
بسم الله الرحمن الرحیم

The Evolving Management of Relapsed/Refractory Myeloma: Clinical, Economic, and Patient-Centric Strategies for Managed Care Pharmacy Professionals

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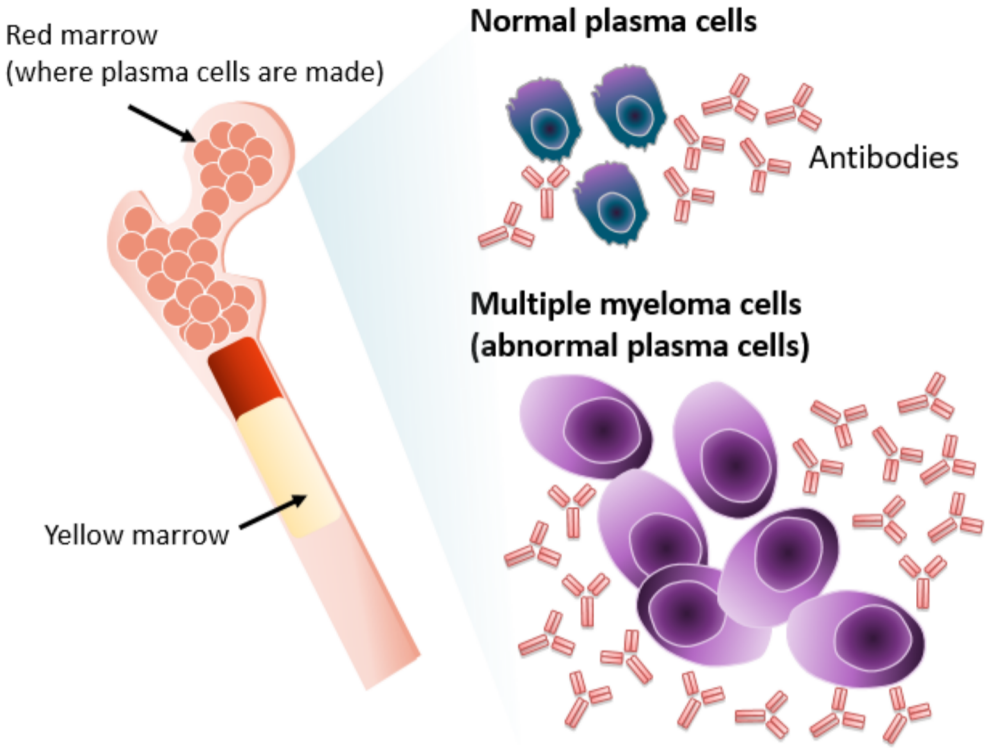
Multiple Myeloma

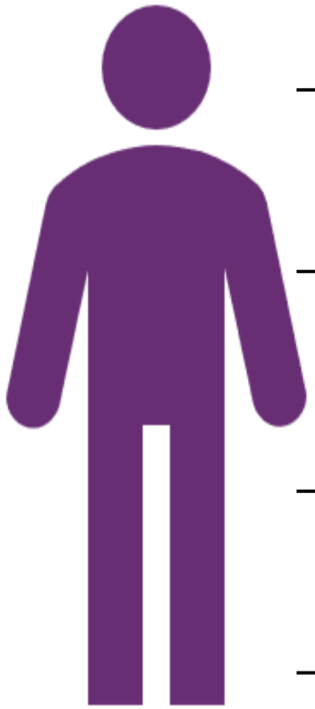
- Malignant neoplasm of clonal plasma cells
  - Abnormal plasma cells accumulate in BM
- Formation of abnormal Abs (monoclonal immunoglobulins)
  - M-protein/paraproteins
  - Abnormal light chain proteins
- Results in organ/immune dysfunction
  - Abnormal antibodies
  - Cytokines
  - Dysfunctional pathways



Rajkumar. Mayo Clin Proc. 2016;91:101. van de Donk. Lancet. 2021;397:10272. Rajkumar. Am J Hematol. 2020;95:548.

