PRACTICE POINTS

Experts Debate: TREATMENT DECISIONS IN RELAPSED/REFRACTORY MULTIPLE MYELOMA

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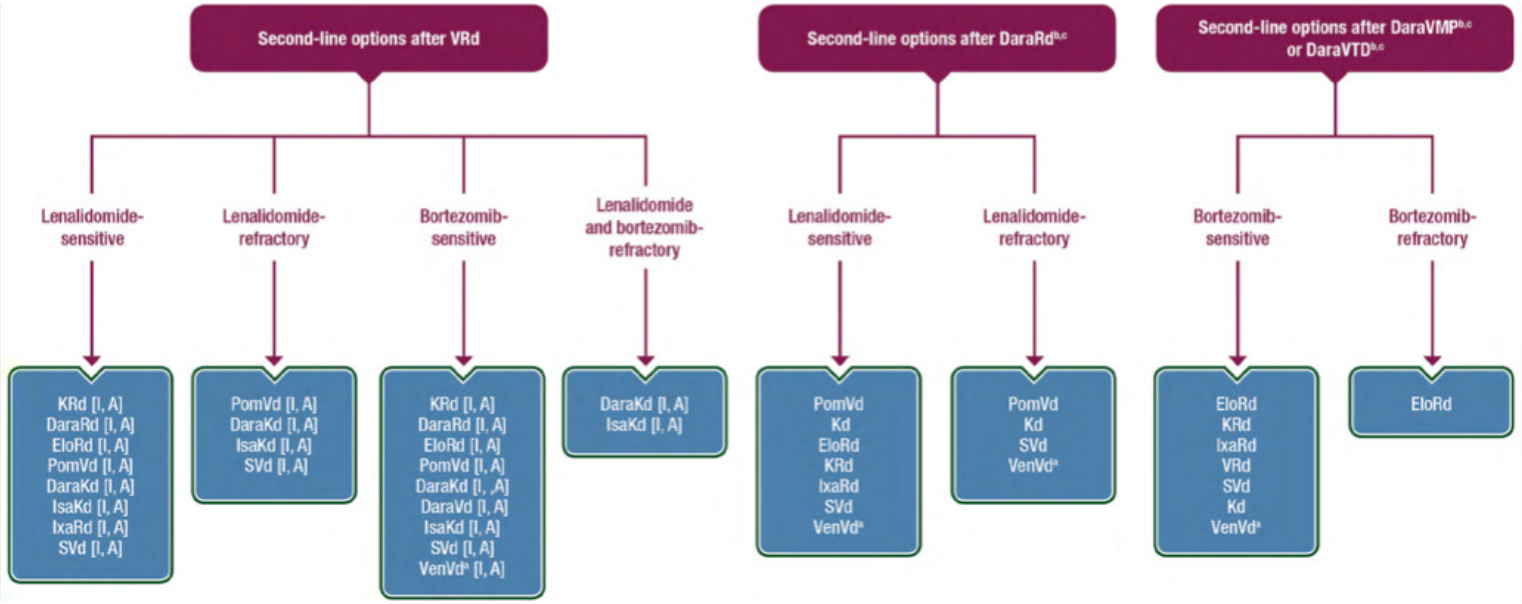
Debate #1: What is the Optimal Partner for CD38 Therapy at First Relapse – Proteasome Inhibitor (PI) or Immunomodulatory Drug (IMiD)?

Treatment Options for Patients at First Relapse



[a] Patients with t(11;14). [b] Patients who progress while on monthly daratumumab are considered as daratumumab-refractory. [c] All recommendations for patients who receive front-line therapy with daratumumab-based therapies are based on panel consensus as there are no trials evaluating regimens in second-line therapy that include patients refractory or exposed to daratumumab.

Dara, daratumumab; Elo, elotuzumab; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; Kd, carfilzomib/dexamethasone; MM, multiple myeloma; PomVd, pomalidomide/bortezomib/dexamethasone; Rd, lenalidomide/dexamethasone; S, selinexor; Vd, bortezomib/dexamethasone; Ven, venetoclax; VMP, bortezomib/melphalan/prednisone; VRd, bortezomib/lenalidomide/dexamethasone; VTD, bortezomib/thalidomide/dexamethasone.

Dimopoulos MA, et al. *Ann Oncol*. 2021;32:309-322.

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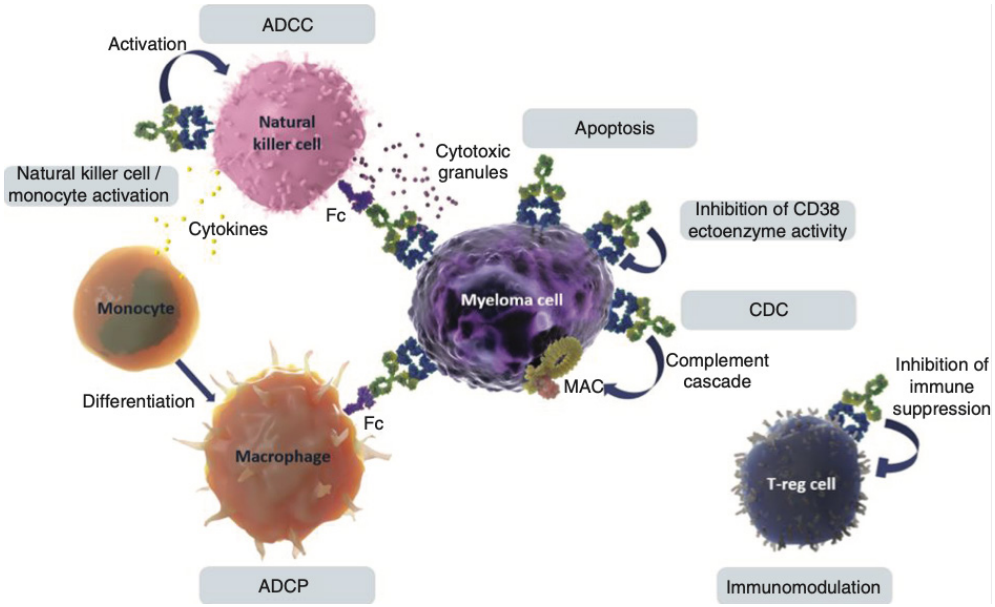
Isatuximab Summary

