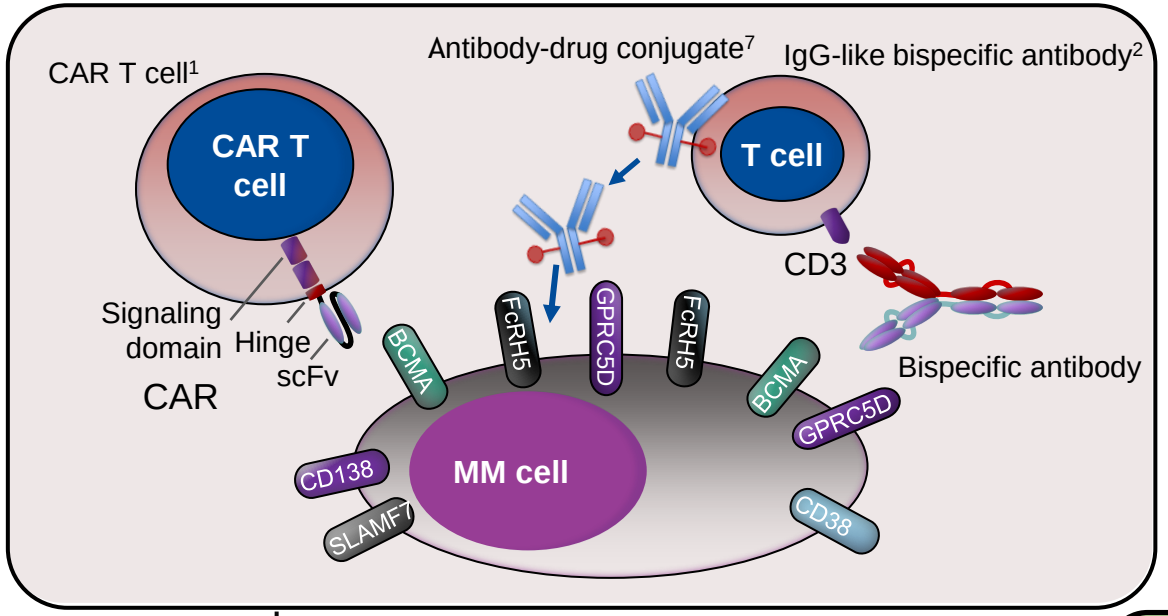
92 different treatment regimens were used, demonstrating lack of defined SOC

The data presented are provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.

[a] Response review committee assessed. CI, confidence interval; CR, complete response; DOR, duration of response; NE, not evaluable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; sCR, stringent complete response SOC, standard of care; VGPR, very good partial response.

1. Gandhi UH, et al. *Leukemia.* 2019;33(9):2266-2275. 2. Moreau P, et al. *Ann Oncol.* 2017;28(supp; 4):iv52-iv61. 3. Mateos MV, et al. *Leukemia.* 2022;36(5):1371-1376.

New-generation Immunotherapies — Particularly BCMA-targeted Therapies — Are Meeting This Need



BCMA:[3]
- Selectively overexpressed in plasma cells
- Promotes proliferation and survival of MM cells

GPRC5D:[4,5]
- Highly and selectively expressed in MM
- Distribution is similar to but independent of BCMA

FCRH5:[6]
- High levels of expression on MM cells
- Normally expressed in plasma cells only

- **ADC:**
  Belantamab
- **BISPECIFICS:**
  Teclistamab
  Talquetamab
  Elranatamab
  Linvoseltamab
  TNB-383B
  Alnuctamab
  Cevostamab
- **CAR T:**
  Ide-cel
  Cilta-cel
  p-BCMA-101
  CT053
  ALLO-715

Idecabtagene vicleucel (ide-cel), ciltacabtagene autoleucel (cilta-cel), and teclistamab are currently FDA-approved for the treatment of adults with R/R MM after **≥4 prior lines of therapy** including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 mAb.

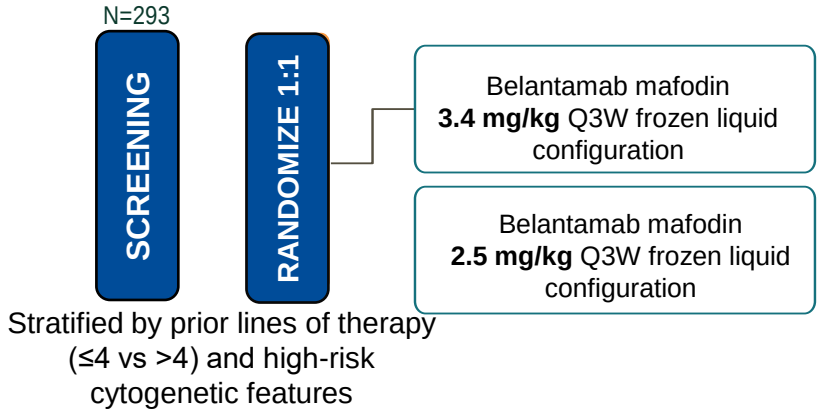
As of Nov. 2022, belantamab mafodotin is being withdrawn from the US market

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; FcRH5, Fc receptor-like 5; GPRC5D, GPRC5D, G-protein coupled receptor family C group 5 member D; Ig, immunoglobulin; scFv, single chain variable fragment.

1. Rodríguez-Lobato LG, et al. *Front Oncol.* 2020;10:1243. 2. Pillarisetti K, et al. *Blood Adv*. 2020;4(18):4538-4549. 3. Yu B, et al. *J Hematol Oncol*. 2020;13(1):125. 4. Verkleij CPM, et al. *Blood Adv.* 2020;5(8);2195-2215. 5. Smith EL, et al. *Sci Transl Med*. 2020;11:eaau7746. 6. Li J, et al. *Cancer Cell*. 2017;31(3);383-395. 7. Bruins WSC, et al. *Front Immunol*. 2020;11:1155.
Images adapted from Verkleij CPM, et al. *Curr Opin Oncol*. 2020;32(6):664-6671 and Bruins WSC, et al. *Front Immunol*. 2020;11:1155; Reuters. 11/22/22. https://reut.rs/3WjwzJY.

BCMA-ADC: Belantamab Mafodotin

Pivotal **DREAMM-2** Study: Single-agent belantamab mafodotin (GSK2857916) in patients with R/R MM refractory to proteosome inhibitors (PIs), immunomodulatory agents, and refractory and/or intolerant to anti-CD38 mAbs



	Belantamab mafodotin 2.5 mg/kg (n=97)	Belantamab mafodotin 3.4 mg/kg (n=99)
ORR	32% (97.5% CI: 21.7–43.6)	35% (97.5% CI: 24.8–47.0)
mPFS	2.8 months (95% CI: 1.6–3.6)	3.9 months (95% CI: 2.0–5.8)
CR	5 (5%)	3 (3%)
mDOR	11.0 months	6.2 months
mOS	13.7 months	14 months

Toxicity profile:

- Ocular events (keratopathy in >70% of any grade [46% and 42%, G3-4]); any-grade thrombocytopenia in 38% and 57%of the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively.
- Responders, half of them, had a treatment hold for ≥3 cycles and were able to restart. Most (88%) maintained or improved response during the dose delay.

As of November 2022, belantamab mafodotin is being withdrawn from the US market based on phase 3 data from the DREAMM-3 confirmatory trial which failed to meet FDA Accelerated Approval regulation requirements. Accelerated approval had allowed use of belantamab mafodotin 2.5 mg/kg for adult R/R MM after ≥4 prior therapies including an anti-CD38 mAb, a proteasome inhibitor, and an immunomodulatory agent. Currently treated patients may enroll in a compassionate use program for continued access.

Lonial S, et al. EHA 2020. Poster EP970; Lonial S, et al. *Cancer.* 2021;127(22):4198-4212; Belantamab mafodotin-blmf. FDA prescribing information. Updated 2/28/2022; Reuters. 11/22/22. https://reut.rs/3WjwzJY.

Ide-cel BCMA-CAR T: KarMMa Trial

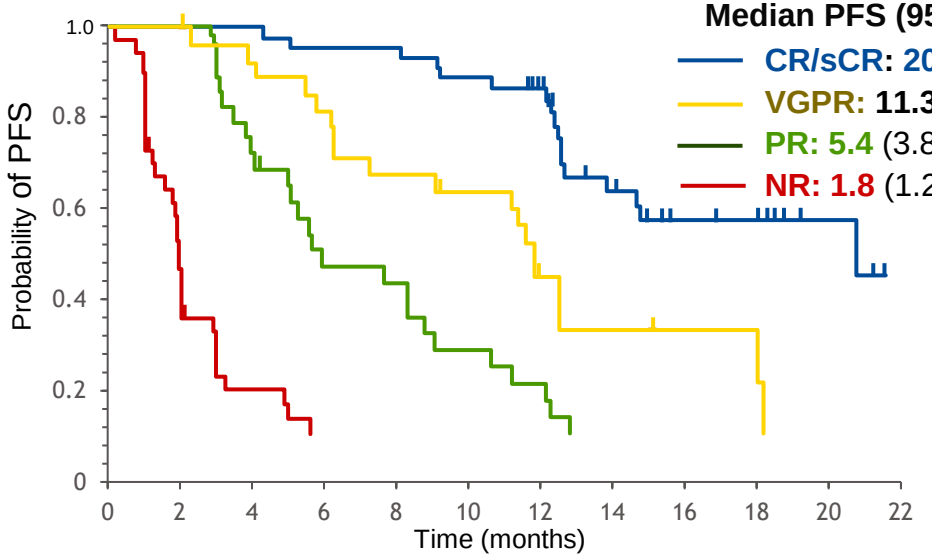
Clinical OLYMPICS℠

- Phase 2 study (N=128) of idecabtagene vicleucel (ide-cel) doses of 150-450 × 10^6 CAR^+ T cells in R/R MM (median, 6 prior lines; 84% triple refractory).
  - ORR: 73%; CR/sCR: 33% (All ide-cel treated; N=128)
  - ORR: 81%; CR/sCR: 39% (dose 450 x 10^6 ; n=54)

Progression-Free Survival

Median PFS (95% CI), months

- **CR/sCR: 20.2** (12.3, NE)
- **VGPR: 11.3** (6.1, 12.2)
- **PR: 5.4** (3.8, 8.2)
- **NR: 1.8** (1.2, 1.9)



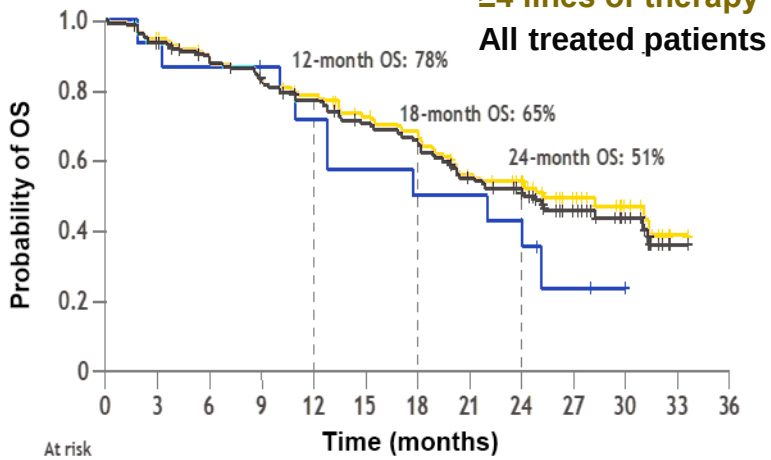
CR/sCR	42	42	42	40	39	37	26	16	11	8	4	0
VGPR	25	25	22	20	16	14	8	3	2	0	0	
PR	27	16	10	9	5	1	0	0	0	0	0	
NR	34	8	83	70	64	56	35	19	13	8	4	0

- Median PFS: 20.2 months in patients with CR/sCR
- Median PFS: 8.8 months in all patients treated

Overall Survival by Prior Lines of Therapy

Median OS (95% CI), months

- **3 lines of therapy** **22.0** (10.0, NE)
- **≥4 lines of therapy** **25.2** (19.9, NE)
- **All treated patients** **24.8** (19.9, 31.2)



At risk												
3 lines of therapy	15	14	13	13	10	8	7	7	5	2	0	0
≥ 4 lines of therapy	113	106	94	87	80	71	65	52	43	24	14	1	0
All ide-cel-treated patients	128	120	107	100	90	79	72	59	48	26	14	1	0

Median OS: 24.8 months in all ide-cel-treated patients

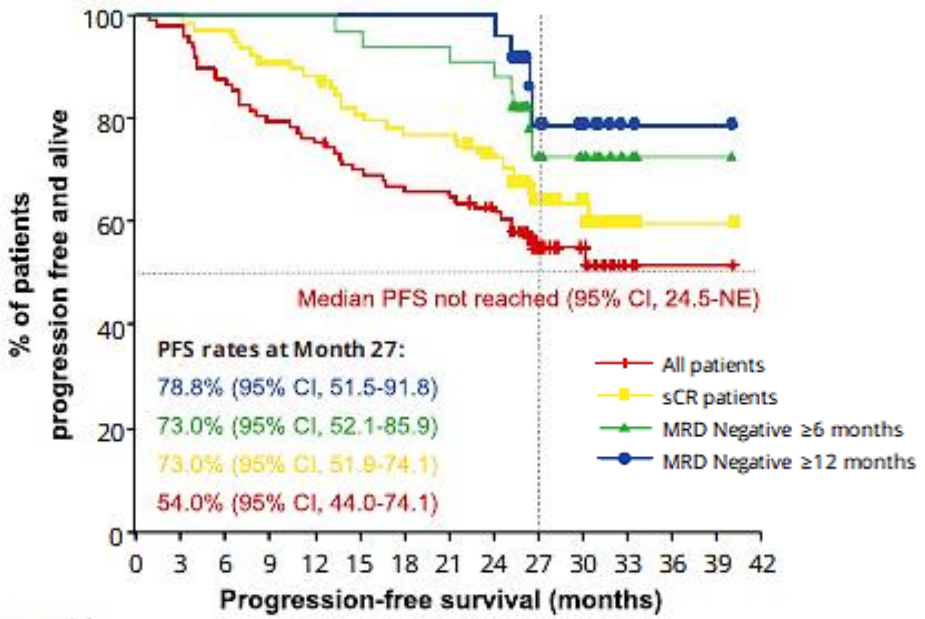
Munshi NC, et al. *N Engl J Med*. 2021;384(8):705-716. Oriol A, et al. Poster presented at EHA 2021; EP1009.

Data cut-off date: 21 December 2020. [a] CRS graded according to Lee criteria [Lee DW, et al. Blood 2014;124:188–95]; [b] NT events were graded according to the NCI CTCAE v4.03; [c] One patient with NT previously graded as maximum grade 1 NT has been changed to grade 3 to align with underlying sign of grade 3 encephalopathy. CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; NR, not reached; NT, neurological toxicity.

