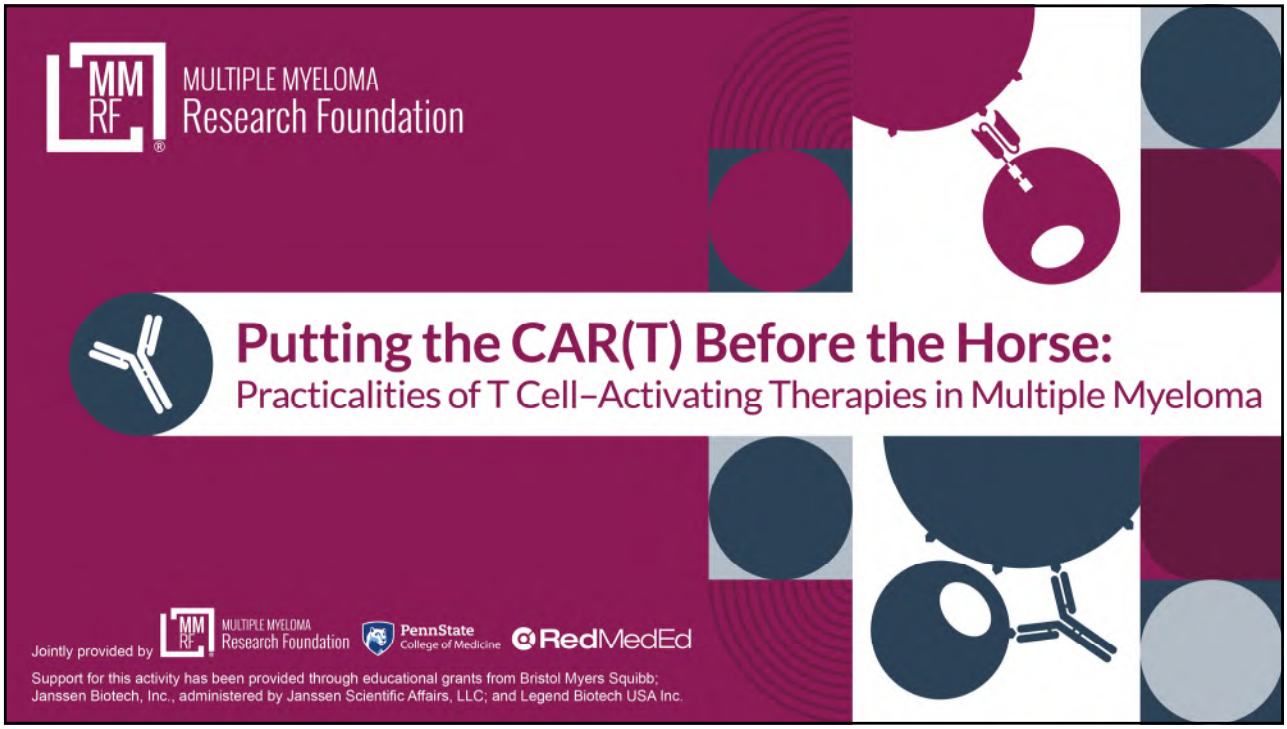

1

CAR T-Cell Therapy, Clinical Safety, and Efficacy

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2

Disclosures

Dr. Lentzsch has disclosed the following relevant financial relationships:

Consultant/Advisor: Takeda, GSK, Regeneron

Data Safety Monitoring Board: Janssen, BMS, Adaptive

Research Grant: Sanofi, Zentalis

Patent and Royalties: CAEL-101

3

CAR T Has Reached Standard-of-Care Status for Multiple Myeloma in the U.S.

Mar 2021 Ide-cel

FDA NEWS RELEASE

FDA Approves First Cell-Based Gene Therapy for Adult Patients with Multiple Myeloma

Share Tweet Linkedin Email Print

Feb 2022 Cilta-cel

FDA NEWS RELEASE

FDA Approves ciltacabtagene autoleucel for relapsed or refractory multiple myeloma

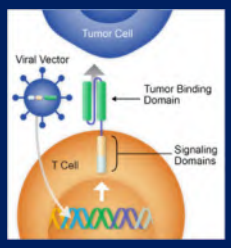
Share Tweet Linkedin Email Print

These are the first regulatory approved CAR Ts that are not targeting CD19.

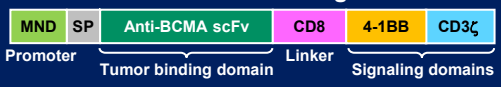
4

Autologous BCMA CAR T in Pivotal Trials

Idecabtagene vicleucel (Ide-cel, bb2121)

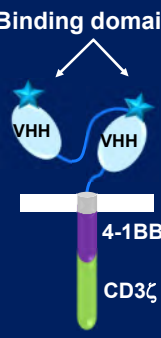


ide-cel CAR design



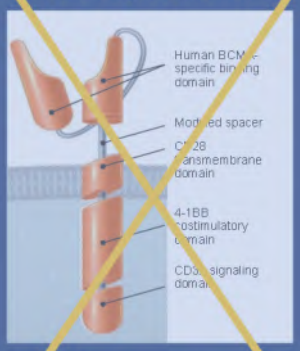
FDA approved

Ciltacabtagene autoleucel (Cilta-cel, JNJ-68284528)



FDA approved

~~**Orvacabtagene autoleucel (Orva-cel, JCARH125)**~~



~~Study discontinued. Next-generation CAR T in trial.~~

Munshi NC et al. *N Engl J Med.* 2021;384:705.
Berdeja JG et al. *Lancet.* 2021;398:314.
Mailankody S et al. *J Clin Oncol.* 2020;38. Abstract 8504.

5

KarMMa-1 Study (Ide-cel)

Response	CAR+ T cells			
	150 × 10^6 (n=4)	300 × 10^6 (n=70)*	450 × 10^6 (n=54)*	Ide-cel treated (n=128)
Overall response rate (%)	50	69	82	73
Complete response rate (%)	25	29	39	33
CR/sCR and MRD-negative	25	24	28	26
CR/sCR and MRD not evaluable	0	4	11	7
VGPR	25	14	26	20
PR	0	26	17	21

*Regulatory agency–approved dose

PFS by Target Dose

CAR+ T cells	Median PFS, mos (95% CI)
150 × 10^6	2.8 (1.0–NE)
300 × 10^6	5.8 (4.2–8.9)
450 × 10^6	12.1 (8.8–12.3)
Ide-cel treated	8.8 (5.6–11.6)

- **PFS increased with higher target dose and depth of response**
- **Median PFS was 12 mos at 450 × 10^6 CAR+ T cells**
- **Median PFS was 20 mos in patients with CR/sCR**

Munshi NC et al. *N Engl J Med.* 2021;384:705.

6

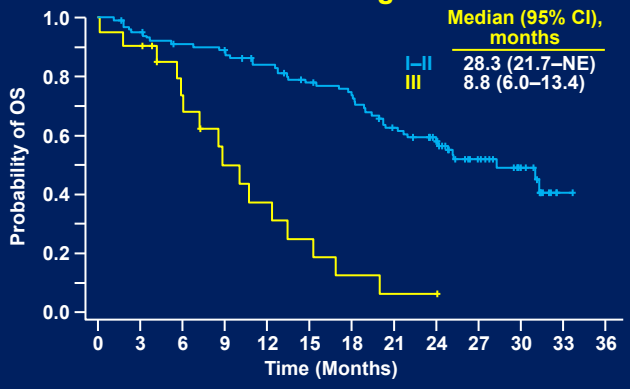
KarMMA-1 Study (Ide-cel) Long-Term Follow-Up

- OS is not decreased for older patients or those with extramedullary or triple-refractory disease
- OS is decreased in patients with R-ISS stage III

OS in high-risk patient subgroups

		Median OS (95% CI), months
Age	<65 y	21.7 (17.1–31.2)
	≥65 y	28.3 (20.2–NE)
Extramedullary disease	No	NE (21.3–NE)
	Yes	20.2 (15.5–28.3)
Triple refractory	No	31.2 (19.9–NE)
	Yes	21.7 (18.2–NE)

R-ISS Stage

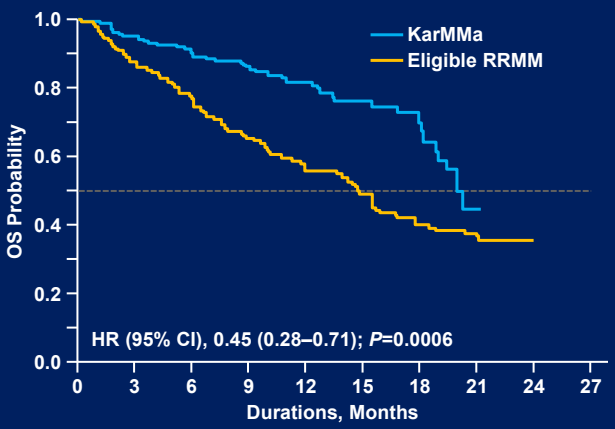


Anderson LD et al. *J Clin Oncol.* 2021;39. Abstract 8016.

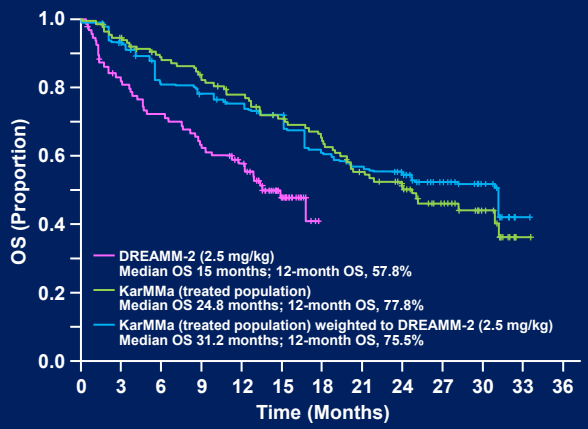
7

KarMMa-1 (Ide-cel) Comparison With Other Therapies

Ide-cel (KarMMa-1) vs Real-World Experience[1]



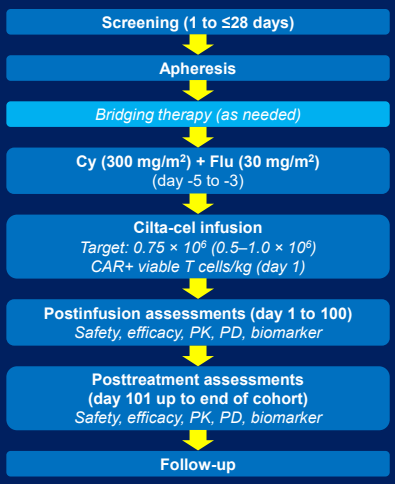
Ide-cel (KarMMa-1) vs Belantamab (DREAMM-2)[2]



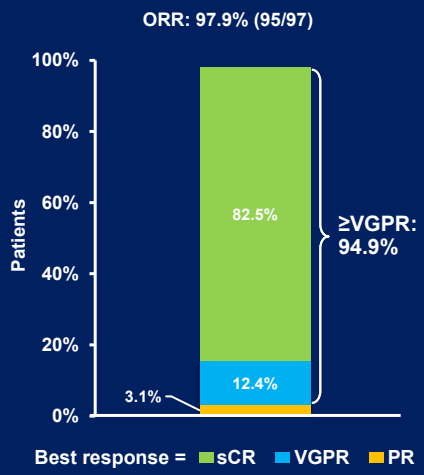
1. Figure 3 from Jagannath S, et al. KarMMa-RW: comparison of idecabtagene vicleucel with real-world outcomes in relapsed and refractory multiple myeloma. Blood Cancer J. 2021 Jun 18;11(6):116. Available through Creative Commons Attribution 4.0 International License. http://creativecommons.org/licenses/by/4.0/ 2. Rodriguez-Otero P et al. *Blood.* 2021;138. Abstract 1978.

8

CARTITUDE-1 Study (Cilta-cel)



- Study population
  - 3 or more prior lines of therapy
  - Triple class and CD38 mAb exposed
- Median 2-yr follow-up



Martin T et al. Ciltacabtagene autoleucel, an anti–B-cell maturation antigen chimeric antigen receptor T-cell therapy, for relapsed/refractory multiple myeloma: CARTITUDE-1 2-year follow-up. *J Clin Oncol.* 2022 Jun 4;JCO2200842. © 2022 American Society of Clinical Oncology.

9

CARTITUDE-1 Study (Cilta-cel)

Progression-Free Survival

	Median PFS, mos (95% CI)	27-month PFS rate, % (95% CI)
All patients	Not reached (24.5–NE)	54.9 (44.0–64.6)
sCR patients		64.2 (51.9–74.1)

Overall Survival

27-month OS rate, 70.4%; median OS not reached)

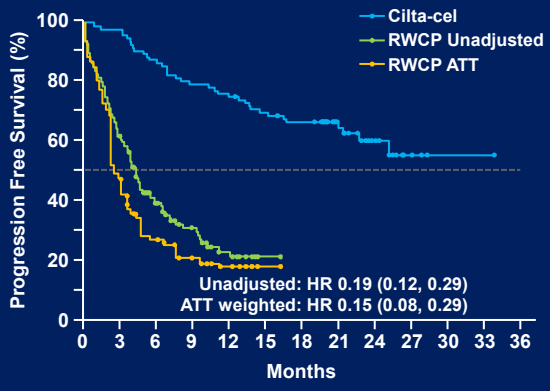
Martin T et al. *J Clin Oncol.* 2022 Jun 4;JCO2200842.

10

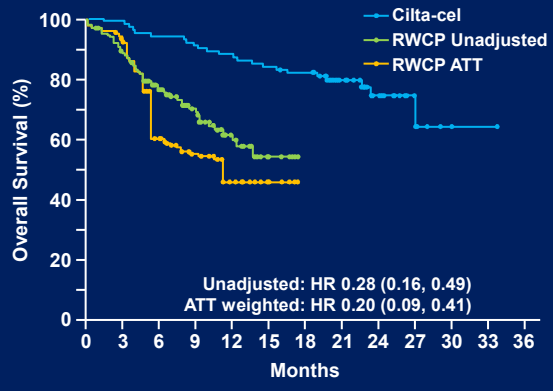
Cilta-cel CARTITUDE-1 vs LocoMMotion Real-World Prospective Study: PFS and OS Is Better With CAR T

- LocoMMotion (NCT04035226) patients with RRMM, triple-class exposed treated with SOC regimens
- LocoMMotion patient distribution 91% Europe, 9% U.S.