Isatuximab: a CD38-directed cytolytic antibody



FDA approved:

- In combination with pomalidomide and dexamethasone for patients who have received at least 2 prior therapies including lenalidomide and a PI
- In combination with carfilzomib and dexamethasone for patients who have received 1-3 prior lines of therapy

DOSING

10 mg/kg IV every week for 4 weeks, followed by every 2 weeks until disease progression or toxicity

- Premedicate with dexamethasone, acetaminophen, H2 antagonists, and diphenhydramine

- Counsel patients on infusion-related reactions, neutropenia, second primary malignancies, cardiac toxicities, interference with laboratory tests, and embryo-fetal toxicity

Moreau P, et al. *Future Oncol.* 2020;16:4347-4358. SARCLISA. Package insert. sanofi-aventis U.S., LLC; 2021.

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Experts Debate: Treatment Decisions in Relapsed/Refractory Multiple Myeloma

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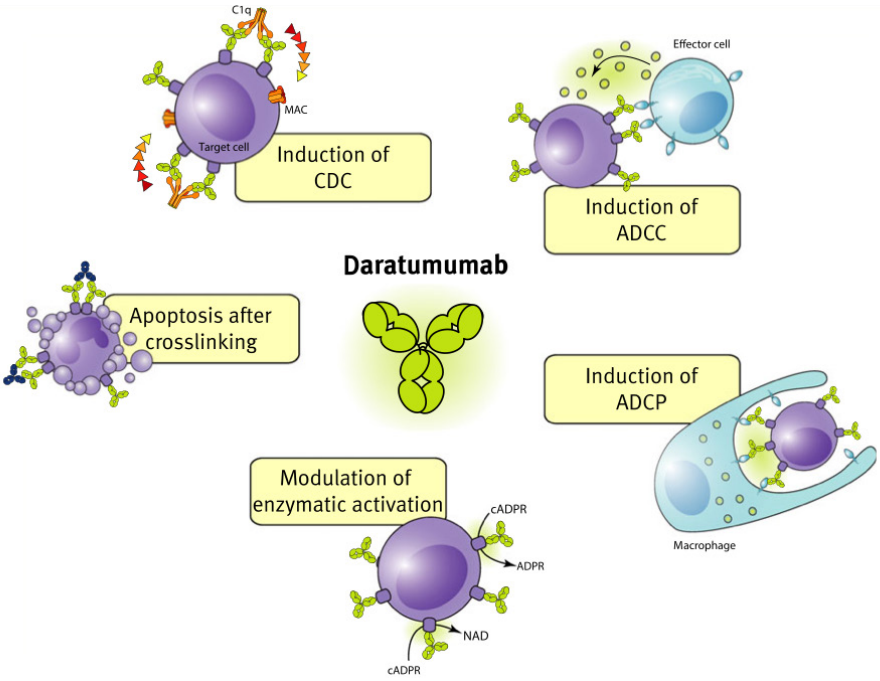
Daratumumab Summary

Daratumumab: a CD38-directed cytolytic antibody



FDA approved:

- Newly diagnosed MM: in combination with Rd, VMP, and VTd
- 1-3 prior therapies: in combination with Vd, Kd, Pd, or as monotherapy

DOSING

Recommended dose is 16 mg/kg actual body weight

- Premedicate with corticosteroids, antipyretics, and antihistamines

- **Warnings and precautions**: Infusion-related reactions, interference with cross-matching and RBC antibody screening, neutropenia, thrombocytopenia, and embryo-fetal toxicity

van de Donk NWCJ, et al. *Immunol Rev.* 2016;270(1):95-112. DARZALEX. Package insert. Janssen Biotech, Inc.; 2022.

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Debate #2: Is MRD Assessment Useful for Treatment Decisions?