Cilta-cel BCMA CAR T: CARTITUDE-1 Trial

- Phase 1b/2 study (N=97) of ciltacabtagine autoleucel (ciltra-cel) 0.75 x 10^6/kg in R/R MM (median, 6 prior lines; 82.5% triple refractory).
  - ORR: 97.9% (sCR rate, 82.5%)
  - 92% of MRD-evaluable patients were MRD-negative

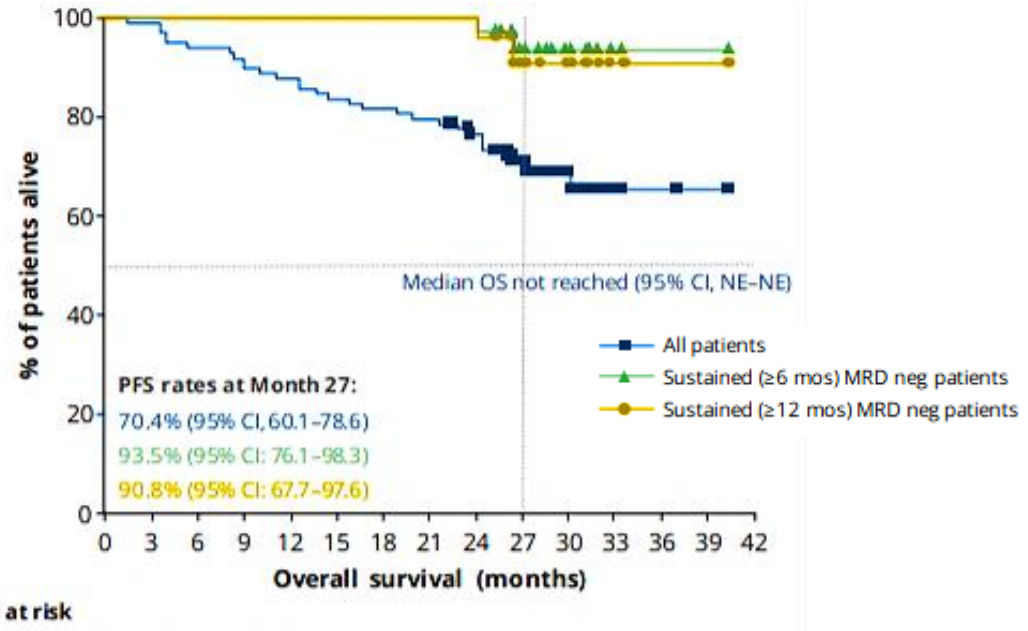
Progression-free Survival



Patients at risk

MRD negative ≥ 12 months	24	24	24	24	24	24	24	24	24	11	8	2	1	1	0
MRD negative ≥ 6 months	34	34	34	34	34	33	32	32	31	13	10	3	1	1	0
sCR patients	80	80	78	73	71	64	62	61	55	27	17	3	1	1	0
All patients	97	95	85	77	74	67	64	63	57	27	17	3	1	1	0

Overall Survival

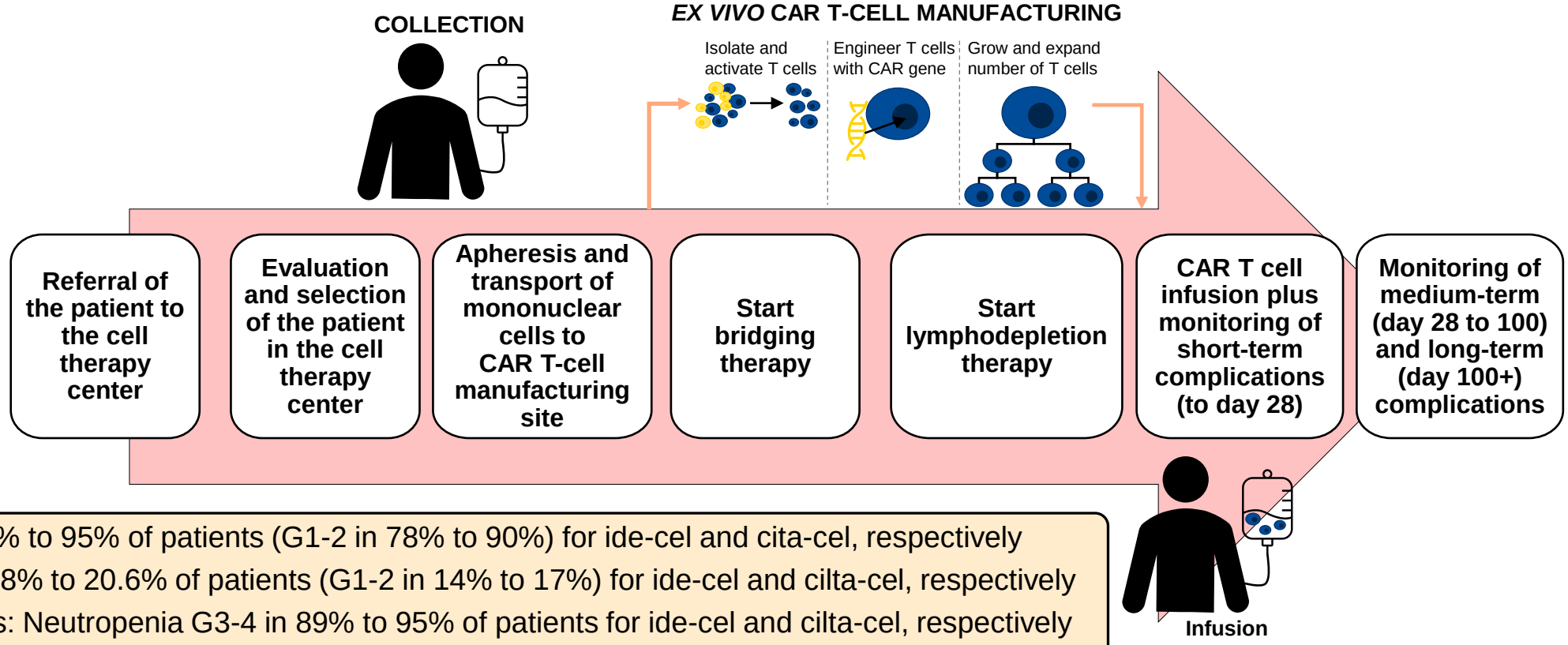


Patients at risk

All Patients	97	96	91	88	85	81	79	77	71	42	22	6	2	1	0
Sustained (≥ 6 mos) MRD neg	34	34	34	34	34	34	34	34	34	18	11	3	1	1	0
Sustained (≥ 12 mos) MRD neg	24	24	24	24	24	24	24	24	24	13	9	2	1	1	0

Usmani S, et al. ASCO 2022. Abstract 8028.

Overview of the Global CAR T-cell Therapy Process



- CRS in 84% to 95% of patients (G1-2 in 78% to 90%) for ide-cel and cita-cel, respectively
- ICANs in 18% to 20.6% of patients (G1-2 in 14% to 17%) for ide-cel and cilta-cel, respectively
- Cytopenias: Neutropenia G3-4 in 89% to 95% of patients for ide-cel and cilta-cel, respectively
- Infections: 69% and 58% of patients overall for ide-cel and cilta-cel, respectively

CAR, chimeric antigen receptor. CRS, cytokine release syndrome. ICANS, immune effector cell-associated neurotoxicity syndrome.

Moran D. The potential of CAR T-cell therapy and the myeloma patient journey. Myeloma Today. Available from: https://indd.adobe.com/view/07583bc3-3af4-4a8d-a14247cb2c8a6402; Raje N, et al. *N Engl J Med.* 2019;380(18):1726-1737; Turtle CJ, et al. *Sci Transl Med.* 2016;8:355ra116; Yakoub-Agha I, et al. *Haematologica* 2020;105(2):297-316; *Ex vivo* CAR T-cell manufacturing image reproduced with permission from Dana-Farber Cancer Institute. Available from: www.dana-farber.org/cellular-therapies-program/car-t-cell-therapy/how-car-t-cell-therapy-works/; Process flowchart reproduced with permission from Moran D. Available from: https://indd.adobe.com/view/07583bc3-3af4-4a8d-a142-47cb2c8a6402.

BCMA-bispecific mAbs: Efficacy

Product	N	TCR	Efficacy at the RP2D	Schedule of Administration
Alnuctamab (CC-93269)[1]	30	66.7%	Overall: ORR: 43% RC: 17% MTD: 10 mg (n=9): **ORR 88% (CR 44%)**	Weekly IV × 3 cycles Every other week × 3 cycles > 7 cycles: Monthly *Now SC formulation
Teclistamab[2]	165	77.6%	**MajesTEC-1** Phase 1 (n=40) Phase 2 (n=125) Dose 1.5 mg/kg SC; **ORR 63% CR/sCR: 39.4%** Median PFS: 11.3 months	Weekly and SC
Elranatamab[3]	94	95.7%	**MagnetisMM-3** Phase 2 (n=94) **ORR: 60.6%** at the dose of 12/32 and 76 mg	SC weekly SC every other week (C7+)
Linvoseltamab (REGN5458)[4]	73	89%	Dose 200 to 8000 mg (n=24); **ORR 75% CR/sCR 16%**	Weekly IV × 16 weeks Every other week later
ABBV-383B (TNB-383B)[5]	124	82%	All patients: ORR: 57% RC: 14%. Median PFS: 10.4 months Dose = 60 mg (n=60): **ORR 60% CR 17%**	IV every 3 weeks. No step-up doses

Most BCMA×CD3 bispecific mAbs have been evaluated in triple-class-refractory MM patients.
ORR is ~60 to 80% and covers the unmet need. Follow-up is short and there are no mature data for PFS, DOR, or OS; median PFS appears to be ~10 months

The data in the table are provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.
BCMA, B-cell maturation antigen; IV, intravenous; mAb, monoclonal antibody; MTD, maximum tolerated dose; ORR, overall response rate; RP2D, recommended Phase 2 dose; SC, subcutaneous.

1. Costa LJ, et al. presented at EHA 2020; Abstract S205; 2. Moreau P, et al. *N Engl J Med*. 2022;387(6):495-505; 3. Lesokhin A, et al. presented at ASCO 2022. Abstract 8006; 4. Zonder, et al. presented at ASH 2021; Abstract 160; 5. Voorhees P, et al. IMS: plenary presentation.

New Guidelines for Managing R/R MM: Is This the Present?

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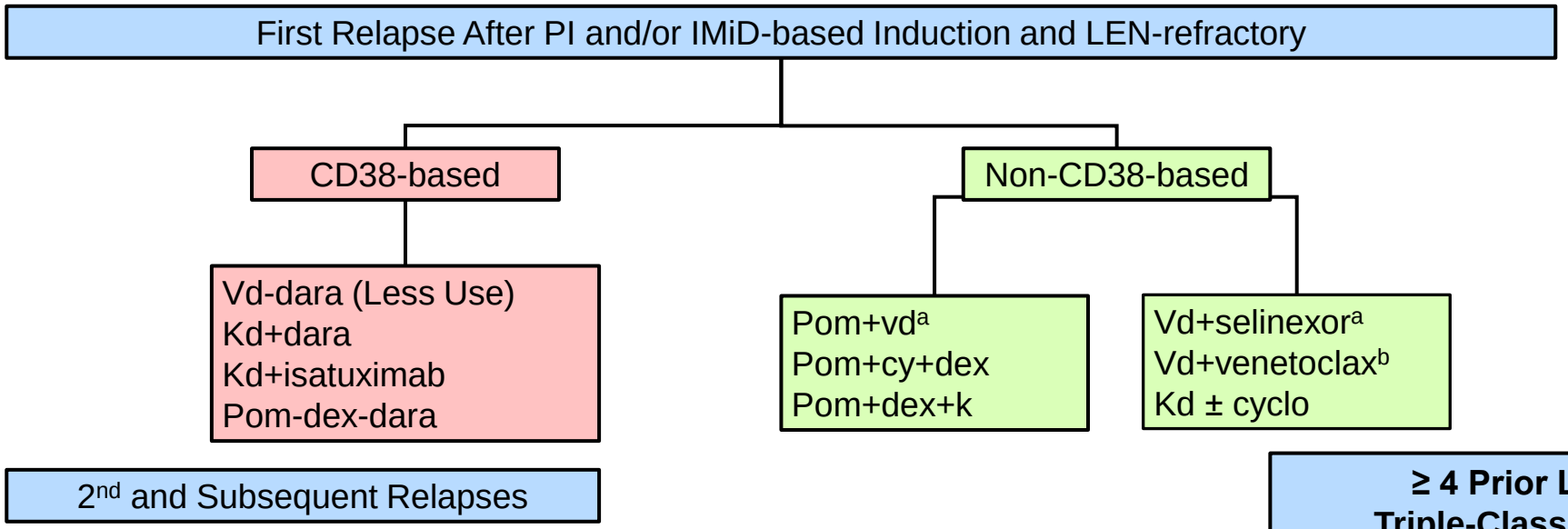


2nd and Subsequent Relapses

Pom-dex + isatuximab
Pom-dex + elotuzumab
Pom-dex + daratumumab

Selinexor-dex/selinexor-based combos
Iberdomide
Mezigdomide
Modakafusp……

≥ 4 Prior Lines & Triple-Class Exposed

Belantamab mafodotin*

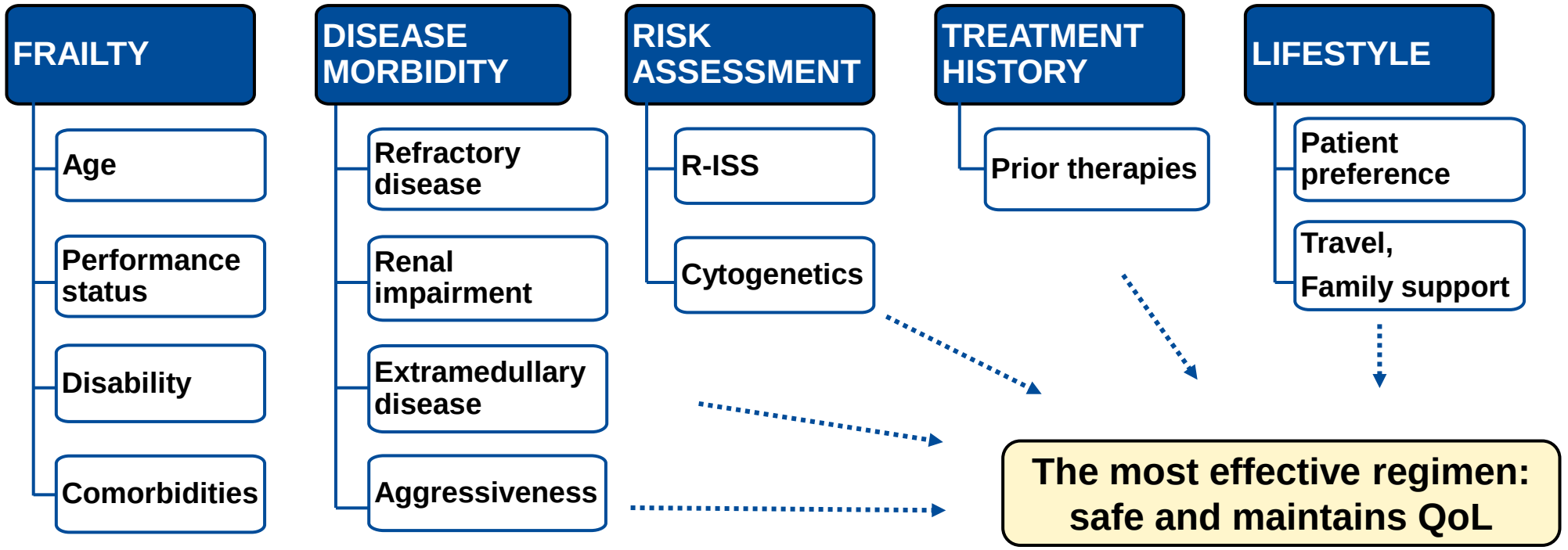
Cell Therapy
CAR-T Cell therapy

Bispecific mAbs

*As of Nov. 2022, belantamab mafodotin is being withdrawn from the US market

[a]Based On Phase 3 Randomized Trials.
[b] Venetoclax-based combinations for patients with T(11;14) and/or overexpression of Bcl-2.
CAR, Chimeric Antigen Receptor; Cy, Cyclophosphamide; Dara, Daratumumab; Dex, Dexamethasone; Imid, Immunomodulatory Drug; K, Carfilzomib; LEN, Lenalidomide; mAbs, Monoclonal Antibody; PI, Proteasome Inhibitor; POM, Pomalidomide; RRMM, Refractory/Relapsed Multiple Myeloma; V, Bortezomib.
Adapted from: Dimopoulos M, et al. *Ann Oncol.* 2021;32(3):309-322. Reuters. 11/22/22. https://reut.rs/3WjwzJY

How Are Patient- and Disease-related Factors Relevant for the Right Choice?



QoL, quality of life.

Chen X, et al. *Clin Interv Aging*. 2014;9:433-441. Chng WJ, et al. *Leukemia.* 2016;30(5):1071-1078. Chung T-H, et al. *PLoS One*. 2013;20:e66361. Clegg A, et al. *Lancet.* 2013;381(9868:752-762. Faiman BM, et al. *Clin J Oncol Nurs*. 2011;15(suppl):66-76. Greipp PR, et al. *J Clin Oncol.* 2005;23(15):3412-3420. Handforth C, et al. *Ann Oncol*. 2015;26(6):1091-1101. Jhaveri M, et al. *Haematologica.* 2016;101(suppl 1):E1312. Merz M, et al. *Haematologica.* 2016;101(suppl 1):P650. Miceli TS, et al. *Clin J Oncol Nurs*. 2011;15(suppl):9-23. Palumbo A, et al. *Blood.* 2015;125(13):2068-2074. Ramsenthaler C, et al. *BMC Cancer*. 2016;16:427. Sonneveld P, et al. *Leukemia*. 2013;27(10):1959-1969. Tatarczuch M, et al. *Haematologica.* 2017;102(suppl 2):E1457. Williams LA, et al. *J Clin Oncol*. 2016;34:e18127.

Chronological Age/Frailty Score

- There is no age cut-off for CAR-T or bispecific mAbs in myeloma
- Although frailty score has not been evaluated, all patients have to be fit enough to meet all of the required criteria. In most cases, patients present with a PS ECOG <2.
- But....

	Ide-cel (All treated) (N=128)	Cilta-cel (N=97)	Bispecific mAbs (pooled data)
Age, median	**61 yrs (up to 78)**	**60 (up to 75)**	**64 (up to 92)**

More elderly patients with more comorbidities will be eligible for bispecific mAbs

Munshi NC, et al. *N Engl J Med*. 2021;384(8):705-716; Usmani S, et al. ASCO 2022. Abstract 8028; Möller MD, et al. *Curr Opin Oncol*. 2021;33(6):648-657; Schoenbeck KL, Wildes TM. *Lancet Healthy Longev*. 2022;3(9):e579-e580.; Mateos MV, personal comment.