Progression-Free Survival



Overall Survival



Mateos M et al. *Blood.* 2021;138. Abstract 550.

11

BCMA CAR T Pivotal Trials: Toxicities

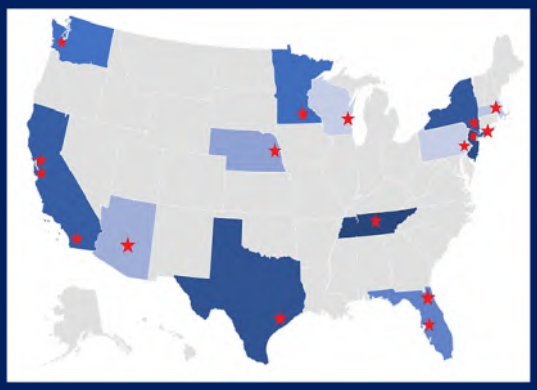
	Ide-Cel: Phase 2 (KarMMA-1)[1] N=128	Cilta-Cel: Phase 1b/II (CARTITUDE-1)[2,3] N=97
CRS, any Gr/≥ Gr 3	84%/5%	95%/4%
Onset day median (range)	1 (1–12)	7 (1–12)
Duration, days median (range)	5 (1–63)	4 (1–97)
ICANS, any Gr/≥ Gr 3	18%/3%	22%/11%*
Drug use	Toci: 52% Steroid: 15%	Toci: 69% Steroid: 22% Anakinra: 19%

*Delayed-onset movement and neurocognitive symptoms noted in 12%, 8% Gr3 or higher.

1. Munshi NC et al. *N Engl J Med.* 2021;384:705. 2. Reprinted from *The Lancet* 398(10297), Berdeja JG, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study, P314-P324. Copyright 2021, with permission from Elsevier. 3. Martin T et al. *J Clin Oncol.* 2022 Jun 4;JCO2200842.

12

CAR T Access Remains an Issue



Survey of 20 centers.
Responses from 15 centers.

	Median (range)
Annual CAR T infusions (all diseases, on/off trial) pre-/during COVID	50–100 (<50, 100–300)
CAR T infusion volume for MM in 2021	10–50 (<5, 50–100)
Patients on wait list (since ide-cel approval)	20 (5–100)
Number of FDA approved CAR T slots given per month	1 (0–4)
Duration a patient is on waiting list	6 (3–8) months
Outcomes of patients on wait list FDA approved CAR-T CAR-T trial non-CAR-T trial hospice or death	 25% (0%–64%) 25% (0%–50%) 25% (0%–50%) 25% (25%–75%)

Kourelis T et al. Ethical challenges with CAR T slot allocation with idecabtagene vicleucel manufacturing access. *J Clin Oncol.* 40(16);suppl (June 01, 2022):e20021-e20021. © 2022 by American Society of Clinical Oncology. https://ascopubs.org/doi/pdf/10.1200/JCO.2022.40.16_suppl.e20021?role=tab

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Challenges With Patient Selection for Commercial CAR T Slots

- Most likely to make it to leukapheresis
- Most likely to make it to CAR T dosing
- Most likely to achieve clinical response

Maximize total benefit

- Lottery
- Time spent on waiting list

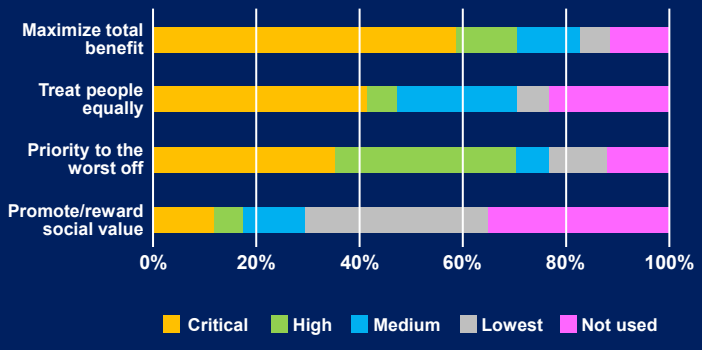
Treat people equally

- Highest myeloma disease burden
- Most comorbidities (ex: not eligible for clinical trials)
- No other myeloma treatment option left

Priority to the worst off

- Older patient: retired and accomplished physician scientist
- Younger patient: still working and financial provider for family with young children

Promote/reward social value



Kourelis T et al. *J Clin Oncol.* 2022;40. Abstract e20021.

14

Conclusions

- 2 FDA-approved CAR T-cell options: ide-cel and cilta-cel
- Ida-cel and cilta-cel have a similar safety profile
  - **CRS**: ide-cel 85% and cilta-cel 95%
  - **ICANs**: ide-cel 18% and cilta-cel 22%
- ORR
  - Ide-cel @450 × 10^6 CAR T cells → ORR 82.5%, CR 39%
  - Cilta-cel → ORR 92.7% and CR 82.5%
- **12 months median PFS** seems to be longer with cilta-cel:
  - Ide-cel 12 mos at 450 × 10^6 CAR+ T cells
  - Cilta-cel median PFS not reached → 27 months PFS 54.9%
- ? CAR T cells up front to replace ASCT?

15

Bispecific Antibodies for Multiple Myeloma: Clinical Safety and Efficacy

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Director, Judy and Bernard Briskin Center for Multiple Myeloma Research
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City of Hope Medical Center
Duarte, California

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Disclosures

Dr. Krishnan has disclosed the following relevant financial relationships:

Consultant/Advisor: Adaptive Biotechnologies, Artiva, AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Pfizer, Regeneron, Sanofi, Sutro BioPharma

Research Grant: Janssen

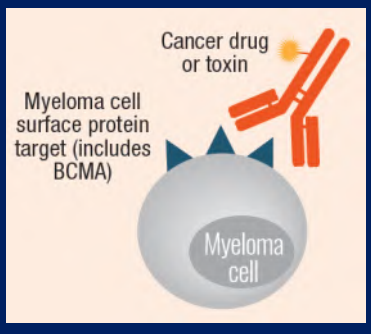
Speakers Bureau: Amgen, Bristol Myers Squibb, GlaxoSmithKline, Takeda

Stock Ownership: Bristol Myers Squibb

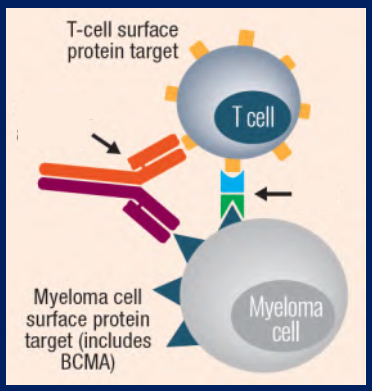
17

Anti–Multiple Myeloma Immunotherapeutic Agent Structures

Antibody–drug conjugate



T-cell bispecific antibodies



Lancman G et al. *Hematology Am Soc Hematol Educ Program*. 2020:264.

18

Bispecific Antibodies Clinical Trials in Multiple Myeloma

- AMG420 (BCMA×CD3)
- Pavurutamab (AMG701; BCMA × CD3)
- Alnuctamab (CC93269; BCMA × CD3)
- Elranatamab (PF06863135; BCMA × CD3)
- Linvoseltamab (RGN5458; BCMA × CD3)
- Teclistamab (JNJ64007957; BCMA × CD3)
- TNB-383B (BCMA × CD3)
- Talquetamab (JNJ64407564; GPRC5D × CD3)
- Cevostamab (BFCR4350A; FCRH5 × CD3)
- GBR1342 (CD38 × CD3)
- AMG424 (CD38 × CD3)

Lancman G et al. *Hematology Am Soc Hematol Educ Program*. 2020:264.

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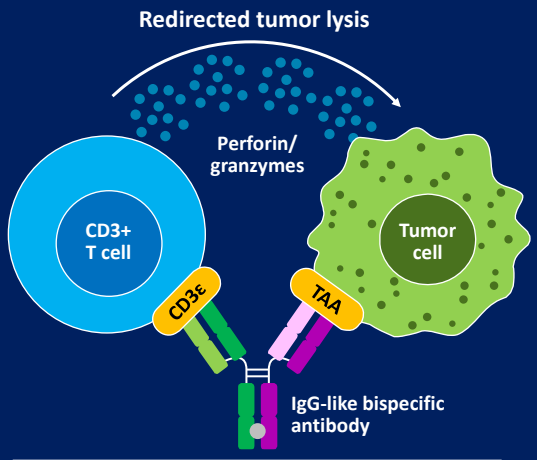
Bispecific Antibodies

Bispecific antibodies bind MM cell (multiple targets available) and to T lymphocyte



CD3 bispecific T-cell redirection mechanism of action in cancer immunotherapy

Figure 1 from Singh A, et al. Overcoming the challenges associated with CD3+ T-cell redirection in cancer. *Br J Cancer*. 2021 Mar;124(6):1037-1048. Available through Creative Commons Attribution 4.0 International License. http://creativecommons.org/licenses/by/4.0/

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BCMA (B-Cell Maturation Antigen)

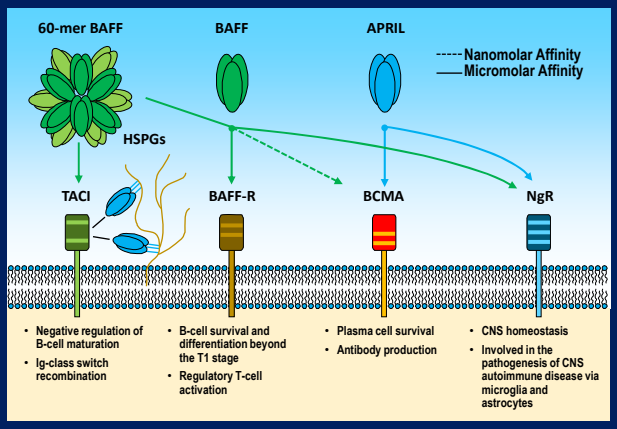
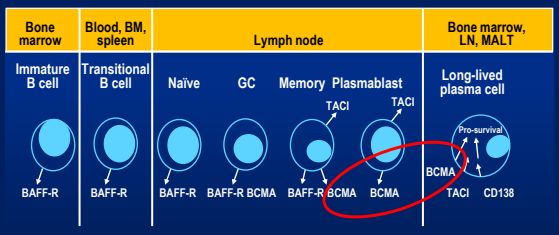


Figure 2 from Hengeveld PJ, Kersten MJ. B-cell activating factor in the pathophysiology of multiple myeloma: a target for therapy? *Blood Cancer J.* 2015 Feb 27;5(2):e282. Available through Creative Commons Attribution 4.0 International License. http://creativecommons.org/licenses/by/4.0/ion from AACR.

- Receptor for BAFF and APRIL
- Expressed on mature B-cell subsets, PCs, and plasmacytoid DCs
- Maintains plasma cell homeostasis
  - BCMA-/- mice have normal B cell #s, impaired PC survival



Reprinted from *Clin Cancer Res.* 2013;19(8). Maus MV, June CH. Zoom zoom: racing CARs for multiple myeloma, 1917-1919. With permission from AACR.

21

MajesTEC-1: Teclistamab Phase 2 Study Design

MajesTEC-1 is a first-in-human, phase 1/2, open-label, multicohort, multicenter dose-escalation study to evaluate teclistamab in patients with RRMM who previously received ≥3 prior lines of therapy and were triple-class exposed

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

POSTTREATMENT

Follow-up 2 years after LPI

Primary end point: ORR
Key secondary end points: DOR, ≥VGPR, ≥CR, sCR, TTR, MRD status, PFS, OS, safety, pharmacokinetics, immunogenicity, PRO

Moreau P et al. *N Engl J Med.* 2022;387:495.

22

MajesTEC-1: Patient Demographics and Baseline Characteristics

- N=165
- Median age, 64 years (33–84)
- Median prior lines of therapy, 5.0 (2–14)
- Exposure status
  - Triple-class exposed, 100%
  - Penta-drug exposed, 70.3%
- Refractory status
  - Triple-class exposed, 77.6%
  - Penta-drug exposed, 30.3%
  - Refractory to last line of therapy, 89.7

Moreau P et al. *N Engl J Med.* 2022;387:495.

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MajesTEC-1: Overall Response Rate for Teclistamab Monotherapy

Response (%)	Teclistamab
Overall response rate, % (n)	63 (104/165)
≥Complete response rate (%)	39.4
≥VGPR response rate (%)	58.8
sCR	32.7
CR	6.7
VGPR	19.4
PR	4.2

- At a median follow-up of 14.1 months (range: 0.3–24.4)
  - ORR of 63% (95% CI: 55.2–70.4) represents a substantial benefit for patients with triple-class–exposed disease
- Median time to first response: 1.2 months (range: 0.2–5.5)
- MRD negativity rate (by next-generation sequencing)
  - 26.7% at a threshold of 10^{-5}
  - In patients who achieved ≥CR, the MRD-negativity rate was 46%

Moreau P et al. *N Engl J Med.* 2022;387:495.

