Developments With BCMA-Directed Bispecific Antibodies in Relapsed/Refractory Multiple Myeloma: Clinical Updates and Future Directions for Therapy

Pre-read materials

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Current Paradigms in Multiple Myeloma Therapy

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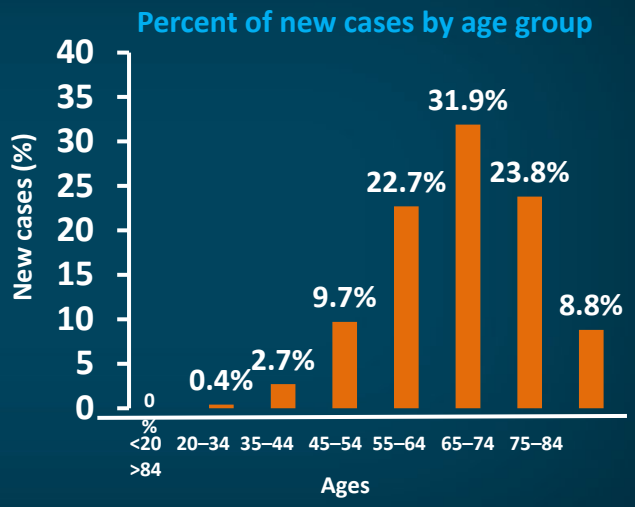
Multiple Myeloma

- MM is a plasma-cell malignancy that will occur in an estimated 35,730 people in 2023 and will be responsible for an estimated 12,590 deaths in the United States alone
- Median age at diagnosis is 69 years, with most patients presenting between the ages of 65 and 74 years



Siegel RL, et al. *CA Cancer J Clin*. 2023;73:17-48. Adapted from National Cancer Institute (NCI). Myeloma—cancer stat facts (https://seer.cancer.gov/statfacts/html/mulmy.html). Accessed 11/4/2023.

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Options for Relapsed/Refractory Multiple Myeloma

Multiple therapies are available in relapsed/refractory setting, including

- Exportin-1 (XPO1) inhibitor—selinexor
- Signaling lymphocyte activation molecular family 7 (SLAMF7) antibody—elotuzumab
- BCMA-targeted chimeric antigen receptor T-cell (CAR T) therapies—idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel)
- BCMA-directed bispecific antibodies—teclistamab, elranatamab
- GPRC5D-directed bispecific antibody—talquetamab

BCMA = B-cell maturation antigen; CAR T = chimeric antigen receptor T-cell therapy.

Raje NS, et al. *Lancet Haematol*. 2022;9:e143-e161. National Comprehensive Cancer Network (NCCN). Multiple myeloma V1.2024 (www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf). Accessed 11/4/2023.

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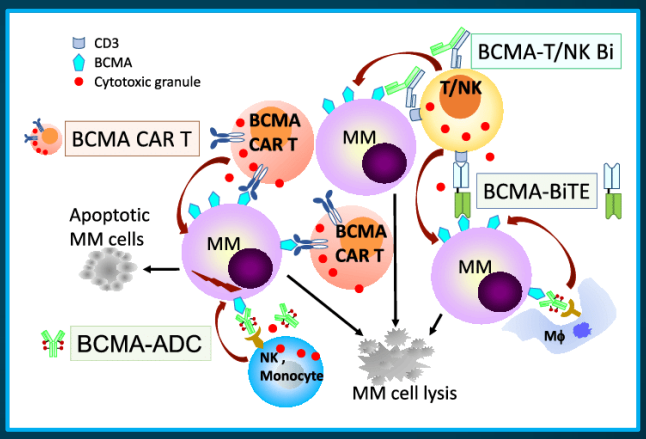
BCMA as Therapeutic Target

- B-cell maturation antigen (BCMA) is highly and specifically expressed on plasma blasts and plasma cells
- Anti-BCMA antibodies are detected in patients in remission after donor lymphocyte infusion, with graft-vs-tumor response
- BCMA mRNA and protein are more highly expressed on malignant cells than on normal plasma cells

Strategies for targeting BCMA



ADC = antibody drug conjugate; Bi = bispecific full-length immunoglobulin; BiTE = bispecific T-cell engager; Mø = macrophage; mRNA = messenger ribonucleic acid; NK = natural killer (cell).
Cho SF, et al. *Front Immunol*. 2018;9:1821.

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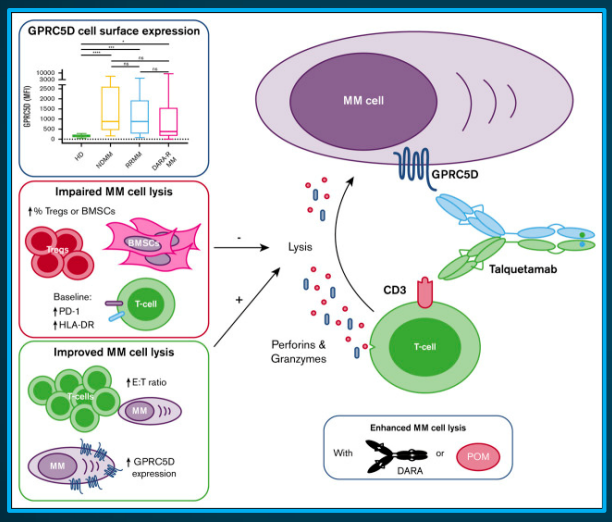
GPRC5D as a Therapeutic Target