Organ Function

- Normal organ function is required for both CAR-T cells and bispecific mAbs, but CAR-T therapy requires a more stringent evaluation

Both CAR-T and bispecific mAbs do require: • >1000 granulocytes, 50 to 75,000 platelets, Performance status of 0 to 1, no symptoms/signs of active infection, normal O2 saturation • Electrocardiogram and echocardiogram • Neurologic examination and mini-mental test at baseline		
SPECIFIC EVALUATIONS FOR CAR-T THERAPY		
EVALUATION BY CARDIOLOGIST	**EVALUATION BY NEUROLOGIST**	
• **Electrocardiogram (also for TCE)** • **Echocardiogram (also for TCE)** • **Troponin and NTproBNP** • **NYHA functional class** • **Cardiac MRI if necessary**	• **Neurologic examination (also for TCE)** • **Mini-mental test (also for TCE)** • **Brain MRI at baseline** **Neurologist is contacted at the moment of admission** • Anti-seizure prophylaxis with levetiracetam at 500 mg every 12 hours from the day of infusion	• **Functional respiratory tests** • **Vein access evaluation**

Yakoub-Agha I, et al. *Haematologica.* 2020;105(2):297-316. Presented at the XVI Congress of the Italian Society of Experimental Hematology in Napoli, Italy.

Renal Impairment and High Risk Features

- In clinical trials, administration of CAR-T cells do require a CrCl of at least 45 mL/min
- In clinical trials, administration of BsAbs do require a **CrCl of at least 30 mL/min**

	Ide-cel (All treated) (N=128)	Cilta-cel (N=97)	Bispecific Abs (pooled evaluation)
Prior lines of therapy, median (range)	**6 (3 to 16)**	**5 (3 to 18)**	**5 to 6**
Triple refractory	**84%**	**86%**	**77% to 96%**
Extramedullary disease (EMD)	**39%**	**10%**	**17% to 29%**
High-risk cytogenetics	**35%**	**27%**	**21% to 23%**
High tumor burden	**51%**	**22%**	**11% to 20%**

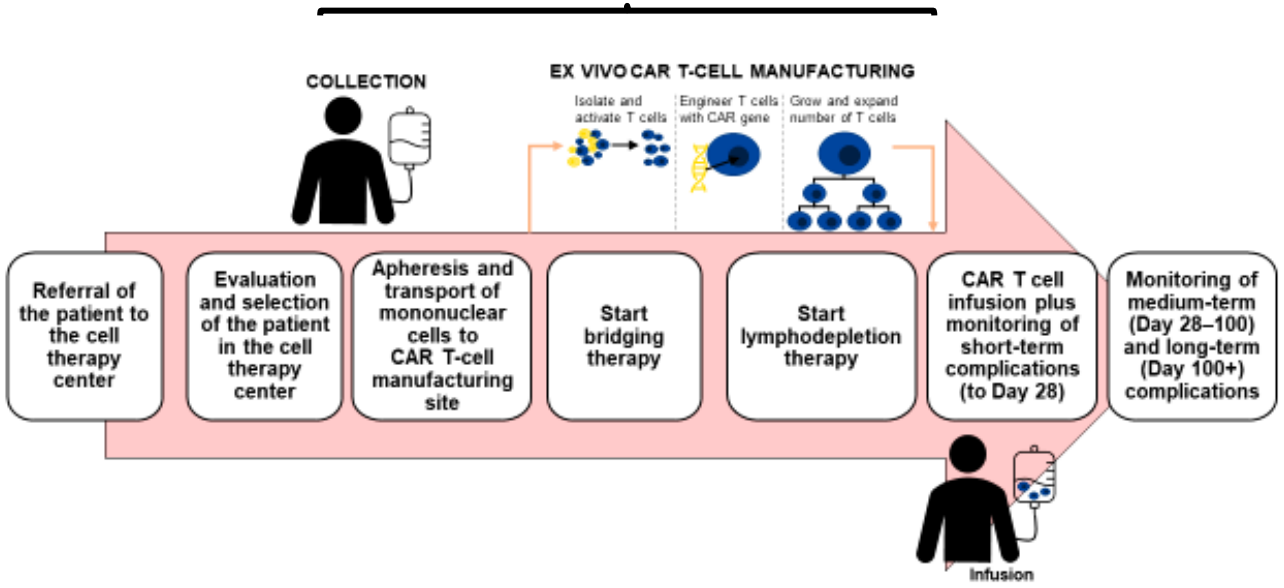
- EMD and/or high-risk cytogenetics and/or high tumor burden should not influence choice
- Efficacy reported with both approaches seems to be a bit inferior in these patient subgroups

These data underscore the challenging nature of these patient populations.

Munshi NC, et al. *N Engl J Med*. 2021;384(8):705-716..Usmani S, et al. ASCO 2022. Abstract 8028. Mateos MV. Personal communication

Disease Morbidity

Vein-to-vein time: 6 to 8 weeks



Rate of disease progression, time for communication of patient referral with the CAR-T center, and manufacturing time must be considered before moving forward with the CAR-T procedure.

Which bispecific mAb do you want?
They are ready for administration

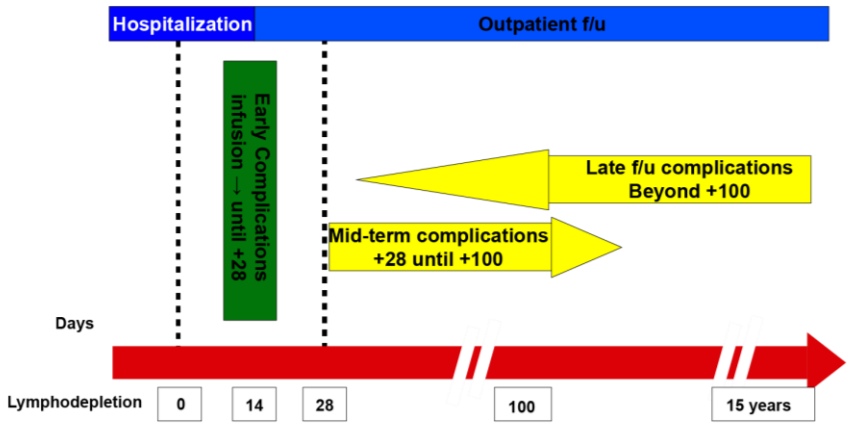
If the disease is rapidly progressing or very aggresive, it is more appropriate to use off- the-shelf product, bispecific mAbs.

This factor is crucial now – considering that these therapeutic options are available for heavily pretreated patients with MM – but may be less relevant in the future as these options move to earlier lines of therapy and more patients in biochemical relapse become eligible.

Lifestyle: Family and Social Support

- Although relevant for all patients and therapies, CAR-T therapy requires more social support as there are few centers in each country authorized to deliver CAR-Ts

CAR-Ts



- Hospitalization from lymphodepletion until day +10-14
- Most protocols require staying within 60 min drive of the hospital[1]
- Weekly evaluation (or more frequent if required)
- Neurologic and cardiac follow-up until +100

Bispecific mAbs

- Hospitalization for priming doses and until full dose on D1C1 to mitigate the CRS development
- Outpatient administration will be possible
- Most of them are administered SC
- Short follow-up after hospital discharge not required
- Continuous therapy in the outpatient setting

CRS, cytokine release syndrome; D1C1, day 1, cycle 1; IV, intravenous; SC, subcutaneous

1. Yakoub-Agha I, et al. *Haematologica.* 2020;105(2):297-316. Mateos MV. Personal communication.

Toxicity as a Consideration

- CRS rate is lower for BCMA bispecific Abs than BCMA CAR-Ts
- ICANS rate is also lower for BCMA bispecific Abs
- Cytopenias are common and they are restricted to the priming-doses and first full dose with BCMA bispecific mAbs and to the first month after CAR-T
- Infections are frequent with both approaches; prophylaxis is recommended
- IVIG support is available
- BCMA bispecific Abs might improve the infection rate through the incorporation of drug holidays in the treatment schedule

Summary

- New immunotherapies strategies, such as ADCs, BCMA bispecific mAbs, and CAR-T can cover unmet medical need in triple-class-refractory patients with ≥4 prior therapies today.
- Optimal therapeutic selection is not simple, but some patient and disease-based factors can influence decision making: more frail, lower CrCl, rapidly progressing patients are more eligible for BCMA bispecific mAbs.
- BCMA bispecific mAbs are off-the-shelf therapies with a broader availability than CAR-Ts and with many possibilities to improve efficacy through combinations, earlier use, or even as a complement to CAR-T.

BCMA-Targeted Therapies in R/R MM: A New Era

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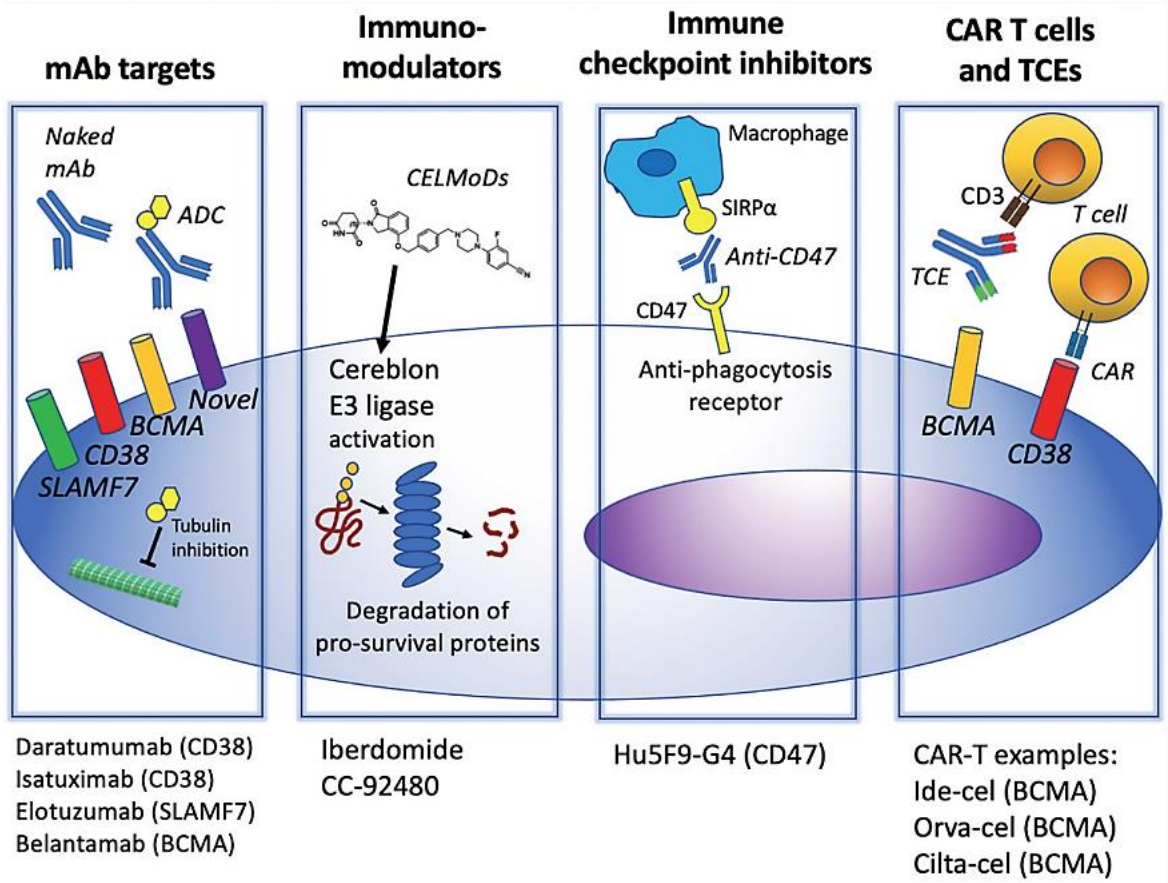
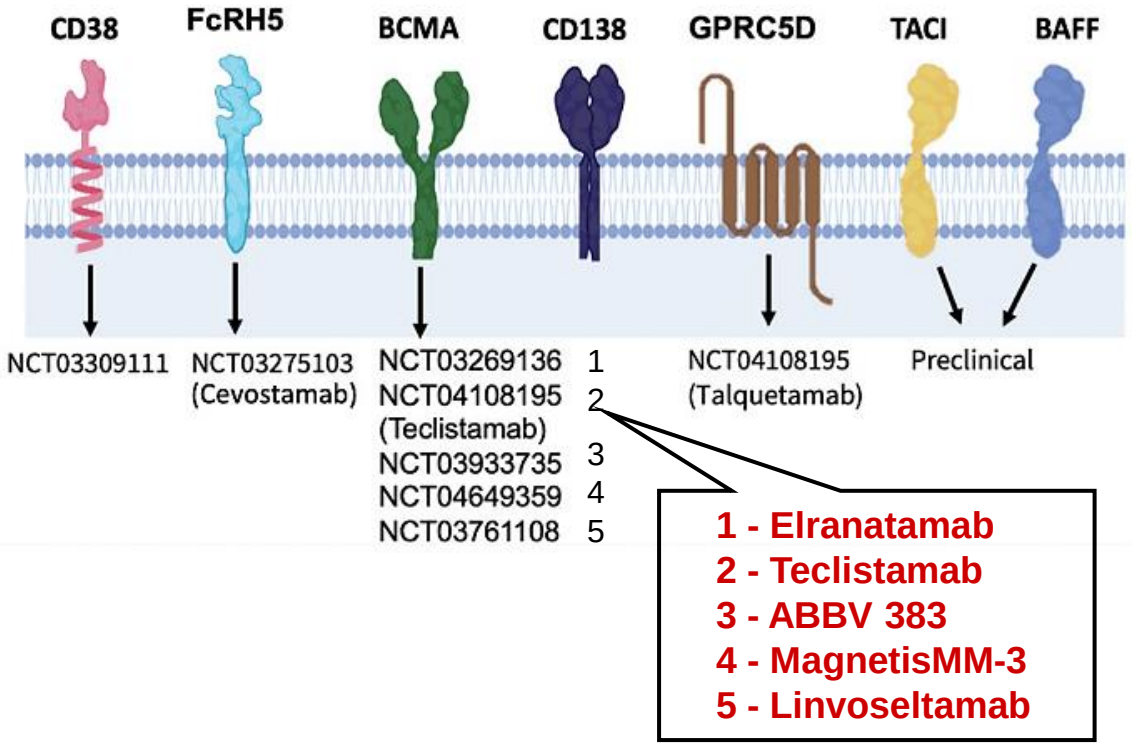
Promise of Immune Therapy

Clinical OLYMPICS℠

- Using a person's own immune system to **target malignant cells**
- A broad anti-tumor immune response has the potential to **target the different tumor clones**, including malignant precursor cell populations
- Immune response provides the potential for **memory and long-term surveillance**

Immunotherapy for Myeloma

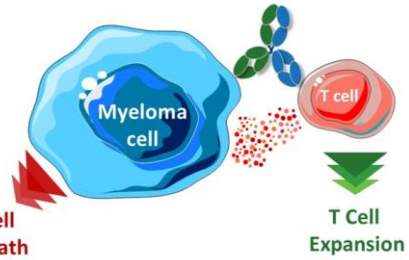




Teclistamab is FDA-approved for adults with R/R MM who have received ≥4 prior lines of therapy, including a proteosome inhibitor, an immunomodulatory agent, and an anti-CD38 mAb.

Braunstein M, et al. *Expert Rev Hematol*. 2021;14(4):377-389.
S. Jagannath, personal communication.