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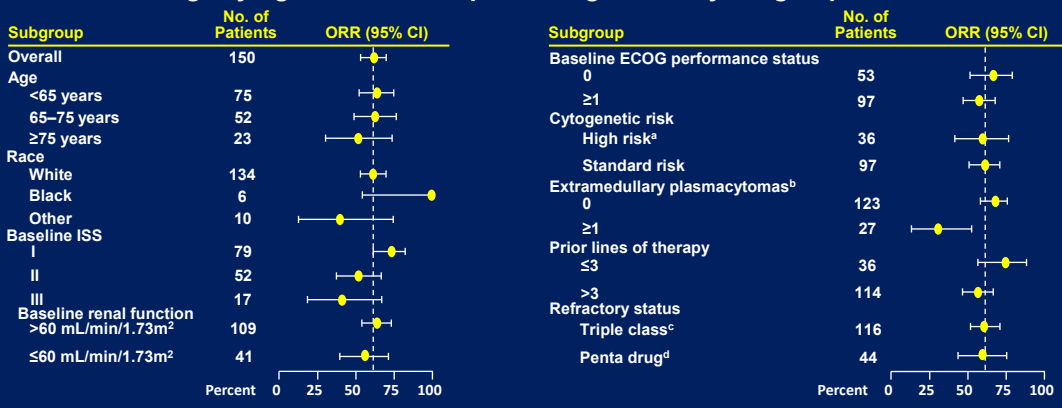
MajesTEC-1: ORR Across Subgroups

ORR was consistent across clinically relevant subgroups, including high cytogenetic risk and penta-drug refractory subgroups



Moreau P et al. *Blood.* 2021;138. Abstract 896.
Moreau P et al. *N Engl J Med.* 2022;387:495.

[a]del(17p), t(4:14), and/or t(14;16); [b]Soft tissue plasmacytomas not associated with the bone were included; [c]≥1 PI, ≥1 IMiD, and ≥ 1 anti-CD38 mAb; [d]≥2 PI, ≥2 IMiD, and ≥ 1 anti-CD38 mAb.

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MajesTEC-1: Duration of Response

- Median DOR 18.4 months
- Median PFS 11.3 months
- Median OS 18.3 months

Moreau P et al. *N Engl J Med.* 2022;387:495.

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MajesTEC-1: Response Durability

- Responses were durable and deepening over time

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MajesTEC-1: Adverse Events

Any grade

- Hematologic
  - Neutropenia, 70.9%
  - Anemia, 52.1%
  - Thrombocytopenia, 40%
- Nonhematologic
  - CRS, 72.1%
  - Diarrhea, 28.5%
  - Fatigue, 27.9%
  - Nausea, 27.3
  - Pneumonia, 18.2%
  - COVID-19, 17.6%
  - Neurotoxic event, 14.5%

Grade 3/4

- Hematologic
  - Neutropenia, 64.2%
  - Anemia, 37%
  - Thrombocytopenia, 21.2%
- Nonhematologic
  - CRS, 0.6%
  - Diarrhea, 3.6%
  - Fatigue, 2.4%
  - Nausea, 0.6
  - Pneumonia, 12.7%
  - COVID-19, 12.1%
  - Neurotoxic event, 0.6%

Moreau P et al. *N Engl J Med.* 2022;387:495.

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BCMA-Directed Bispecific Antibodies in Development

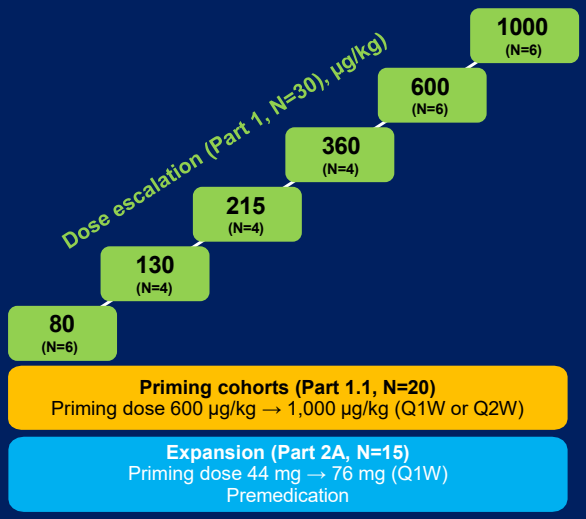
	Current Phase
Teclistamab	**Approved!**
Elranatamab	3
AMG 701	1/2
REGN5458	1/2
CC-93269	1
ABBV-383	1

Moreau P, Touzeau C. *Blood*. 2022;139:3681.

29

MagnetisMM-1: Elranatamab Monotherapy

- Dose escalation (Part 1, n=30): elranatamab 80–1,000 µg/kg weekly
- Priming cohorts (Part 1.1, n=20): single priming dose (600 µg/kg) followed 1 week later by full dose (1,000 µg/kg) q1w or q2w
- Expansion (Part 2A, n = 15): single priming dose (44 mg) followed by full dose (76 mg) weekly
  - Premedication was given with priming dose and first full dose
- Data cutoff was July 26, 2021

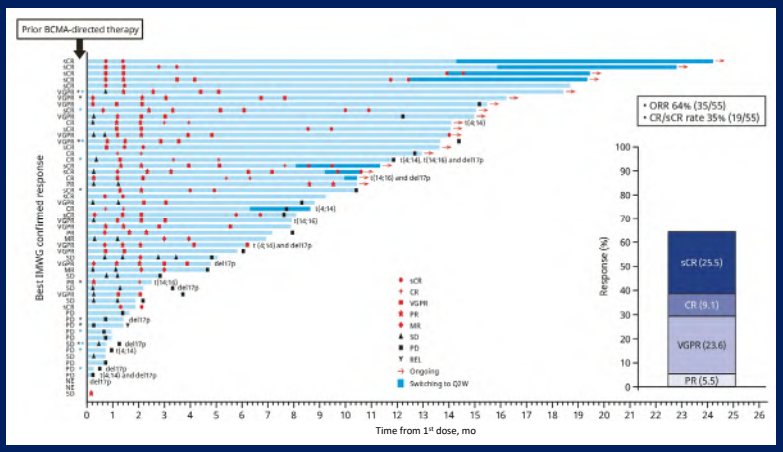


Sebag M et al. *Blood*. 2021;138. Abstract 895.

30

MagnetisMM-1: Response

- N=55, Median follow-up: 10.6 mo
- ORR: 64%
  - ≥CR: 35% (all evaluable patients MRD-negative [13/13])
  - 54% ORR in patients with prior BCMA-directed therapy



Jakubowiak AJ et al. *J Clin Oncol.* 2022;40. Abstract 8014.

31

MagnetisMM-1: Adverse Events

Treatment Emergent Adverse Events	Grade 1	Grade 2	Grade 3	Grade 4	Total (n=55)
Hematologic, n (%)					
Neutropenia	0	2 (3.6)	14 (25.5)	25 (45.5)	41 (74.5)
Anemia	2 (3.6)	8 (14.5)	26 (47.3)	0	36 (65.5)
Lymphopenia	0	0	3 (5.5)	26 (47.3)	29 (52.7)
Thrombocytopenia	7 (12.7)	6 (10.9)	5 (9.1)	10 (18.2)	28 (50.9)
Nonhematologic, n (%)					
Cytokine release syndrome	28 (50.9)	20 (36.4)	0	0	48 (87.3)
Injection site reaction	27 (49.1)	4 (7.3)	0	0	31 (56.4)
Diarrhea	12 (21.8)	8 (14.5)	2 (3.6)	0	22 (40.0)
Fatigue	6 (10.9)	13 (23.6)	3 (5.5)	0	22 (40.0)

Jakubowiak AJ et al. *J Clin Oncol.* 2022;40. Abstract 8014.

32

BCMA Bispecifics

- High response rates
- Subcutaneous administration (schedule?)
- Durable?
- Efficacy after other BCMA-directed therapies
- Combination strategies
- TRIMM study: teclistamab + dara + pom

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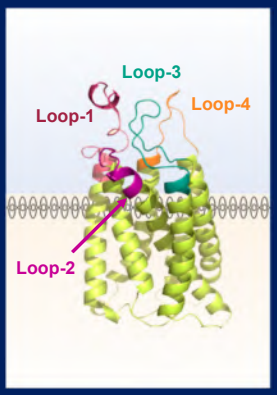
GPRC5D: G Protein-Coupled Receptor Class C Group 5 Member D

- Orphan G protein–coupled receptor of unknown function
- Limited expression in healthy human tissue, primarily in plasma cells and hair follicles[1-2]
- Highly expressed in myeloma cells and associated with poor prognostic factors in multiple myeloma[1-3]
- No known shed peptides or extracellular domain shedding (reduced risk for sink effect)
- Ideal target for CD3 redirection

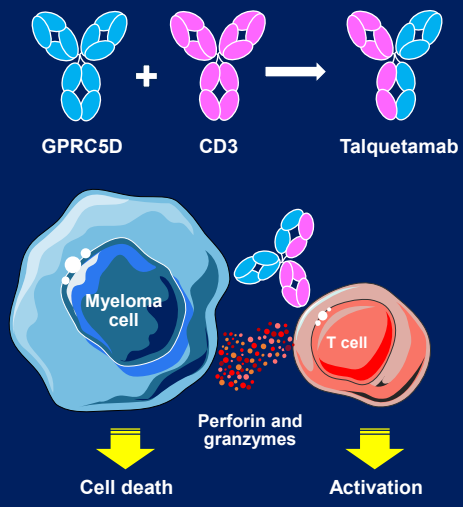


1. Smith EL et al. *Sci Transl Med.* 2019;11:eaau7746.
2. Pillarisetti K et al. *Blood.* 2020;135:1232.
3. Atamaniuk J et al. *Eur J Clin Invest* 2012;42:953.

34

Talquetamab: GPRC5D×CD3 Bispecific Antibody

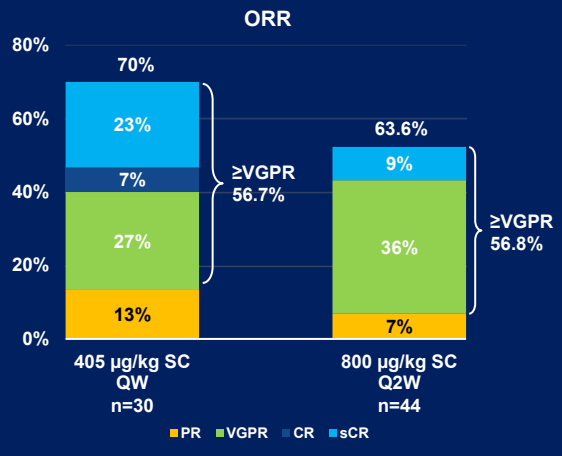
- Talquetamab is a first-in-class antibody that binds to both GPRC5D and CD3
- Talquetamab redirects T cells to GPRC5D-expressing myeloma cells to mediate cell killing
- Antitumor activity was demonstrated in primary myeloma cells and xenograft models of multiple myeloma[1-3]
- First-in-human phase 1 study is ongoing to evaluate talquetamab in patients with RRMM (NCT03399799)



1. Smith EL et al. *Sci Transl Med*. 2019;11:eaau7746.
2. Verkleij CPM et al. *Blood Adv*. 2021;5:2196.
3. Pillarisetti K et al. *Blood*. 2020;135:1232.

35

Talquetamab: Overall Response Rate



Response	405 µg/kg SC QW (n=30)	800 µg/kg SC Q2W (n=44)
Median follow-up, mos (range)	13.2 (1.1–24.0)	7.7 (0.7–16.0)
ORR, n (%)	21 (70.0)	28 (63.6)
Triple-class–refractory patients, n/N (%)	15/23 (65.2)	23/34 (67.6)
Penta-drug–refractory patients, n/N (%)	5/6 (83.3)	9/12 (75)
Median tie to first confirmed response, mos (range)	0.9 (0.2–3.8)	1.2 (0.3–6.8)

Minnema MC et al. *J Clin Oncol*. 2022;40. Abstract 8015.

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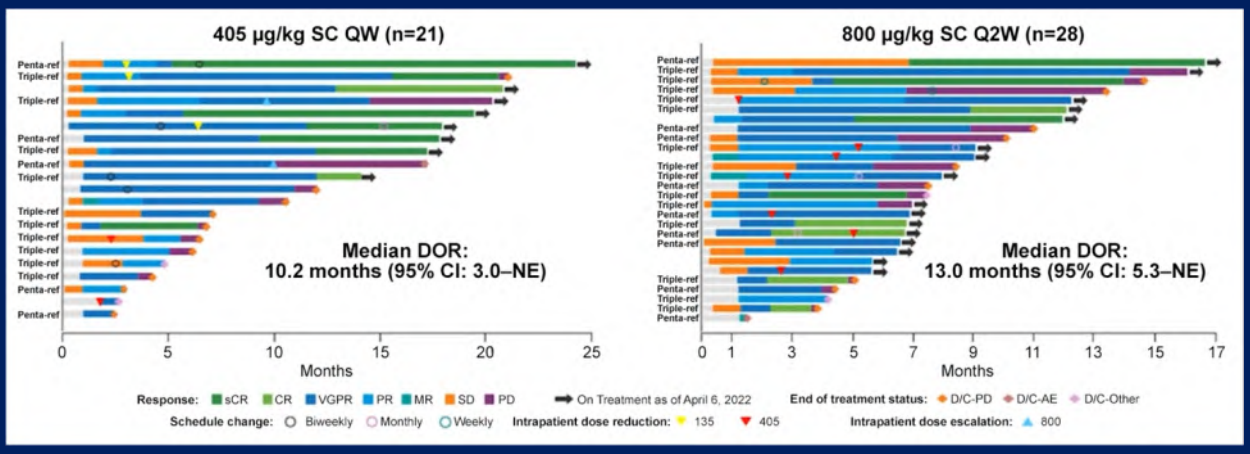
Talquetamab: Duration of Response



Minnema MC et al. *J Clin Oncol*. 2022;40. Abstract 8015.