Slide credit: ProCE.com and clinicaloptions.com

Clinical Presentation: Myeloma Defining Event



C **Hypercalcemia**
Confusion, constipation

- ~15% of patients
  - Due to renal ± bone involvement

R **Renal Failure**
Electrolytes disturbances

- 20%-40% have an elevated creatinine
  - Can be reversible with treatment

A **Anemia**
Fatigue, weakness, SOB

- ~75% of patients
  - Due to renal and marrow involvement

B **Bone Disease**
Osteolytic lesions, fractures

- 80% of patients have osteolytic lesions
  - 58% of patients report bone pain

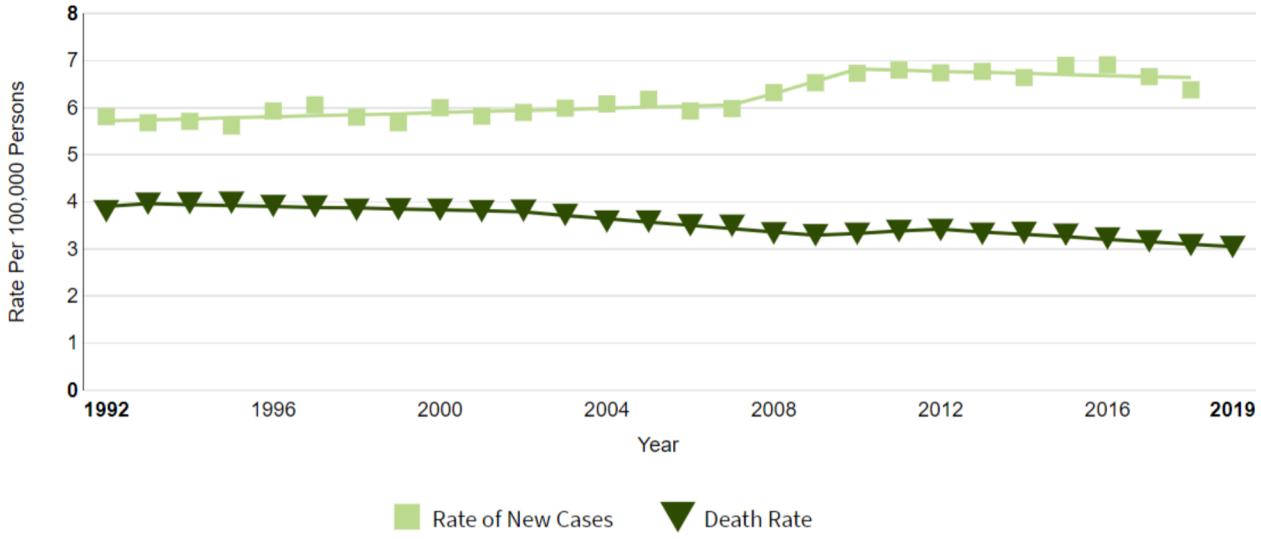
Rare Presentation

Infections → decreased function of IgG and T-lymphocyte function
Hyperviscosity → headache, blurred vision, epistaxis, oral bleeding, confusion
Neurologic disease → neuropathy, cord compression, intracranial plasmacytomas

Rajkumar. Mayo Clin Proc. 2016;91:101. Kyle. Mayo Clin Proc. 2003;78:21.
Palumbo. NEJM. 2011;364:1046. Talamo. Clin Lymphoma Myeloma Leuk. 2010;10:464.

Epidemiology of Myeloma

- Incidence
  - 2022 cases: 34, 470
  - 1.8% of cancer cases
  - 7.1 per 100,2000 per yr
- Mortality
  - 2022 deaths: 12,640
  - 2.0% of cancer deaths
  - 3.2 per 100,000 per yr
- Survival
  - 55.6% 5-yr relative survival



Siegel. CA Cancer J Clin. 2022;72:7-33. seer.cancer.gov/statfacts/html/mulmy.html

Slide credit: ProCE.com and clinicaloptions.com

IMWG Criteria for Diagnosis of MM

MGUS	Smoldering Myeloma	Active or Symptomatic Multiple Myeloma
▪ M protein < 3 g/dL ▪ Clonal plasma cells in BM < 10% ▪ No myeloma-defining events	▪ M protein ≥ 3 g/dL (serum) or ≥ 500 mg/ 24 hrs (urine) ▪ Clonal plasma cells in BM ≥ 10% to 60% ▪ No myeloma-defining events	▪ Underlying plasma cell proliferative disorder ▪ AND ≥ 1 SLiM-CRAB* feature

*S: Sixty percent clonal bone marrow plasma cells
Li: Serum free Light chain ratio ≥ 100 (involved kappa) or ≤ .01 (involved lambda)
M: MRI studies with > 1 focal lesion (> 5 mm in size)

C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN
R: Renal insufficiency (CrCl < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET/CT)

Rajkumar. Lancet Oncol. 2014;15:e538.

