Agenda

Introduction

Where we stand with antibodies and CAR-T: regulatory updates

Pharmacy Clinical Consult Sessions

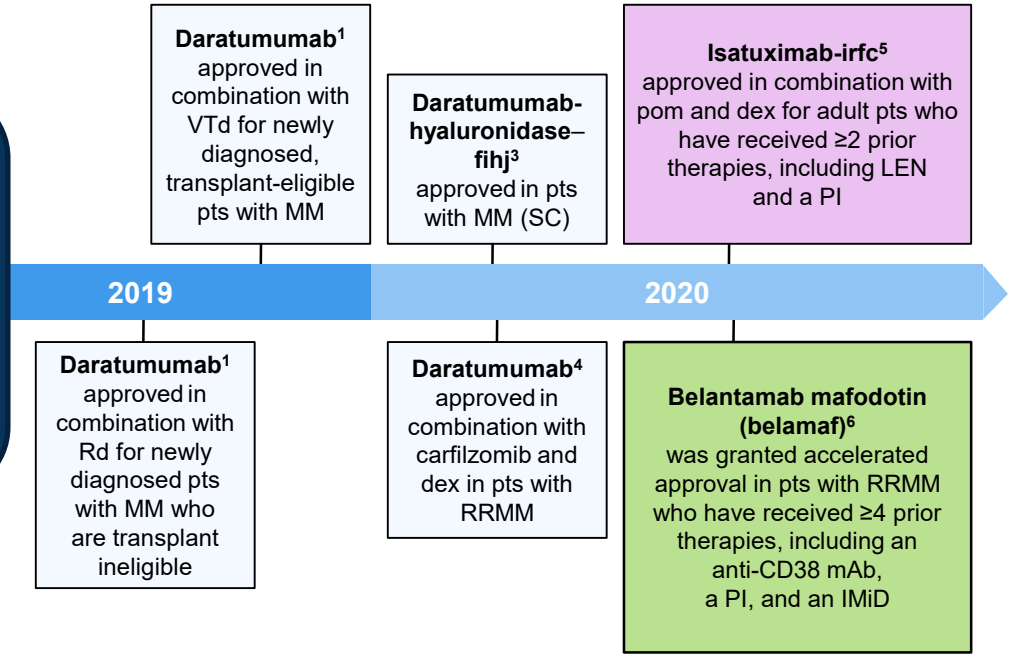
Case discussions and mini lectures on the evidence supporting antibodies and cellular therapy in RRMM and the role of pharmacists in patient care

CAR-T, chimeric antigen receptor T cell; RRMM, relapsed/refractory multiple myeloma.

Antibody Therapy in MM: Recent Approvals

Prior to 2019[1,2]

- ✓ Single-agent daratumumab approved in RRMM
- ✓ Daratumumab and elotuzumab approved in RRMM in combination with active doublets and triplets
- ✓ First approval of daratumumab combination therapy in NDMM (transplant ineligible)
- ✓ Daratumumab split-dosing regimen



CD, cluster of differentiation; dex, dexamethasone; IMiD, immunomodulatory drug; LEN, lenalidomide; mAb, monoclonal antibody; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; PI, proteasome inhibitor; pom, pomalidomide; Rd, lenalidomide and dexamethasone; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; VTd, bortezomib, thalidomide, and dexamethasone.

1. Darzalex (daratumumab) Prescribing Information. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX-pi.pdf. 2. Empliciti (elotuzumab) Prescribing Information. https://packageinserts.bms.com/pi/pi_empliciti.pdf. 3. Faspro (daratumumab-hyaluronidase–fihj) Prescribing Information. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX+Faspro-pi.pdf. 4. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-carfilzomib-and-daratumumab-dexamethasone-multiple-myeloma. 5. Sarclisa (isatuximab-irfc) Prescribing Information. http://products.sanofi.us/Sarclisa/sarclisa.pdf. 6. Blenrep (belantamab mafodotin-blmf) Prescribing Information. https://gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Blenrep/pdf/BLENREP-PI-MG.PDF.

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First Approval of BCMA CAR-T Therapy in MM and Additional Antibody Indications

Prior to 2019[1,2]

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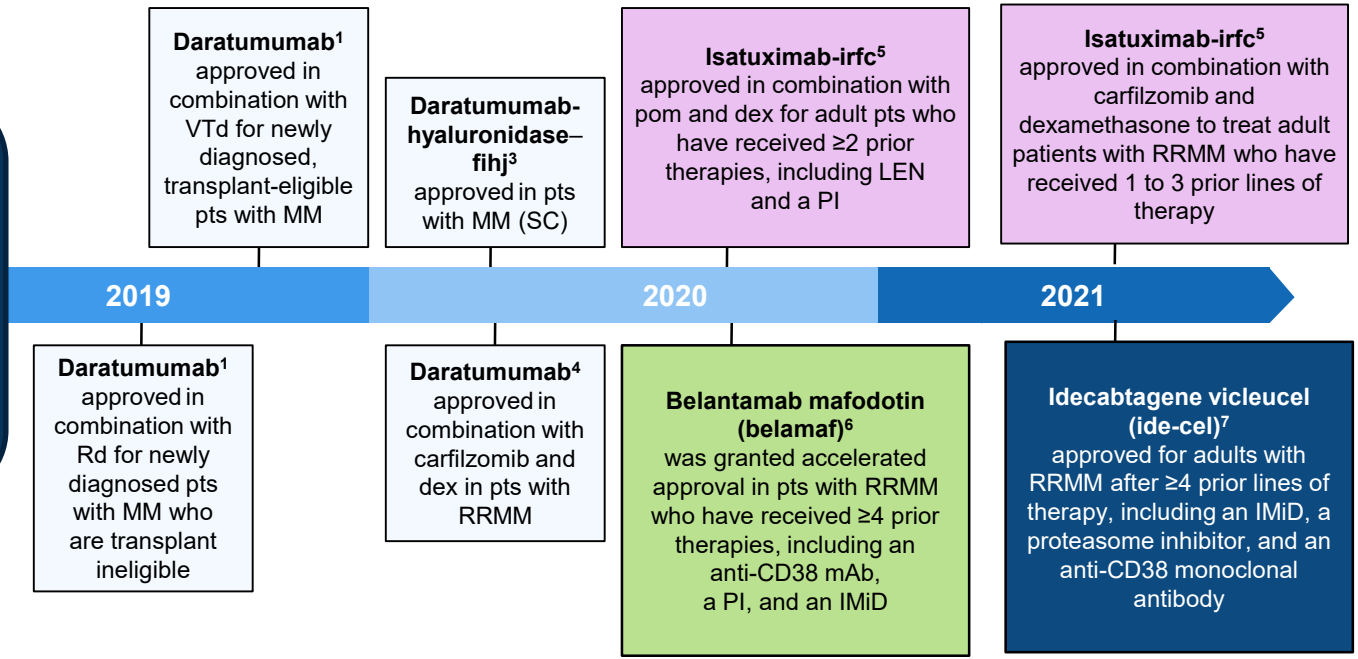

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Clinical Consult: A Patient Relapsing After ASCT and Lenalidomide Maintenance

- **Alex, a 56-year-old man with newly diagnosed symptomatic MM, PS of 0-1, ASCT eligible**
  - Receives VRd induction
  - Based on response (CR), proceeds to ASCT
  - Followed by lenalidomide maintenance
- **After 2 years, Alex shows signs of progression**

Is he eligible for an antibody-based triplet? Would his extended exposure to lenalidomide inform the choice of subsequent therapy?

ASCT, autologous stem cell transplant; CR, complete response; MM, multiple myeloma; PS, performance status; VRd, bortezomib, lenalidomide, and low-dose dexamethasone.

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Clinical Consult: Role of Pharmacy in Developing Appropriate Next Steps for This Patient

Provide education/counseling when starting a new treatment regimen

- Subcutaneous formulation preferred over IV daratumumab

Review all medications and screen for drug–drug interactions

Assess the impact of comorbidities, disease cytogenetics, and/or prior treatment toxicities on treatment selection

Recommend interventions for supportive care concerns

Submit appeals to insurance for denied medications

IV, intravenous.

Role of Antibodies in RRMM
NCCN Recommendations[1]

Preferred Antibody-Based Regimens, Category 1
Daratumumab + Vd or Kd or Rd
Isatuximab + pom-dex

Preferred category 1 triplets without antibodies: KRd, ixazomib + Rd, pomalidomide + Vd

Other Recommended Options With Antibody Components
Belantamab mafodotin
Daratumumab + VCd or pom-dex
Elotuzumab + Rd (category 1)
Elotuzumab + pom-dex or Vd

dex, dexamethasone; Kd, daratumumab and carfilzomib; KRd, carfilzomib, lenalidomide, and dexamethasone; NCCN, National Comprehensive Cancer Network; pom, pomalidomide; Rd, lenalidomide and dexamethasone; RRMM, relapsed/refractory multiple myeloma; VCd, bortezomib, cyclophosphamide, and dexamethasone; Vd, bortezomib and dexamethasone.

1. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. Version 5.2021. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf.

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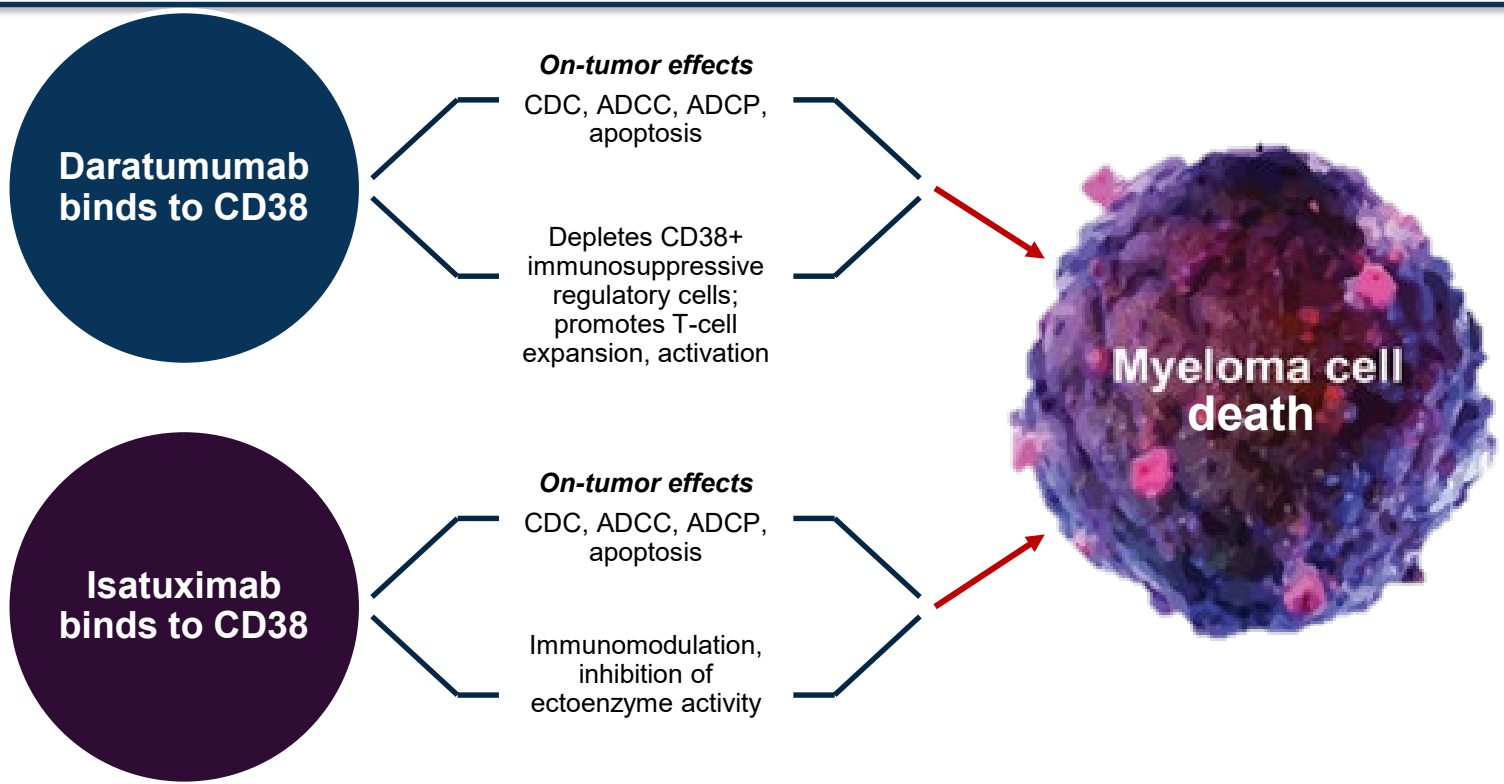
How CD38 Antibodies Work[1,2]



ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CD, cluster of differentiation; CDC, complement-dependent cytotoxicity.

1. Dimopoulos MD et al. 62nd American Society of Hematology Annual Meeting and Exposition (ASH 2020). Abstract 2325. 2. Moreau P et al. ASH 2020. Abstract 2316.

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IV Daratumumab in RRMM
Combination With Carfilzomib

- Building on prior studies testing the addition of daratumumab to IMiD and PI regimens, **CANDOR** tested a triplet with daratumumab and a carfilzomib platform[1]
- ***With ~11 months of additional follow-up, KdD continues to show PFS benefit in this RRMM population***

Outcomes, mo	KdD (n = 312)	Kd (n = 154)
Median PFS by ORCA	28.6	15.2

HR = 0.59 (0.45-0.78)

HR, hazard ratio; IMiD, immunomodulatory drug; IV, intravenous; Kd, daratumumab and carfilzomib; KdD, daratumumab, carfilzomib, and dexamethasone; ORCA, Onyx Response Computer Algorithm; PFS, progression-free survival; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma.

1. Dimopoulos MD et al. ASH 2020. Abstract 2325.

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SC Daratumumab in RRMM
Combination With Pomalidomide

- **APOLLO** tested SC daratumumab in combination with a pomalidomide platform in RRMM[1]
- ***After 16.9 months of median follow-up, the addition of SC daratumumab to pom-dex significantly improved PFS and led to a 37% reduction in risk of progression or death***

Outcomes, mo	D-Pd (n = 151)	Pd (n = 153)
Median PFS	12.4	6.9
HR = 0.63; *P* = .0018		
Median PFS in len-refractory pts	9.9	6.5

dex, dexamethasone; D-Pd, daratumumab, pomalidomide, and dexamethasone; HR, hazard ratio; len, lenalidomide; Pd, pomalidomide and dexamethasone; PFS, progression-free survival; pom, pomalidomide; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous.

1. Dimopoulos MD et al. ASH 2020. Abstract 412.

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Daratumumab Dosing

	SC[1]	IV[2]
Dosing	1,800 mg flat dose (15 mL)	16 mg/kg in 1,000 mL (dose 1), then 500 mL
Administration *Weekly for 8 weeks, then every other week for 16 weeks, then monthly*	SC push over 3-5 minutes	Infusion rates vary based on dose; range from ~1.5 to 8 hours
Comments/suggestions for pharmacy practice	Observe after cycle 1, day 1	Potential for split dose for cycle 1 and give 8 mg/kg over days 1 and 2

IV, intravenous; SC, subcutaneous.

1. Darzalex Faspro (daratumumab and hyaluronidase-fihj) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761145s000lbl.pdf.
2. Darzalex (daratumumab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761036s013lbl.pdf.

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Practical Considerations With Daratumumab for Pharmacists

AEs include hypersensitivity reactions, myelosuppression, fatigue, and risk for HBV reactivation

- Screen for hepatitis B core antibody and surface antigen prior to initiation and initiate prophylaxis if needed

Can interfere with the tests used to identify a patient's blood type

- Pretherapy blood screening and molecular phenotype tests can ensure the patient's blood type if RBC transfusion is required

AE, adverse event; HBV, hepatitis B virus; RBC, red blood cell.

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Hypersensitivity Reactions and Premedication With Antibodies in MM[1-3]

	IV Daratumumab	SC Daratumumab	Isatuximab
Hypersensitivity reactions, %	48	11	38-40
Required premedications	• Acetaminophen 650-1,000 mg • Diphenhydramine 25-50 mg • Dexamethasone 20 mg (pre/post infusion) OR • Methylprednisolone 100 mg	• Acetaminophen 650-1,000 mg • Diphenhydramine 25-50 mg • Dexamethasone 20 mg OR • Methylprednisolone 100 mg	• Acetaminophen 650-1,000 mg • Diphenhydramine 25-50 mg • Dexamethasone 40 mg • H_2 antagonist

H_2, histamine 2; IV, intravenous; MM, multiple myeloma; SC, subcutaneous.

1. Darzalex (daratumumab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761036s013lbl.pdf.
2. Darzalex Faspro (daratumumab and hyaluronidase-fihj) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761145s000lbl.pdf.
3. Sarclisa (isatuximab-irfc) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761113s000lbl.pdf.

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Clinical Consult: What If Alex Had Presented With a Clinically Significant Comorbid Condition?

- **Alex, a 56-year-old man with newly diagnosed symptomatic MM, PS of 0-1, ASCT eligible**
  - Receives VRd induction
  - Based on response (CR), proceeds to ASCT
  - Followed by lenalidomide maintenance
- **After 2 years, Alex shows signs of progression**
  - Testing confirms renal impairment, with eGFR 40 mL/min

ASCT, autologous stem cell transplant; CR, complete response; eGFR, estimated glomerular filtration rate; MM, multiple myeloma; PS, performance status; VRd, bortezomib, lenalidomide, and low-dose dexamethasone.