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Talquetamab: Safety Profile

AEs (≥20% of Total SC population)	405 µg/kg SC QW (n=30)		800 µg/kg SC Q2W (n=44)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic, n (%)				
Neutropenia	20 (66.7)	18 (60.0)	18 (40.9)	15 (34.1)
Anemia	17 (56.7)	9 (30.0)	21 (47.7)	12 (27.3)
Lymphopenia	12 (40.0)	12 (40.0)	18 (40.9)	18 (40.9)
Leukopenia	12 (40.0)	9 (30.0)	10 (22.7)	8 (18.2)
Thrombocytopenia	11 (36.7)	7 (23.3)	10 (22.7)	5 (11.4)
Nonhematologic, n (%)				
CRS	23 (76.7)	1 (3.3)	35 (79.5)	0
Skin-related AEs	20 (66.7)	0	32 (72.7)	1 (2.3)
Dysgeusia	19 (63.3)	NA	25 (56.8)	NA
Nail-related AEs	18 (60.0)	0	15 (34.1)	0
Rash-related AEs	14 (46.7)	1 (3.3)	13 (29.5)	7 (15.9)
Dysphagia	12 (40.0)	0	12 (27.3)	0
Pyrexia	11 (36.7)	0	10 (22.7)	0
Fatigue	10 (33.3)	1 (3.3)	12 (27.3)	0
Dry mouth	9 (30.0)	0	25 (56.8)	0
Weight decreased	9 (30.0)	0	19 (43.2)	1 (2.3)
Nausea	9 (30.0)	0	9 (20.5)	0

- Most common AEs were CRS, skin-related events, and dysgeusia
  - Dysgeusia managed with supportive care and dose adjustments
- Cytopenias were mostly confined to step-up and cycle 1–2 doses and generally resolved within 1 week
- Infections occurred in 46.7% of patients at 405 µg/kg SC QW and 38.6% at 800 µg/kg SC Q2W (grade 3/4: 6.7%/9.1%)
- No patients died due to drug-related AEs

Minnema MC et al. *J Clin Oncol*. 2022;40. Abstract 8015.

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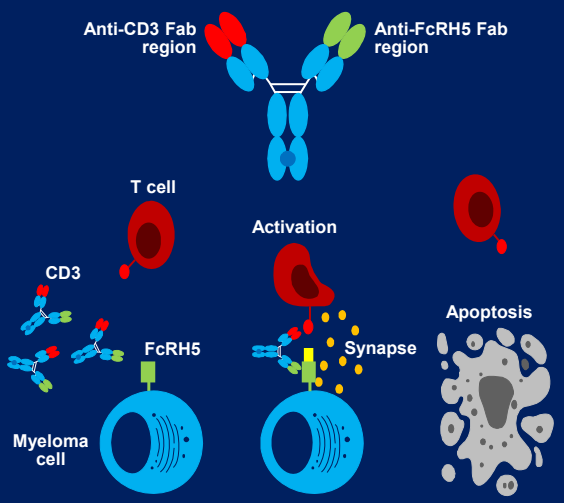
Cevostamab: FcRH5×CD3 Bispecific Antibody

- Fc receptor-homolog 5 (FcRH5)
  - Expressed on myeloma cells with near 100% prevalence[1]
  - Expression on myeloma and plasma cells > normal B cells[1]
- Cevostamab
  - Humanized IgG-based T-cell–engaging bispecific antibody[1]
  - Targets FcRH5 on myeloma cells and CD3 on T cells[1]
- Ongoing phase I dose-escalation and expansion trial (NCT03275103) evaluating safety and activity of cevostamab monotherapy in patients with RRMM[2]

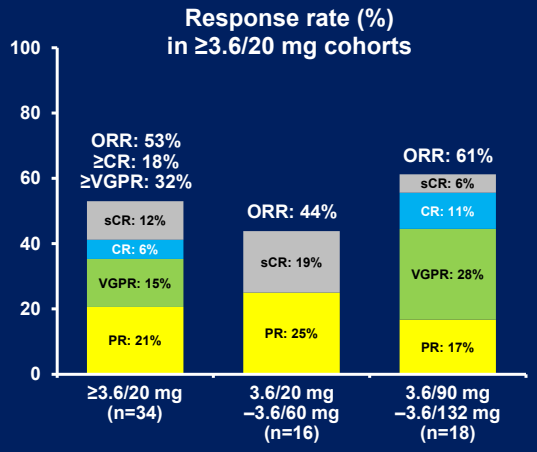


1. Li J et al. *Cancer Cell*. 2017;31:383.
2. Cohen AD et al. *Blood*. 2020;136. Abstract 292.

39

Cevostamab: Response Rate

- 51/53 patients efficacy evaluable; no response in ≤3.6/10.8 mg cohorts
- ORR* in ≥3.6 mg/20 mg cohorts
  - 53% (18/34) in all patients
  - 41% (7/17) in penta-drug refractory patients
  - 63% (5/8) in patients with prior anti-BCMA
- Median time to first response/best response: 29.5 days (range: 21–105)/ 57.5 days (range: 21–272)
- Response irrespective of target expression level in patients assessed to date
- MRD negativity by NGS (<10−5) detected in 6/7 evaluable patients with ≥VGPR



*Best response of PR, VGPR, CR, or sCR by IMWG uniform response criteria 2016
Cohen AD et al. *Blood*. 2020;136. Abstract 292.

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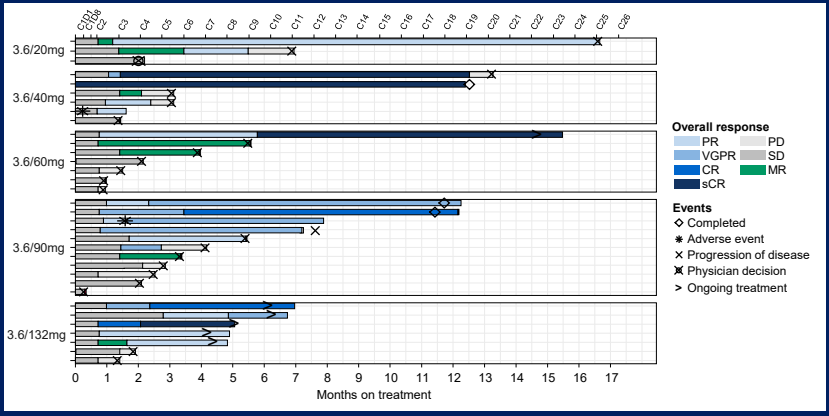
Cevostamab: Response Duration



- Median follow-up in responders: 10.3 months (range: 2.7–19.5)
- 8 patients with duration of response ≥6 months
- 4 patients continued in response after treatment discontinuation*

*2 patients completed 17 cycles of treatment and 2 patients discontinued treatment prematurely due to AEs

Cohen AD et al. *Blood.* 2020;136. Abstract 292.

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Cevostamab: Adverse Events

N (%)	All Gr (N=53)	All Gr 3–4 (N=53)
Hematologic AEs (≥15%)		
Platelet count decreased*	17 (32)	13 (25)
Anemia	15 (28)	10 (19)
Neutropenia	9 (17)	8 (15)
Lymphocyte count decreased	8 (15)	8 (15)
Non-hematologic AEs (≥15%)		
Cytokine release syndrome	40 (76)	1 (2)
Hypomagnesemia	15 (28)	0
Diarrhea	15 (28)	1 (2)
Infusion-related reaction	12 (23)	0
Hypokalemia	11 (21)	2 (4)
Hypophosphatemia	10 (19)	5 (9)
Nausea	10 (19)	0
Fatigue	9 (17)	2 (4)
AST increased	8 (15)	1 (2)

*Platelet count decreased includes the terms *thrombocytopenia* and *platelet count decreased*; †AE considered by the investigator to be related to study treatment

- Median follow-up: 8.1 months (range: 0.2–30.4)
- 28 patients with serious AEs
  - Treatment-related† events (13 patients) in ≥2 patients were CRS (6 patients)
- 5 patients (9%) with AEs leading to withdrawal
  - Treatment-related events (2 patients) were pneumonitis (1 patient) and meningitis (1 patient)
- 7 pts (13%) with Gr 5 AE (malignant neoplasm progression, 5 patients; respiratory failure, 2 patients)
  - No treatment-related Gr 5 events
- 1 patient (2%) with DLT of Gr 3 pneumonia in the 3.6/90 mg cohort; MTD not reached

Cohen AD et al. *Blood.* 2020;136. Abstract 292.

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Conclusions

- T cell–directed therapies current state; advanced disease
- Unknown
  - Sequencing, same targets?
  - Renal failure
  - CNS disease

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Dana-Farber Cancer Institute

BRIGHAM AND WOMEN'S HOSPITAL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Options for Patients Who May Not Have Access to CAR T or Bispecifics

Paul G. Richardson, MD
R. J. Corman Professor of Medicine
Harvard Medical School
Clinical Program Leader and Director of Clinical Research
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Disclosures

Dr. Richardson has disclosed the following relevant financial relationships:

Consultant/Advisor: **AstraZeneca, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Karyopharm Therapeutics, Oncopeptides, Protocol Intelligence, Regeneron, Sanofi, Secura Bio, Takeda**

Research Grants: **Bristol Myers Squibb/Celgene, Karyopharm Therapeutics, Oncopeptides, Takeda**

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Treatment of MM Is a Marathon, Not a Sprint
Strategic and Practical Considerations Key

- **Treatment options rapidly diminish with each progression**
- **Goal in advanced RRMM: stop further progression, maintain disease control, preserve QoL**

Adapted from Borrello I. *Leuk Res.* 2012;36:S3.
Richardson PG et al. *Blood Cancer J.* 2018;8:109.

46

Treatment of MM in 2022: Multiple Therapies Approved or Under Investigation

Backbone/standard-of-care agents				Recent approvals / later relapse			Emerging therapies for MM		
IMiDs	PIs	mAbs	HDACis	ADCs	Targeted therapies	CAR T-cell therapies	CELMoDs	BiTEs/ bispecifics	Others
Lenalidomide	Bortezomib*	Daratumumab (CD38)	Panobinostat‡	Belantamab mafodotin	Selinexor	Idecabtagene vicleucel	Iberdomide†	Teclistamab (BCMA × CD3)	CAR NK cell therapies†
Pomalidomide	Carfilzomib	Isatuximab (CD38)	Vorinostat†		Venetoclax	Ciltacabtagene autoleucel	Mezigdomide†	Elranatamab† (BCMA × CD3)	Immune checkpoint inhibitors†
Thalidomide	Ixazomib	Elotuzumab (SLAMF7)			Melflufen†‡¶			Pavurutamab† (BCMA × CD3)	Immuno-cytokines†
	Marizomib†							Talquetamab†§ (GPRC5D × CD3)	
								Cevostamab† (FcRH5 × CD3)	

KEY TARGETS, 2022
- Genomic abnormalities
- Target and overcome mutations
- Critical role of combination and continuous therapy
- Evolving position and timing of ASCT
- Excess protein production
- Target protein degradation
- Immune suppression
- Restore anti-MM immunity

*Also approved in combination with liposomal doxorubicin; †Not currently approved in RRMM; ‡FDA approval withdrawn. ¶Positive recommendation from CHMP for full EMA approval; §Granted FDA Breakthrough Therapy designation.

Adapted from Richardson PG. 8th COMy World Congress, Paris, France, May 2022.
Moreau P et al. *Lancet Oncol*. 2021;22:e105.

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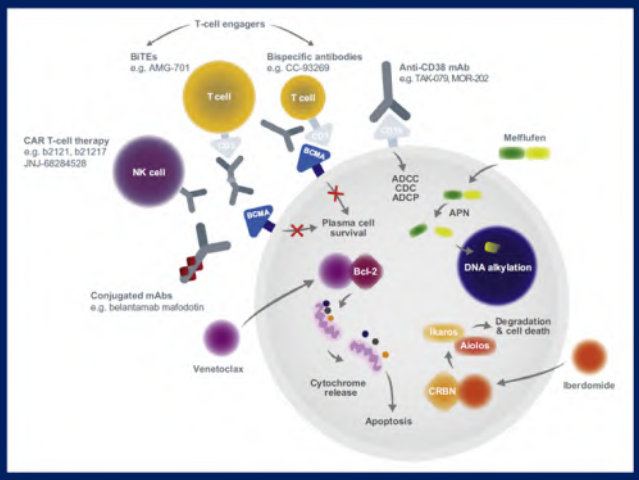
Selected Emerging Treatment Options for MM 2022: Novel MOAs

- Novel mechanisms of action are urgently needed and are being brought forward into early relapse and NDMM
- Emerging role of cellular therapies (CAR T-cell therapies), bispecific antibodies, and more
- Continued promise of small molecules and targeted agents (eg, peptide drug conjugates, CELMoDs, venetoclax)
- Further development of novel combinations (eg, with belantamab mafodotin, selinexor, immunoconjugates)



Richardson PG. 13th Annual IMWG Summit, Vienna, Austria, June 2022.
Adapted from *Blood Rev* 49. Ramasamy K, et al. Improving outcomes for patients with relapsed multiple myeloma: Challenges and considerations of current and emerging treatment options. Copyright 2021, with permission from Elsevier.

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Immune Therapy Approaches in MM

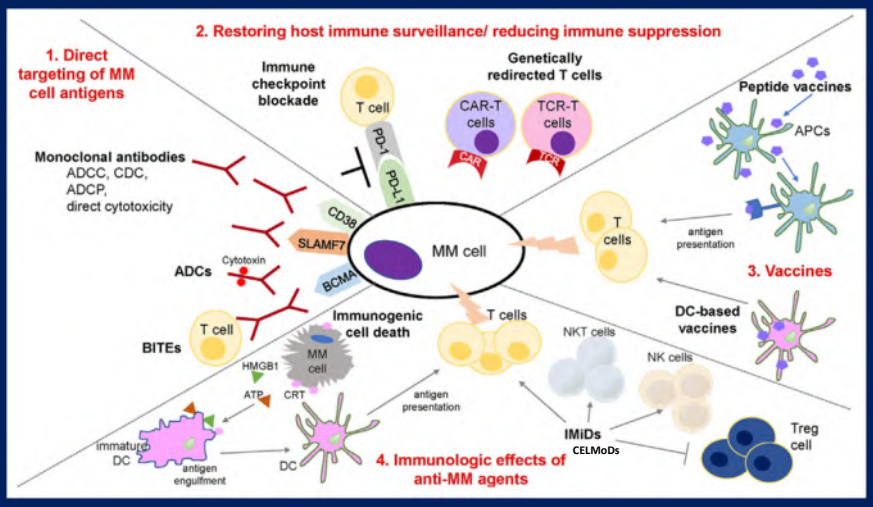

Figure 1 from Yamamoto L, et al. Harnessing the immune system against multiple myeloma: challenges and opportunities. *Front Oncol.* 2021;10:606368. Copyright © 2021 Yamamoto, Amodio, Gulla, and Anderson.