Slide credit: clinicaloptions.com

Diagnosis of Myeloma Defining Event/Staging

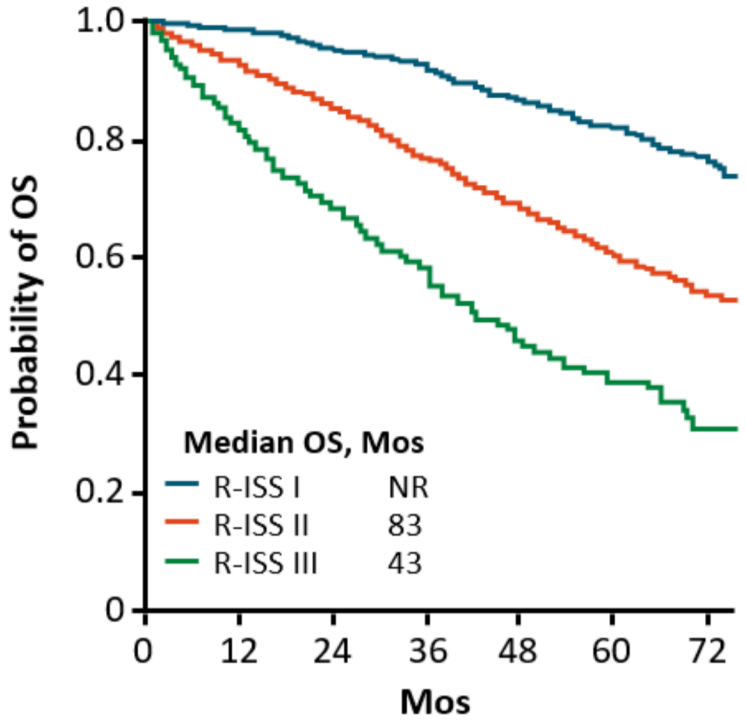
CRAB Criteria
Hypercalcemia: ▪ Serum calcium >1 mg/dL higher than the ULN or >11 mg/dL
Renal insufficiency: SCr >2 mg/dL; CrCl <40 mL/min
Anemia: ▪ Hb >2 g/dL below the lower limit of normal ▪ Hb <10 g/dL
Bone lesions: ▪ ≥1 osteolytic lesions on skeletal radiography, CT, or FDG PET/CT
SLiM Criteria
S (60%): clonal BM plasma cells ≥60%
Li (Light chain): ▪ Involved:uninvolved serum FLC ratio ≥100 ▪ Involved FLC concentration ≥10 mg/dL
M (MRI): >1 focal lesions on MRI studies ≥5 mm

Stage	International Staging System	Revised-ISS	5-Yr OS, %
I	▪ Serum β_2M <3.5 mg/L ▪ Albumin ≥3.5 g/dL	▪ ISS stage I plus: • Standard risk by FISH • LDH ≤ULN	82
II	▪ Not ISS stage I or stage III	▪ Not R-ISS stage I or III	62
III	▪ Serum β_2M ≥5.5 mg/L	▪ ISS stage III plus: • High risk by FISH *or* • LDH >ULN	40

Rajkumar. ASCO Educational Book. 2016;36:e418. Rajkumar. Lancet Oncol. 2014;15:e538. Rajkumar. Mayo Clin Proc. 2016;91:101.

Revised ISS

ISS Definition	
I	▪ Serum albumin ≥ 3.5 g/dL *AND* ▪ β_2-M < 3.5 mg/L
II	▪ Not stage I or III
III	▪ β_2-M ≥ 5.5 mg/dL
R-ISS Definition	
I	▪ ISS stage I *AND* ▪ Normal LDH ▪ No t(4;14), t(14;16), or del(17p)
II	▪ Not stage I or III
III	▪ ISS stage III *AND* ▪ Serum LDH > ULN *OR* ▪ With t(4;14), t(14;16), or del(17p)



Palumbo. J Clin Oncol. 2015;33:2863.