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Clinical Consult: Role of Pharmacy in Managing This Patient With Relapsed MM and Renal Impairment

Recommend any necessary dose modifications to MM-directed therapy due to organ function or tolerability concerns

Screen concomitant medications for renal dose adjustments

- For example, acyclovir, trimethoprim/sulfamethoxazole, entecavir, gabapentin, and pregabalin all require dose adjustments

Avoid nephrotoxic agents when possible and closely monitor renal function

Which CD38 monoclonal antibody would you choose?

CD, cluster of differentiation; MM, multiple myeloma.

Isatuximab in RRMM (ICARIA-MM)
Combination With Pomalidomide

- The **ICARIA-MM** trial tested isatuximab + Pd vs Pd alone in RRMM[1]
- ***Isa-Pd substantially improved PFS and responses and led to FDA approval in RRMM (adults receiving ≥2 prior therapies, including lenalidomide and a PI***

	Isa-Pd (n = 154)	Pd (n = 153)
Median PFS, mo	11.53	6.47

HR = 0.596; *P* = .001

Responses with Isa-Pd vs Pd
- ORR: 60% vs 35%
- VGPR: 27% vs 7%

FDA, Food and Drug Administration; HR, hazard ratio; Isa, isatuximab; ORR, overall response rate; Pd, pomalidomide and dexamethasone; PFS, progression-free survival; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; VGPR, very good partial response.

1. Attal M et al. *Lancet*. 2019;394:2096-2107.

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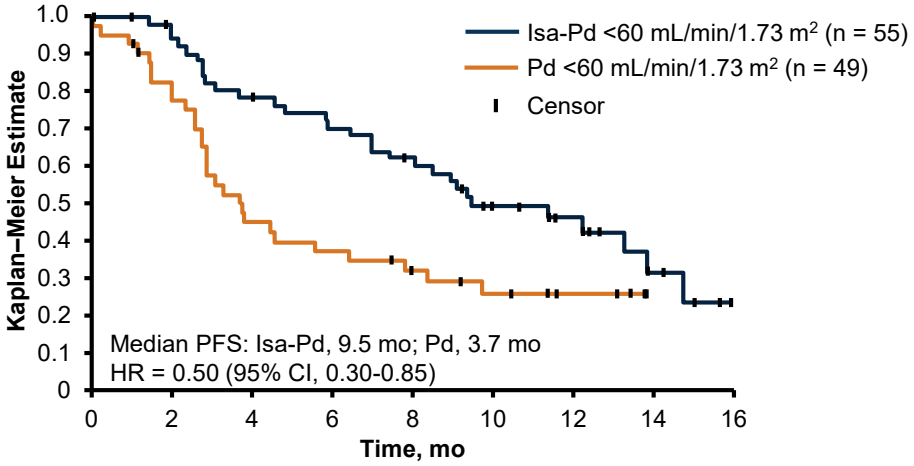
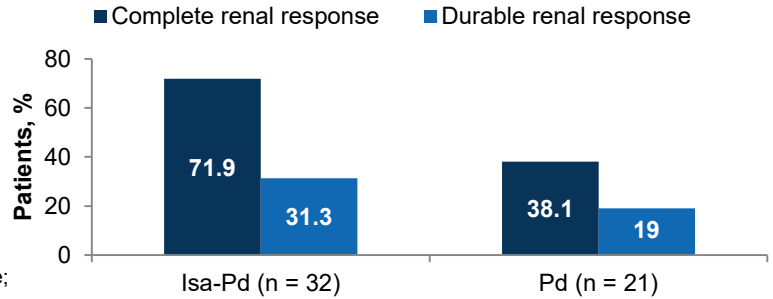
Outcomes With Isa-Pd in Patients With Renal Impairment
ICARIA Subgroup Analysis

- In patients with renal impairment, the addition of Isa to Pd improved PFS, ORR, and renal response rates[1]

- Isa pharmacokinetics were comparable between the subgroups, suggesting no need for dose adjustment in patients with renal impairment[1]





HR, hazard ratio; Isa, isatuximab; ORR, overall response rate; Pd, pomalidomide and dexamethasone; PFS, progression-free survival.

1. Dimopoulos MD et al. *Leukemia.* 2021;35:562-572.

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IKEMA: Isatuximab Plus a Carfilzomib Platform in RRMM

- The phase 3 **IKEMA** trial assessed Isa-Kd vs Kd in RRMM[1]
- **Isa-Kd resulted in a statistically significant improvement in PFS, corresponding to a 47% reduction in the risk of progression or death (leading to recent FDA approval)**

	Isa-Kd (n = 179)	Kd (n = 123)
Median PFS, mo	Not reached	19.15

HR = 0.531; *P* = .0007

- The MRD negativity rate with Isa-Kd was approximately 30% in the ITT population vs 13% in the Kd arm

- Isa-Kd showed a consistent benefit across multiple subgroups, including elderly patients, those with high-risk cytogenetics, and renally impaired patients

FDA, Food and Drug Administration; HR, hazard ratio; Isa, isatuximab; ITT, intent to treat; Kd, daratumumab and carfilzomib; MRD, minimal residual disease; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma.

1. Moreau P et al. ASH 2020. Abstract 2316.

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Isatuximab Dosing[1]

	IV
Dosing	10 mg/kg
Administration	*Every week for 4 weeks followed by every 2 weeks until disease progression or unacceptable toxicity* Infusion rate: ~3.5 hours
Comments	To date, not studied in patients who previously received daratumumab SC formations are being investigated in MM (NCT04045795)[2]

IV, intravenous; MM, multiple myeloma; SC, subcutaneous.

1. Sarclisa (isatuximab-irfc) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761113s000lbl.pdf.
2. https://clinicaltrials.gov/ct2/show/NCT04045795.

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Practical Considerations With Isatuximab for Pharmacists[1]

- AEs reported in clinical trials include infusion reactions (38%), upper respiratory tract infections (28%), and diarrhea (26%)
- Because of interference with serological testing, type and screen patients prior to starting therapy
  - Inform blood banks that a patient has received isatuximab
- For grade ≥2 infusion reactions, interrupt therapy and manage medically
- Neutropenia: monitor CBC periodically during treatment, and monitor patients with neutropenia for signs of infection

AE, adverse event; CBC, complete blood count.

1. Sarclisa (isatuximab-irfc) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761113s000lbl.pdf.

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Antibodies in NDMM: A Snapshot of the Evidence and Next Steps

MAIA

Established dara + Rd triplet as upfront therapy in NDMM (ASCT ineligible)[1]

GRIFFIN, CASSIOPEIA

Studies showing the efficacy of 2 quadruplets: dara + VRd or VTd, respectively (ASCT eligible)[4,5]

ALCYONE

Quadruplet with dara + VMP in ASCT-ineligible NDMM[2]

IsaKia

Phase 3 trial testing isa + KRd in NDMM (ASCT eligible; NCT04483739)[3]

ASCT, autologous stem cell transplant; dara, daratumumab; isa, isatuximab; KRd, carfilzomib, lenalidomide, and dexamethasone; NDMM, newly diagnosed multiple myeloma; Rd, lenalidomide and dexamethasone; VMP, bortezomib, melphalan, and prednisone; VRd, bortezomib, lenalidomide, and low-dose dexamethasone; VTd, bortezomib, thalidomide, and dexamethasone.

1. Facon T et al. *N Engl J Med*. 2019;380:2104-2115. 2. Mateos M-V et al. *Lancet*. 2020;395:132-141.
3. https://clinicaltrials.gov/ct2/show/NCT04483739. 4. Moreau P et al. *Lancet*. 2019;394:29-38. 5. Kaufman J et al. ASH 2020. Abstract 549.

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Audience Q&A

How have you been recommending or modifying the dosing and scheduling of CD38 antibodies during the COVID pandemic?

CD, cluster of differentiation; COVID, coronavirus disease.

Clinical Consult: Treatment Choices for a Patient With RRMM and Prior Antibody Therapy

- **Helen, a 73-year-old woman with RRMM who has failed 4 lines of prior therapy**
  - Therapeutic history includes exposure to a multiagent proteasome inhibitor, an IMiD, and antibody platforms (daratumumab)
  - PS of 1
  - Has a history of pseudophakia and 1 vascular event and has had cataract surgery

Is she a candidate for BCMA ADC therapy?

ADC, antibody–drug conjugate; BCMA, B-cell maturation antigen; IMiD, immunomodulatory drug; PS, performance status; RRMM, relapsed/refractory multiple myeloma.