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Multiple Therapies Approved or Under Investigation in RRMM

Backbone/standard-of-care agents				Recent approvals/later relapse			Emerging therapies for MM		
IMiDs	PIs	mAbs	HDACis	ADCs	Targeted therapies	CAR T-cell therapies	CELMoDs	BiTEs/ bispecifics	Others
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Pomalidomide	Carfilzomib	Isatuximab (CD38)	Vorinostat†		Venetoclax	Ciltacabtagene autoleucel	Mezigdomide†	Elranatamab† (BCMA × CD3)	Immune checkpoint inhibitors†
Thalidomide	Ixazomib	Elotuzumab (SLAMF7)			Melflufen†‡¶			Pavurutamab† (BCMA × CD3)	Immuno-cytokines†
	Marizomib†							Talquetamab†§ (GPRC5D × CD3)	
								Cevostamab† (FcRH5 × CD3)	

Several agents have been recently approved for later relapses in RRMM; these agents are moving up the treatment algorithm and being investigated in combination regimens with the standard-of-care backbone regimens

*Also approved in combination with liposomal doxorubicin; †Not currently approved in RRMM; ‡FDA approval withdrawn. ¶Positive recommendation from CHMP for full EMA approval; §Granted FDA Breakthrough Therapy designation.

Adapted from Richardson PG. 8th COMy World Congress, Paris, France, May 2022.
Moreau P et al. *Lancet Oncol.* 2021;22:e105.

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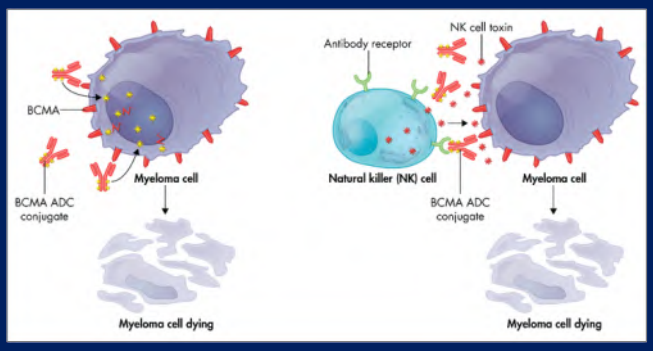
Belantamab Mafodotin: BCMA-Targeted ADC

First ADC approved in RRMM (2020)



Adapted from Figure 2 of Cho S-F, et al. Targeting B cell maturation antigen (BCMA) in multiple myeloma: potential uses of BCMA-based immunotherapy. *Front Immunol* 2018;9:1821.
Trudel S et al. *Lancet Oncol* 2018;19:1641.
Richardson PG et al. *Blood Cancer J* 2020;10:106.

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Belantamab Mafodotin: Initial Approval Based on DREAMM-2 in Heavily Pretreated RRMM

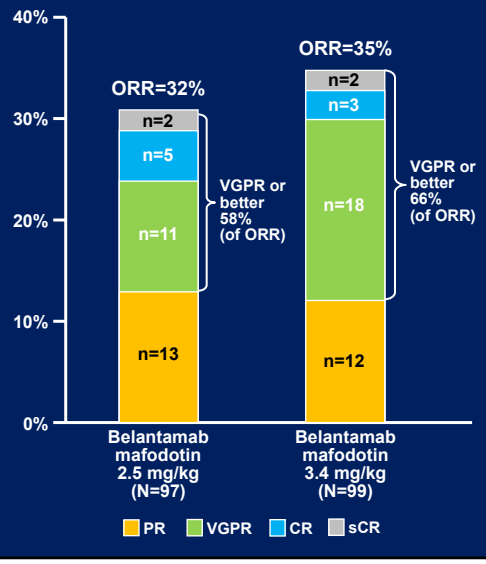
Patients

- Median age: 65 and 67 years
- High-risk cytogenetics: 42% and 47%
- Median prior lines of therapy: 7 and 6
- 90% and 89% lenalidomide-refractory
- 76% and 75% bortezomib-refractory
- 100% and 92% daratumumab-refractory

Safety

- 72% overall rate of keratopathy*
- Grade 3/4 keratopathy in 27% (2.5 mg/kg) and 21% (3.4 mg/kg) of patients
- Grade 3/4 thrombocytopenia in 20% and 33%, anemia in 20% and 25%, respectively
- 3% discontinued due to corneal event
- 2.5 mg/kg chosen for further studies

	Belantamab mafodotin 2.5 mg/kg (n=97)	Belantamab mafodotin 3.4 mg/kg (n=99)
ORR	32%*	35%
Median DOR, months	11.0	6.2
Median PFS, months	2.8	3.9
Median OS, months	13.7*	14.0



Reprinted from *Lancet Oncol* 21(2). Lonial S, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. 207-221. Copyright 2020, with permission from Elsevier.
*Updated: Lonial S et al. *Cancer*. 2021;127:4198.

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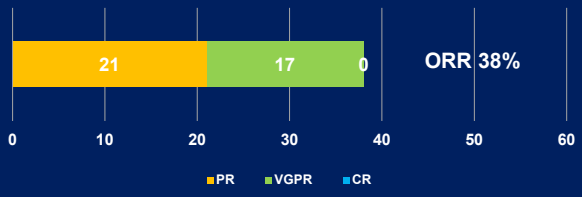
DREAMM-5: Belantamab Mafodotin + Nirogacestat

Rationale

- Nirogacestat is a gamma-secretase inhibitor that may increase cell-surface levels of BCMA
- This may augment belantamab mafodotin activity by increasing target expression

24 patients treated with combination

- 10 in dose-escalation
- 14 in expansion cohort
- Median of 4.5 / 4.0 prior lines of therapy
- EMD in 20% / 29%
- Patients received a median of 8.5 (range 1–29) / 4.0 (1–9) cycles



Outcomes

- ORR: 38%
- Clinical benefit rate (≥MR): 38%
- Rate of ≥ stable disease: 75%
- Median follow-up 12–34.5 weeks (early results)

Safety

- 100% had AEs (83% had grade ≥3 AEs)
  - Ocular events 54% (13%)
  - Grade ≥3 thrombocytopenia 21%
- 29% had AEs leading to dose reductions
  - 13% discontinuations due to AEs

Lonial S et al. *J Clin Oncol.* 2022;40. Abstract 8019.

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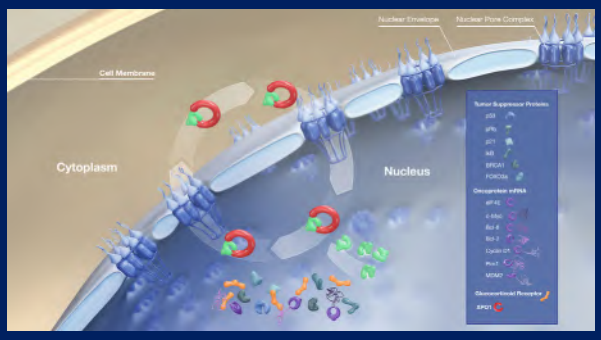
Other Novel Targeted Agents for RRMM: Selinexor Mechanism of Action: Inhibition of XPO1

XPO1 overexpression

1. Enables cancer cells to escape tumor suppressor proteins (TSPs) mediated cell cycle arrest and induction of apoptosis
2. Correlates with poor prognosis and drug resistance



Inhibition of XPO1 impacts tumor cells via 3 core mechanisms

1. Increases nuclear levels and activation of TSPs
2. Traps oncoprotein mRNA in the nucleus leading to reduced oncoprotein levels
3. Retains activated glucocorticoid receptor in the nucleus

Selinexor is an oral selective XPO1 inhibitor; preclinical data demonstrate that, in MM models, selinexor:

- Reactivates multiple TSPs relevant to MM, inhibits NF-kB signaling and reduces c-Myc levels
- Reactivates GR signaling in combination with dexamethasone
- Demonstrates synergistic activity in combination with bortezomib, pomalidomide, and lenalidomide in vitro and in vivo

1. Gupta A et al. *J Thorac Oncol.* 2017;12:1446. 2. Sun Q et al. *Signal Transduct Target Ther.* 2016;1:16010.
3. Gandhi UH et al. *Clin Lymphoma Myeloma Leuk.* 2018;18:335. 4. Gravina GL et al. *J Hematol Oncol.* 2014;7:85.

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BOSTON Trial: Selinexor-Vd vs Vd in Patients With MM Who Had Received 1–3 Prior Therapies (FDA Approved)

Phase 3 trial (N=402)

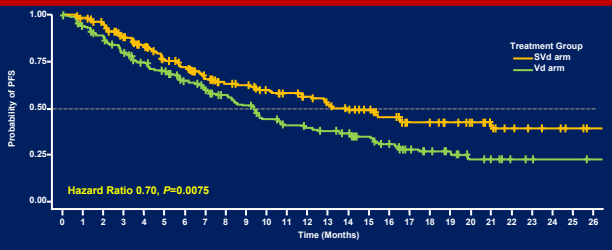
- 195 SVd vs 207 Vd
- Median of 2 prior therapies

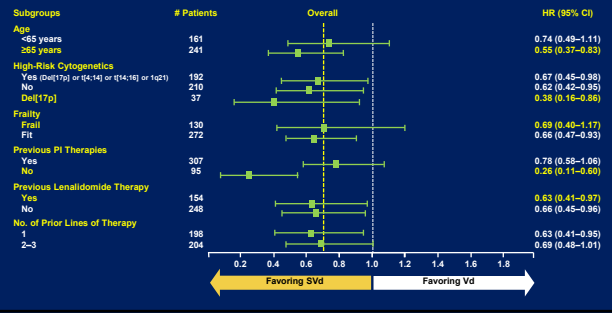
Efficacy

- Median PFS 13.93 vs 9.46 months (HR 0.70)
- ORR 76.4% vs 62.3%
- ≥VGPR 44.6% vs 32.4%
- Median DOR 20.3 vs 12.9 months

Safety

- Higher rates of grade 3–4 thrombocytopenia (39% vs 17%), anemia (16% vs 10%), neutropenia (9% vs 3%), fatigue (13% vs 1%), and cataracts (9% vs 1%) with SVd vs Vd
- Significantly lower rate of PN (32% vs 47%) and grade ≥2 PN (21% vs 34%)
- Grade ≥3 PN: 4.6% vs 8.8%





Dimopoulos MA et al. *J Clin Oncol.* 2020;38. Abstract 8501.
Reprinted from *The Lancet* 396(10262), Grosicki S, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial, 1563-1573. Copyright 2020, with permission from Elsevier.

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Other Selinexor Combinations in RRMM

Study	Phase	ClinicalTrials.gov	Setting	Primary endpoint	Initial completion
BENCH	3	NCT04939142	• 1–3 prior lines • Relapsed or refractory MM	PFS	July 2024
NCI-2020-13697	2	NCT04756401	• 1–3 prior lines • Selinexor + Dara-Kd	MRD-negativity rate	September 2023
STOMP	1/2	NCT02343042	• Multiple settings • Combinations with Pom-dex, Vd, Rd, Pom-Vd, Dara-dex, Kd, Ixa-dex, Elo-Pom-dex, Belamaf-dex, Dara-Pom-dex	MTD/RP2D ORR	January 2025
SELIBORDARA	2	NCT03589222	• ≥3 prior lines • Selinexor + Dara-Vd	ORR	August 2023
SCOPE	1/2	NCT04764942	• ≥2/3 prior lines • Selinexor-Pom-dex ± carfilzomib	MTD ORR	March 2025
EMN29	3	NCT05028348	• 1–4 prior lines • Selinexor-Pom-dex vs Elo-Pom-dex	PFS	July 2023
NCI-2014-01199[1]	1	NCT02199665	• ≥2 prior lines • Selinexor + Kd	MTD	July 2022
Pro2020-0369	2	NCT04661137	• Refractory to/disease progression on prior carfilzomib-, pomalidomide-, or daratumumab-containing regimen • Selinexor + Kd, Pom-dex, Dara-dex	ORR	January 2023
ClaSPd	2	NCT04843579	• Selinexor + clarithromycin + Pom-dex	ORR, AEs	November 2023
SELVEDge	2	NCT05530421	• Selinexor + venetoclax + dex in t(11;14)-positive RRMM	ORR	December 2025
ATG-010-IIT-MM-001	1/2	NCT04891744	• Selinexor + Thal-dex	ORR	December 2024
ATG-010-IIT-MM-004	2	NCT04941937	• Selinexor + Thal-dex/Rd/Pom-dex	ORR	December 2025
ATG-010-IIT-MM-002	2	NCT04877275	• Selinexor + Doxil + Cyclo + dex	ORR	December 2024

1. Jakubowiak AJ et al. *Br J Haematol.* 2019;186:549.

56

Other Novel Combinations: Dara-K-Pom-dex in RRMM

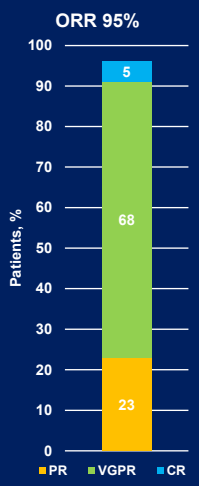
Dara given per APOLLO

- Plus weekly carfilzomib
- Pomalidomide
- Dexamethasone

24 RRMM patients; median of 2 prior regimens

- All had received lenalidomide and a PI
- 54% prior pomalidomide; 13% prior carfilzomib
- All were refractory to last prior therapy

13% del17p; 8% t(14;16); 46% gain of 1q



12-month PFS: 86.2%

Grade 3/4 hematologic AEs:

- Neutropenia 46%
- Thrombocytopenia 25%

Non-hematologic AEs:

- Fatigue 42%
- Dyspnea 38%
- ALT/AST increased 29%
- Insomnia 21%
- Neuropathy 17%

Dara-Ixa-Pom-dex also being studied in RRMM, with ORR of 80% (28% sCR, 20% VGPR) seen to date1

Yee AJ et al. *J Clin Oncol*. 2022;40. Abstract 8012.
1. Kumar AD et al. *J Clin Oncol*. 2022;40. Abstract 8041.