Slide credit: clinicaloptions.com

Prognostic Factors

- **Tumor cell related**
  - Presence of high-risk cytogenetics

Mayo Clinic Risk Stratification		
Risk	Standard	High*
Criteria	Trisomies: t(11;14) t(6;14)	t(14;16) del(17p) t(4;14) t(14;20) gain(1q)
% of newly diagnosed patients	75	25

*May include patients with double-hit (any 2) or triple-hit (any 3) high-risk factors

- **Tumor-burden related**
  - Durie-Salmon stage
  - International Staging System
  - Extramedullary disease
  - High lactate dehydrogenase
- **Patient related**
  - Age
  - Performance status
  - Renal failure → serum β_2M
  - Frailty (IMWG guidelines): *http://www.myelomafrailtyscorecalculator.net/*

Mikhael. Mayo Clin Proc. 2013;88:360. Rajkumar. Am. J. Hematol. 2020;95:548. Palumbo. Blood. 2015;125:2068.

Summary of Frontline MM Treatment Approach

Treatment Suggestions

- Goal is to maximize initial disease response (sCR, MRD[-])
- Backbone agents: steroids, PIs, IMiDs ± anti-CD38 mAbs
- Quad >/= triplet >>doublet regimens
- Choosing regimens → individual patient and tumor factors, prior exposure

Tips for Transplant Patients

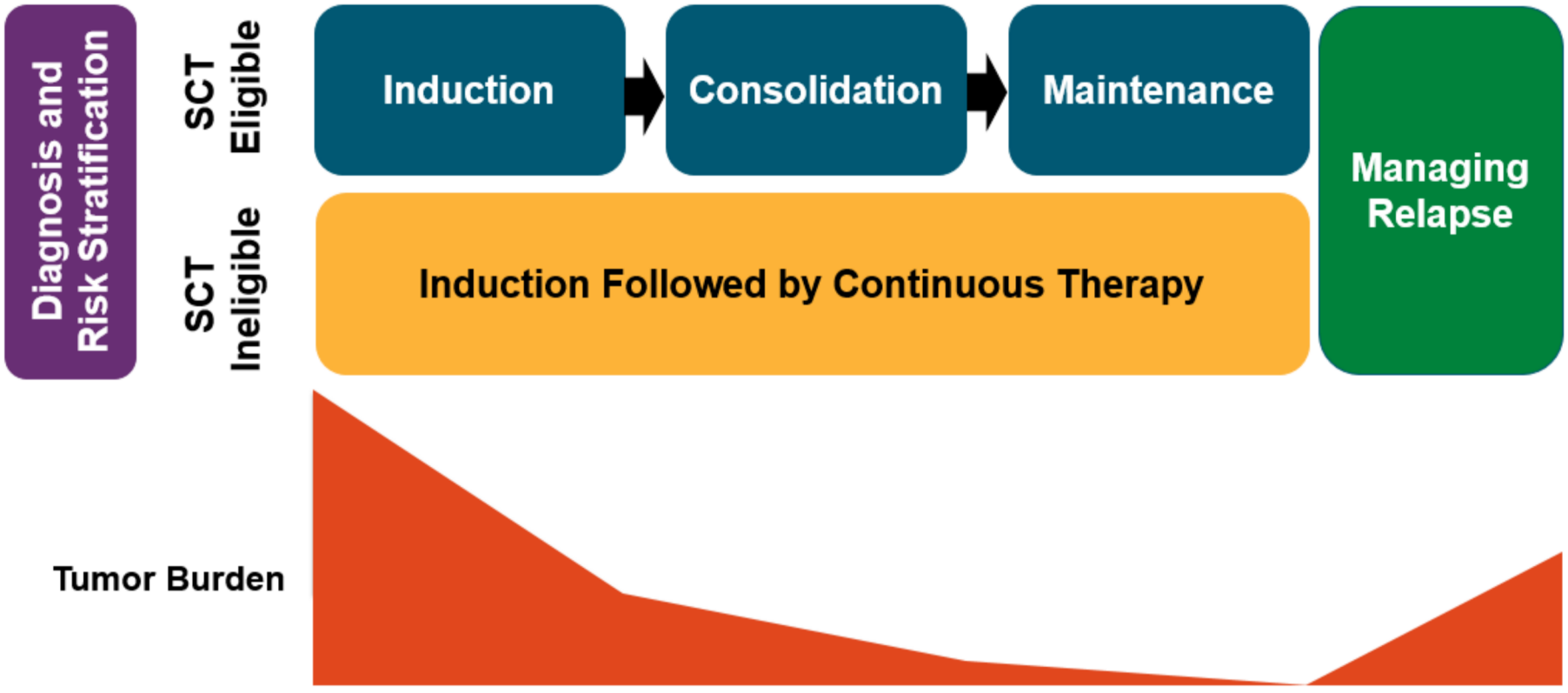
- Every patient who is a candidate should go to aHCT
- Age and renal function are not contraindications
- Limit exposure to myelotoxic agents and consider harvesting cells before prolonged exposure to lenalidomide and/or daratumumab