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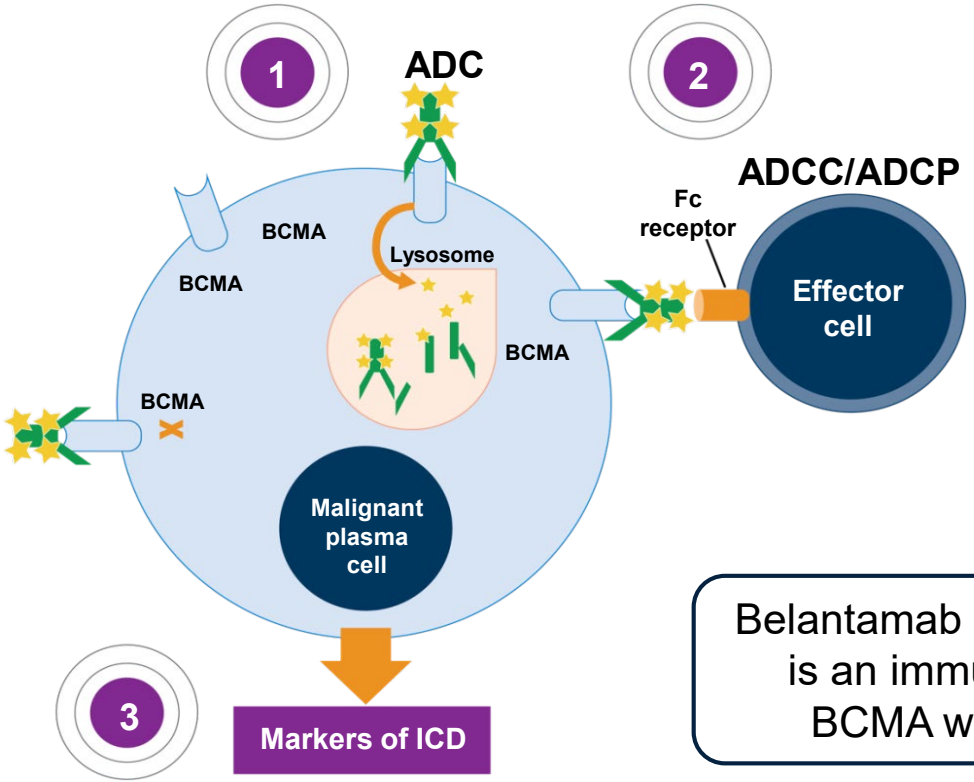
Clinical Consult: Role of Pharmacy in Developing a Management Plan for This Patient

- Coordinating REMS program
- Monitoring for ocular events/eye examination timing
- Need for premedications?
- Prepare to counsel patient and staff on safety expectations with belamaf

REMS, Risk Evaluation and Mitigation Strategy.

Belantamab Mafodotin: MOA and Early Evidence[1]



Belantamab mafodotin (GSK2857916) is an immunoconjugate targeting BCMA with a multimodal MOA

ADC, antibody-drug conjugate; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; BCMA, B-cell maturation antigen; Fc, fragment crystallizable; ICD, immunogenic cell death; MOA, mechanism of action.

1. Lonial S et al. *Lancet Oncol*. 2020;21:207-221.

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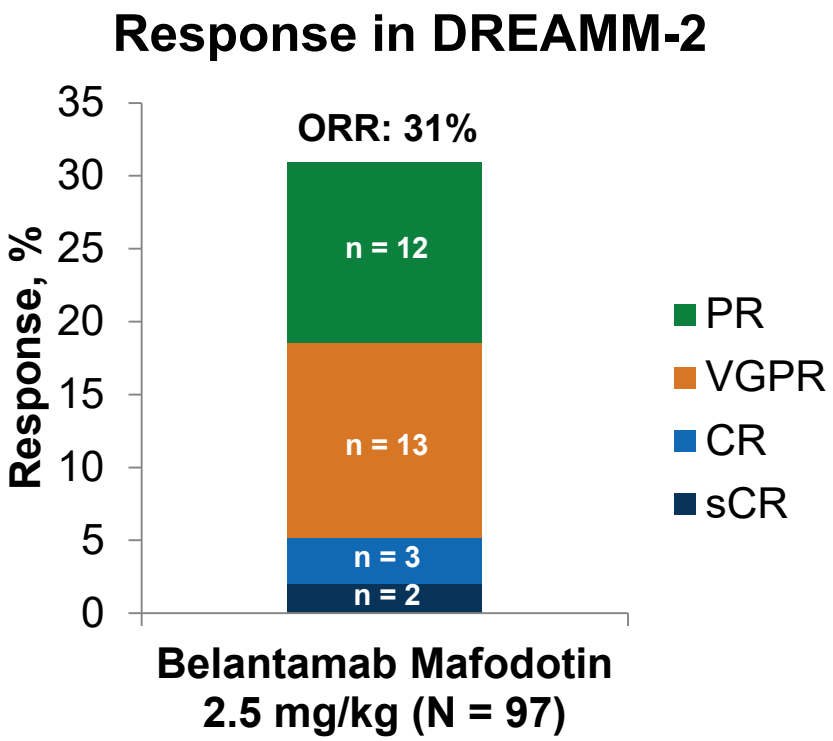
DREAMM-2: Single-Agent Belantamab Mafodotin in Heavily Pretreated RRMM

- In the **DREAMM-2 trial**, single-agent belantamab mafodotin showed clinically meaningful activity and manageable safety in patients with heavily pretreated RRMM[1]
- ***After longer follow-up, clinically meaningful responses were sustained despite dose modifications with longer follow-up***



CR, complete response; ORR, overall response rate; PR, partial response; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; VGPR, very good partial response.

1. Lonial S et al. 2020 American Society of Clinical Oncology Virtual Scientific Program (ASCO 2020). Abstract 8536.

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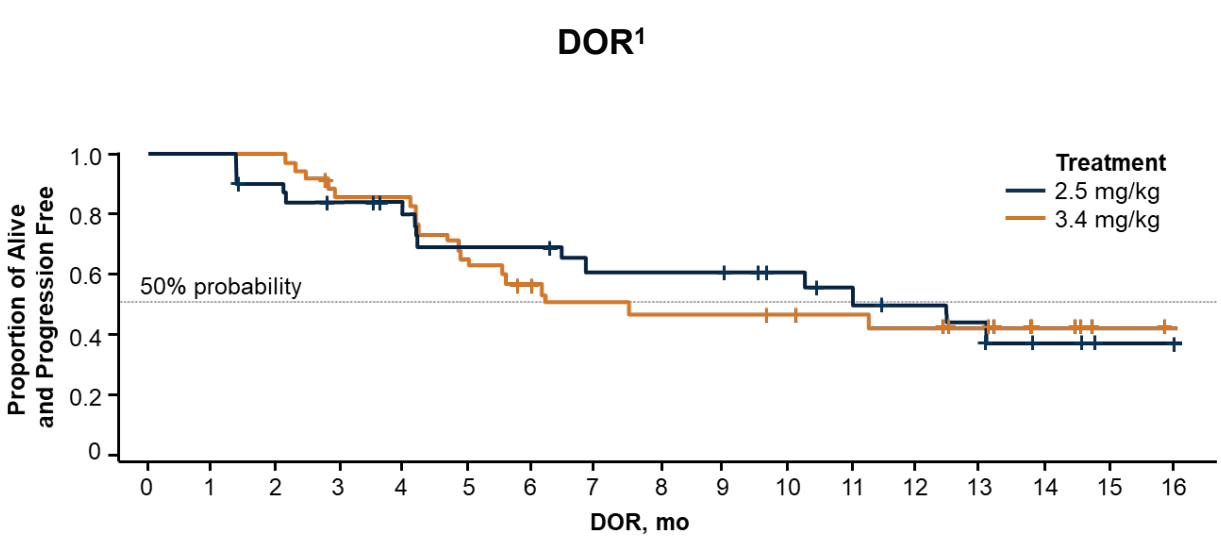
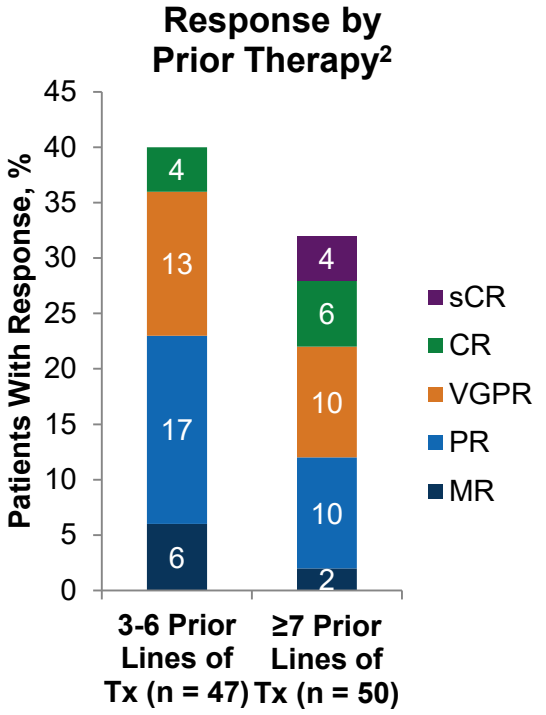
DOR and Response by Prior Therapy With Belantamab Mafodotin (DREAMM-2)