Advantages and Disadvantages of MRD Detection Methods

Table 1 Advantages and disadvantages of MRD detection methods

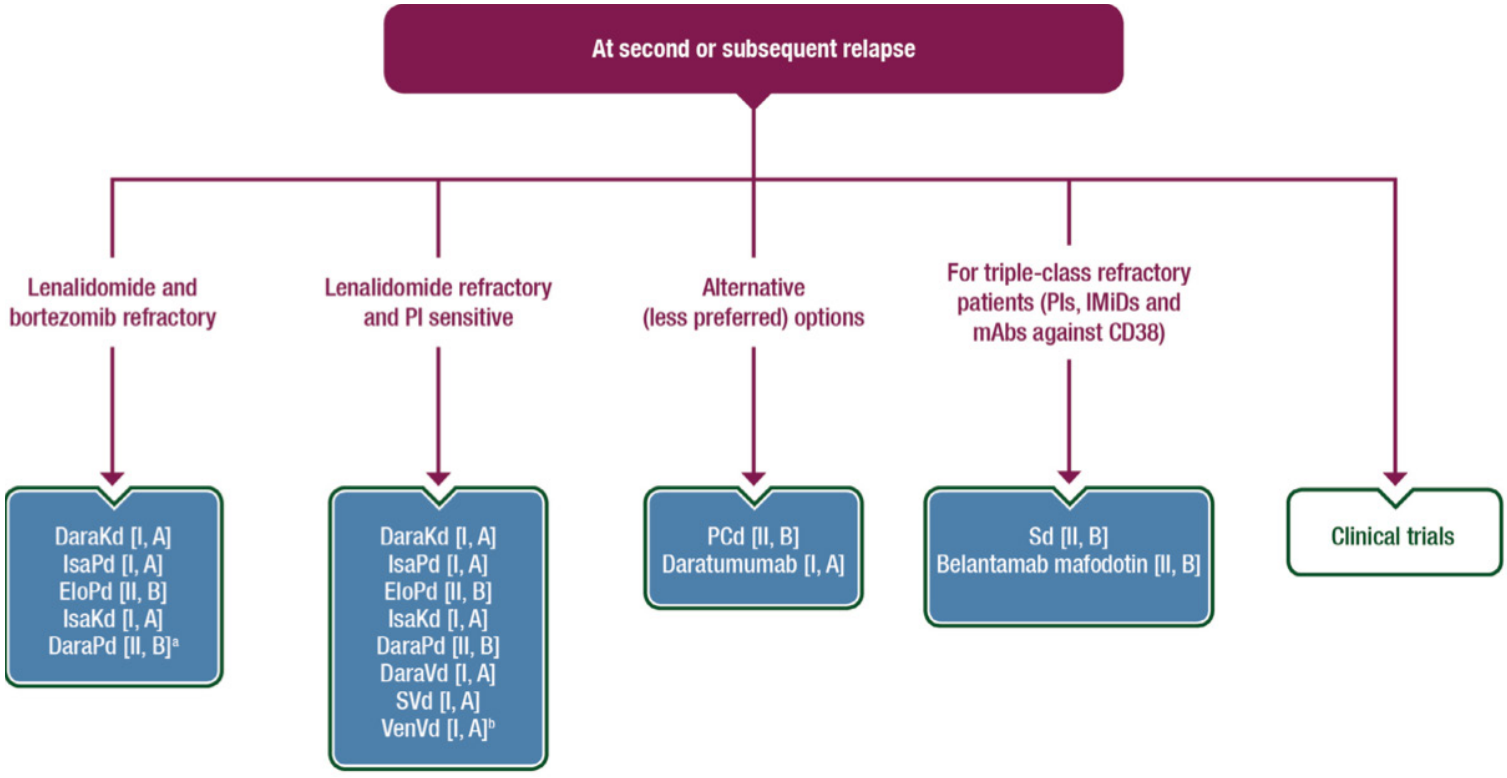
Techniques	Sensitivity	Advantages	Disadvantages
MFC --- Identification of MM cells by Flow cytometry analysis of MM-specific cell surface antigens.	10^{-4} (4–6 colour) 10^{-5} (8–10 colour)	1) Strong applicability (90–100%) 2) Fast, economical and efficient; 3) Built-in evaluation of sample quality; 4) Not affected by SHM and clonal evolution.	1) Need to be tested within 24-48 h; 2) Data analysis needs professional knowledge and technology; 3) Complex data visualization; 4) Cannot detect cytogenetic characteristics.
NGF ---Optimized version of MFC with higher sensitivity.	10^{-6}	1) Nearly 100% applicability; 2) EuroFlow Consortium standardization; 3) Highly automated; 4) Based on the analysis of large numbers of cells;	1) Need to be tested within 24-48 h; 2) Cannot detect clonal evolution; 3) Complex data analysis.
ASO-qPCR ---Identification of MM cells by amplifying MM-specific immuno-globulin gene rearrangement.	10^{-5}	1) Wide range of applications (it can be used in almost all laboratories); 2) Fully standardized detection method and data interpretation standards; 3) No need to process bone marrow samples immediately;	1) The applicability is reduced to 42–75% when using universal primers; 2) The construction of a standard curve will consume a large number of limited bone marrow DNA samples; 3) May provide false negative results.
NGS --- Identification of MM cells by sequencing the IGH/IGK/IGL loci.	10^{-6}	1) No need to process samples immediately and no need for a standard curve; 2) Can capture almost all Ig gene rearrangements; 3) Uses consensus primers for clonality detection and subsequent MRD analysis; 4) Adaptive Biotechnologies (Seattle, WA, US) standardization;	1) May be affected by SHM; 2) No sample built-in test; 3) It is time-consuming, labor-intensive, expensive, and cannot be universally used in clinics and laboratories; 4) Interpretation of results is really difficult, requiring high expertise.
FDG-PET/CT --- Identification of MM cells by assessing tumor metabolic aberration	Spatial resolution limit of approximately 5 mm	1) Residual active clonal plasma cells can be detected in residual osteolytic lesions; 2) Accurately maps the sites of bone and extra-medullary disease; 3) It is complementary to cellular or molecular-based techniques;	1) May provide false positive results, for example: recent use of chemotherapy or/and growth factors to induce bone marrow reconstitution; 2) May provide false negative results, for example: lack of hexokinase enzyme or use of high-dose steroids; 3) Significant cost.

ASO-qPCR, allele-specific oligonucleotide quantitative polymerase chain reaction; FDG-PET/CT, positron emission tomography with computed tomography using 18F-deoxyglucose; MFC, multiparameter flow cytometry; MRD, measurable residual disease; NGF, next-generation flow cytometry; NGS, next-generation sequencing.

Ding H, et al. *Biomark Res*. 2021;9:75.

Debate #3: What is the Optimal Class of Agents for Triple-Class-Refractory MM – Immunotherapy or Small Molecule Inhibitors?

Treatment Options for Patients at Second or Subsequent Relapse



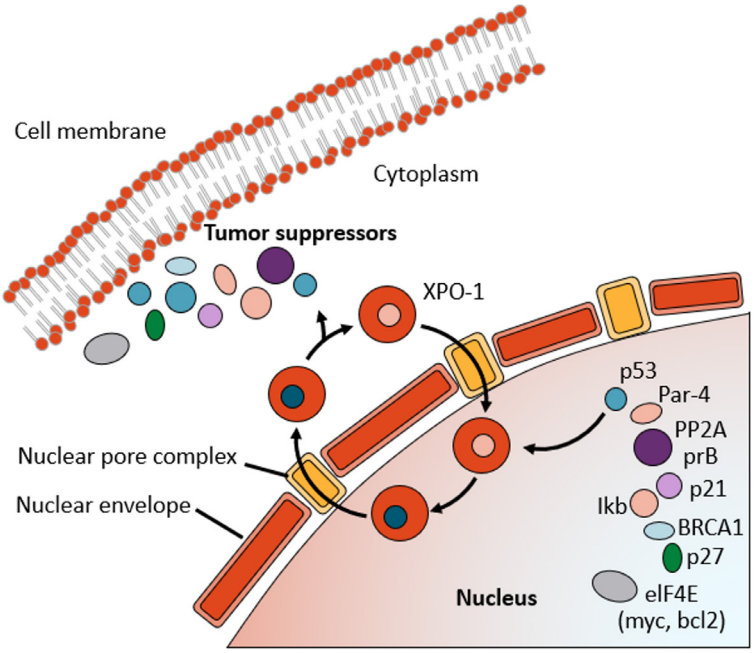
[a] Only phase IB data are published for DaraPd. Publication of phase III data are expected in 2021. [b] For patients with t(11;14).