MajesTEC-1 Trial: Teclistamab (JNJ-64007957)



Teclistamab (JNJ-64007957) is a humanized IgG-4 bispecific DuoBody® antibody that binds to BCMA and CD3

Endpoints

- **Primary:** ORR
- **Secondary:** DOR, TTR, MRD status, PFS, OS, safety, pharmacokinetics, immunogenicity, PRO

Screening

Cohort A

(Triple-class exposed)

Key eligibility criteria

- Measurable MM
- RRMM, ≥3PL
- Prior PI, IMiD, and anti-CD38
- No prior BCMA therapy

Treatment

Week 1

- Step-up doses of teclistamab SC (0.06 and 0.3 mg/kg)

Cycles 1+

- Weekly treatment dose of teclistamab SC 1.5 mg/kg
- Continue until progressive disease

Post-treatment

Follow-up

2 years after LPI

Patient Characteristics

Time since initial diagnosis, median (range) in years		6.0 (0.8 to 22.7)
Prior lines of therapy, median (range)		5.0 (2 to 14)
Prior stem cell transplantation, n (%)		135 (81.8)
Refractory status, %	Triple-class refractory	128 (77.6)
	Penta-drug refractory	50 (30.3)
	Refractory to last line of therapy	148 (89.7)

Study status as of 16 March 2022

Screened N=165

↓

Phase 1 = 40
Phase II = 125

↓

Primary safety = 165
Primary efficacy = 150

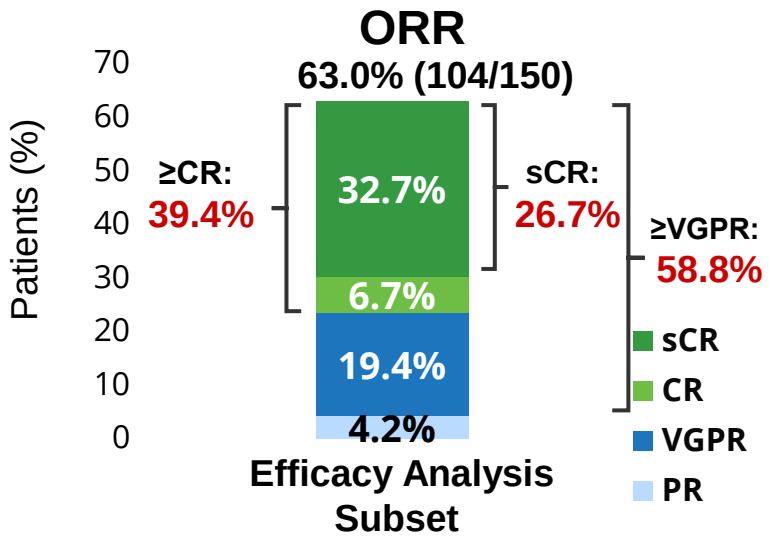
↓

Median duration of treatment, 5.9 mo

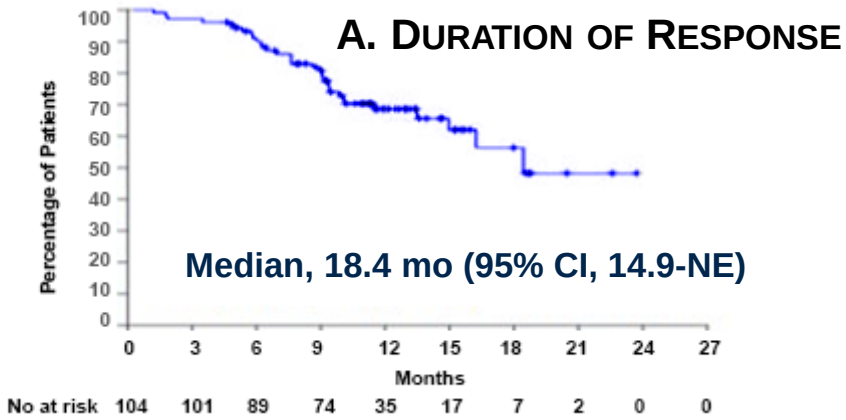
Median follow-up, 14.1 mo (range: 0.5±18)

Moreau P, et al. *N Engl J Med*. 2022;387(6):495-505.

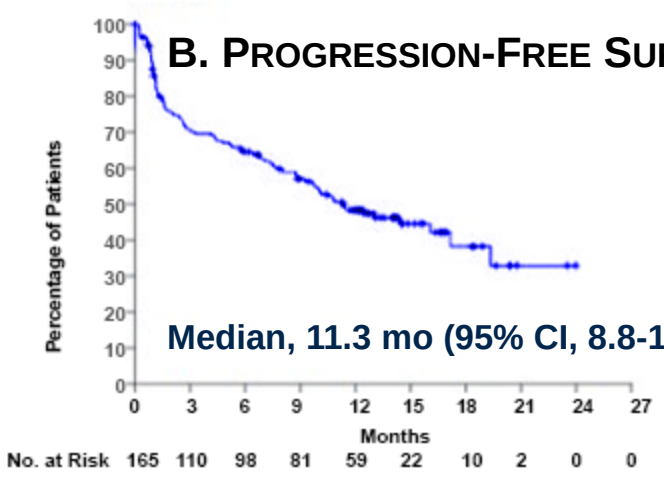
Teclistamab Efficacy

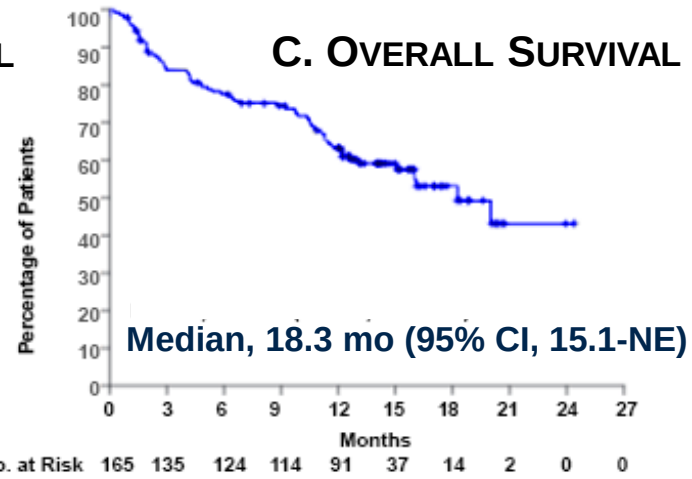


*In patients who achieved ≥CR, the MRD-negativity rate was 46%



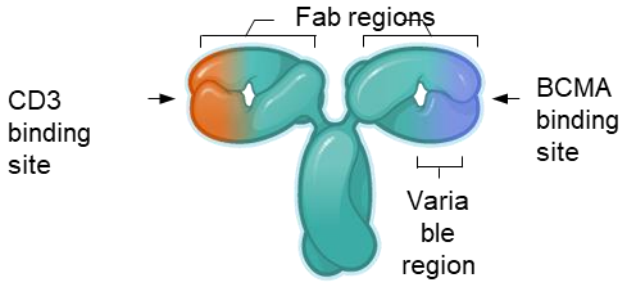
SAFETY ANALYSIS SET (N=165)		
AEs ≥20%, n (%)	**Any Grade**	**Grade 3/4**
Neutropenia	117 (70.9)	106 (64.2)
Anemia	86 (52.1)	61 (37.0)
Thrombocytopenia	66 (40.0)	35 (21.2)
Lymphopenia	57 (34.5)	54 (32.7)
CRS	**119 (72.1)**	**1 (0.6)**
ICANs	**9 (5.5)**	**0**
Deaths (Gr 5)		19





Moreau P, et al. *N Engl J Med*. 2022;387(6):495-505.

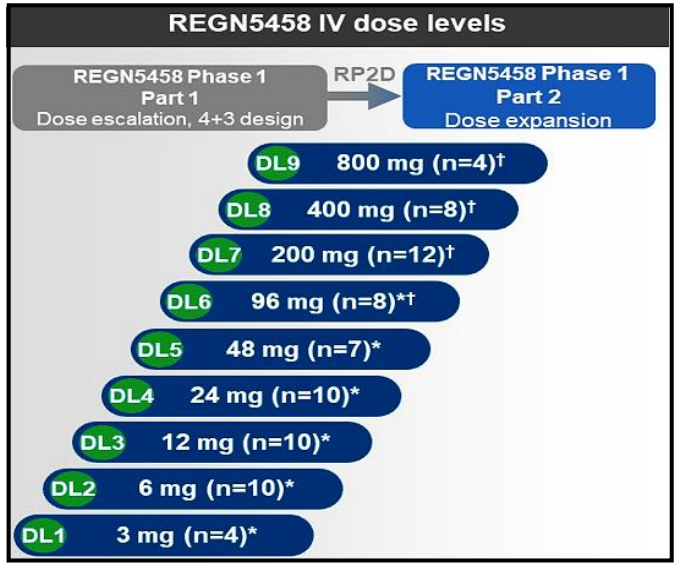
Linvoseltamab (REGN5458)

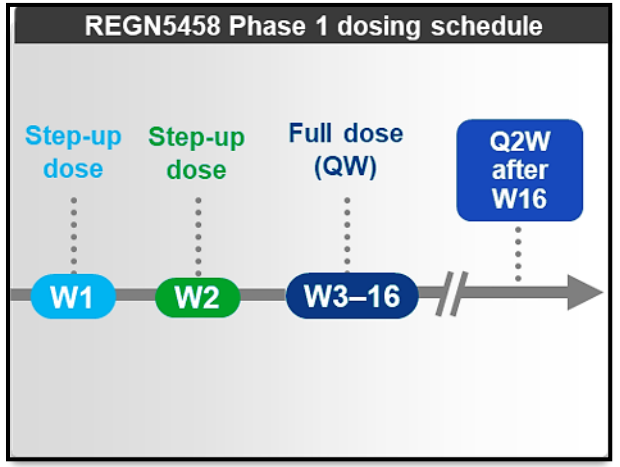


REGN 5458 is a human IgG-4 BCMAxCD3 bispecific antibody developed using ***Veloci-Bi***

N≈73

- Active MM by IMWG; non-secretory MM allowed
- Relapsed/refractory (or intolerance) to ≥3 lines of therapy including an IMiD, a PI, and an anti-CD38 Ab, or double-refractory to an IMiD and PI and progressed on or after an anti-CD38 Ab





ENDPOINTS

- **Primary:** Safety, tolerability, DLTs
- Recommended Phase 2 dose (RP2D)
- **Secondary:** ORR, DOR, PFS, MRD status, and OS

PATIENT CHARACTERISTICS

Median age (range) in years		64 (41 to 81)
No. of prior antimyeloma regimens, median (range)		5 (2 to 17)
Prior autologous SCT, n (%)		47 (64)
Refractory status, n (%)	Proteasome inhibitor	70 (96)
	Anti-CD38 Ab (daratumumab/isatuximab)	70 (96)
	Immunomodulatory drug	69 (95)
Progressed-refractory, n (%)	Triple-refractory	65 (89)
	Quad-refractory	51 (70)
	Penta-refractory	28 (38)

Study status as of 30 Sept 2021

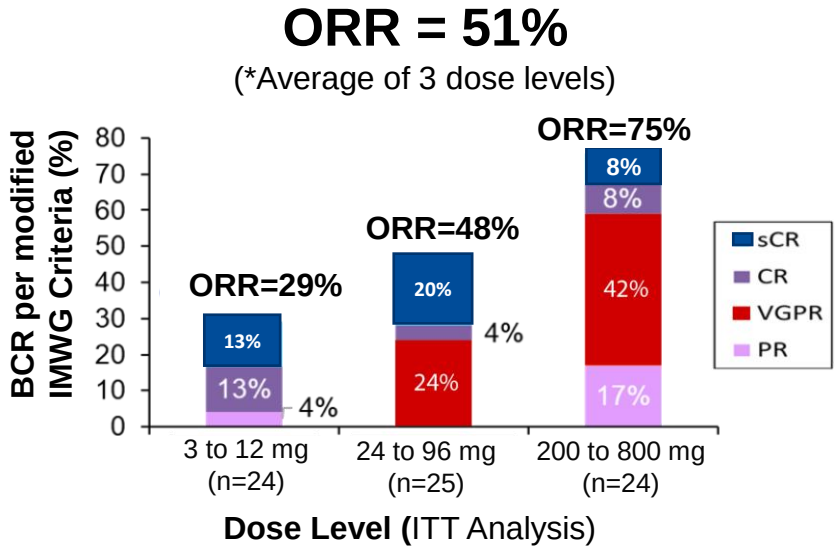
Screened N=73

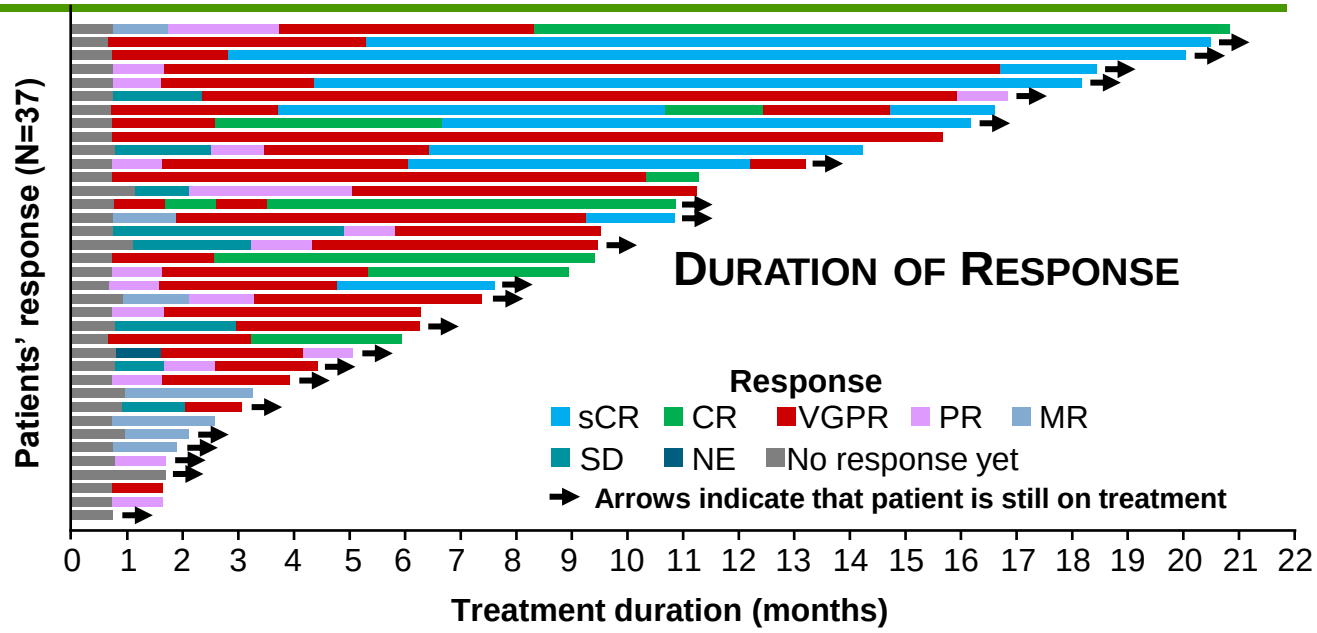
- Phase 1 Part 1. Dose escalation, 4+3 design
- Phase 1 Part 2 Dose expansion

Median follow-up, 23 mo (9 to 46)

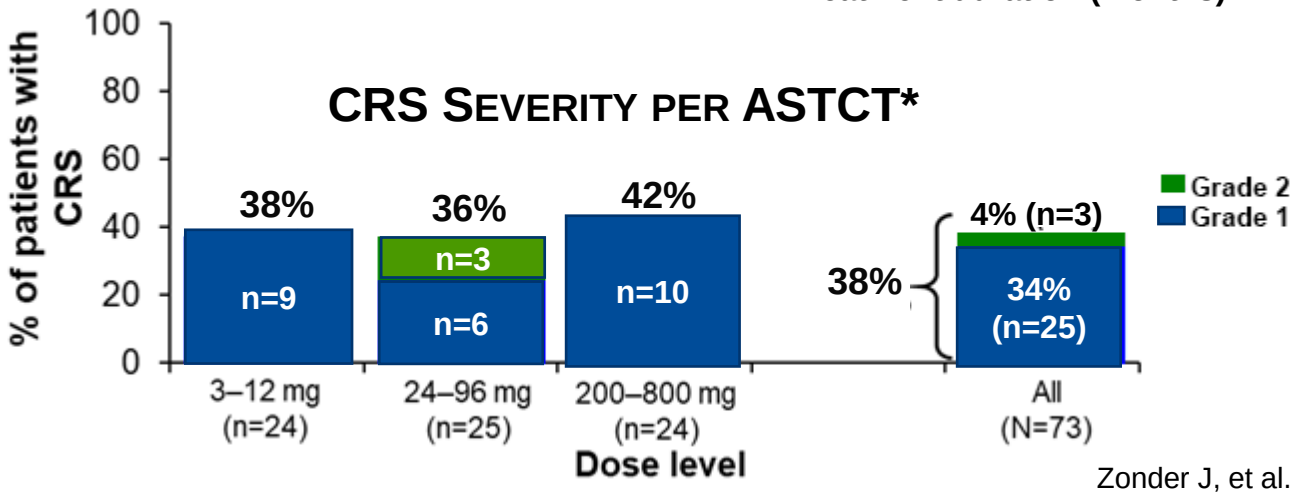
Zonder J, et al. IMS. 2022;OAB-056.

Linvoseltamab Efficacy





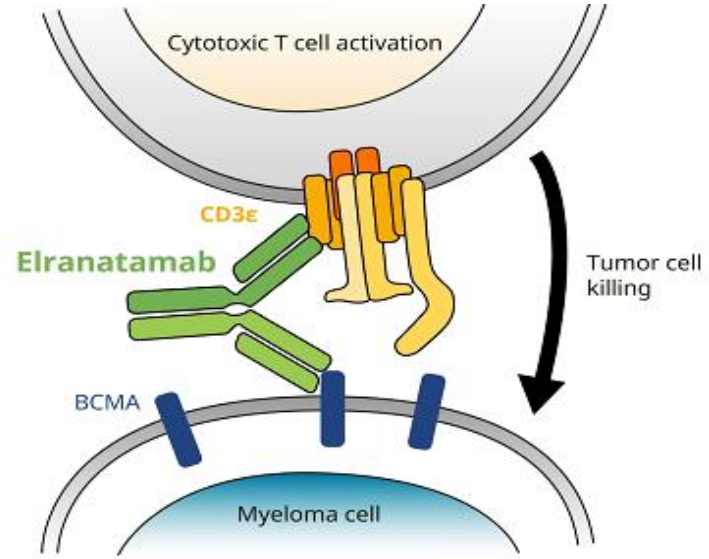
SAFETY ANALYSIS SET (N=73)		
AEs ≥20%, n (%)	**Any Grade**	**Grade 3/4**
Neutropenia	17 (23)	16 (22)
Anemia	23 (32)	17 (23)
Thrombocytopenia	15 (21)	10 (13)
Lymphopenia	17 (23)	14 (20)
CRS	**28 (38)**	**0 (0)**
ICANs	**3 (4)**	**0 (0)**
Death (unrelated)	5 (7)	5 (7)



Zonder J, et al. IMS. 2022;OAB-056.