CR, complete response; DOR, duration of response; MR, minimal response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

1. Lonial S et al. ASCO 2020. Abstract 8536. 2. Lonial S et al. ASH 2020. Abstract 1417.

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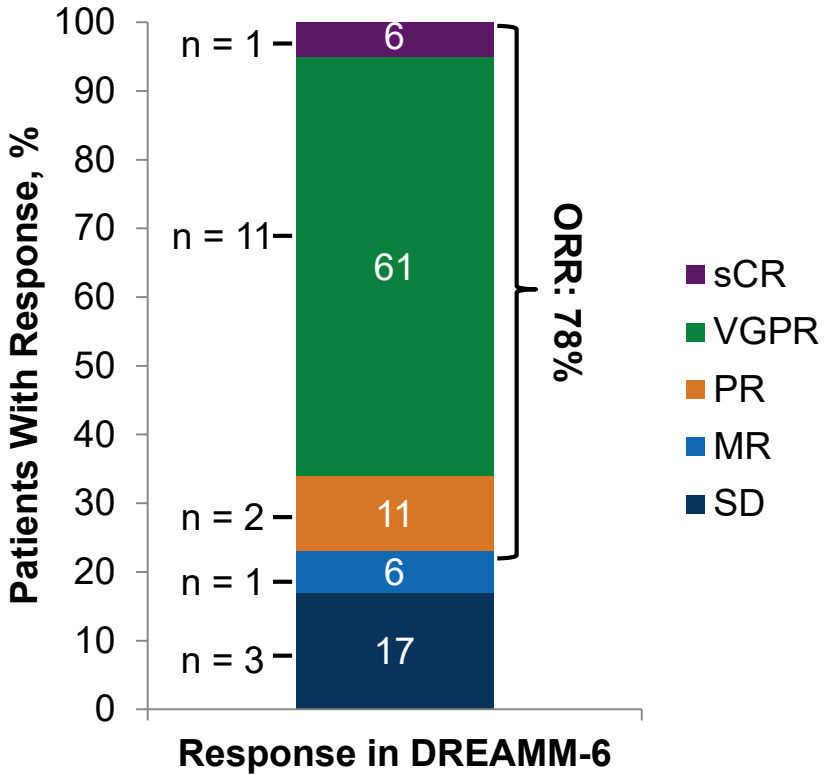
DREAMM-6: Belantamab Mafodotin + Vd

- **DREAMM-6** tested belamaf in combination with Vd (multiarm study) in RRMM[1]
- ***Belamaf 2.5 mg/kg Q3W with standard-of-care Vd appears to be active and safe in patients receiving ≥3 prior lines of therapy (including bortezomib and daratumumab)***



Belamaf, belantamab mafodotin; MR, minimal response; ORR, overall response rate; PR, partial response; Q3W, every 3 weeks; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; SD, stable disease; Vd, bortezomib and dexamethasone; VGPR, very good partial response.

1. Popat R et al. ASH 2020. Abstract 1419.

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Belamaf Dosing and Administration Recommendations[1,2]

- Dosing: 2.5 mg/kg as an IV infusion over approximately 30 minutes once every 3 weeks[1]

- Prescribers must be certified with the program by enrolling and completing training in REMS program[2]
  - Patients must be enrolled in REMS program and comply with monitoring

- Counsel patients about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose

Belamaf, belantamab mafodotin; IV, intravenous; REMS, Risk Evaluation and Mitigation Strategy.

1. Blenrep (belantamab mafodotin-blmf [belamaf]) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761158s000lbl.pdf.
2. https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=403.

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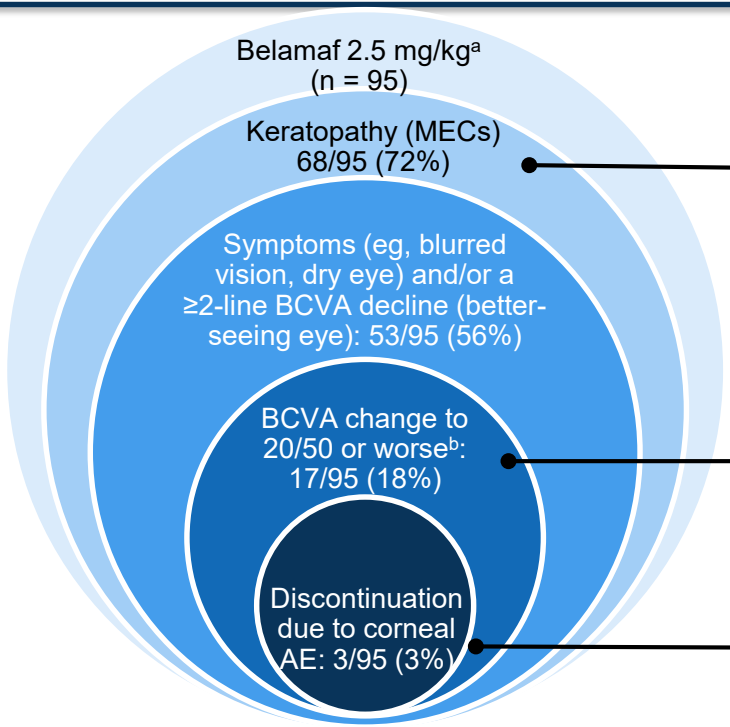
Keratopathy Can Occur With or Without Symptoms[1]



In patients with keratopathy (MECs) events grade ≥2 per KVA, 48% (29/60) had >1 event

Of these patients, 76% (13/17) had 1 event and 24% (4/17) had 2 events (no patients had >2 events)

1 patient discontinued due to keratopathy (MECs), 1 due to blurred vision, and 1 due to reduced BCVA

1 patient experienced a worsening of BCVA to 20/200 in their better-seeing eye who recovered to baseline[c]

1 patient developed a grade 4 corneal ulcer[d]

AE, adverse event; BCVA, best-corrected visual acuity; belamaf, belantamab mafodotin; CTCAE, Common Terminology Criteria for Adverse Events; KVA, Keratopathy and Visual Acuity; MEC, microcyst-like epithelial changes.

[a] Only data from the approved dose of 2.5 mg/kg are presented. [b] Better-seeing eye; represents threshold at which activities of daily living (eg, legal driving) become affected. [c] 20/200, the threshold for legal blindness in many countries. [d] CTCAE scale event grading: 1 patient (with a history of cataract surgery in the right eye) developed a central corneal ulcer that resolved 9 days after onset with the use of topical antibiotics.

1. Lonial S et al. ASH 2020. Abstract 3224.

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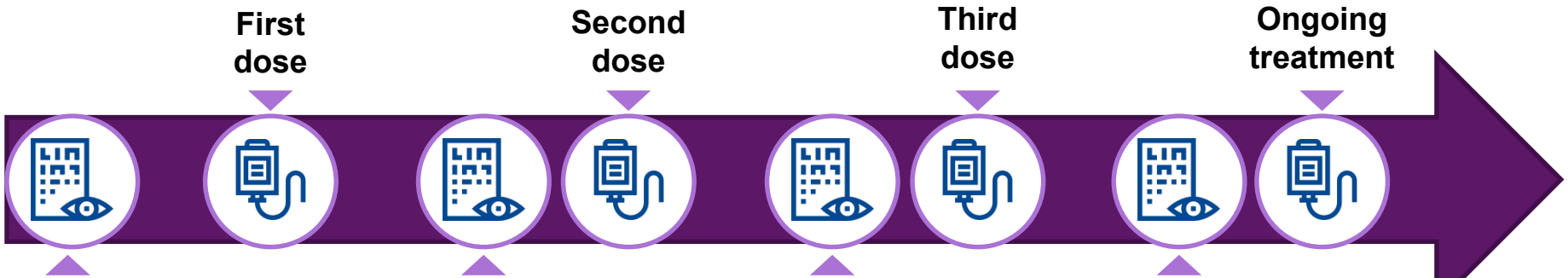
Monitoring and Preventive Measures for Ocular Toxicity With Belamaf[1]

Pharmacy can coordinate *ophthalmic examinations (visual acuity and slit lamp); baseline examinations* ***within 3 weeks prior to the first dose***

Follow-up examination ***at least 1 week after the previous dose and within 2 weeks prior to the next dose***

Use preservative-free lubricant eye drops at least 4x daily starting with the first infusion until the end of treatment ***(no benefit with steroid drops)***



Baseline eye exam, including slit lamp and visual acuity, prior to initial dose

Eye exam prior to each dose

Eye exam prior to each dose

Eye exam prior to each dose

Belamaf, belantamab mafodotin.