Dara, daratumumab; Elo, elotuzumab; IMiD, immunomodulatory drug; Isa, isatuximab; Kd, carfilzomib/dexamethasone; mAb, monoclonal antibody; MM, multiple myeloma; PCd, pomalidomide/cyclophosphamide/dexamethasone; Pd, pomalidomide/dexamethasone; PI, proteasome inhibitor; S, selinexor; Sd, selinexor/dexamethasone; Vd, bortezomib/dexamethasone; Ven, venetoclax.

Dimopoulos MA, et al. *Ann Oncol*. 2021;32:309-322.

Selinexor Summary

Selinexor: an XPO1 inhibitor that induces nuclear retention and activation of TSPs and the GRPs in the presence of steroids and suppresses oncoprotein expression



FDA approved:

- In combination with Vd after ≥1 previous therapy
- In combination with dex after ≥4 previous therapies and refractory to ≥2 PIs, ≥2 IMiDs, and an anti-CD38 mAb

DOSING WITH Vd — **100 mg PO (five 20-mg tablets) once weekly**

DOSING WITH DEX — **80 mg PO (four 20-mg tablets) on days 1 and 3 of each week**

- Patients should take 5-HT3 antagonists and/or other antinausea agents (eg, olanzapine) prior to and during treatment with selinexor

- Counsel patients on what to expect when receiving selinexor; advise patients to maintain adequate fluid and caloric intake; help patients with tools to ensure compliance with oral therapy

XPOVIO. Package insert. Karyopharm Therapeutics Inc.; 2021. Gravina GL, et al. *J Hematol Oncol.* 2014;7:85. Culjkovic-Kraljacic B, et al. *Cell Rep.* 2012;2:207-215.

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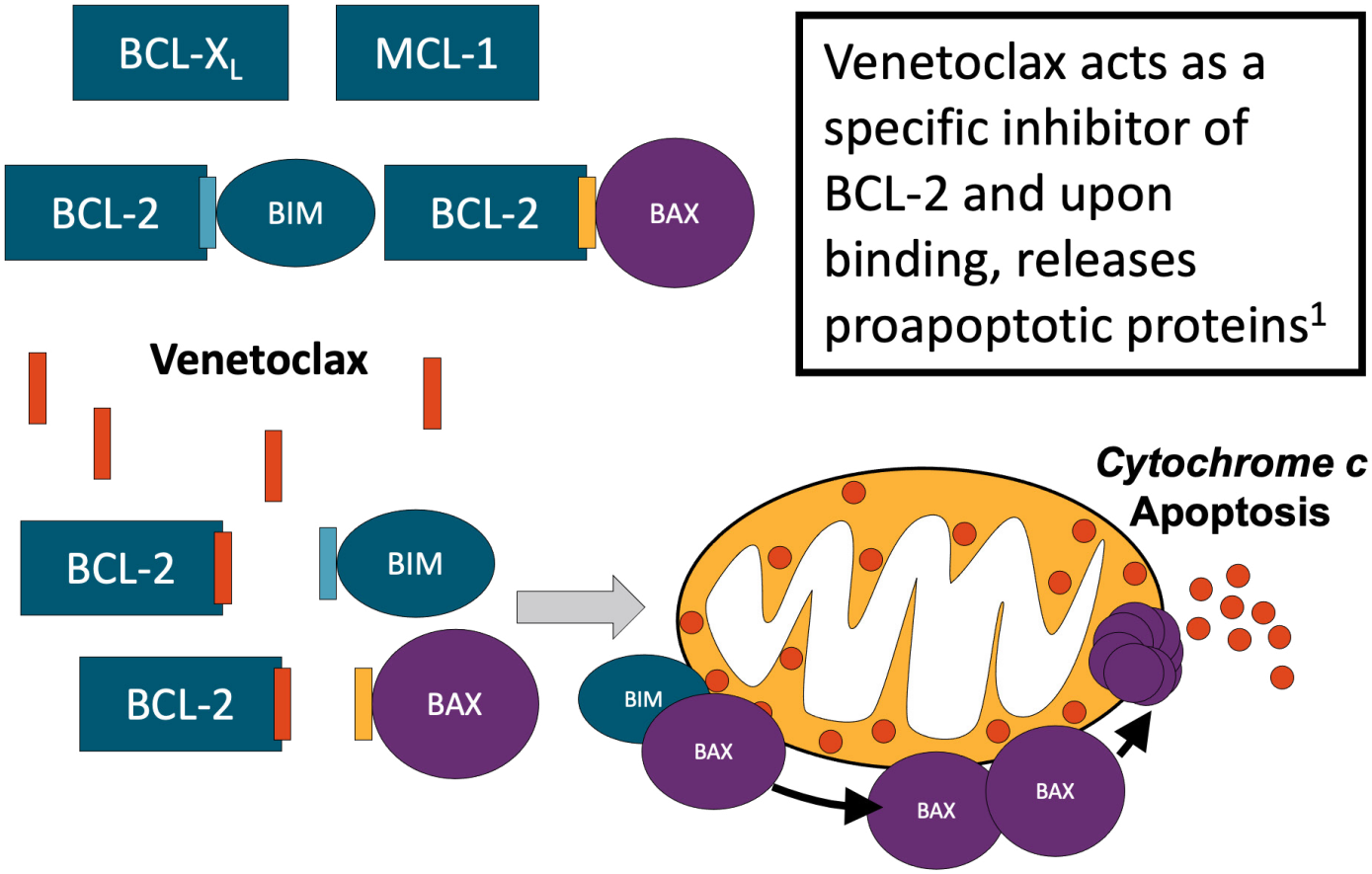
Venetoclax Summary