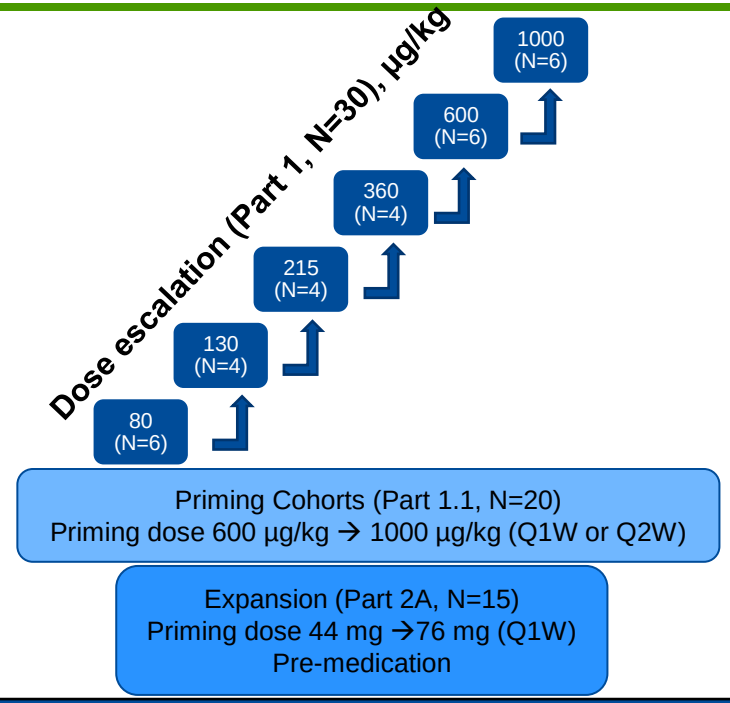
MagnetisMM-1 Trial: Elranatamab (PF-06863135)

Clinical OLYMPICS℠



N≈55

- R/R MM
- Prior IMiD and PI, and anti-CD38 mAb required
- Measureable disease by IMWG criteria
- ANC: ≥1.0 x 10⁹/L; platelets: ≥25 x 10⁹/L; Hb: ≥8 g/dL
- Prior BCMA-directed therapy allowed



Study status as of 23 March 2022

Screened N=55

SC dose escalation (µg/kg):

80(n=6)
130 (n=4)
215 (n=4)
360 (n=4)
600 (n = 6)
1000 (n=6) µg/kg weekly

ENDPOINTS

- **Primary:** ORR
- **Secondary:** Safety, CRS, DLT, PK, immunogenicity

PATIENT CHARACTERISTICS

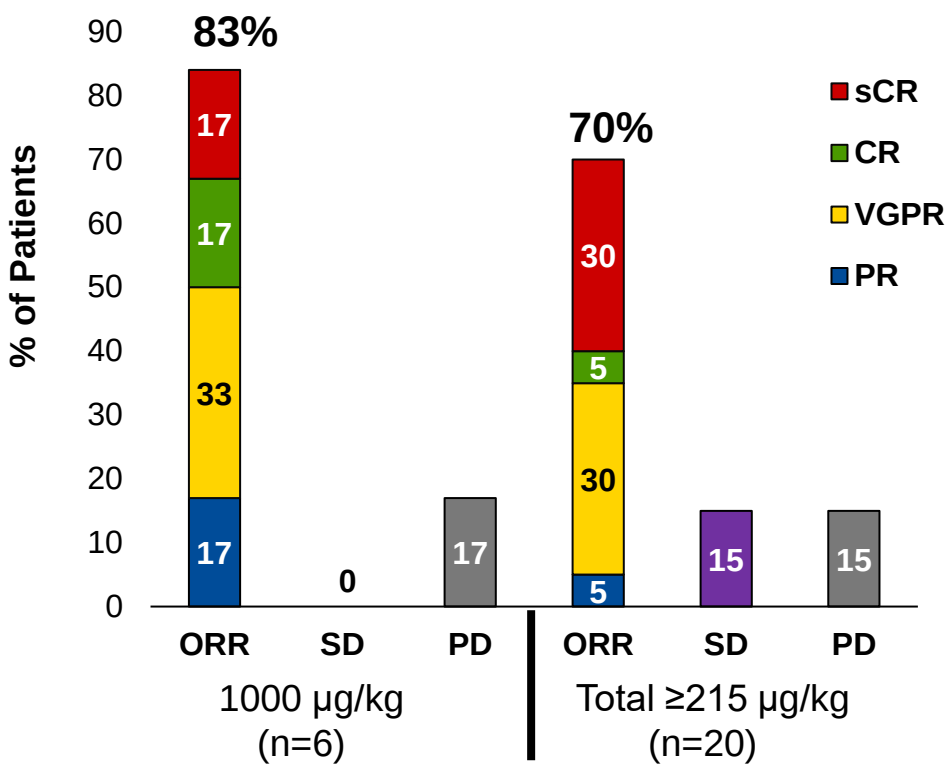
Median age, y (range) in yrs	64.0 (42 to 80)
No. of prior antimyeloma regimens, median (range)	6.0 (2 to 15)
Prior IMiDs, N(%)	55 (100.00)
Prior anti-CD38 therapy , n (%)	54 (98.2)
Prior BCMA-targeted therapy, n (%)	12 (21.8)

Sebag, et al. ASH 2021; Abstract 895.

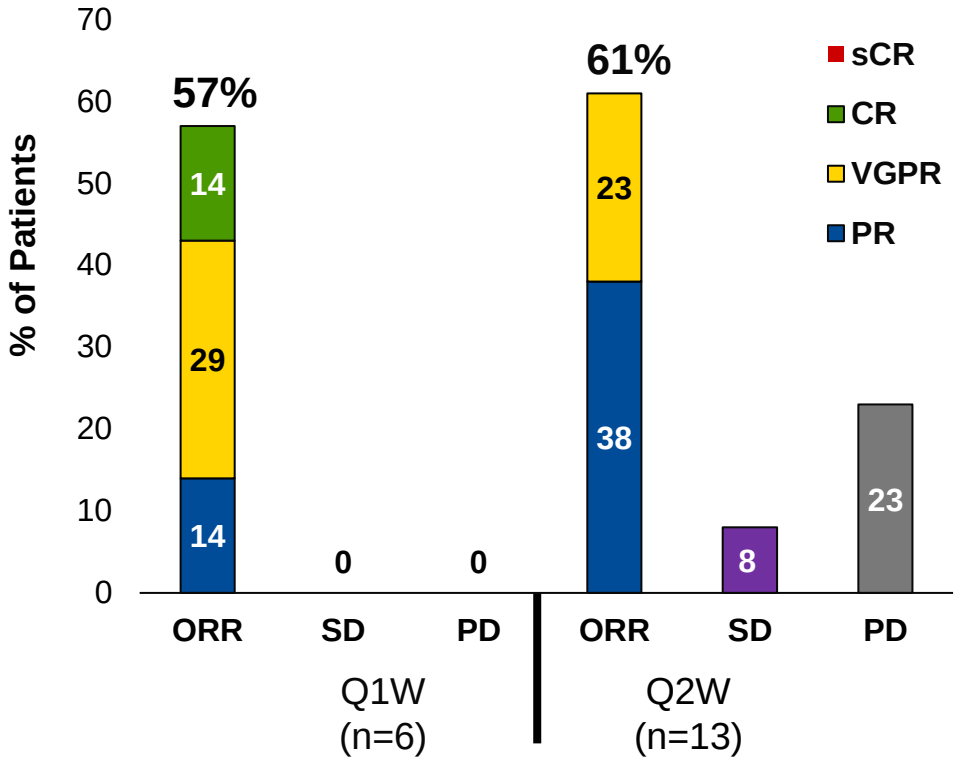
Elranatamab Efficacy

Clinical OLYMPICS℠

Investigator-Assessed IMWG Responses of the Dose Escalation Cohort



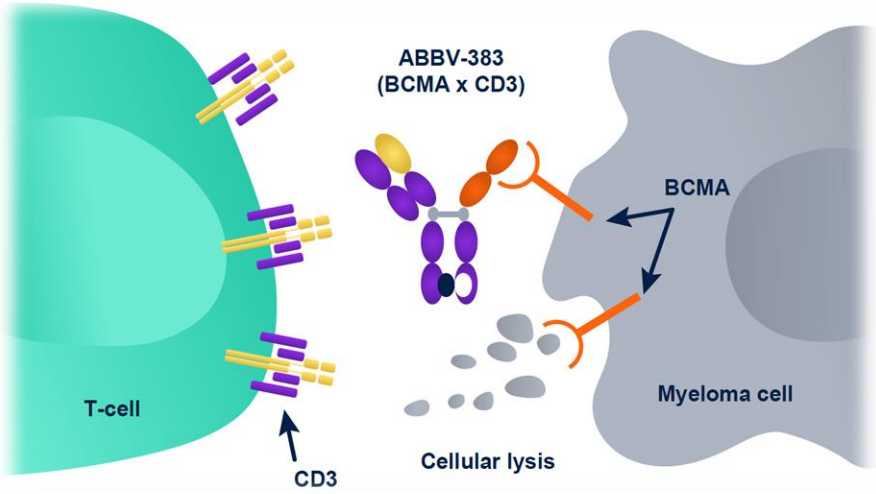
Investigator-Assessed IMWG Responses of the Priming Cohort (n=20)



- ORR was 83% at 1000 µg/kg (RP2D) and 70% in the total efficacious group.
- With a median follow-up of 7.5 months, the ORR was 57% for those dosed once a week and 61% for the twice weekly dosing group.
- ORR at the RP2D of 1000 mg/kg was 69% (9/13 patients: 5 from the expansion cohort and 4 from the priming cohort.

Sebag, et al. ASH 2021; Abstract 895. Khan and Bhurke. Multiple Myeloma Hub. Feb 2022.

ABBV-383B (TNB-383B)

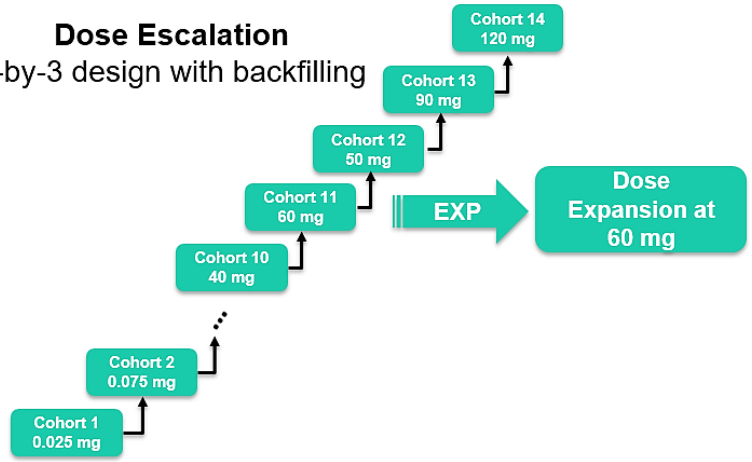


ABBV-383
Fully human, IgG4 Ab,
One IgH and IgL – CD3 low affinity
IgH – BCMA high affinity

N=124

- Patients with RRMM (≥3 prior lines including a PI, an IMiD, and an anti-CD38 mAb)
- Not considered candidates for therapies known to provide clinical benefit
- Hgb ≥8 g/dL, ANC ≥1 × 109/ L, platelets ≥50 × 109/ L
- ECOG ≤2
- eGFR ≥30 mL/min
- Prior BCMA-targeted therapy prohibited

Dose Escalation
3-by-3 design with backfilling



Study status as of 08 Jan 2022

Screened N=124

R-ISS Stage at initial diagnosis:

Stage I – 19 (15%)
Stage II – 23 (19%)
Stage III – 38 (31%)

Dose escalation (mg):

Cohort 1 (0.025 mg)
Cohort 2 (0.075 mg)…

Cohort 10 (40 mg)
Cohort 11 (60 mg)
Cohort 12 (50 mg)
Cohort 13 (90 mg)
Cohort 14 (120mg)

ENDPOINTS

- **Primary:** Safety/tolerability, PK, and determination of RP2D
- **Secondary:** Clinical activity (per IMWG criteria 2016)

PATIENT CHARACTERISTICS

Median age (range) in yrs		68 (35 to 88)
No. of prior antimyeloma regimens, median (range)		5 (3 to 15)
Prior autologous SCT, n (%)		100 (81)
Refractory status, n (%)		120 (97)
Progressed-refractory, n (%)	Double-refractory	104 (84)
	Triple-refractory	102 (82)

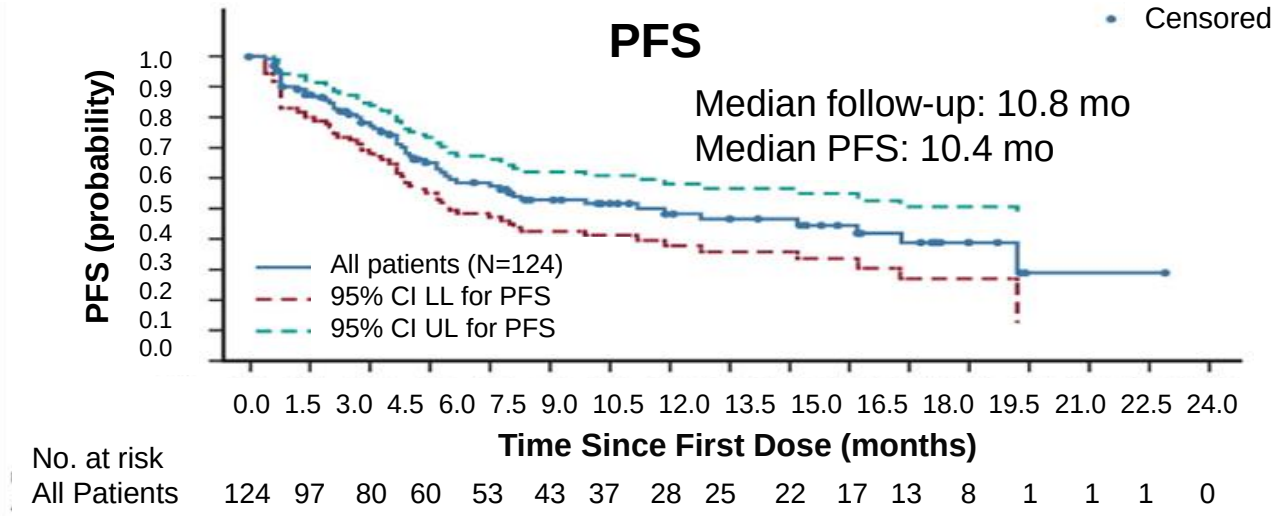
D'Souza A, et al. *J Clin Oncol*. 2022;40(31):3576-3586.

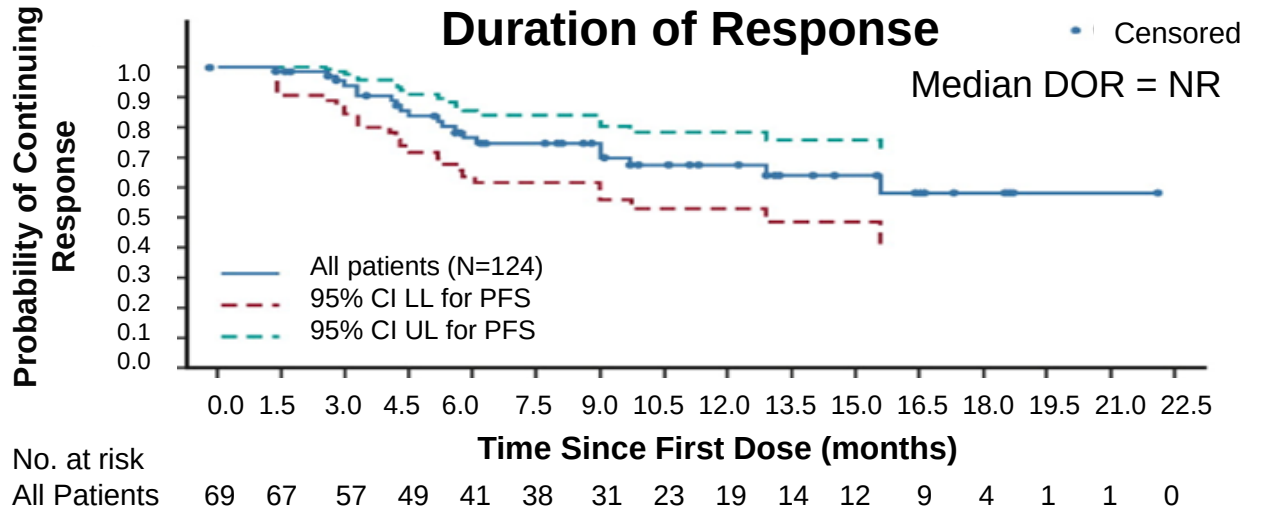
ABBV-383B (TNB-383B)

Clinical OLYMPICS℠

Overview of Efficacy	40 mg ESC + EXP (n=79)	60 mg EXP (n=49)	Total (N=122)
ORR, No. (%)	54 (68)	29 (59)	69 (57)
Best overall response, No. (%)			
sCR	16 (20)	4 (8)	21 (17)
CR	13 (16)	7 (14)	14 (11)
VGPR	14 (18)	8 (16)	17 (14)
PR	11 (14)	10 (20)	17 (14)

Safety Analysis Set (N=124)		
AEs ≥20%, n (%)	**Any Grade**	**Grade 3/4**
Neutropenia	32 (27)	26 (22)
Anemia	29 (25)	17 (14)
Thrombocytopenia	26 (22)	13 (11)
Lymphopenia	18 (15)	15 (13)
CRS	**64 (54)**	**3 (3)**
ICANs	**2 (2)**	**NR**
Death (unrelated)	NR	7 (Gr 5)





D'Souza A, et al. *J Clin Oncol*. 2022;40(31):3576-3586.