1. Blenrep (belantamab mafodotin-blmf [belamaf]) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761158s000lbl.pdf.

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Additional Pharmacy Practice Recommendations for Use of Belantamab Mafodotin

- Eye care
  - When counseling on preservative-free artificial tears: 2-4 drops in each eye 4 times daily
  - Cooling eye mask may be applied during infusion
  - Instruct patients to avoid contact lenses
  - Dose holds for higher-grade events

- Platelet transfusions may be needed for thrombocytopenia

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Take-Homes on Belamaf and the Role of Pharmacy

- Activity shown in heavily pretreated patients
  - Most responses occur early in therapy and are prolonged in duration
- The possibility of ocular adverse events requires ongoing monitoring, counseling, and scheduled lubricant eye drops
  - Blurred vision, dry eyes, photophobia
  - Most events occur within the first 2 cycles and are reversible with drug holds and/or dose reductions
- Infusion reactions may occur; no premedications are recommended unless treatment-emergent events occur

Belamaf, belantamab mafodotin.

Clinical Consult: An Alternate Scenario

- **Reimagining Helen's case: a 73-year-old woman with RRMM who has failed 4 lines of prior therapy**
  - Therapeutic history includes exposure to a multiagent proteasome inhibitor, an IMiD, and antibody platforms (daratumumab)
  - PS of 1
  - Has a history of pseudophakia and 1 vascular event and has had cataract surgery
  - Patient elects to pursue treatment with CAR-T therapy

CAR-T, chimeric antigen receptor T cell; IMiD, immunomodulatory drug; PS, performance status; RRMM, relapsed/refractory multiple myeloma.

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Why CAR-T Therapy Is an Option for This Patient and the Role of Pharmacy in Subsequent Care

BCMA CAR-T is a highly effective and now approved option in heavily pretreated MM

- Including for patients exposed to prior IMiD, PI, and CD38 antibody therapy

Role of pharmacy in care coordination with cellular therapy

- Educating staff and patients on the CAR-T process and the unique efficacy and safety profiles
- Coordination of lymphodepletion (premedication, avoid steroids)
- ICANS/CRS: develop protocols for use of tocilizumab, steroids

BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; CD, cluster of differentiation; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; IMiD, immunomodulatory drug; PI, proteasome inhibitor.

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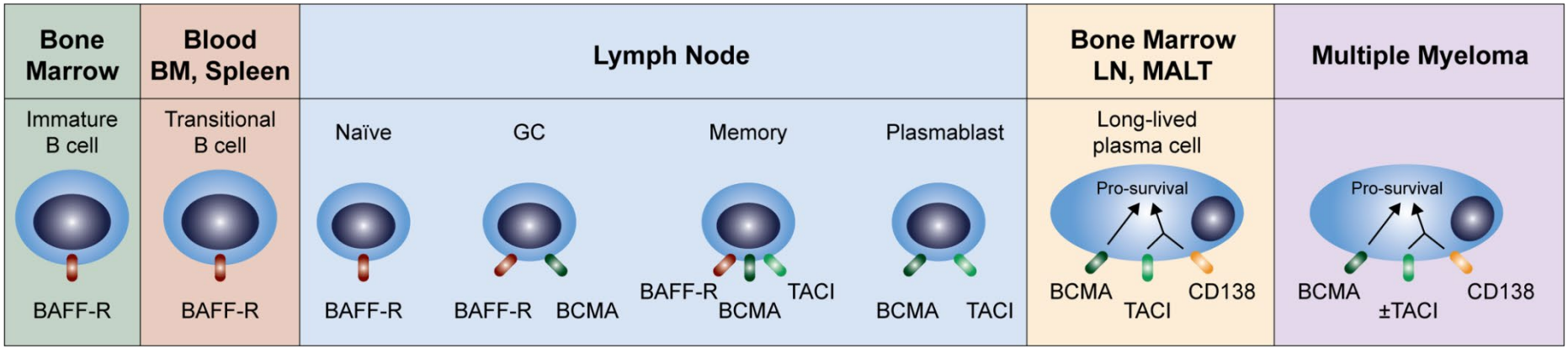
B-Cell Maturation Antigen (BCMA): A Near-Perfect Target in MM[1]



A rationale for the development of BCMA-targeting antibodies and CAR-T therapy

BAFF-R, B-cell activating factor receptor; BM, bone marrow; CAR-T, chimeric antigen receptor T cell; CD, cluster of differentiation; GC, germinal center; LN, lymph node; MALT, mucosa-associated lymphoid tissue; MM, multiple myeloma; TACI, transmembrane activator and CAML interactor.

1. Seckinger A et al. *Cancer Cell.* 2017;31:396-410.

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Current Status of Cellular Therapy in MM

BCMA CAR-T Constructs in MM	Status
Idecabtagene vicleucel	FDA approved
Ciltacabtagene autoleucel	Phase 1/2
CT053	Phase 1/2
bb21217 (ide-cel with alterations to ex vivo processing)	Phase 1
P-BCMA-101	Phase 1/2
Allo-715 (“off-the-shelf” allogeneic CAR-T)	Phase 1

BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; FDA, Food and Drug Administration; ide-cel, idecabtagene vicleucel; MM, multiple myeloma.

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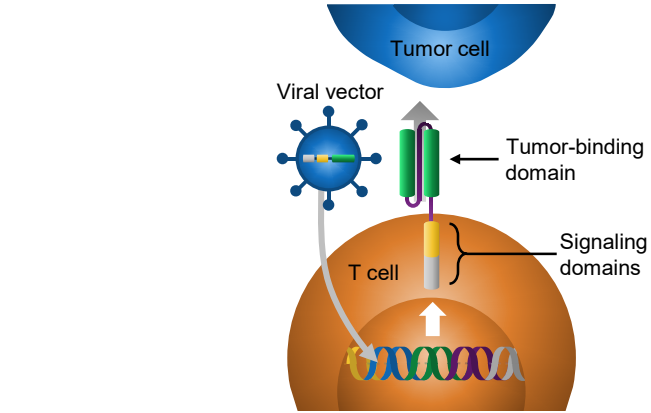
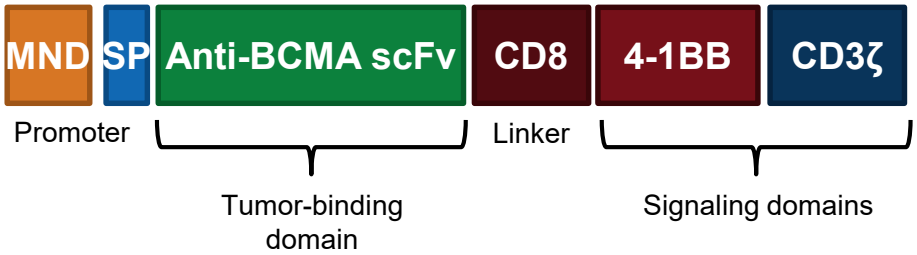
Idecabtagene Vicleucel (Ide-Cel) in RRMM

- BCMA-directed CAR-T cell construct ide-cel showed promising efficacy in a phase 1 study of patients with RRMM[1]
  - ORR of 89.5%, CR of 36.9% at the 450 x 10^6 dosing level

- This led to the phase 2 KarMMa trial assessing the efficacy and safety of ide-cel in patients with triple-class–exposed RRMM



Ide-Cel CAR Design



BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; CD, cluster of differentiation; CR, complete response; MND, dl587 Rev-binding site substituted; ORR, overall response rate; RRMM, relapsed/refractory multiple myeloma; scFv, single-chain antibody fragment; SP, signal peptide.