Maintenance

- Given proven PFS ± OS benefit, maintenance remains important role
- Optimal duration varies (cost, toxicity, adherence, MRD status)

NCCN. Clinical Practice Guidelines in Oncology. Multiple Myeloma v5.2022.

MM Treatment Paradigm



Slide credit: clinicaloptions.com

Definition of Relapsed and Refractory Myeloma

- Relapsed/refractory myeloma[1,2]
  - Meets IMWG criteria for PD[3]
  - RR MM: progression on therapy in patients who obtain ≥ minor response or progress within 60 days of most recent therapy
  - Primary refractory MM: progression on therapy without having achieved at least minor response
  - Relapsed MM: meets IMWG criteria for PD but does not fit definition of RR or primary refractory MM

IMWG Criteria for PD[3]

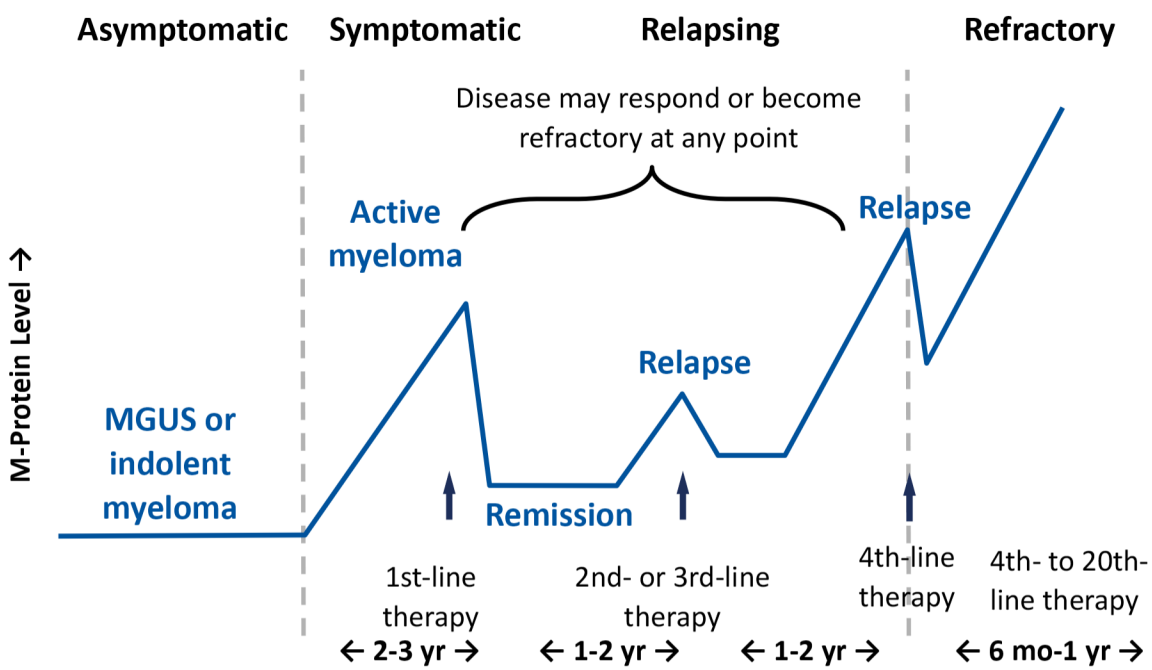
≥ 25% increase from nadir in:

- Serum or urine M-protein (absolute increase ≥ 0.5 g/dL* and ≥ 200 mg/24 hrs, respectively), *or*
- Difference between involved and uninvolved FLC levels† (absolute increase > 100 mg/L), *or*
- Bone marrow plasma cells‡ (absolute increase ≥ 10%), *or*
- New lesions (≥ 50% increase in SPD of > 1 lesion or longest diameter of previous lesion > 1 cm in short axis), *or*
- Circulating plasma cells (≥ 50% increase [minimum 200 cells/μL] if only measure of disease)

*If lowest M component ≥ 5 g/dL, increase must be ≥ 1 g/dL.
†In patients without measurable serum/urine M-protein.
‡In patients without measurable serum/urine M-protein or involved FLC.

1. Nooka. Blood. 2015;125:3085. 2. Rajkumar. Blood. 2011;117:4691. 3. Kumar. Lancet Oncol. 2016;17:e328.

Myeloma Can Be Treated, but Not Cured



- **Relapsed/refractory MM (R/R MM)**
  - Progression after achieving at least minor response *or* progression within 60 days of most recent therapy
- **Primary refractory MM**
  - Progression without achieving at least minor response
- **Relapsed MM**
  - Progressive disease but does not fit definition of relapsed/ refractory or primary refractory

Durie. International Myeloma Foundation Concise Review. 2018. Lonial. Clin Cancer Res. 2011;17:1264.