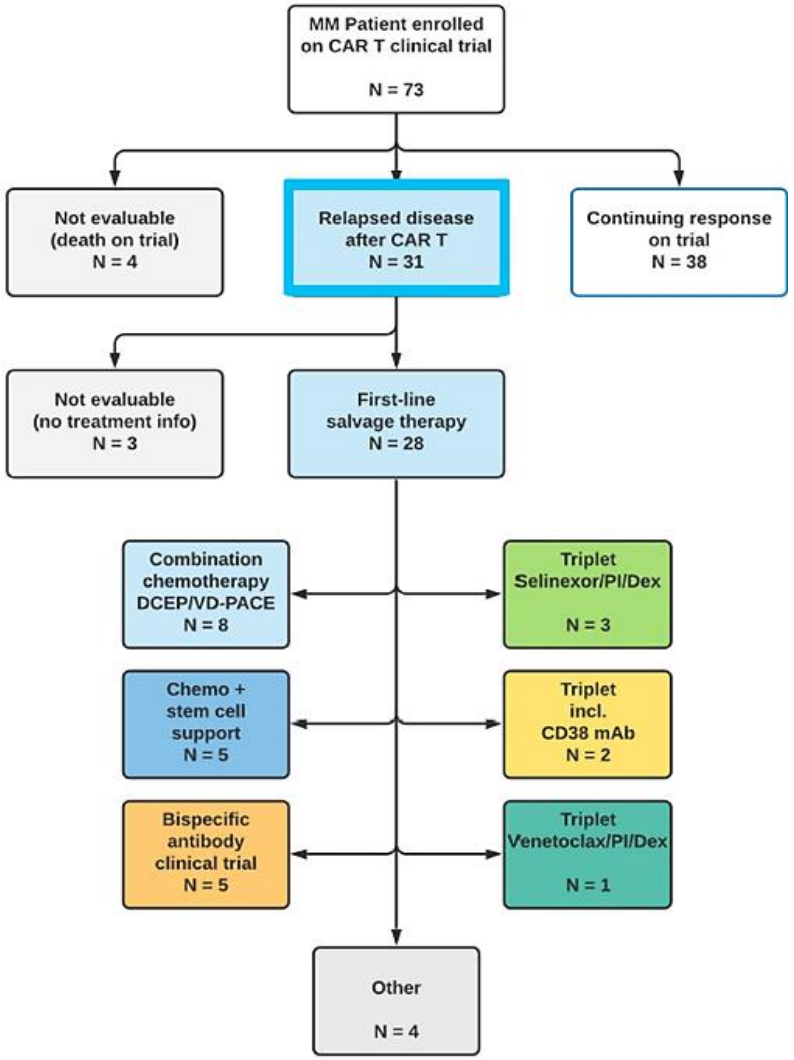
Bispecific Antibodies: Summary

	Teclistamab[1]	Linvoseltamab (REGN5458)[2]	Elranatamab[3] (PF-3135)	ABBV-383[4]	Cevostamab[5]* (FcRH5-CD3)	Talquetamab[6]* (GPRC5D-CD3)
Patients	157	73	55	124	161	74
No. of prior regimens, median	6	5	6	5	6	5.5
Triple refractory, %	128 (82)	65 (89)	50 (90.9)	102 (82)	136 (84.5)	57 (77)
ORR, %	**65%**	**51%**	**69%**	**57%**	**46%***	**67%***
≥ CR %	40%	43%	5%	28%	9%*	25.3%*
CRS (all grades), %	89 (55)	28 (38)	48 (87.3)	71 (57)	130 (80.7)	58 (78.4)
CRS Grade 3/4, %	0%	0%	0%	2%	1.2%	1.4%*
ICANS	7	3	6	2	23	NR
Neutropenia all grade (Grade 3/4), %	61 (48)	23 (20)	71 (67)	37 (34)	39 (37)	51 (45)
Infection %	60	23	NR	41	48	43*

*Calculations were generated from 2 subgroups averaged

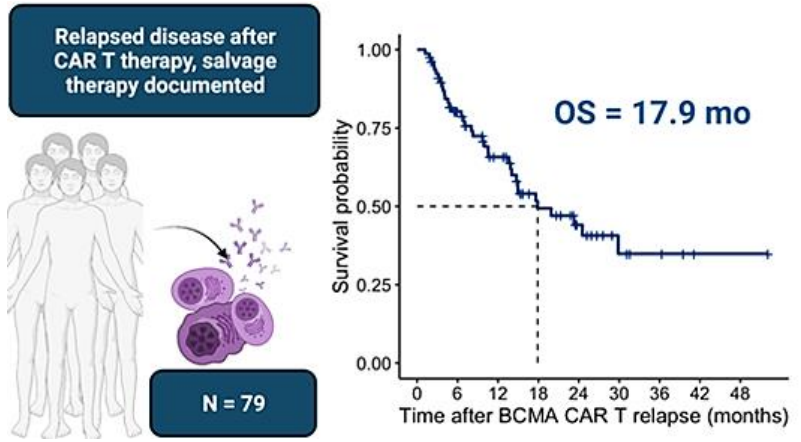
(1) Usmani SZ, et al. *Lancet.* 2021;398(1030):665-674. (2) Richter, et al. EHA 2022. (3) Sebag, et al. ASH 2021; Abstract 895. (4) D'Souza A, et al. *J Clin Oncol*. 2022;40(31):3576-3586. (5) Trudel, et al. ASH 2021; Abstract 157. (6) Minnema, et al. ASCO 2022; Abstract 8015.

Treatment After CAR-T Failure

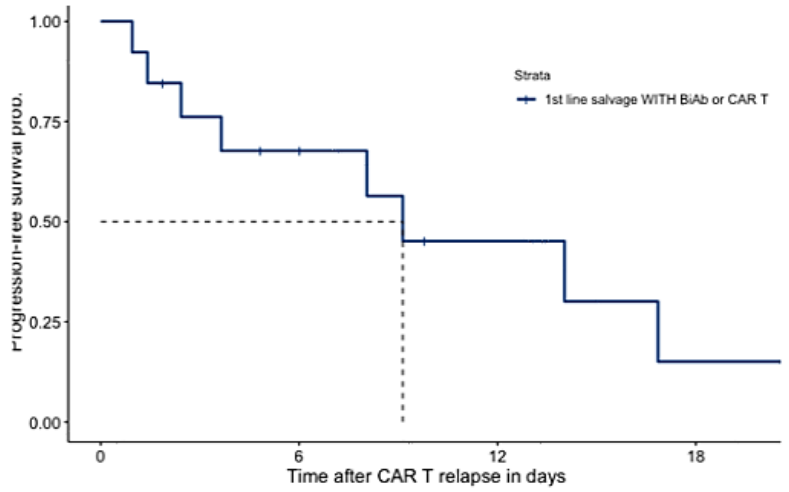


Overall Survival

ORR: 45.1%
Median PFS: 3.5 mos
Median OS: 17.9 mos



PFS for Bispecific Ab

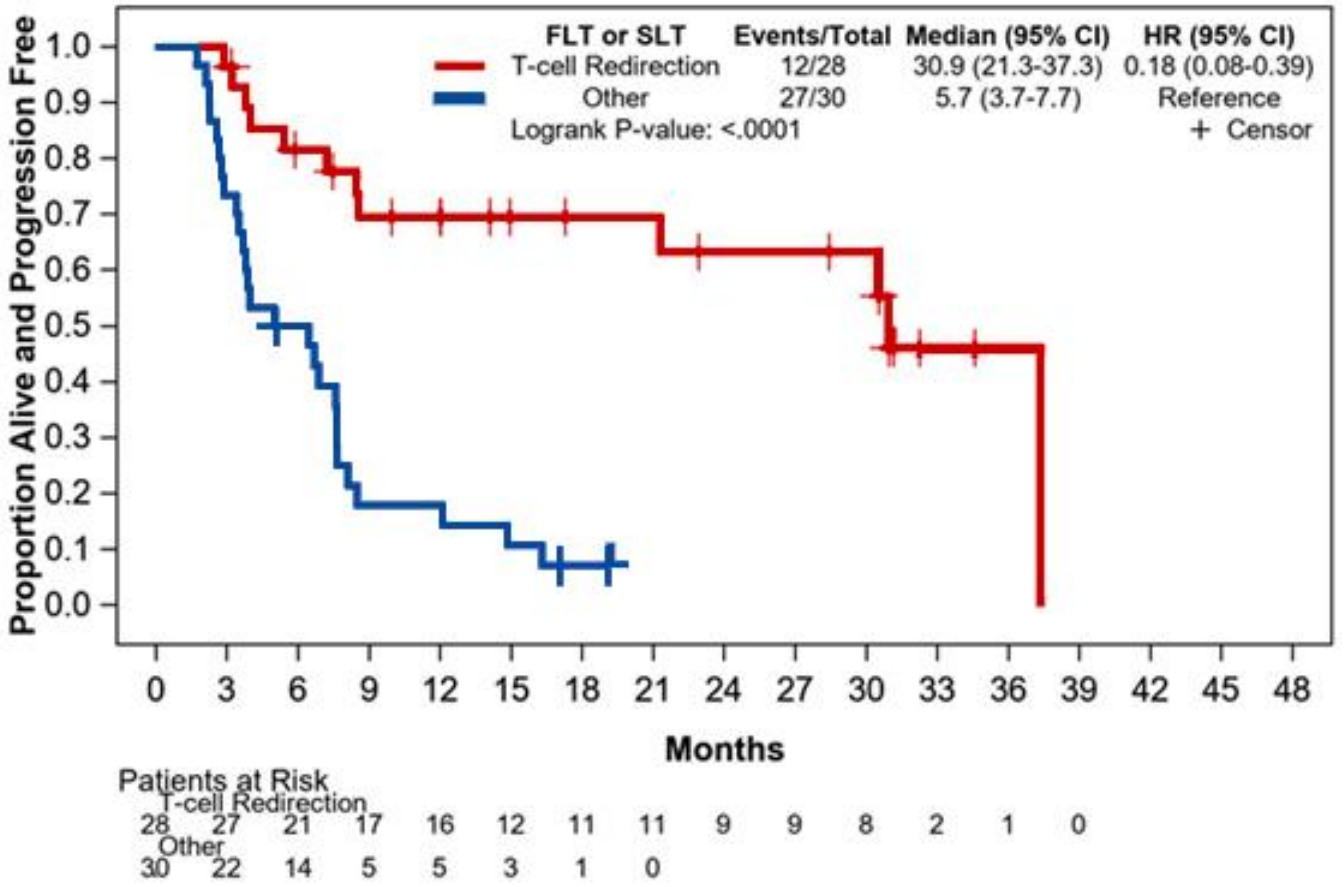


Van Oekelen O, et al. *Blood.* 2022. Online ahead of print.

Treatment After Bispecific Ab Failure

Clinical OLYMPICS℠

Patient on First Bispecific Ab Trial	= 115
Progressed and went to 1st Salvage	= 58
Chemotherapy Salvage	= 39
Second Bispecific Ab	= 10
CAR-T	= 9
Progressed and went to 2nd Salvage	= 37
Chemotherapy 2nd Salvage	= 27
Second Bispecific Ab	= 5
CAR-T	= 5



Mouhieddine TH, et al. *Blood Adv.* 2022. Online ahead of print.

Conclusion

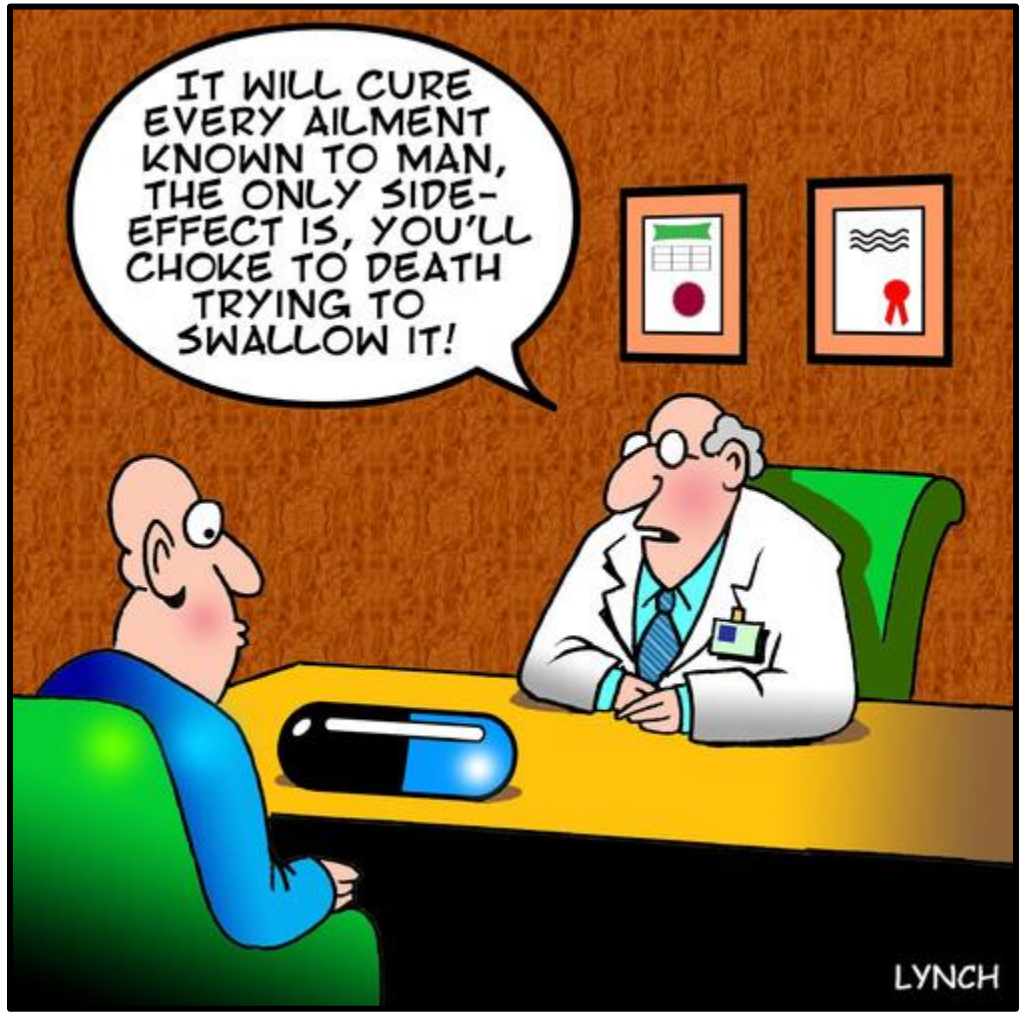
- Anti-BCMA CAR-T cells and bispecific antibodies targeting BCMA/CD3 are indicated for the treatment of triple class exposed and failing ≥4 lines of therapy
  - High response rate (70%)
  - Durable remission (median 12 mo+)
  - PFS of ~12 months
- Several BCMA- and non-BCMA directed CAR-T cells and bispecifics in clinical trial show great promise
- Patients failing BCMA targeted bispecific Ab or CAR-T can be rescued by non-BMCA targeted bispecific Ab
- Sequential use of CAR-T cells and bispecific antibodies in earlier lines of therapy may lead to potential cure in myeloma
- Understanding the tumor cell antigen expression, immune microenvironment and T cell fitness may help guide the choice of therapy and its success

BCMA-Targeted Therapies in R/R MM: Safety First

James Hoffman, MD
Associate Professor, Clinical Medicine
Division of Myeloma (Hematology)
Sylvester Comprehensive Cancer Center (SCCC)
University of Miami
Miami, Florida

Nice of them to leave the bad news to me...
Side Effects — How often and how bad?