1. Lin Y et al. ASH 2020. Abstract 131.

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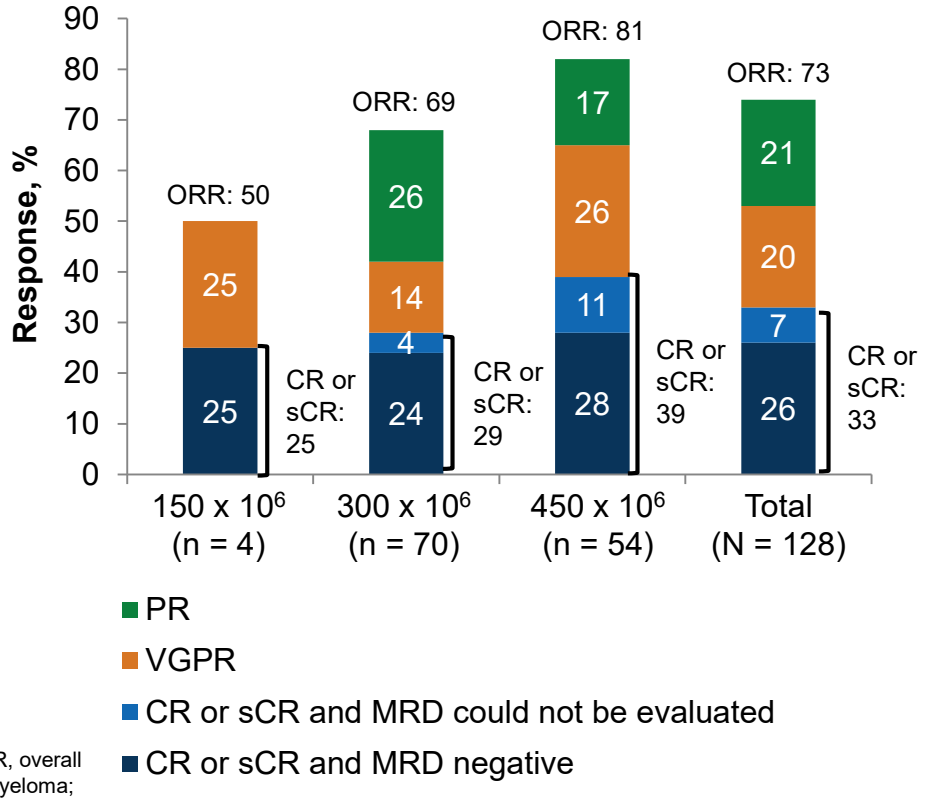
KarMMa: Pivotal Study of Ide-Cel in RRMM

- KarMMa: phase 2 study of ide-cel in RRMM; including double- and triple-refractory patients (IMiD, PI, and an anti-CD38 antibody)[1]
- **Ide-cel induced responses in a majority of heavily pretreated patients with RRMM (leading to FDA approval); MRD-negative status was achieved in 26% of treated patients**



CD, cluster of differentiation; CR, complete response; FDA, Food and Drug Administration; ide-cel, idecabtagene vicleucel; IMiD, immunomodulatory drug; MRD, minimal residual disease; ORR, overall response rate; PI, proteasome inhibitor; PR, partial response; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; VGPR, very good partial response.

1. Munshi N et al. *N Engl J Med.* 2021;384:705-716.

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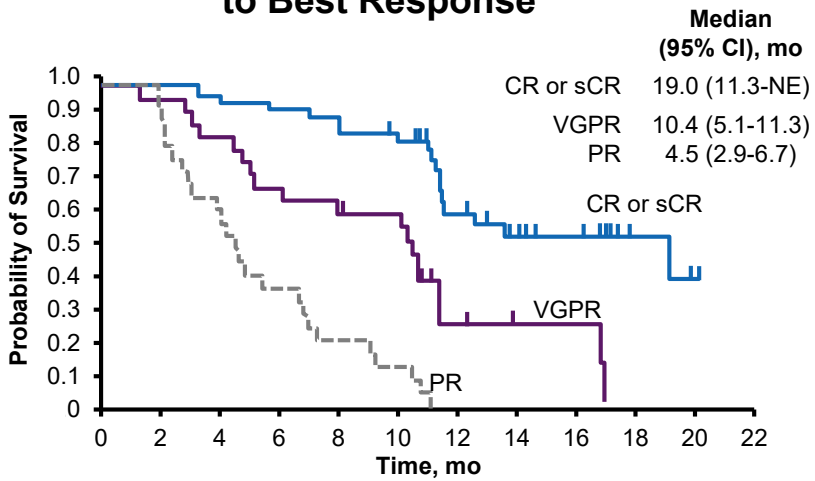
KarMMa: DOR and Survival[1]

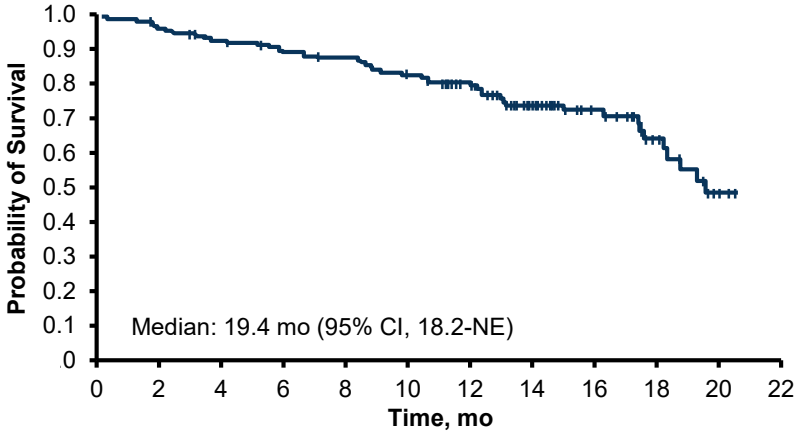
Duration of Response According to Best Response



No. at Risk												
CR or sCR	42	42	40	39	36	34	18	13	10	4	1	0
VGPR	25	24	21	17	15	14	4	2	2	0	0	–
PR	27	23	14	9	5	3	0	0	0	0	0	–

CAR+ T cells in 29 of 49 patients (59%) at 6 months and 4 of 11 patients (36%) at 12 months after infusion

Overall Survival



No. at Risk												
	128	122	114	108	104	97	82	55	38	27	12	0

- Median OS of 19.4 months
- OS of 78% at 1 year

CAR, chimeric antigen receptor; CI, confidence interval; CR, complete response; DOR, duration of response; NE, not evaluable; OS, overall survival; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

1. Munshi N et al. *N Engl J Med.* 2021;384:705-716.

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Ide-Cel Safety Experience From KarMMa[1]

Common AEs included

- Neutropenia (91%), anemia (70%), and thrombocytopenia (63%)

CRS reported in 107 (84%) patients

- 7 (5%) had CRS grade ≥3

Neurotoxicity: 4 patients (3%) with grade 3 events

AE, adverse event; CRS, cytokine release syndrome; ide-cel, idecabtagene vicleucel.

1. Munshi N et al. *N Engl J Med*. 2021;384:705-716.

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The Practical Shape of CAR-T Therapy in MM

Patient found to be eligible for CAR-T

- ✓ *Example: MM patient relapsing after ≥4 lines of therapy, triple refractory*
- ✓ *Do not consider CAR-T therapy for patients with active infection or inflammatory disorders*
- ✓ *Increase apheresis structure; increase outpatient infusion capacity; SOPs for fever triage*

Referred to specialized/ expert center for period of intensive therapy

- ✓ *Lymphodepletion prior to CAR-T infusion*
- ✓ *Watch for neurotoxicity, CRS; IL-6 antibody for higher-grade events*
- ✓ *Neurotoxicity: steroid-based management*
- ✓ *Grading and management guidelines available from ASTCT and NCCN*

Longer-term follow-up

- ✓ *Monitor for relapse/recurrence*

ASTCT, American Society for Transplantation and Cellular Therapy; CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; IL-6, interleukin 6; MM, multiple myeloma; NCCN, National Comprehensive Cancer Network; SOP, standard operating procedure.

Ide-Cel Dosing and Administration Recommendations[1]

- Administer a lymphodepleting chemotherapy regimen of cyclophosphamide and fludarabine before ide-cel infusion
- Confirm the patient's identity prior to infusion
- Premedication: acetaminophen and an H_1-antihistamine
  - Avoid prophylactic use of dexamethasone or other systemic corticosteroids
- Confirm availability of tocilizumab prior to infusion
- Ide-cel dosing based on the number of CAR-positive T cells
  - Recommended dose range: 300 to 460 × 10^6 cells; administer at a certified healthcare facility

CAR, chimeric antigen receptor; H_1, histamine 1; ide-cel, idecabtagene vicleucel.

1. Abecma (idecabtagene vicleucel) Prescribing Information. https://www.fda.gov/media/147055/download.

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Recommendations for Managing CRS[1]

	Tocilizumab	Steroids
Grade 1 Symptoms require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)	• Onset ≥72 hours after infusion: treat symptomatically • Onset <72 hours after infusion: 8 mg/kg IV over 1 hour (not to exceed 800 mg)	Consider dexamethasone 10 mg IV every 24 hours
Grade 2 Symptoms require and respond to moderate intervention Oxygen requirement <40% FiO_2 or hypotension responsive to fluids, or low dose of one vasopressor, or grade 2 organ toxicity	• 8 mg/kg IV over 1 hour (not to exceed 800 mg) • Repeat every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen • Max of 3 doses in a 24-hour period; max total of 4 doses	Consider dexamethasone 10 mg IV every 12-24 hours
Grade 2: *If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose/frequency of dexamethasone (20 mg IV every 6 to 12 hours); if no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times per day*[a]		

CRS, cytokine release syndrome; FiO_2, fraction of inspired oxygen; IV, intravenous.