Venetoclax: a selective, potent, oral BCL-2 inhibitor



Venetoclax acts as a specific inhibitor of BCL-2 and upon binding, releases proapoptotic proteins[1]

- Induces cell death in MM cell lines and primary samples, especially those with t(11;14) translocation

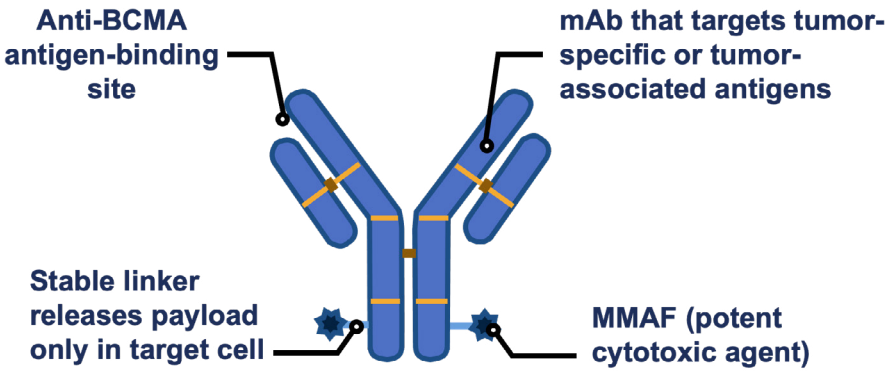
- t(11;14) translocation is associated with increased dependency upon BCL-2 for MM cell survival[3]

- Venetoclax is **not currently FDA approved** for myeloma but can be considered for off-label use in some circumstances

1. Kapoor I, et al. *Cell Death Dis*. 2020;11:941. 2. Touzeau C, et al. *Leukemia*. 2018;32:1899-1907. 3. Kumar. S, et al. *Blood*. 2017;130:2401-2409.

Belantamab Mafodotin Summary

Belantamab mafodotin: humanized, afucosylated, IgG1 BCMA-targeted ADC that neutralizes soluble BCMA



Cytotoxic agent	MMAF (highly potent auristatin)
Afucosylation	Enhanced antibody-dependent cellular cytotoxicity (ADCC)
Linker	Stable in circulation

FDA approved:

- For patients with R/R MM after ≥4 previous therapies including an anti–CD-38 mAb, a PI, and an IMiD

DOSING

2.5 mg/kg IV once every 3 weeks as infusion over 30 minutes

- Systemic steroids not required prior to initial infusion or in combination with belantamab, but patients should be monitored for infusion-related reactions
- Belantamab is only available through REMS program due to potential for ocular toxicity
- Counsel patients on what to expect when receiving belantamab, including about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose

Tai YT, et al. *Blood.* 2014;123:3128-3138. Trudel S, et al. *Lancet Oncol.* 2018;19:1641-1653. Trudel S, et al. *Blood Cancer* J. 2019;9:37. BLENREP. Package insert. Research Triangle Park: GlaxoSmithKline; 2020.

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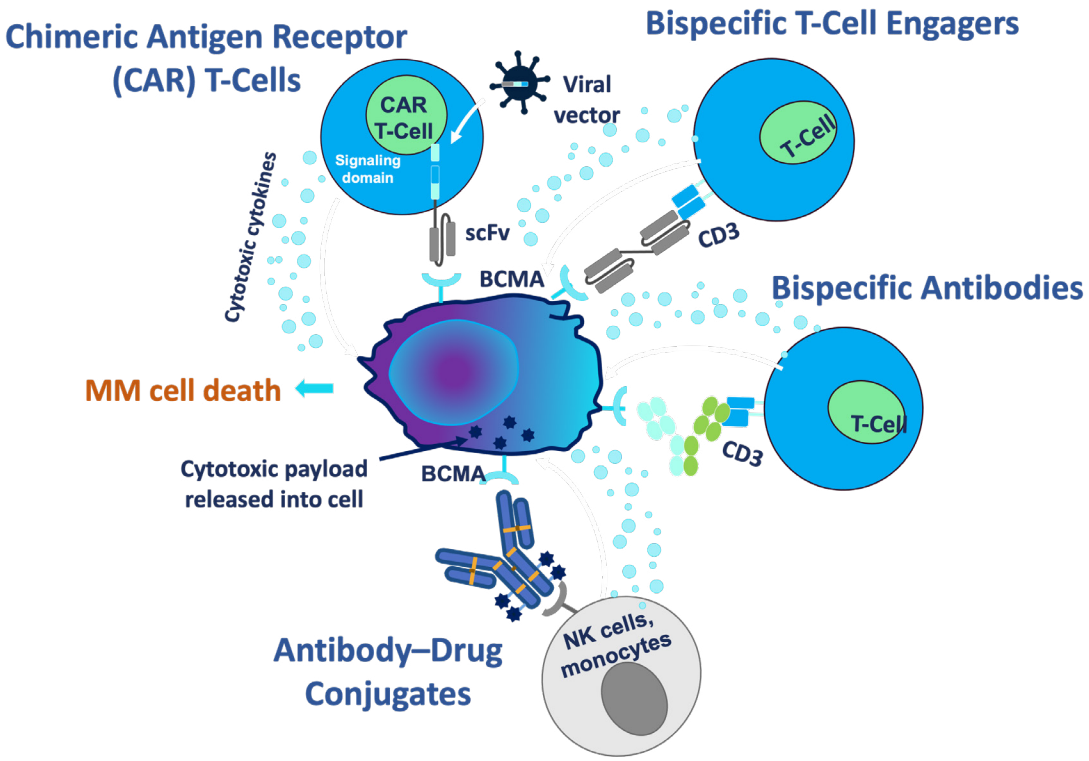
Debate #4: What is the Optimal Immunotherapy for Targeting BCMA – CAR T-Cells or Bispecific Antibodies?