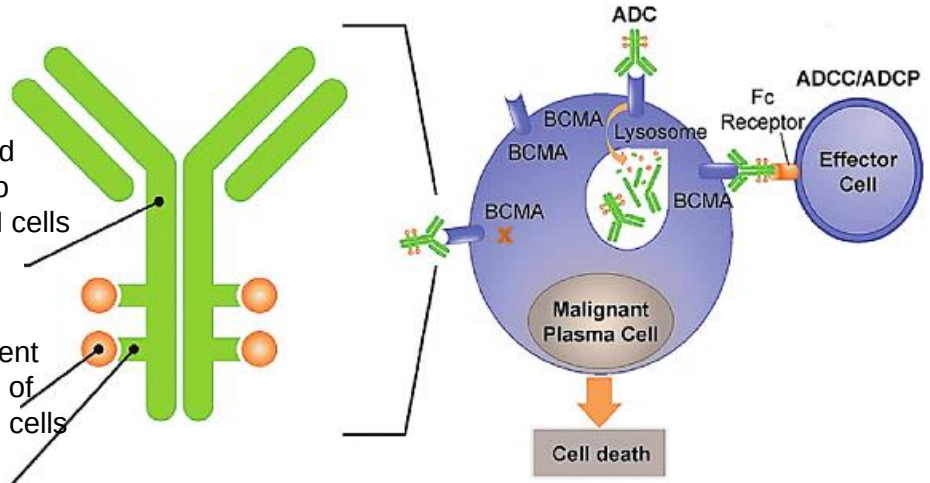
Clinical OLYMPICS℠



Targeting BCMA – What Could Go Wrong?

Clinical OLYMPICS℠

BELANTAMAB MAFODOTIN*



Anti-BCMA, humanized IgG1 mAb that binds to BCMA-expressing MM cells

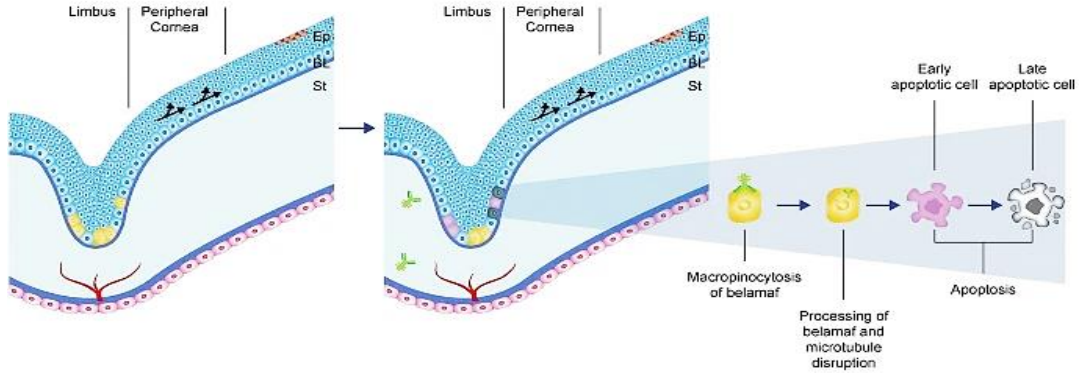
MMAF, microtubule-disrupting cytotoxic agent that leads to apoptosis of BCMA-expressing MM cells

Protease-resistant, maleimidocaproyl linker that joins MMAF to the mAb

*As of Nov. 2022, belantamab mafodotin is being withdrawn from the US market.

Normal conditions

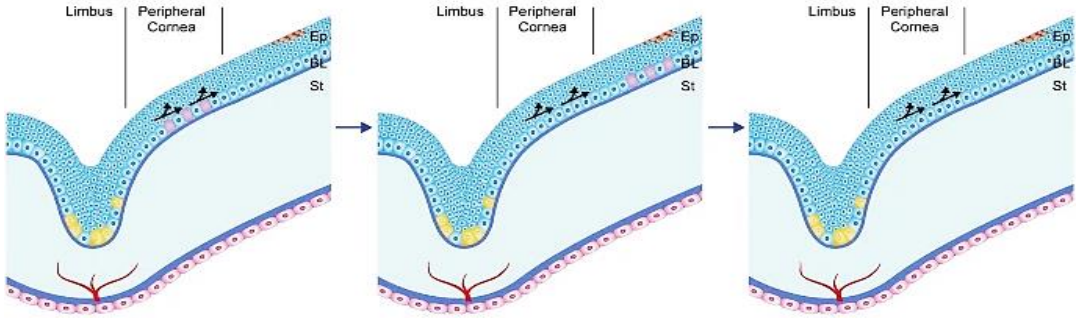
Internalization: Belantamab mafodotin enters the cornea, is internalized by limbal epithelial stem cells, and induces apoptosis



Migration of early apoptotic corneal epithelial cells to peripheral cornea (MECs observed but no symptoms)

Migration of early and late apoptotic corneal epithelial cells to central cornea (MECs observed & symptoms reported)

Migration of early and late apoptotic corneal epithelial cells to central cornea (MECs observed & symptoms reported)



Farooq AV, et al. *Ophthalmol Ther.* 2020;9(4):889-911; Reuters. 11/22/22. https://reut.rs/3Wjwz.

Phase 2 DREAMM2: Most Common AEs (≥15%) and Grade ≥3 AEs (≥5%)

Median follow up: 12.4 mo (0.1 to 17.9)	Belantamab mafodotin 2.5 mg/kg, N=94: No. Patients, %	
	ANY GRADE	GRADE ≥3
Any Event	93 (98)	80 (84)
Eye examination finding		
Keratopathy	68 (72)	44 (46)
Change in BCVA	51 (54)	29 (31)
Thrombocytopenia	36 (38)	21 (22)
Anemia	26 (27)	20 (21)
Blurred vision	24 (25)	4 (4)
Nausea	24 (25)	0 (0)
Pyrexia	22 (23)	4 (4)
AST increased	20 (21)	2 (2)
Infusion-related reaction	20 (21)	3 (3)
Fatigue	15 (16)	2 (2)
Neutropenia	14 (15)	10 (11)
Dry eye	14 (15)	1 (1)
Hypercalcemia	14 (15)	7 (7)
Lymphocyte count decreased	13 (14)	12 (13)
Pneumonia	9 (9)	6 (6)

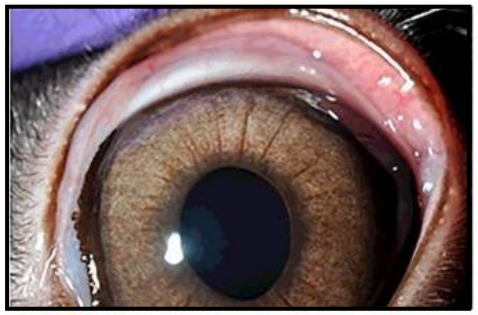
Lonial S, et al. *Cancer.* 2021;127(22): 4198-4212.

Ocular Toxicity

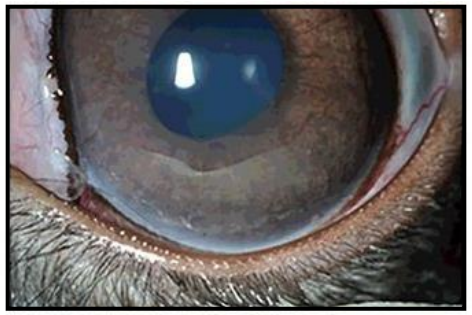
- Mechanism not completely understood.
- Class effect for MMAF-containing ADCs
- Keratopathy = damage to the corneal epithelium (eg, ulcers)
- Eye exams before every dose in DREAMM-2
- Dose modifications
- Topical steroids did not help in DREAMM-2

Rabbit Eye Images

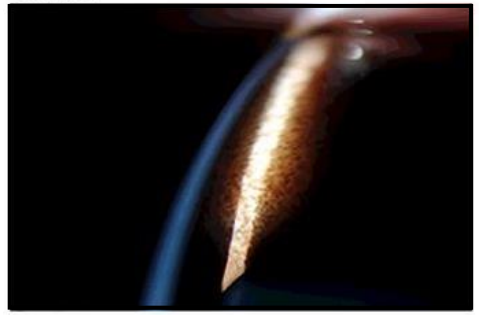
Control



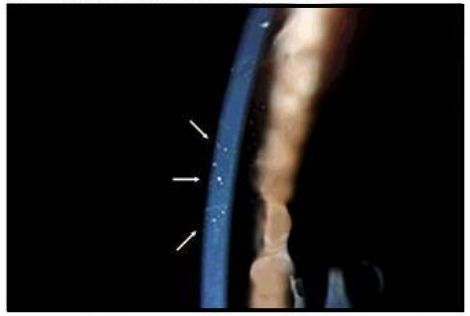
Mirvetuximab soravtansine



Control



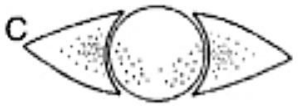
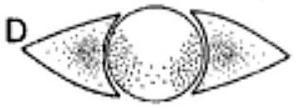
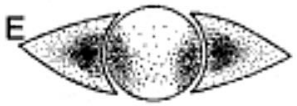
Mirvetuximab soravtansine



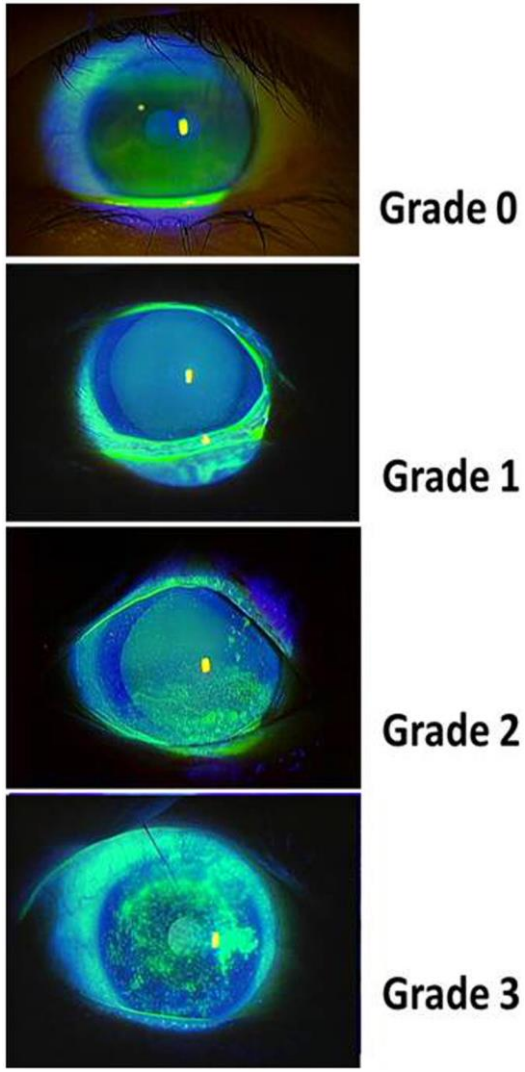
GSK ODAC Belamaf-Slit Lamp

Matulonis UA, et al. *Clin Cancer Res*. 2019;25(6):1727-1736.

Keratopathy Scoring

PANEL	GRADE	CRITERIA	DOT COUNT	LOG	VERBAL DESCRIPTOR
A 	0	Equal to or less than panel A	1	0	Absent
B 	I	Equal to or less than panel B, greater than A	10	1.0	Minimal
C 	II	Equal to or less than panel C, greater than B	32	1.5	Mild
D 	III	Equal to or less than panel D, greater than C	100	2.0	Moderate
E 	IV	Equal to or less than panel E, greater than D	316	2.5	Marked
>E	V	Greater than panel E	>316	>2.5	Severe

This figure depicts the grading panels, their numerical grade, the dot count and log numbers, as well as the verbal descriptor for each grade



Bron AJ, et al. *Cornea*. 2003;22(7):640-650.

Characteristics of Corneal Events from Eye Exam

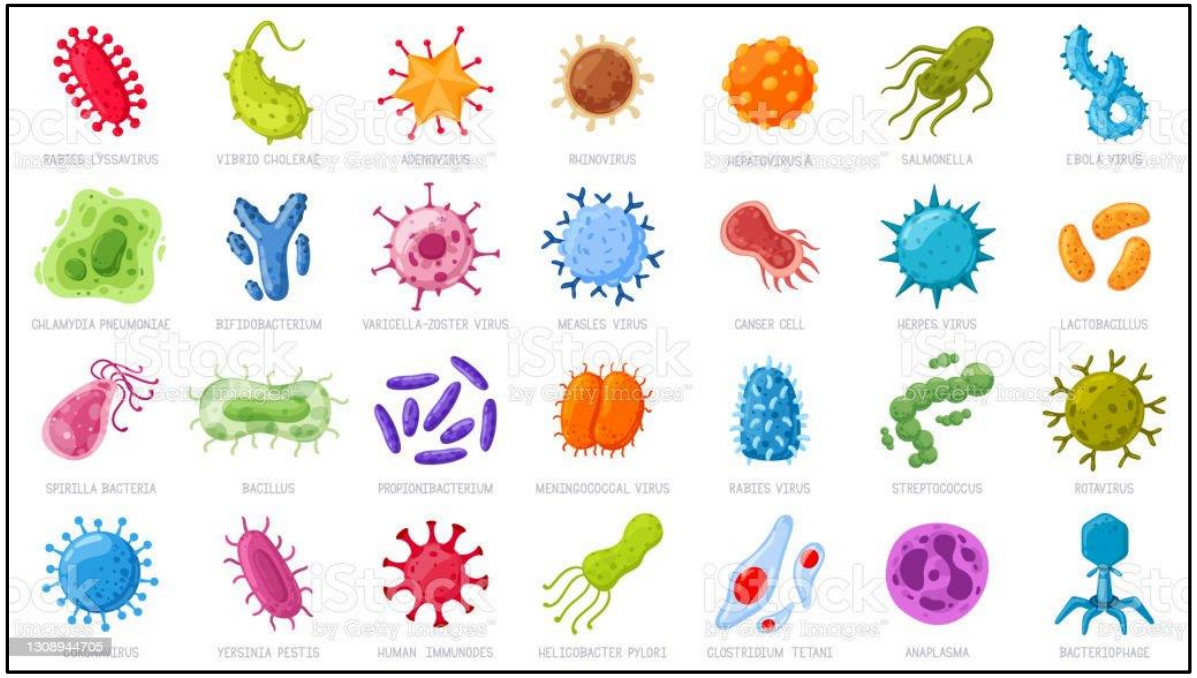
	Belantamab Mafadotin	
	Primary Analysis Data (21 Jun 19)	
	2.5 mg/ kg (N=95)	3.4 mg/kg (N=99)
Patients with Corneal Exam Findings (MECs), n (%)	67 (71)	76 (77)
Maximum Grade for Corneal Exam Findings (MECs), n/N (%)		
Grade 1	8/95 (8)	6/99 (6)
Grade 2	17/95 (44)	29/99 (29)
Grade 3	42/95 (44)	40/99 (40)
Grade 4	0	1/99 (1)
Patients with BCVA Changes	50 (53)	48 (48)
Grade 1	6/95 (6)	3/99 (3)
Grade 2	17/95 (18)	21/99 (22)
Grade 3	25/95 (26)	22/99 (22)
Grade 4	2/95 (2)	2/99 (2)

- 77% of patients Grade 3-4 recovered to Grade 1 or better as of last follow-up
- 94% of visual changes recovered

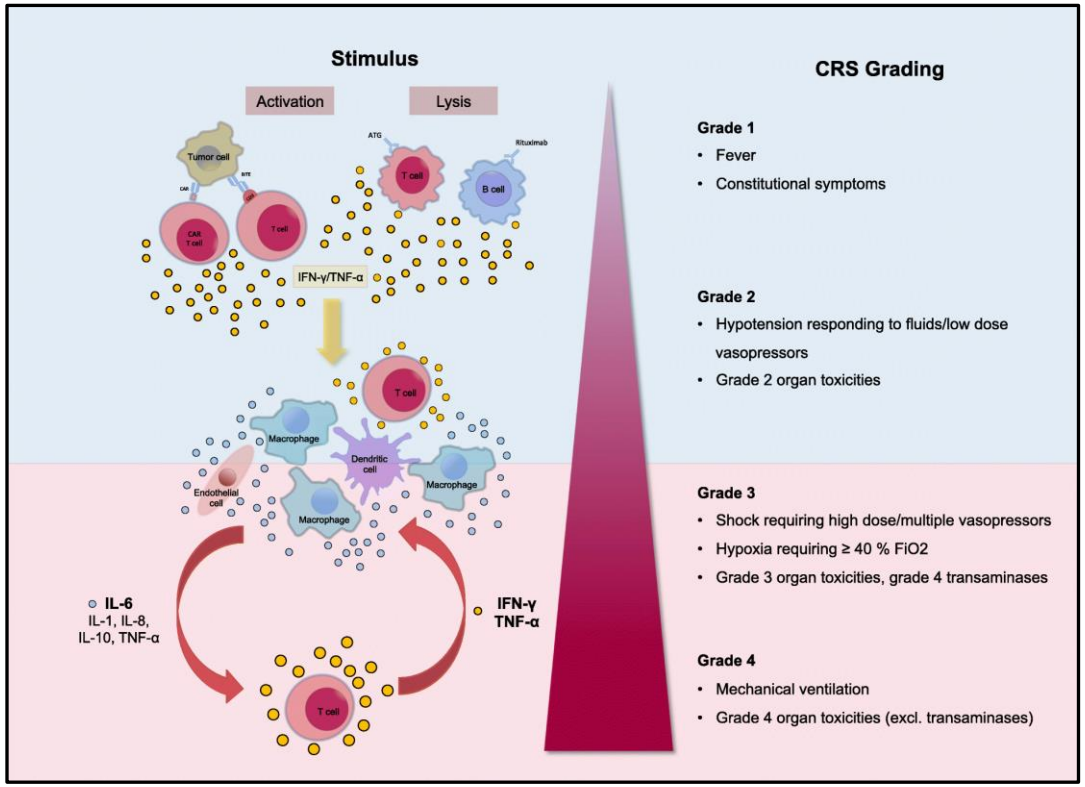
Farooq AV, et al. *Ophthalmol Ther.* 2020;9(4):889-911.