- G protein–coupled receptor, class C, group 5, member D (GPRC5D)
- Expressed on malignant plasma cells to a greater degree than on normal plasma and immune cells
- Expression in normal tissue limited to skin cells that express hard keratins (eg, hair follicles, filiform papillae of the tongue)
- Potential for dysgeusia and skin/nail toxicity

Smith EL, et al. *Sci Transl Med.* 2019;11:eaau7746. Verkleij CPM, et al. *Blood Adv.* 2021;5:2196-2215. Inoue S, et al. *J Invest Dermatol.* 2004;122:565-573.

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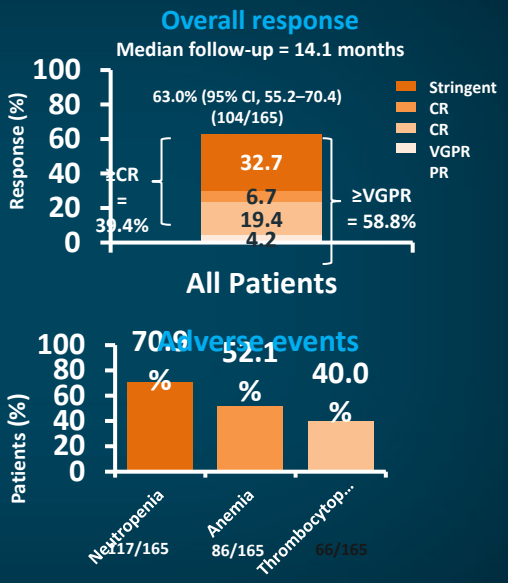
Teclistamab: MajesTEC-1 Trial Efficacy Results

- **MajesTEC-1**
  - 2 step-up doses of 0.05 mg/kg and 0.3 mg/kg; then 1.5 mg/kg SC weekly
  - ORR = 63.0%; 39.4% had CR or better
  - Median DoR = 18.4 months
  - Median PFS = 11.3 months
- Separate study (n = 38) with prior BCMA-targeted treatment, ORR = 40%
  - 26% developed grade 3 to 4 infections
- **Safety**
  - Cytokine release syndrome = 72.1%; grade 1 (50.3%), grade 2 (21.2%)
    - 33% of patients had ≥2 CRS events
    - 36.4% of patients with CRS required tocilizumab



CI = confidence interval; PR = partial response; SC = subcutaneous(ly); VGPR = very good partial response.

Moreau P, et al. *N Engl J Med*. 2022;387:495-505. Touzeau C, et al. *J Clin Oncol*. 2022;40(16 suppl); Abstract 8013. FDA news release 10/25/2022 (www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-teclistamab-cqyv-relapsed-or-refractory-multiple-myeloma). Accessed 11/4/2023. Teclistamab [Package Insert]. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=54e0f974-ccee-44ea-9254-40e9883cee1e.

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Teclistamab: Results of Every-Other-Week Dosing

- Of 104 responders, 60 patients in the pivotal MajesTEC-1 trial transitioned from weekly to every-other-week teclistamab dosing after achieving response
- Among patients switching from weekly to every-other-week dosing
  - CR rate: 82% (49/60)
  - VGPR rate: 18% (11/60)
- From the date of switch to every-other-week dosing
  - Median DOR: 20.5 months
  - At a median follow-up of 11.1 months from the switch, 67% of patients (40/60) remained in ongoing response
- Patients receiving less frequent dosing generally had deep responses to therapy
- Results suggest feasibility of long-term response with less frequent dosing

CR = complete response; VGPR = very good partial response.

Usmani SZ, et al. *J Clin Oncol*. 2023;41(suppl 16); Abstract 8034.

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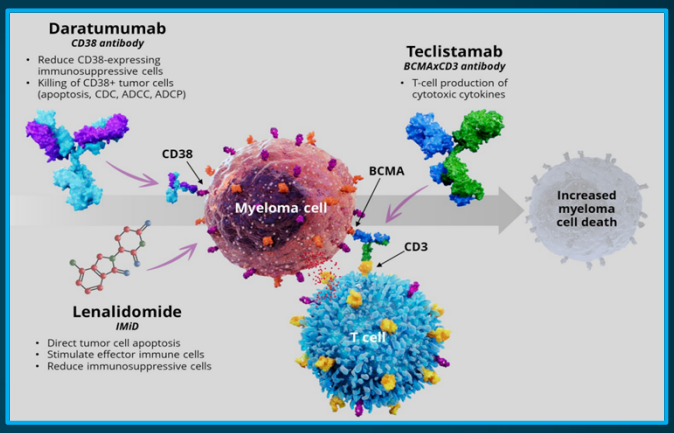
Teclistamab: MajesTEC-2 Study Design

- Phase 1b multicohort MajesTEC-2 (NCT04722146) trial evaluated combination therapy with teclistamab, daratumumab, and lenalidomide in patients with R/R MM
- Eligibility criteria included
  - Presence of measurable MM
  - Prior use of 1 to 3 lines of therapy, including IMiD and PI
- Primary endpoints included safety and dose-limiting toxicity



The combination of teclistamab, daratumumab and lenalidomide is an investigational combination and is not FDA-approved for the management of relapsed/refractory multiple myeloma.
ADCC = antibody-dependent cellular cytotoxicity; ADCP = antibody-dependent cellular phagocytosis; CDC = complement-dependent cytotoxicity; IMiD = immunomodulatory drug; PI = proteasome inhibitor.