57

Ixa-Pom-Dex: Randomized Phase 2 Alliance Study A061202

Randomize

Arm 1
28-day cycle
Pomalidomide 4 mg on days 1–21
Dexamethasone 40* mg on days 1, 8, 15, and 22

Arm 2*
28-day cycle
Pomalidomide 4 mg on days 1 – 21
Dexamethasone 40* mg on days 1, 8, 15, and 22
Ixazomib 4 mg on days 1, 8, 15

Crossover at PD

Treatment until PD, toxicity, or patient preference

Primary end point
- PFS

Secondary end points
- ORR, depth of response, DOR, OS, safety

Stratification factors

- High-risk vs standard-risk cytogenetics (FISH)
- Prior PI exposure (Yes/No)
- ISS stage I and II vs III disease at registration

Patients (n=80)

- ≥18 years of age
- Relapsed MM
- 1 prior line of therapy; progression on frontline lenalidomide
- PI-naïve/sensitive disease

*Arm 2 derived from Phase 1/2 study of IXA POM dex in RRMM ~ double refractory disease; ORR 52%, CBR 59% (n=29)
Voorhees PM et al. *Am J Hematol*. 2021;1-9.

Voorhees P et al. *HemaSphere* 2022;6. Abstract P968.

58

Ixa-Pom-Dex: Randomized Phase 2 Alliance Study A061202

Response	Pom-dex (n=39)	Ixa-Pom-dex (n=38)
ORR (95% CI)	43.6% (27.8%–60.4%)	63.2% (46.0%–78.2%)
sCR/CR	2.6%	0.0%
VGPR	2.6%	29.0%
PR	38.5%	34.2%
≥VGPR	5.1%	29.0%
Median DOR (months, range)	12.3 (2.8–42.3+)	23.7 (1.8–40.9+)

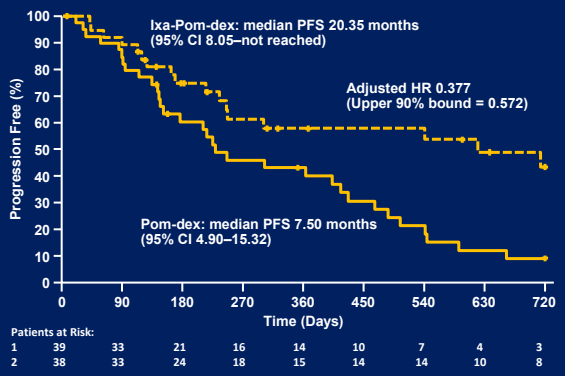
Pom-dex

- Grade 3/4 AEs included lymphopenia 26%, neutropenia 21%, anemia 13%, and fatigue 15%

Ixa-Pom-dex

- Grade 3/4 AEs included lymphopenia 40%, neutropenia 37%, anemia 16%, fatigue 16%, and hyperglycemia 11%
- No increase in discontinuation or dose adjustments for toxicity
- No COVID-related deaths and no treatment-related mortality in either arm

PFS at data lock



No difference in OS between arms to date

- 80 patients registered: 3 found to be ineligible, with 77 randomized and evaluable.

Voorhees P et al. *HemaSphere.* 2022;6. Abstract P968.
Voorhees P et al. IMS 2022. Abstract P282.

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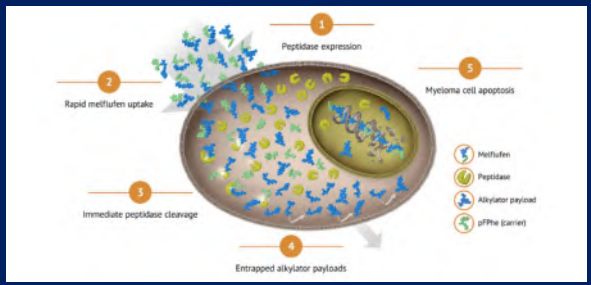
Other Novel Targeted Agents: Melflufen–Cytotoxic Drug–Peptide Conjugate

- Melphalan flufenamide: novel targeted cytotoxic drug–peptide conjugate mechanism[1]
- Rapidly taken up by plasma cells due to high lipophilicity
- Once inside, aminopeptidases cleave the compound and release melphalan "warhead," where it causes maximal DNA damage to MM
- Active in melphalan and other alkylator resistance
- Potent activity in extramedullary disease
- Targeting "stemness?"
- Current dosing/dexamethasone is IV q28d; no mucositis or alopecia seen
- Granted FDA priority review in August 2020 and approved in March 2021
- FDA approval provisionally held, October 2021
- EMA review completed, CHMP recommended full approval, June 2022



Preclinical findings

- MM cells exquisitely sensitive to melflufen, including melphalan- and bortezomib-resistant cells[2,3]
- BMSCs more sensitive to melflufen than melphalan[4]
- Cytotoxicity of melflufen in MM cells not affected by co-culture with BMSCs
- Overcomes 17p deletion in resistant MM

1. Adapted from Richardson PG et al. *HemaSphere.* 2020;4. Abstract EP945. 2. Chauhan D et al. *Clin Cancer Res.* 2013;19:3019.
3. Ray A et al. *Br J Haematol.* 2016;174:397. 4. Gebraad A et al. *Cells.* 2022;11:1574.

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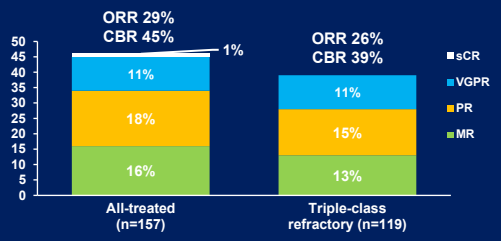
HORIZON (OP-106) Phase 2 Trial in RRMM: Melflufen-dex in Pom- and/or CD38 mAb-Refractory Patients

Dosing
- Melflufen 40 mg IV on Day 1 + dex 40 mg days 1, 8, 15, and 22 in 28-day cycles

Patients
- RRMM with ≥2 prior lines, including IMiD and PI
- Refractory to Pom and/or anti-CD38 mAb

Safety
- Grade ≥3 neutropenia 79%, thrombocytopenia 76%, anemia 43%
- Grade ≥3 pneumonia 10%, hypophosphatemia 8%
- SAEs 49%; AEs leading to melflufen discontinuation 22%

Population	Median OS, months	Median PFS, months	Median DOR, months
ITT (N=157)	11.6	4.2	5.5
Triple-class refractory (n=119)	11.2	3.9	4.4
EMD (n=55)	6.5	2.9	5.5



ORR in 55 patients with EMD: 24%

Richardson PG et al. Melflufen and dexamethasone in heavily pretreated relapsed and refractory multiple myeloma. *J Clin Oncol.* 2021;39(7):757-767. © 2020 by American Society of Clinical Oncology. https://ascopubs.org/doi/10.1200/JCO.20.02259?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

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OCEAN (OP-103) Phase 3 Trial in RRMM: Melflufen-dex vs Pom-dex

- Phase 3, randomized, open-label, controlled, head-to-head, comparison study

SCREENING (day −21 to −1)

Key eligibility criteria
- Patients with RRMM
- Aged ≥18 years
- 2–4 prior lines of therapy including lenalidomide (within 18 months of randomization) and a PI
- Refractory to lenalidomide and to last line of therapy
- ECOG PS ≤2 (N=495)

RANDOMIZATION

1:1 Randomization

Stratified by
- Age (<75 vs ≥75 y)
- Prior lines of therapy (2 vs 3-4)
- ISS score (I vs ≥II or III)

TREATMENT (28-day cycles until disease progression or unacceptable toxicity)
- Melflufen (40 mg IV, day 1 of each cycle) + Dexamethasone (40 mg PO weekly)[b,c]
- Pomalidomide (4 mg po, days 1–21 of each cycle) + Dexamethasone (40 mg PO weekly)[b,c]

EoT — **FOLLOW-UP**[a]

Primary end point
- PFS assessed by IRC per IMWG uniform response criteria[c]

Key secondary end points
- ORR
- OS
- Safety and tolerability[d]

ECOG PS, Eastern Cooperative Oncology Group performance status; EoT, end of treatment; IMWG, International Myeloma Working Group; IRC, Independent Review Committee; ISS, International Staging System; IV, intravenous; PO, orally; y, years.

Schjesvold FH et al. *Lancet Haematol* 2022;9(2):E98.

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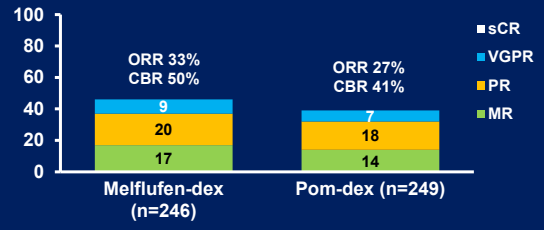
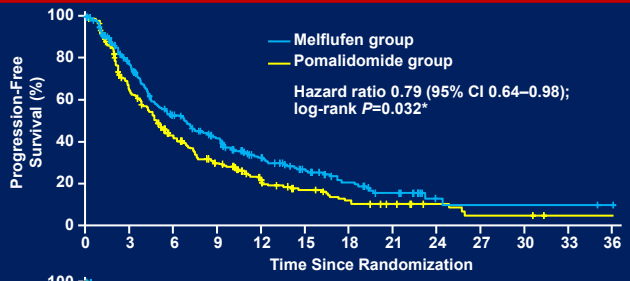
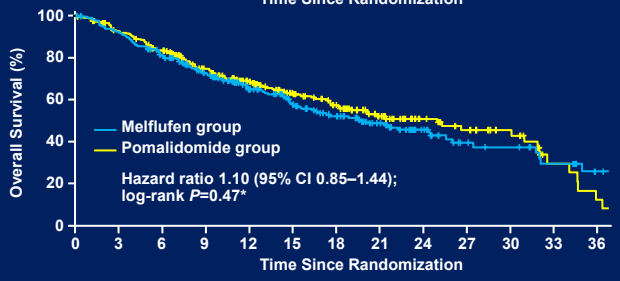
OCEAN (OP-103) Phase 3 Trial in RRMM: Melflufen-dex vs Pom-dex



- Superior PFS with Melflufen-dex vs Pom-dex
- No difference in OS on ITT analysis
- Post-hoc, pre-specified analysis: OS in favor of Melflufen-dex in patients without prior ASCT and in favor of Pom-dex in patients with prior ASCT
- ~ >3 years post ASCT subgroup ~ clear benefit





Reprinted from *Lancet Haematol* 9(2). Schjesvold FH, et al. Melflufen or pomalidomide plus dexamethasone for patients with multiple myeloma refractory to lenalidomide (OCEAN): a randomised, head-to-head, open-label, phase 3 study, e98-e110. Copyright 2022, with permission from Elsevier.

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Other Novel Targeted Agents: Venetoclax, Selective Inhibitor of BCL-2

Potent selective inhibitor of BCL-2

Oncogene *BCL-2* located on chromosome 11

t(11;14) (in ~20% of MM patients) activates BCL-2 overexpression; also more common in PCL

Selective binding to BCL-2 frees pro-apoptotic proteins, which associate with the apoptotic effectors BAX and BAK and induce mitochondrial outer membrane permeabilization. Cytochrome c released, activating caspases and triggering cell death.[1]

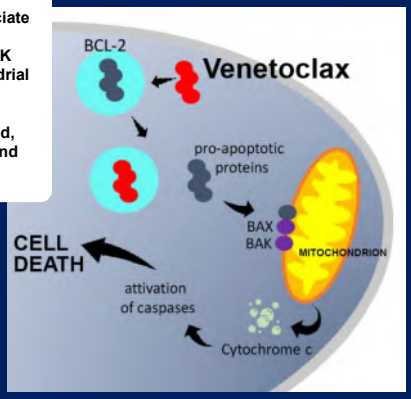

Figure 1 from Sgherza N et al. Novel approaches outside the setting of immunotherapy for the treatment of multiple myeloma: the case of melflufen, venetoclax, and selinexor. *Front Oncol.* 2021; 11:716751. Copyright © 2021 Sgherza, Curci, Rizzi, and Musto.

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Other Novel Targeted Agents: Venetoclax – Clinical Activity

BELLINI: Venetoclax + Vd (n=194) vs placebo-Vd (n=97)[1]	Phase 2 study: Venetoclax + Kd (n=49)[2]	PCL	CANOVA phase 3 trial[6]

• Median PFS 22.4 vs 11.5 months (HR 0.63)
• Specific activity in t(11;14) RRMM patients
  • Median PFS not reached vs 9.5 months (HR 0.11) in t(11;14) patients
  • Median PFS not reached vs 9.9 months (HR 0.21) in patients with t(11;14) and/or high BCL2 expression
• But higher mortality overall with venetoclax+Vd (6% vs 1% grade 5 AEs)
	• ORR 80% (92% in t(11;14) patients)
	• ≥CR 41% (54% in t(11;14) patients)
	• Median DOR 19.7 months
	• Median PFS 22.8 months (24.8 months in t(11;14) patients)
	• Grade ≥3 AEs 92%; SAEs 53%
		• Promising preliminary findings in primary PCL and RR disease, specifically with t(11;14) or BCL-2 overexpression[3-5]	• Venetoclax + dex vs Pom-dex in t(11;14)-positive RRMM

1. Kumar SK et al. *Lancet Oncol.* 2020;21(12):1630. 2. Costa LJ et al. *Blood Adv.* 2021;5:3748. 3. Roy T et al. *Leuk Lymphoma.* 2022;63:759.
4. Vo K et al. *J Oncol Pharm Pract.* 2022 Jan 27;10781552221074269. 5. Szita VR et al. *Pathol Oncol Res.* 2022;28:1610276. 6. Mateos MV et al. *J Clin Oncol.* 2020;38. Abstract TPS8554.