BCMA in Multiple Myeloma



- Expressed on late memory B-cells committed to PC differentiation and PCs
- BCMA plays a role in survival of long-lived PCs
- γ-secretase cleaves BCMA from the cell surface, yielding soluble BCMA
- Other targets under investigation
  - GPRC5D
  - FcHR5
  - SLAMF7
  - CD38/138

Cho SF, et al. *Front Immunol.* 2018;10:1821.

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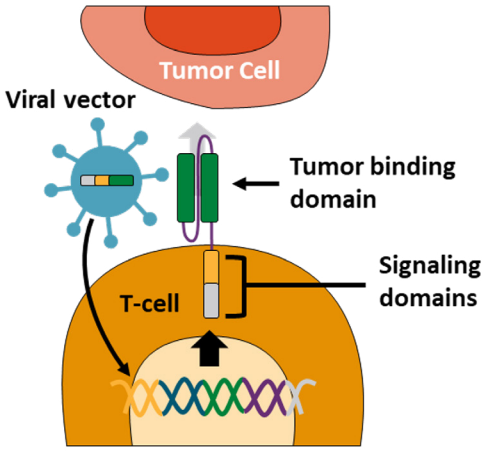
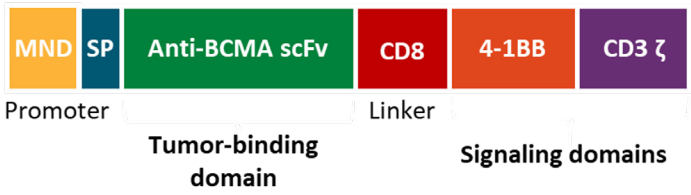
Idecabtagene Vicleucel Summary

Idecabtagene vicleucel: BCMA-directed genetically modified autologous CAR T-cell therapy



Idecabtagene CAR design



FDA approved:

- For patients with R/R MM after ≥4 previous lines of therapy including a PI, an IMiD, and an anti-CD38 mAb

DOSING

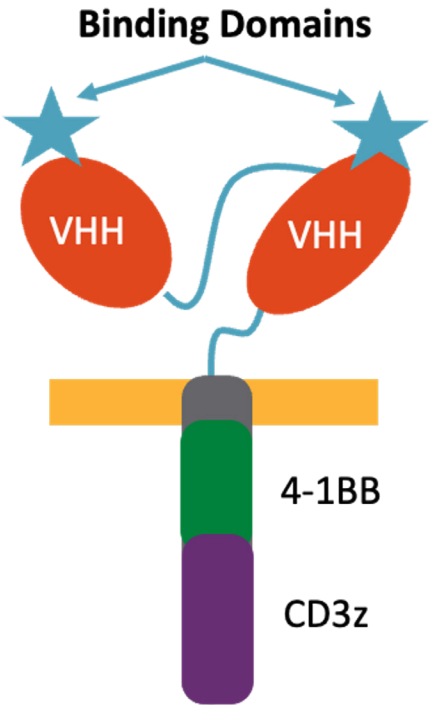
Recommended dose range:
300 to 460 × 10^6 CAR-positive T-cells

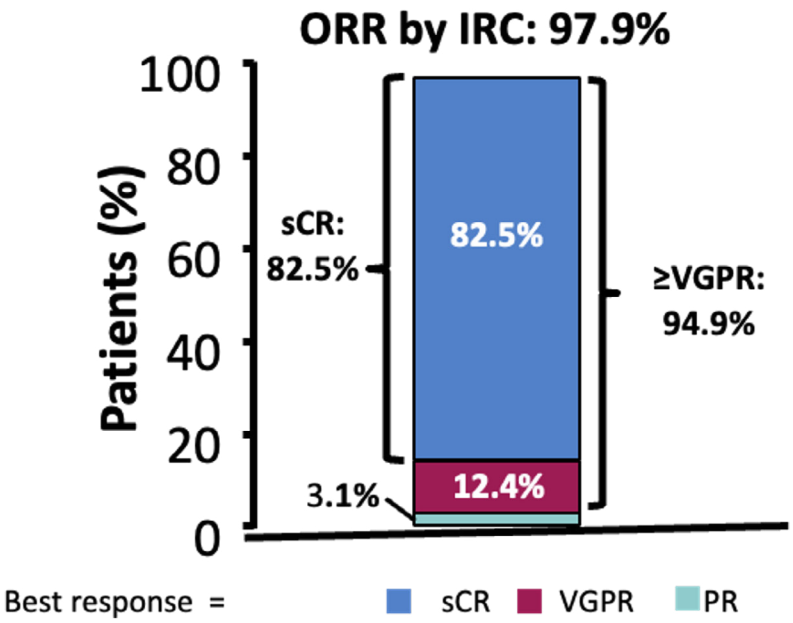
- Must be administered at certified healthcare facility under REMS; lymphodepleting chemotherapy regimen (cyclophosphamide and fludarabine) must be administered before infusion
- Premedicate with acetaminophen and H1-antihistamine, but avoid prophylactic use of systemic corticosteroids (eg, dexamethasone)
- Counsel patients on what to expect when receiving idecabtagene vicleucel, including the risk of CRS and neurotoxicity

ABECMA. Package insert. Summit, NJ: Celgene Corporation, a Bristol-Myers Squibb Company; 2021.

Ciltacabtagene Autoleucel Summary

Ciltacabtagene autoleucel: Contains 2 BCMA-targeting single-chain antibodies designed to confer avidity





Not yet FDA approved

CARTITUDE-1 DOSING

Target: 0.75 × 10^6 CAR T-cells (range 0.5-1 × 10^6)

PATIENT POPULATION

Patients with R/R MM and ≥3 prior regimens or double refractory to IMiD and PI and had received IMiD, PI, and anti-CD38 mAb (N=113)

Berdeja JG, et al. *Lancet.* 2021;398:314-324. Martin T, et al. ASH 2021. Abstr #549.