Searle E, et al. *Blood.* 2022;140(suppl 1):394-396.

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Talquetamab: MonumenTAL-1 Study Design and Phase 2 Dose Recommendations

- MonumenTAL-1 (NCT03399799) phase 1 clinical study enrolled patients who had heavily pretreated R/R MM that had progressed with median of 6 previous lines of therapy or who could not receive these therapies without unacceptable side effects
- CD3 and GPRC5D receptor targeting bispecific antibody talquetamab was administered
  - SC QW, Q2W, or QM at doses ranging from 5 to 1600 µg per kilogram of body weight
- Evaluation of subset of patients receiving talquetamab at recommended phase 2 dose receiving either of 2 schedules
  - 405 µg per kilogram SC QW (n = 30), with ORR of 70% (95% CI, 51–85) at median follow-up of 11.7 months, with median DoR of 10.2 months
  - 800 µg per kilogram SC Q2W (n = 44), with ORR of 64% (95% CI, 48–78) at median follow-up of 4.2 months, with median DoR of 7.8 months

QM = every month; Q2W = every 2 weeks; QW = every week.

Chari A, et al. *N Engl J Med*. 2022;387:2232-2244.

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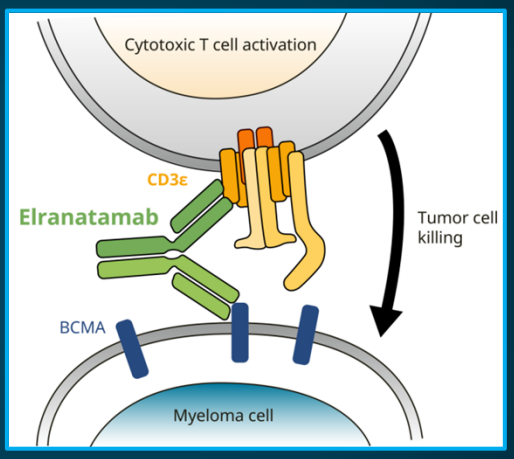
Elranatamab: Overview

- Bispecific BCMAxCD3 T-cell engaging antibody
- In phase 1 MagnetisMM-1 clinical study, 55 patients receiving elranatamab monotherapy at doses ≥215 µg/kg and up to 1000 µg/kg SC QW or Q2W demonstrated
  - ORR = 64% (95% CI, 50–75)
  - CR/sCR = 38% (21/55)
  - Median DoR in responders = 17.1 months (95% CI, 11.1 to not evaluable)
- ORR was lower (54%) in 13 patients treated with prior BCMA-directed therapy



Raje N, et al. American Society of Hematology (ASH) 2022; Abstract 158 (https://ash.confex.com/ash/2022/webprogram/Paper166494.html). Accessed 11/4/2023.

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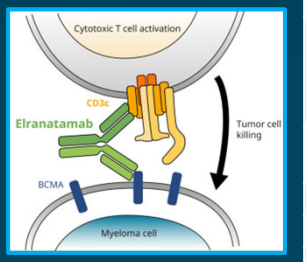
Elranatamab: MagnetisMM-3 Study Design

- MagnetisMM-3 is an open-label, phase 2 study of safety and efficacy of elranatamab monotherapy in patients with R/R MM
- 76 mg SC weekly on 28-day cycle, with 2-step-up priming dose regimen administered during first week
- Results in R/R MM and no prior BCMA-targeted treatment (Cohort A, N = 123) presented at ASH 2022



Bispecific BCMAxCD3 T-cell engaging antibody

Baseline characteristics (N = 123)	
Median age, median (range)	68.0 (36–89)
Male (%)	55.3
Ethnicity (%)	
White	58.5
Asian	13.0
Black or African American)	7.3
Prior lines of therapy, median (range)	5.0 (2–22)
Triple-class refractory (%)	96.7
Penta-drug refractory (%)	42.3
ECOG PS (%)	
0	36.6
1	57.7
2	5.7
High-risk cytogenetics (%)	25.2
R-ISS III (%)	15.4
Extramedullary disease (%)	31.7

ECOG PS = Eastern Cooperative Oncology Group performance status; R-ISS = Revised International Staging System.

Bahlis NJ, et al. ASH 2022; Abstract 159. Lesokhin AM, et al. *Nat Med*. 2023;29(9):2259-2267. Raje N, et al. American Society of Hematology (ASH) 2022; Abstract 158 (https://ash.confex.com/ash/2022/webprogram/Paper166494.html). Accessed 11/4/2023.

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