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Multiple Therapies Approved or Under Investigation in RRMM

Backbone/standard-of-care agents				Recent approvals/later relapse			Emerging therapies for MM		
IMiDs	PIs	mAbs	HDACis	ADCs	Targeted therapies	CAR T-cell therapies	CELMoDs	BiTEs/ bispecifics	Others
Lenalidomide	Bortezomib*	Daratumumab (CD38)	Panobinostat‡	Belantamab mafodotin	Selinexor	Idecabtagene vicleucel	Iberdomide†	Teclistamab (BCMA × CD3)	CAR NK cell therapies†
Pomalidomide	Carfilzomib	Isatuximab (CD38)	Vorinostat†		Venetoclax	Ciltacabtagene autoleucel	Mezigdomide†	Elranatamab† (BCMA × CD3)	Immune checkpoint inhibitors†
Thalidomide	Ixazomib	Elotuzumab (SLAMF7)			Melflufen†‡¶			Pavurutamab† (BCMA × CD3)	Immuno-cytokines†
	Marizomib†							Talquetamab†§ (GPRC5D × CD3)	
								Cevostamab† (FcRH5 × CD3)	

Multiple emerging therapies for RRMM, including CELMoDs and bispecifics, are being extensively investigated and will further transform the RRMM treatment landscape in the next 5 years, with teclistamab the first to be approved, by EMA, in August 2022

*Also approved in combination with liposomal doxorubicin; †Not currently approved in RRMM; ‡FDA approval withdrawn. ¶Positive recommendation from CHMP for full EMA approval; §Granted FDA Breakthrough Therapy designation.

Adapted from Richardson PG. 8th COMy World Congress, Paris, France, May 2022.
Moreau P et al. *Lancet Oncol.* 2021;22:e105.

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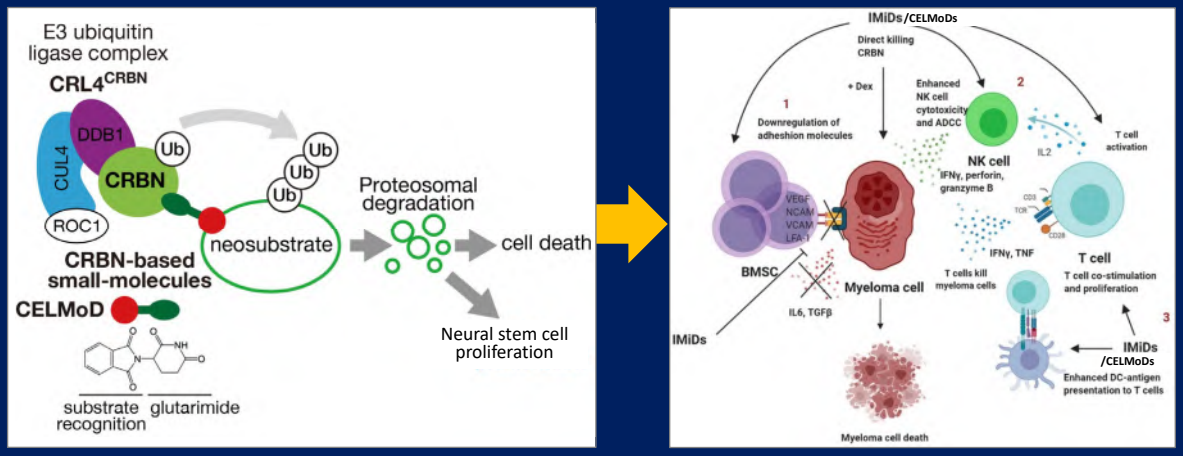
CELMoDs: Iberdomide and Mezigdomide (CC-92480)



1. Lonial S et al. *Lancet Haematol.* Oct 6, 2022 [Epub ahead of print]. 2. Richardson PG et al. *Blood.* 2021;138. Abstract 2731.
(left) Figure 1 from Sato T et al. *Front Cell Dev Biol.* 2021;9:629326. Copyright © 2021 Sato, Ito, and Handa.
(right) Figure 1 from D'Souza C et al. *Front Immunol.* 2021; 12:632399. Copyright © 2021 D'Souza, Prince, and Neeson.

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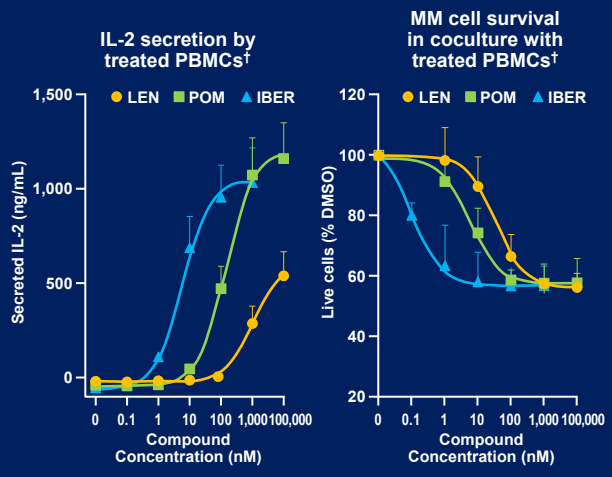
Iberdomide Enhances In Vitro Immune-Stimulatory Activity vs Lenalidomide and Pomalidomide

Compound concentration required for degradation of Ikaros or Aiolos protein in vivo:

EC_{50}, nM^2	Ikaros	Aiolos
Lenalidomide	67	87
Pomalidomide	24	22
Iberdomide	1	0.5



Adapted from Figure 1 of Bjorklund CC, et al. *Leukemia.* 2020;34(4):1197-1201. Copyright © The Authors, 2019. Available through Creative Commons Attribution 4.0 International License. http://creativecommons.org/licenses/by/4.0/
Matyskiela ME et al. *J Med Chem.* 2018;61:535; †Lonial S et al. *Lancet Haematol.* Oct 6, 2022 [Epub ahead of print].

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Iberdomide in RRMM

Study	Phase	ClinicalTrials.gov	Setting	Primary end point	Initial completion
EXCALIBER-RRMM	3	NCT04975997	• 1–2 prior lines • Iberdomide + Dara-dex vs Dara-Vd	PFS	April 2026
ICON	2	NCT04392037	• 2-4 prior regimens • Iberdomide + Cd	PFS	November 2023
I2D IFM2021_03	2	NCT04998786	• 1st relapse • Iberdomide + Ixa-dex	≥VGPR rate	January 2025
CC-220-MM-001	1/2	NCT02773030	• RRMM • Iberdomide + dex, Vd, Dara-dex, Kd	MTD/RP2D ORR	May 2026
TIG-007	1/2	NCT05289492	• RRMM • Iberdomide + EOS884448 ± dex	Safety ORR	February 2024

Iberdomide is being more extensively investigated in NDMM; this is the anticipated primary treatment setting in the future

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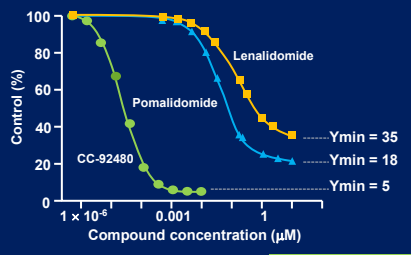
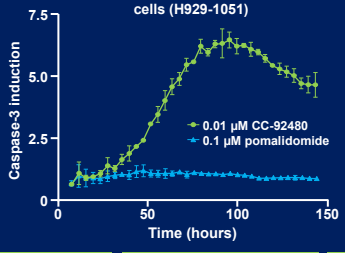
Emerging Novel Therapies: CC-92480 (Mezigdomide), CELMoD

CELMoD agent specifically designed for rapid protein degradation[1,2]
Efficient substrate degradation leading to apoptosis and potent antiproliferative activity in lenalidomide and pomalidomide resistance[3]

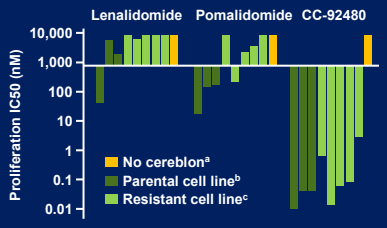
Aiolos degradation efficiency[1]

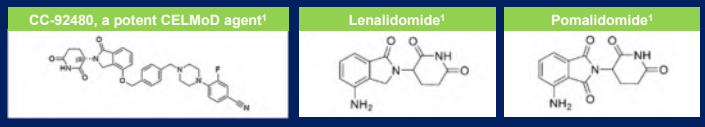


Apoptosis induction kinetics



Antiproliferative activity in lenalidomide/pomalidomide resistance





1. Hansen J et al. *J Med Chem*. 2020;63:6648. 2. Wong L et al. *Blood*. 2019;134. Abstract 1815.
3. Richardson PG et al. *J Clin Oncol*. 2020;38. Abstract 8500.

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Emerging Novel Therapies: CC-92480 (Mezigdomide), CELMoD

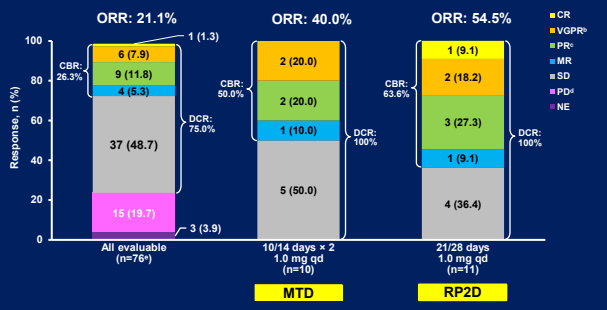
First-in-Human Phase 1 Trial: CC-92480 + Dex[1]

76 heavily pretreated RRMM patients

- 36.8% EMD
- Median 6 prior therapies
- 50% triple-class refractory

Grade 3/4 AEs

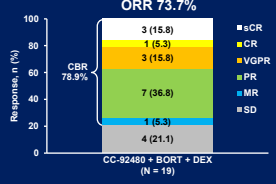
- 64% neutropenia
- 32% anemia
- 16% thrombocytopenia
- 36% infections (14.5% pneumonia)

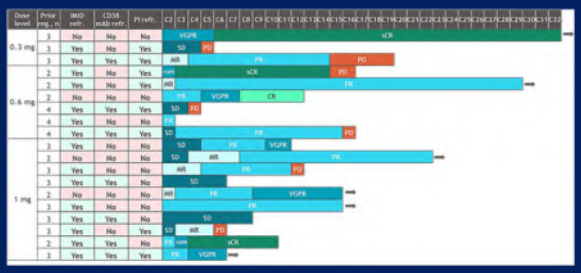


CC-92480-MM-002 Phase 1/2 Study: CC-92480 + Vd[2]

19 heavily pretreated RRMM patients

- Median time to response was 1.2 months (range 0.7–4.9)
- Median duration of response was 10.4 months (95% CI, 9.5, not reached)





1. Richardson PG et al. *J Clin Oncol*. 2020;38. Abstract 8500. 2. Richardson PG et al. *Blood*. 2021;138. Abstract 2731.

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Conclusions and Future Directions

PIs, IMiDs, mAbs have produced significant improvements in PFS and OS in NDMM and in RRMM

- Quadruplets are emerging standards of care in NDMM
- Quadruplet regimens also under investigation in non-transplant setting, with a focus on younger/fit patients
- MRD negativity a key goal of therapy; MRD-adapted therapy emerging – deferred ASCT approach
- Triplets are standards of care in early RRMM

Next wave of immune therapies: mAbs (including ADCs, bispecifics) represent true new novel mechanisms, as well as other immuno-therapeutics (eg, CAR T cells)

- Next-generation standards of care in NDMM and/or at first relapse?
- BCMA-targeted approaches may become a fourth pillar of NDMM treatment
- Baseline immune function is a key barrier to success and may be targetable
- Question of sequencing
- Crucially, are new therapies agnostic to mutational thrust?

Next-generation small molecules/targeted therapy show great promise (eg, selinexor, melflufen, CELMoDS) under investigation in NDMM and RRMM

New insights to mechanisms of drug action are further expanding treatment/immuno-therapeutic opportunities with combinations

- Additional novel immune therapies being investigated later in the treatment course – will move to earlier/first relapse if therapeutic potential emerges

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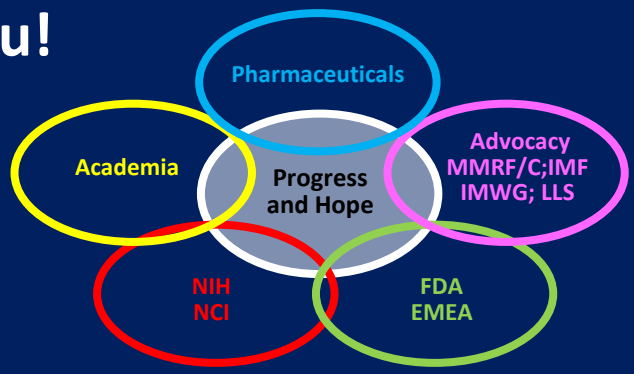
Ongoing MM Collaborative Model for Rapid Translation of Novel Therapeutics From Bench to Bedside 2003–2022

Thank you!