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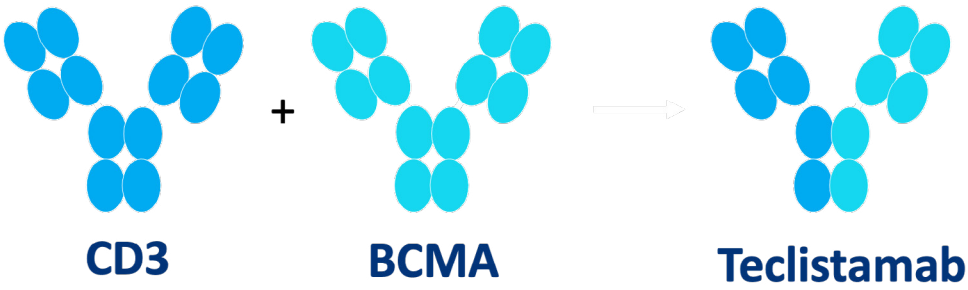
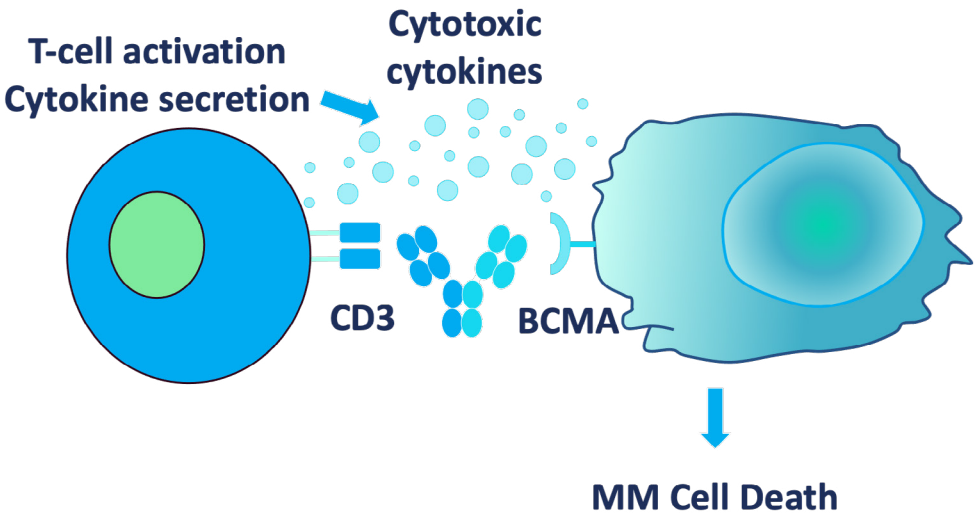
Teclistamab Summary





Not yet FDA approved

- Prognosis is poor for patients who progress on available classes of therapies, with ORR ~30%, mPFS of ~3 months, and mOS between 6 and 11 months[1]

- Teclistamab (JNJ-64007957): a humanized BCMA × CD3 bispecific IgG-4 antibody that redirects CD3+ T cells to BCMA-expressing MM cells

- Teclistamab induces T-cell–mediated killing of MM cells from heavily treated patients and in xenograft models[2-4]

1. Gandhi UH. *Leukemia.* 2019;33:2266-2275. 2. Labrijn AF, et al. *Proc Natl Acad Sci USA.* 2013;110:5145-5150. 3. Frerichs KA, et al. *Clin Cancer Res.* 2020;26:2203-2215. 4. Pillarisetti K, et al. *Blood Adv.* 2020;4:4538-4549.

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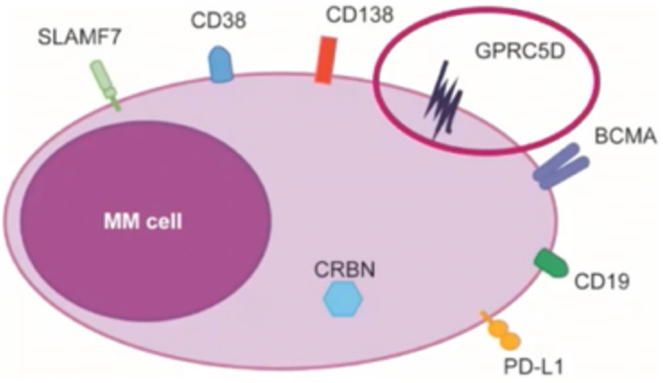
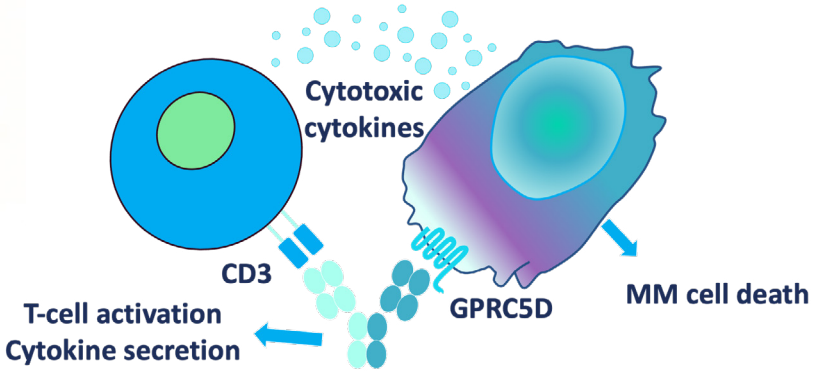
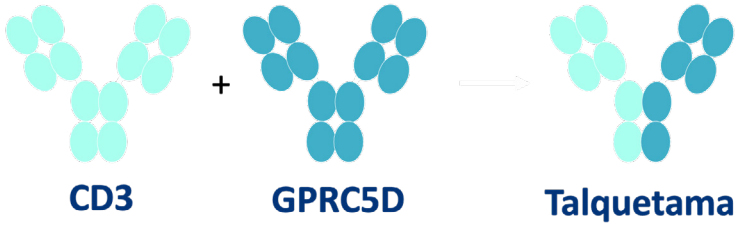
Talquetamab Summary