[a] After 2 doses of tocilizumab, consider alternative anticytokine agents. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.

1. Abecma (idecabtagene vicleucel) Prescribing Information. https://www.fda.gov/media/147055/download.

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Recommendations for Managing CRS[1] (Cont'd)

	Tocilizumab	Steroids
Grade 3 Symptoms require and respond to aggressive intervention Fever, oxygen requirement ≥40% FiO_2, or hypotension requiring high-dose or multiple vasopressors, or grade 3 organ toxicity or grade 4 transaminitis	Manage per grade 2	Administer dexamethasone 10 mg IV every 12 hours
Grade 4 Life-threatening symptoms; requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD), or grade 4 organ toxicity (excluding transaminitis)	Manage per grade 2	Administer dexamethasone 20 mg IV every 6 hours

Grade 3: *If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose/frequency of dexamethasone (20 mg IV every 6 to 12 hours);* ***grade 3 and 4:*** *if no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times per day*[a]

CRS, cytokine release syndrome; FiO_2, fraction of inspired oxygen; IV, intravenous.

[a] After 2 doses of tocilizumab, consider alternative anticytokine agents. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.

1. Abecma (idecabtagene vicleucel) Prescribing Information. https://www.fda.gov/media/147055/download.

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Pharmacy Practice Points for Neurologic Toxicity[1]

- **Monitor** patients for signs and symptoms of neurologic toxicities
- **Rule out other causes** of neurologic signs or symptoms
- **Provide intensive care supportive therapy** for severe or life-threatening neurologic toxicities
- **Pharmacologic and other interventions** for NT include (depending on nature/severity)
  - Nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis
  - Corticosteroids (eg, dexamethasone, methylprednisolone)
  - Hyperventilation and hyperosmolar therapy (eg, for higher-grade cerebral edema)

NT, neurotoxicity.

1. Abecma (idecabtagene vicleucel) Prescribing Information. https://www.fda.gov/media/147055/download.

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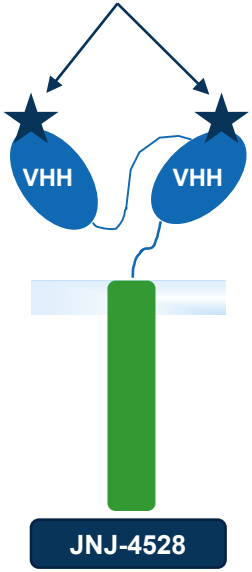
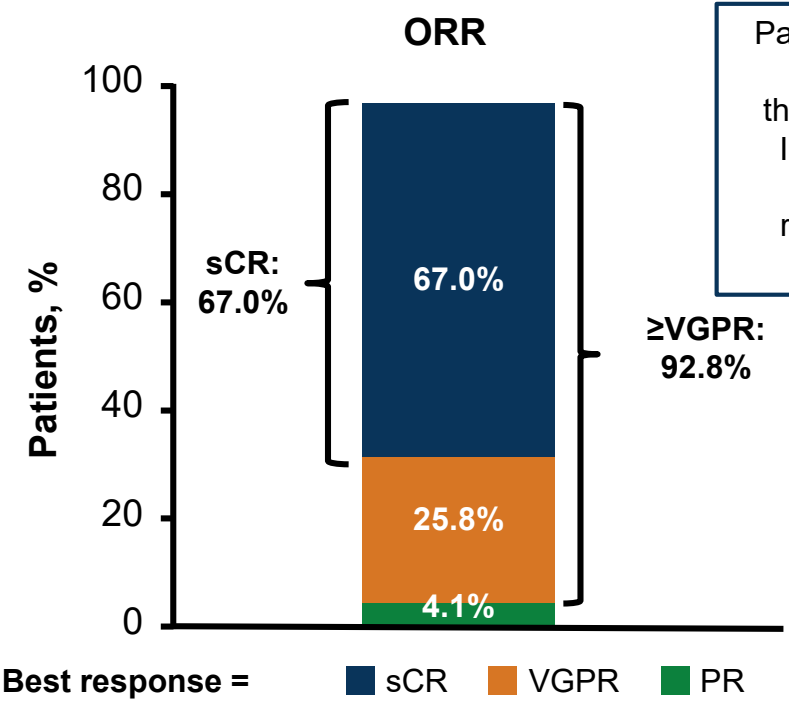
Other BCMA CAR-T Constructs: Ciltacabtagene Autoleucel in RRMM (CARTITUDE)[1]

Binding Domains



JNJ-4528: investigational CAR-T cell therapy made up of 2 BCMA-targeting domains designed to confer avidity plus a 4-1BB costimulatory domain



Patients with PS ≤1 and receiving ≥3 prior therapies, including PI, IMiD, and anti-CD38 therapy, or double-refractory to PIs and IMiDs

BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; CD, cluster of differentiation; IMiD, immunomodulatory drug; ORR, overall response rate; PI, proteasome inhibitor; PR, partial response; PS, performance status; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; VGPR, very good partial response; VHH, variable domain on a heavy chain.

1. Madduri D et al. ASH 2020. Abstract 177.

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Future Directions for Immune-Based Therapy in MM

- **Dual-targeted CAR-T therapy**
- **GPRC5D/CD3 BiTE**
  - Talquetamab[1]
- **FcRH5/CD3 BiTE**
  - Cevostamab[2]
- **BCMA BiTEs**
  - CC-93269[3]
  - Teclistamab
  - Pavurutamab (formerly AMG-701, half-life–extended version of AMG-420)

BCMA, B-cell maturation antigen; BiTE, bispecific T-cell engager; CAR-T, chimeric antigen receptor T cell; MM, multiple myeloma.
1. Chari A et al. ASH 2020. Abstract 290. 2. Cohen AD et al. ASH 2020. Abstract 292. 3. Costa L et al. ASH 2019. Abstract 143.

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Audience Q&A

What is the role of the pharmacist in coordinating care with belantamab mafodotin therapy?

Abbreviations

ADC, antibody–drug conjugate

ADCC, antibody-dependent cellular cytotoxicity

ADCP, antibody-dependent cellular phagocytosis

ASCT, autologous stem cell transplant

ASTCT, American Society for Transplantation and Cellular Therapy

BAFF-R, B-cell activating factor receptor

BCMA, B-cell maturation antigen

BCVA, best-corrected visual acuity

belamaf, belantamab mafodotin

BiTE, bispecific T-cell engager

BM, bone marrow

CAR-T, chimeric antigen receptor T cell

CD, cluster of differentiation

CDC, complement-dependent cytotoxicity

CI, confidence interval

CR, complete response

CRS, cytokine release syndrome

CTCAE, Common Terminology Criteria for Adverse Events

CVVHD, continuous veno-venous hemodialysis

dara, daratumumab

dex, dexamethasone

DOR, duration of response

Fc, fragment crystallizable

FiO_2, fraction of inspired oxygen

GC, germinal center

H_1, histamine 1

H_2, histamine 2

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Abbreviations

HBV, hepatitis B virus

HR, hazard ratio

ICANS, immune effector cell-associated neurotoxicity syndrome

ICD, immunogenic cell death

ide-cel, idecabtagene vicleucel

IL-6, interleukin 6

IMiD, immunomodulatory drug

Isa, isatuximab

Kd, daratumumab and carfilzomib

KdD, daratumumab, carfilzomib, and dexamethasone

KRd, carfilzomib, lenalidomide, and dexamethasone

KVA, Keratopathy and Visual Acuity

len, lenalidomide

LN, lymph node

MALT, mucosa-associated lymphoid tissue

MEC, microcyst-like epithelial changes

MM, multiple myeloma

MND, dl587 Rev-binding site substituted

MOA, mechanism of action

MR, minimal response

MRD, minimal residual disease

NCCN, National Comprehensive Cancer Network

NDMM, newly diagnosed multiple myeloma

NE, not evaluable

NT, neurotoxicity

ORCA, Onyx Response Computer Algorithm

ORR, overall response rate

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Abbreviations

OS, overall survival

PI, proteasome inhibitor

pom, pomalidomide

PR, partial response

PS, performance status

Q3W, every 3 weeks

Rd, lenalidomide and dexamethasone

REMS, Risk Evaluation and Mitigation Strategy

RRMM, relapsed/refractory multiple myeloma

SC, subcutaneous

scFv, single-chain antibody fragment

sCR, stringent complete response

SD, stable disease

SOP, standard operating procedure

SP, signal peptide

TACI, transmembrane activator and CAML interactor

VCd, bortezomib, cyclophosphamide, and dexamethasone

Vd, bortezomib and dexamethasone

VGPR, very good partial response

VHH, variable domain on a heavy chain

VMP, bortezomib, melphalan, and prednisone

VRd, bortezomib, lenalidomide, and low-dose dexamethasone

VTd, bortezomib, thalidomide, and dexamethasone

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