Courtesy of Phil McCarthy MD

14 novel drugs and 30 new FDA-approved drug combos/indications in last 18 years

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MULTIPLE MYELOMA Research Foundation

Panel Discussion & Questions

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Case Study 1

44-year-old man diagnosed with MM presented with extensive bone disease; BM cytogenetics revealed hyperdiploidy with trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19; kyphoplasty performed for severe L2 compression fracture

Treatments

First Line	Second Line	Third Line	Fourth Line
• Lenalidomide + bortezomib + dex • Achieved VGPR • ASCT • Achieved CR by IF • Lenalidomide maintenance post-ASCT • Relapsed after 26 months	• Carfilzomib + pomalidomide + dex • Achieved VGPR • Pomalidomide maintenance for 1 year • Progressed 6 months after maintenance stopped	• Daratumumab + bortezomib + dex • Achieved PR • Biochemical progression after 12 months	• Carfilzomib + cyclophosphamide + dex • Achieved PR • Progressed after 9 month with signs of renal compromise

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Case Study 1

Current Status	BM Biopsy	Cytogenetics and FISH	Labs
• 50 years old • Patient is active • Karnofsky score 80% • Some chronic back pain	• 40% clonal plasma cells	• Persistent hyperdiploidy • FISH negative for: – del 17p – 1q amp	• WBC nL • Hgb 10.5 • Creatinine 2.1 • Calcium nL

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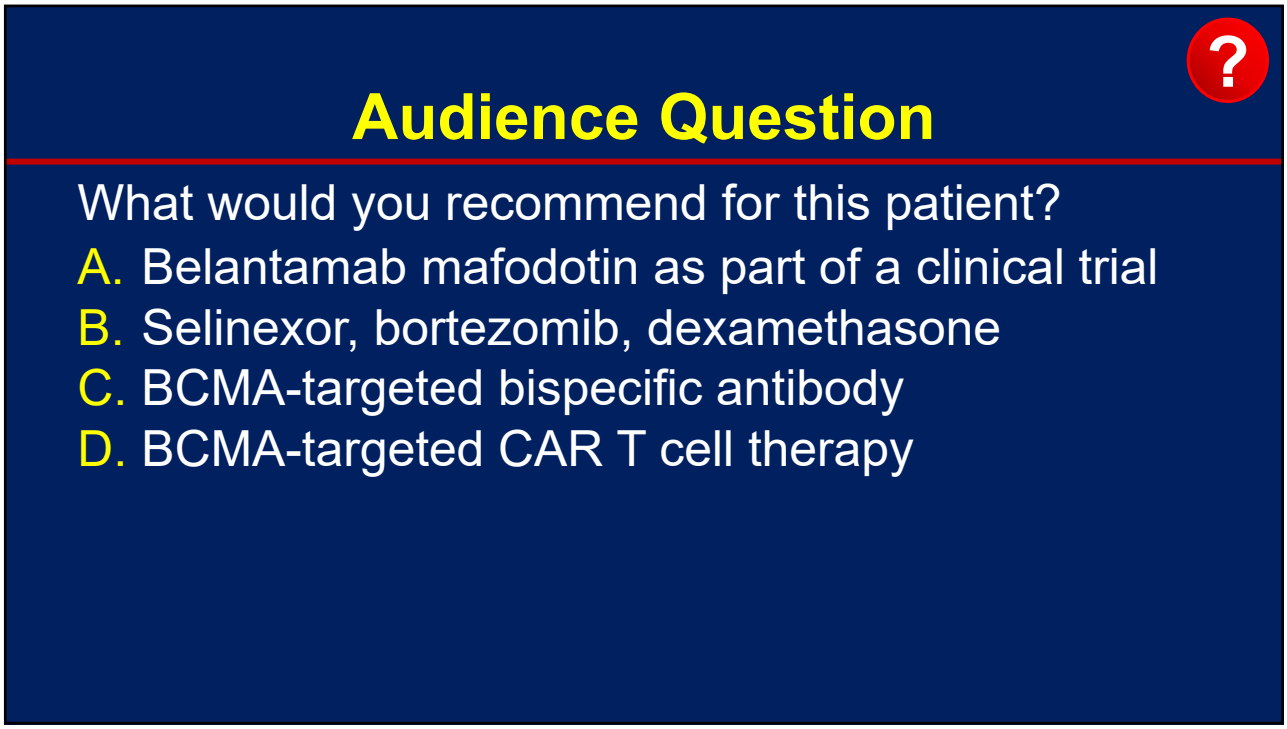
Audience Question
What would you recommend for this patient?
A. Belantamab mafodotin as part of a clinical trial
B. Selinexor, bortezomib, dexamethasone
C. BCMA-targeted bispecific antibody
D. BCMA-targeted CAR T cell therapy

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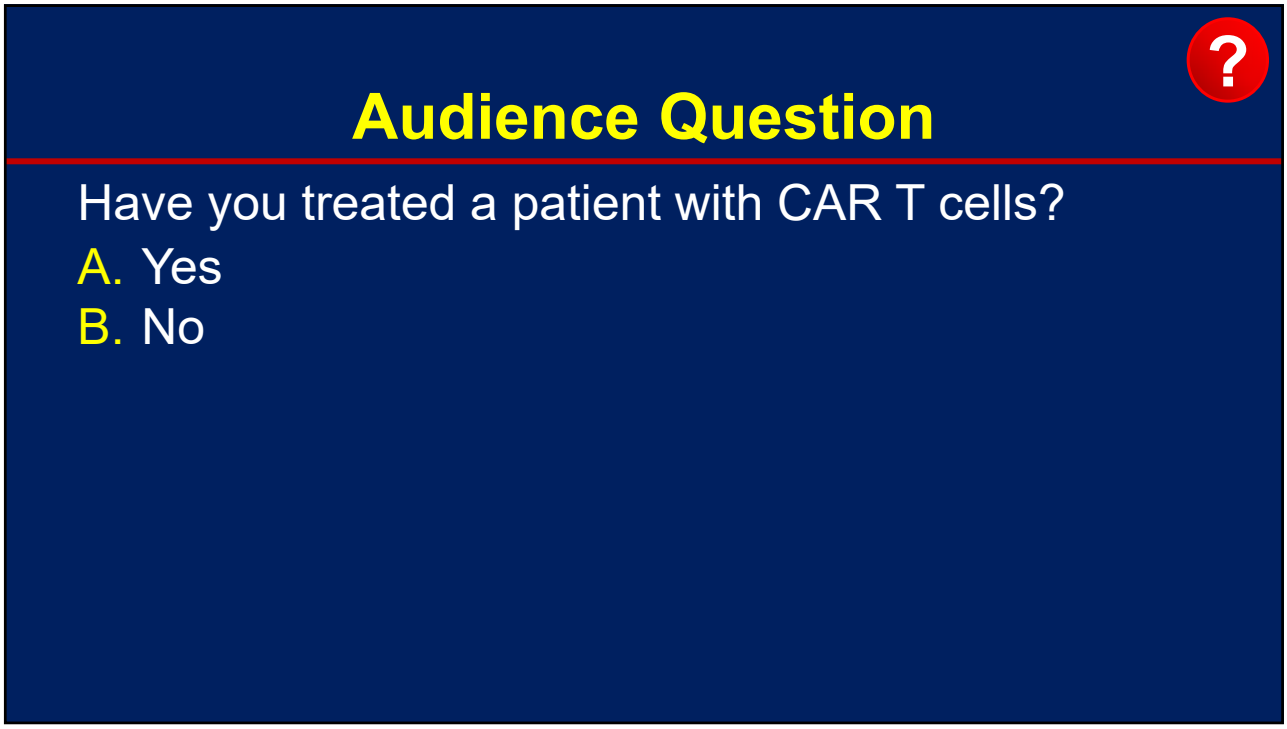
Audience Question
Have you treated a patient with CAR T cells?
A. Yes
B. No

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Case Study 1

50-year-old man 6-years post diagnosis with low-risk hyperdiploid MM has progressed through 4 therapies

Patient and hematologist agree to proceed with CAR T at this time

- Patient hospitalized
- Receives BCMA CAR T
- Within 2 days, patient experiences fever (39.5°C)
- Tachycardic 120
- Mild hypotension 92/68
- No hypoxia
- No mental status change
- WBC 1.2
- Neutrophils 400

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T Cell–activating therapy

Eligibility

Panel discussion questions

- **What makes a patient a candidate for either bispecifics or CAR T cells?**
- **Is there anything about this patient that makes one treatment more suitable than the other?**
- **If this patient was to elect to receive CAR T cell therapy, what are the steps to take to ensure that he receives this therapy?**
  - **Referral process**
  - **Bridging therapy**
  - **Manufacturing slot**
  - **Insurance**
- **What other options are available for this patient if access to CAR T cells is difficult?**

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Audience Question

Based on the patient's symptoms, what is the leading diagnosis?

A. CRS Grade 2
B. CRS Grade 4
C. ICANS
D. Sepsis

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Audience Question

CRS management for this patient includes:

A. Fluids, acetaminophen
B. Fluids, acetaminophen, broad-spectrum antibiotics
C. Fluids, acetaminophen, tocilizumab
D. Fluids, acetaminophen, tocilizumab and broad-spectrum antibiotics

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Case Study 2

73-year-old man diagnosed with IgGκ MM; presented with anemia; 70% plasma cells; BM cytogenetics revealed t(4;14)

Treatments

First Line	Second Line	Third Line	Fourth Line
• Lenalidomide-ixazomib-dex* • Achieved CR • Ixazomib maintenance • Relapsed after 6 years	• Daratumumab-lenalidomide + dex • Achieved VGPR • Len dose reduction due to diarrhea • Light chain progression within 3 years	• Daratumumab-pomalidomide-dex • Progressed after 3 months	• Selinexor-bortezomib-dex • Achieved PR • Significant fatigue, weight loss, thrombocytopenia • Stopped therapy after 2 months • Light chain progression

*As part of a clinical trial (ixazomib not approved for use in patients with newly diagnosed MM)

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Case Study 2

Current Status	BM Biopsy	Cytogenetics and FISH	Labs
• 82 years old • No significant comorbidities • Mild HTN	• 20% clonal plasma cells	• FISH – t(4;14) – del 17p	• WBC 2.5 • Hgb 9 • Creatinine 1.1 • Calcium nL

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Audience Question

What would you recommend for this patient, who is now 82 and has a del(17p) clone?

A. Carfilzomib + cyclophosphamide + dexamethasone
B. Belantamab mafodotin as part of a clinical trial
C. BCMA-targeted bispecific antibody
D. BCMA-targeted CAR T-cell therapy

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Audience Question

Have you treated a patient with a bispecific antibody?

A. Yes
B. No

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Audience Question

What is the major risk for patients receiving T cell–activating therapies?

A. Atypical infection
B. Neurologic complications (eg, ICANS)
C. Pancytopenia
D. Recurrent CRS

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Case Study 2

82-year-old man 6 years post diagnosis with MM; has relapsed from 4 prior lines of therapy.

Patient and hematologist agree to proceed with bispecific therapy at this time

- Patient hospitalized
- Received step-up dosing
- Around cycle 6 contracted COVID-19 infection
- Hospitalized 1 month
  - Multiple anti-COVID therapies in ICU and recovered

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T Cell-activating therapy

Adverse events

Panel discussion questions

- What other options are available for this patient if access to a bispecific antibody is difficult?
- Which AEs should clinicians and patients expect on bispecific T cell–activating therapies?
  - CRS
    - Hallmark: fever
    - Grading
    - Distinguishing from infection?
    - Treatment/management
  - Neurotoxicity/ICANS
    - Features
    - Treatment/management
- Any other unique features?
  - Bispecifics: infection prophylaxis, immune globulin? PJP, pneumonia
  - COVID risk?
  - What about non-BCMA targets (skin, taste, rash)

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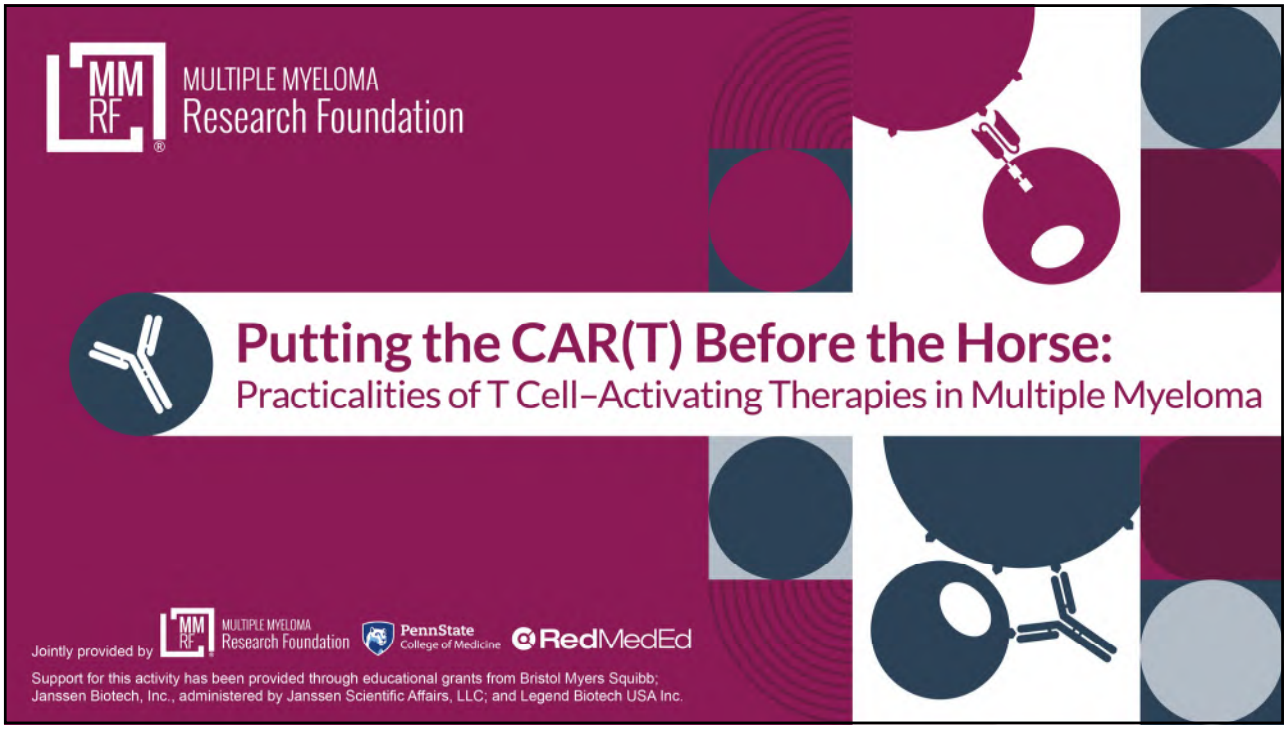

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