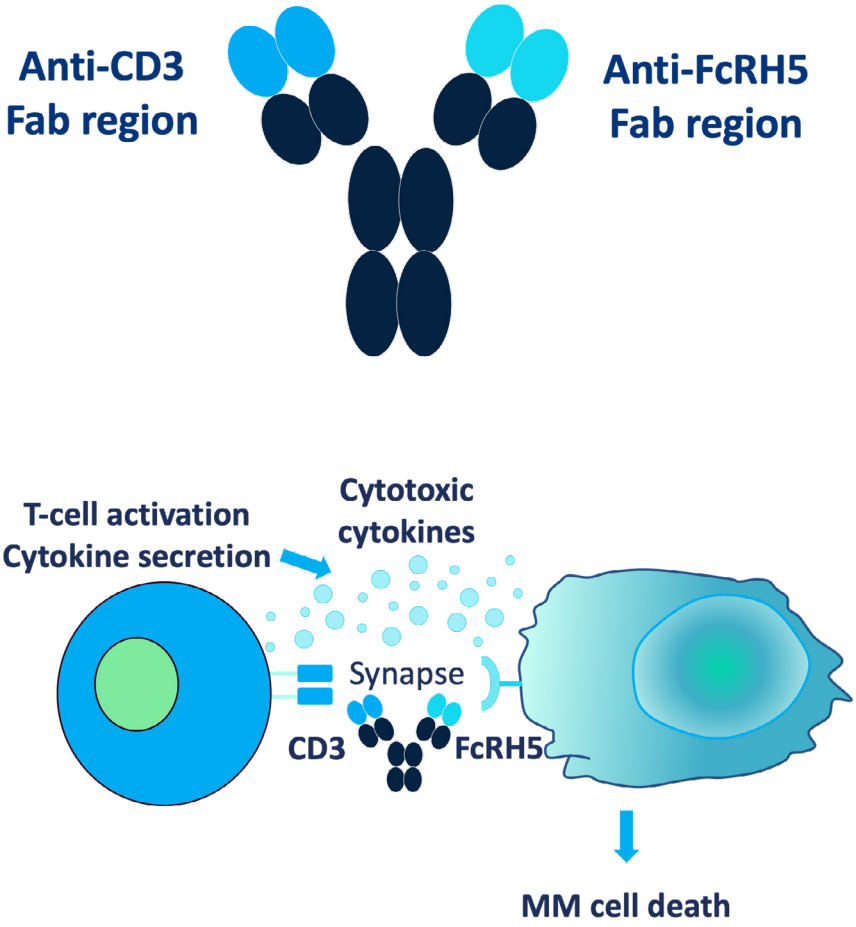
Not yet FDA approved

- GPRC5D × CD3 bispecific antibody
  - Orphan GPCR of unknown function with limited expression in healthy human tissue; primarily plasma cells and hair follicles
  - Highly expressed in MM cells and associated with poor prognostic features in MM
  - No known extracellular shedding

Berdeja JG, et al. ASCO 2021. Abstr #8008.

Cevostamab Summary

Cevostamab - a FcRH5 x CD3 Bispecific Antibody



Not yet FDA approved

- Fc receptor-homolog 5 (FcRH5)
  - Expressed on myeloma cells with near 100% prevalence
  - Also expressed on normal B cells, but higher in myeloma and plasma cells
  - Gene located on chromosome 1

- Cevostamab BFCR4350A:
  - Humanized IgG based FcRH5 × CD3 bispecific antibody

Cohen AD, et al. ASH 2020. Abstr #292.

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Summary of Bispecific Antibodies in R/R MM

Drug	Target	Efficacy	CRS
Teclistamab[1]	BCMA × CD3	65% ORR 40% CR or better	67% (99% were grade 1/2)
TNB-383B[2]	BCMA × CD3	79% ORR; 29% CR (doses ≥40 mg)	52% @ all doses 70 at doses ≥40 mg
Elranatamab[3]	BCMA × CD3	70% ORR; 30% CR/sCR (efficacious dose range 215–1000 µg/kg)	83% (none higher than grade 2)
Talquetamab[4]	GPRC5D × CD3	70% ORR @ 405 µg/kg weekly 71% ORR @ 800 µg/kg biweekly	73% @ 405 µg/kg weekly 78% @ 800 µg/kg biweekly
Cevostamab[5]	FcRH5 × CD3	55% ORR @ 160 mg 37% @ 90 mg	80% any grade 1% grade 3-4
REGN5458[6]	BCMA × CD3	93% ORR @ all dose levels 73% @ 96 and 200 mg	38% (34% grade 1 and 4% grade 2)

1. Moreau P, et al. ASH 2021. Abstr #896. 2. Kumar SK, et al. ASH 2021. Abstr #900. 3. Sebag M, et al. ASH 2021. Abstr #895. 4. Krishnan AY, et al. ASH 2021. Abstr #158. 5. Trudel S, et al. ASH 2021. Abstr #157. 6. Zonder J, et al. ASH 2021. Abstr #160.

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CAR T Cells vs Bispecific Antibodies: Advantages/Disadvantages

	CAR T Cells	Personalized
ADVANTAGES	Bispecific Antibodies	Off the shelf
	Targeted immuno-cytotoxicity	Targeted immuno-cytotoxicity
	Single infusion ("one and done")	No lymphodepletion Minimal steroids
	Potentially persistent	
DISADVANTAGES	FACT-accredited center required (hospitalization likely required)	Initial hospitalization required
	CRS and neurotoxicity; requires ICU and neurology services	CRS and neurotoxicity possible
	Dependent on T-cell health (manufacturing failures)	Dependent on T-cell health (T-cell exhaustion)
	Requires significant social support – caregiver required	Requires continuous administration

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