Bispecifics – What to Worry About

GERMS

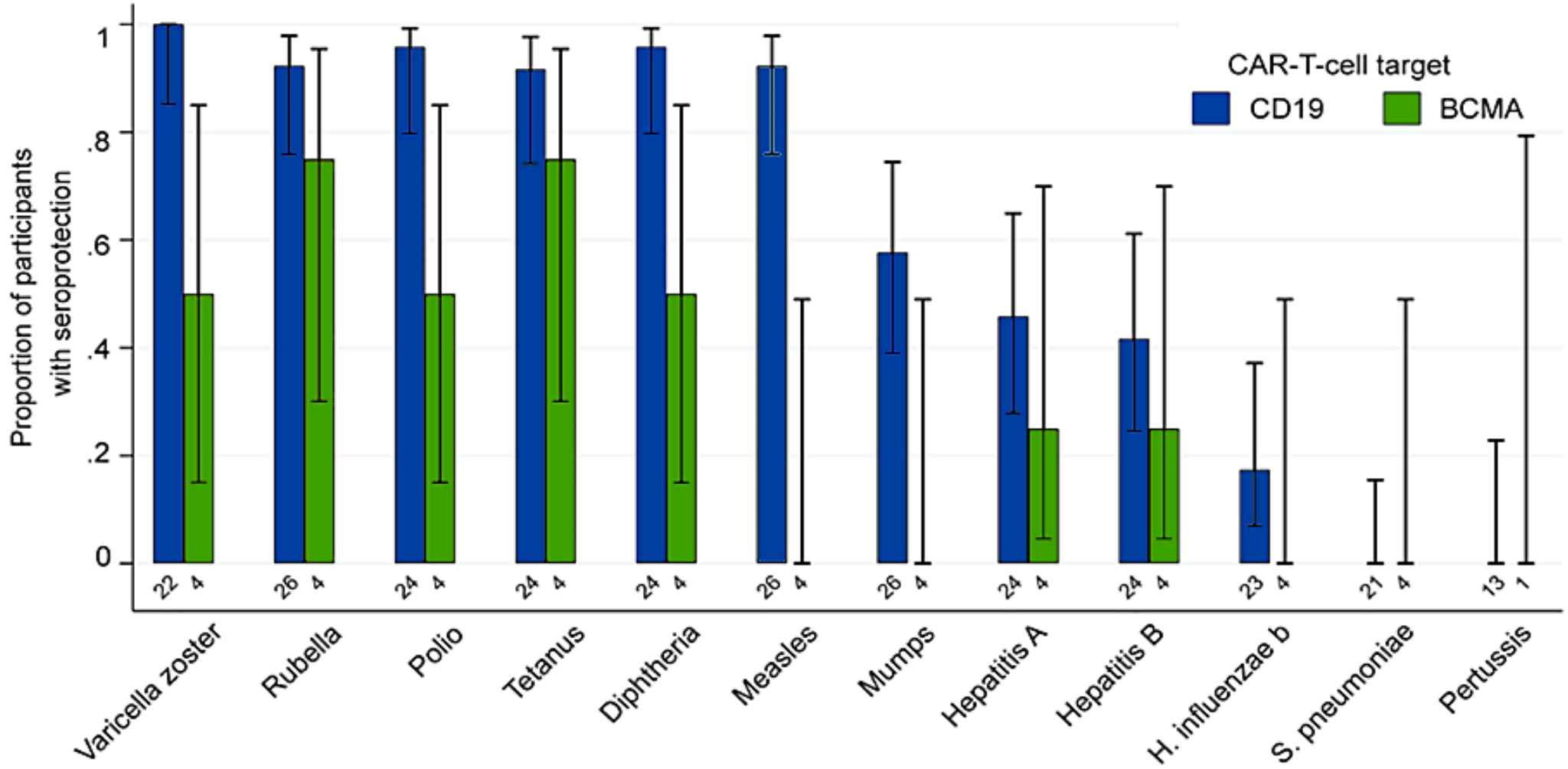


CRS



Istock by getty images. Shimabukuro-Vornhagen A, et al. *J Immunother Cancer.* 2018;6(1):56.

Depleting BCMA: Very Immunosuppressive



Walti CS, et al. *JCI*. 2022 (credit to Jay Speigel MD- SCCC).

BCMA-bispecific mAbs: Safety Profile

	Alnuctamab	Teclistamab[2]	Elranatamab[3]	Linvoseltamab[4] (REGN5458)	TNB383b[5]
CRS (Grade 3-4) Median onset Duration Tocilizumab	**76.7%** (3.3%) 1 (1-9) days 2 (1-6) days 43%	**71.5%** (0.6%) 2 (1-6) days 2 (1-9) days 36.4%	**60.6%** (0%) 2 days 2(1-19) days 45%	**38%** (0%) 10.1 (6-47) hours 14 (0-96) hours 43%	**69%** (4%) 1 (1-2) days 1 (1-8) days
Neurotoxicity (NTX) Grade 3-4 ICANs Median onset Duration Treatment required	Not reported	12.7% 9% 3.5% 2.5 (1-7) days 3 (1-37) days 7.3%	6.4% 1.1% 2.2% 2.5 days 3 (2-6) days	0% 4% (G2)	0%
Cytopenias Grade 3-4 Neutropenia Anemia Thrombopenia	 37% 43% 17%	 57% 34.5% 21.2%	 67.3% 47.3% 27.3%	 22% 23% 13%	 24% 15% 9%
Infections Grade 3-4	30%	63% 35%	52.1% 22.3%	5 exitus infection	28%
Hypogammaglobulinemia as AEs observed in most patients treated with BCMA-CD3 mAbs during therapy.					

The data in the table are provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred. AE, adverse event; BCMA, B-cell maturation antigen; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; mAb, monoclonal antibody; NTX, neurotoxicity.

1. Costa LJ, et al. presented at EHA 2020; Abstract S205; 2. Moreau P, et al. presented at ASH 2021; Abstract 896; 3. Sebag M, et al. presented at ASH 2021; Abstract 895; 4. Zonder, et al. presented at ASH 2021; Abstract 160; 5. Kumar SK, et al. presented at ASH 2021; Abstract 900.

CRS and Infections with Bispecifics

	Pavurutamab (AMG 701)	Elranatamab	Alnuctamab (PF-0683135)	Linvoseltamab (REGN5458)	Teclistamab	TNB383b	Talquetamab	Cevostamab
CRS (G3+)	65 (9)	90 (5)	73 (0)	38 (0)	55 (0)	45 (0)	54 (3)	76 (2)
Infection (G3+)	17 (NR)	NR (26)	NR (30)	47 (18)	52 (15)	21 (14)	28 (8)	NR
Neurotox (G3+)	NR	2.2 (0)	20	12 (0)	5 (1)	NR	6 (2)	28 (0)

Pooled data from variety of sources from most recent data. Dr. Hoffman, personal communication.

Effect of Priming and Premedication on Cytokine Release Syndrome

Clinical OLYMPICS℠

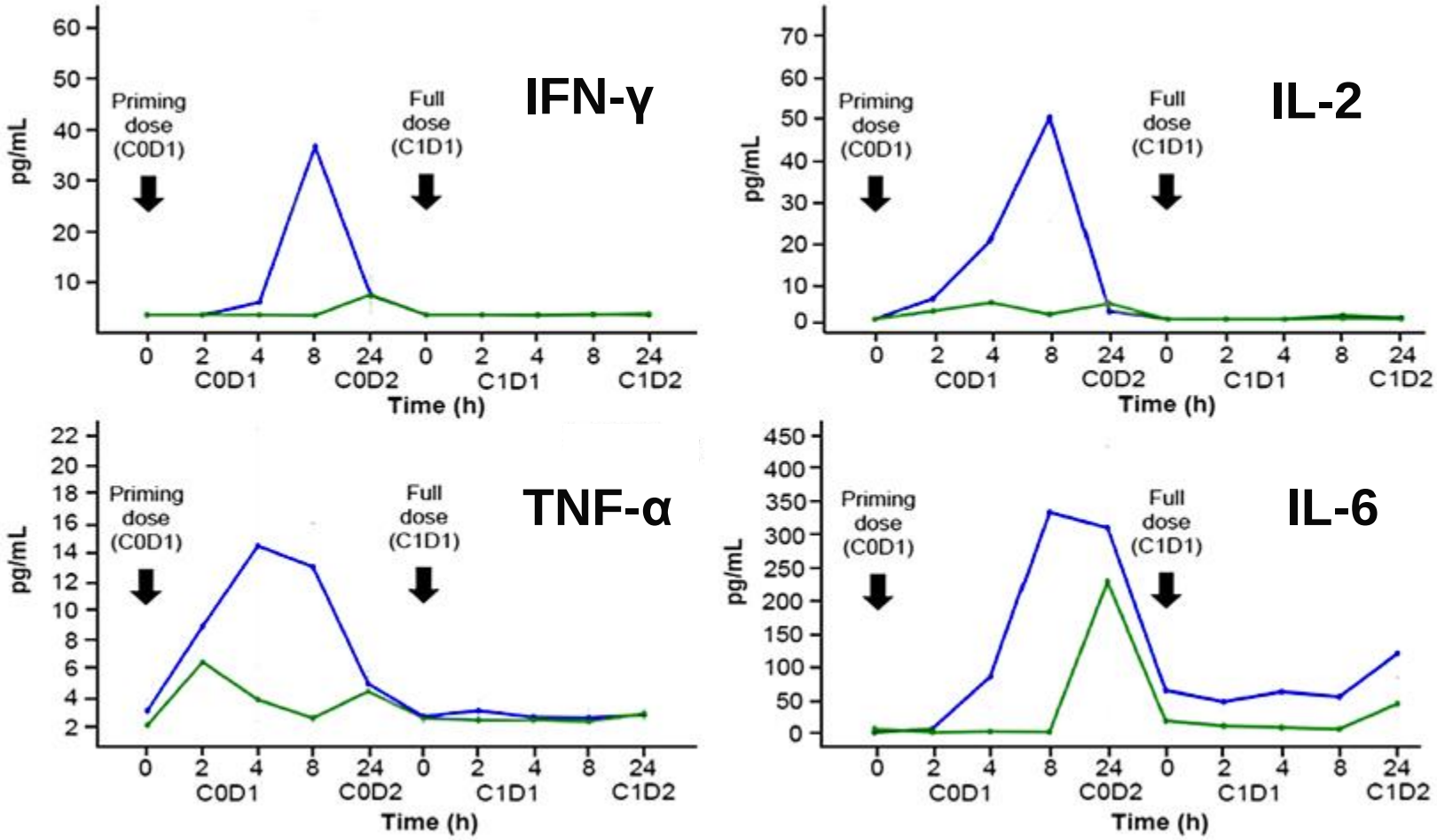
- At the recommended dose (1000 µg/kg or 76 mg fixed dose), CRS was limited to Grade 1 or 2 with no events Grade >2
- Priming (1-step) and premedication reduced the overall incidence and median duration of CRS
- Based on these results, a 2-step priming regimen was implemented within the MagnetisMM program to further mitigate the risk for CRS; premedication with dexamethasone, acetaminophen, and diphenhydramine was administered before each priming dose and the first full dose.
  - This approach was also incorporated in the MajesTEC-1 trial and the approved prescribing information for teclistamab.

	Elranatamab SC at Recommended Monotherapy Dose		
	Dose escalation (Part 1, N=6)	Priming cohorts (Part 1.1, N=20)	Expansion (Part 2A, N=15)
Priming / Pre-medication*	**No/No**	**Yes/No**	**Yes/Yes**
Overall incidence of CRS, n (%)	6 (100)	20 (100)	10 (66.7)
Grade 1	4 (66.7)	10 (50.0)	5 (33.3)
Grade 2	2 (33.3)	10 (50.0)	5 (33.3)
Duration, days, median (range)	4.0 (1 to 10)	3.0 (2 to 7)	3.0 (1 to 4)

Data cutoff was July 26, 2021.
Grading of CRS based on Lee DW, et al. *Biol Blood Marrow Transplant* 2019;25:625.

Sebag M, et al. presented at ASH 2021; Abstract 895. Moreau P, et al. *N Engl J Med*. 2022;387(6):495-505.
Teclistamab-cqyv. FDA prescribing information. Issued 10/25/2022.

Effect of Pre-medication on Cytokine Production



Use of pre-medication with priming reduces acute cytokine production

Sebag M, et al. presented at ASH 2021; Abstract 895.

AE of Special Interest: Infections

Clinical OLYMPICS℠

ELRANATAMAB

Infections were reported in 52.1% (grade 3/4, 22.3%) of patients

n (%)	Cohort A n=94	
	Any grade	Grade 3/4
Infection TEAEs in ≥5% of patients		
COVID-related AE	14 (14.9)	8 (8.5)
Upper respiratory tract infection	10 (10.6)	0
Pneumonia	8 (8.5)	4 (4.3)
Urinary tract infection	5 (5.3)	2 (2.1)
TEAEs of interest		
Pneumocystis jirovecii pneumonia	4 (4.3)	3 (3.2)
CMV infection	4 (4.3)	0
CMV infection reactivation	1 (1.1)	0

TECLISTAMAB

19 patients died from AEs, including

- COVID-19 (n=12)
- PML (n=1)
- PNA (n=1)

ADVERSE EVENTS (SAFETY POPULATION, N=165)

Event	Any Grade	Grade 3 or 4
	No. of Patients (%)	
Any adverse event	165 (100)	156 (94.5)
HEMATOLOGIC		
Neutropenia	117 (70.9)	106 (64.2)
Anemia	86 (52.1)	61 (37.0)
Thrombocytopenia	66 (40.0)	35 (21.2)
Lymphopenia	57 (34.5)	54 (32.7)
Leukopenia	29 (17.6)	17 (7.3)
NONHEMATOLOGIC		
Diarrhea	47 (28.5)	6 (3.6)
Fatigue	46 (27.9)	4 (2.4)
Nausea	45 (27.3)	1 (0.6)
Injection-site Erythema	43 (26.1)	0
Pyrexia	45 (27.3)	1 (0.6)
Headache	39 (23.6)	1 (0.6)
Arthralgia	36 (21.8)	1 (0.6)
Constipation	34 (20.6)	0
Cough	33 (20.0)	0
Pneumonia	**30 (18.2)**	**21 (12.7)**
COVID-19	**29 (17.6)**	**20 (12.1)**
Bone pain	29 (17.6)	6 (3.6)
Back pain	27 (16.4)	4 (2.4)
Cytokine release syndrome	119 (72.1)	1 (0.6)
Neurotoxic event	24 (14.5)	1 (0.6)

Sebag, et al. ASH 2021; Abstract 895. Moreau P, et al. *N Engl J Med*. 2022;387(6):495-505.

What can we do to prevent infections?

Clinical OLYMPICS℠

Contributing Factors

- Lymphopenia
- Hypogammaglobulinemia
- Poor response to vaccines

Prophylaxis?

- Trimethoprim/sulfamethoxazole (or other PCP prophylaxis)
- IVIG
- Tixagevimab co-packaged with cilgavimab

CLINICAL VIGILANCE REMAINS PARAMOUNT

Early antibiotics, chest CT as part of infection workup, COVID/influenza precautions

Hoffman, J. Personal Communication.

Integrating Bispecific Antibodies into Clinical Practice

Clinical OLYMPICS℠

Boxed Warnings

- CRS
- Neurologic toxicity
- REMS

Warnings and Precautions

- Hepatotoxicity
- Infections
- Neutropenia
- Hypersensitivity and other administration reactions
- Embryo-fetal toxicity

STEP-UP DOSING

Dose Schedule	Day	Dose, mg/kg
Step-up dose 1	1	0.06
Step-up dose 2	4	0.3
1st treatment dose	7	1.5
Subsequent weekly treatment doses	One week after 1st treatment dose and weekly thereafter	1.5

Patients should be hospitalized for 48 hours after administration of all doses within step-up dosing schedule

Withhold teclistamab in patients with active infection during the step-up dosing schedule

Teclistamab-cqyv. FDA prescribing information. Updated 10/25/2022.