Slide credit: ProCE.com and clinicaloptions.com

Milestones in Multiple Myeloma Drug Approvals

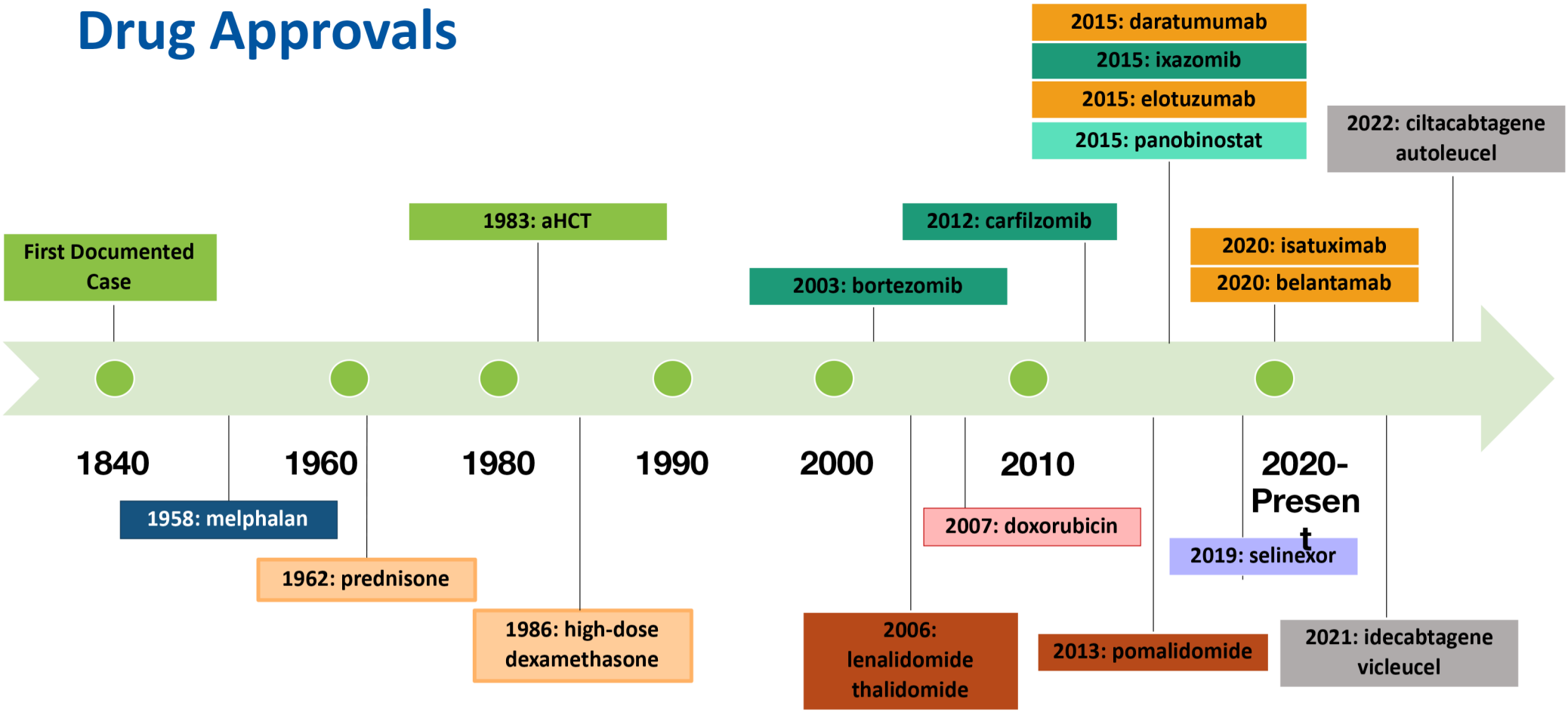
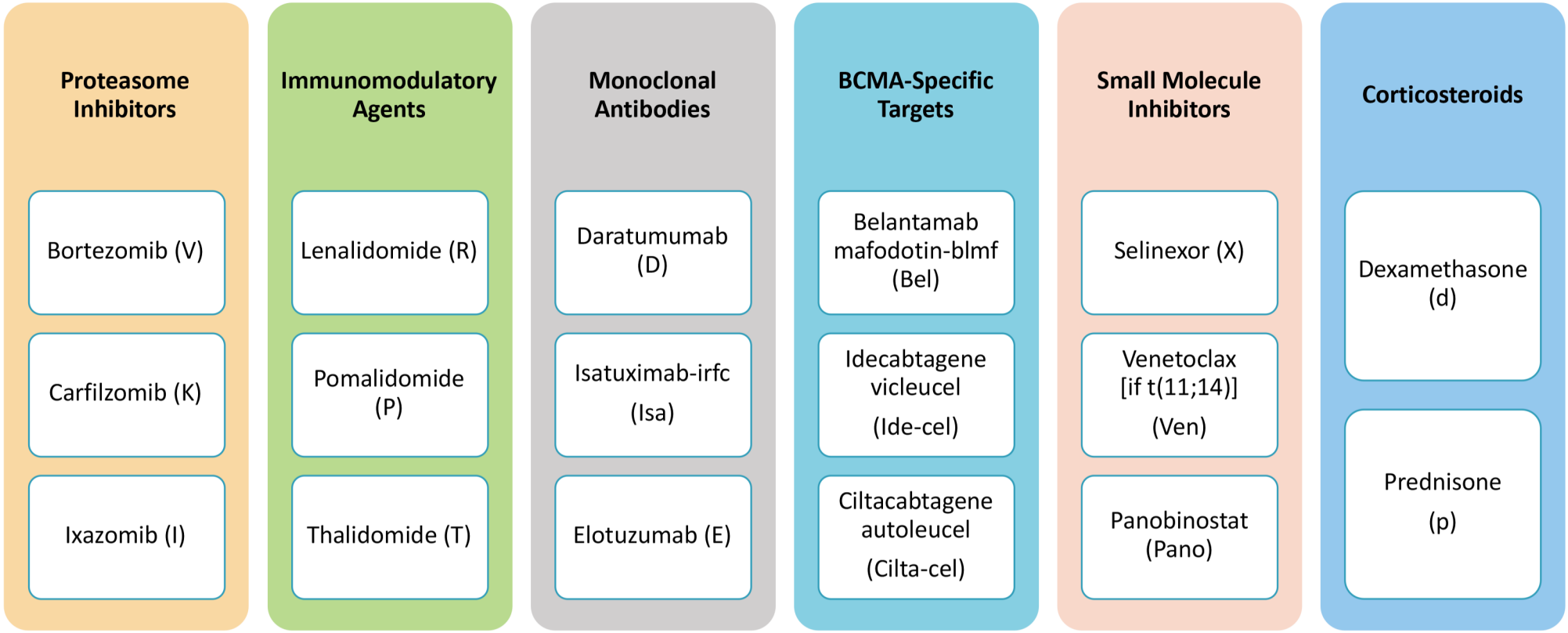


Image adapted from Kyle. Blood. 2008; 111:2962. Raje. NEJM. 2019;380:1726. Li. Circulation. 2016;133:908.

Slide credit: ProCE.com and clinicaloptions.com

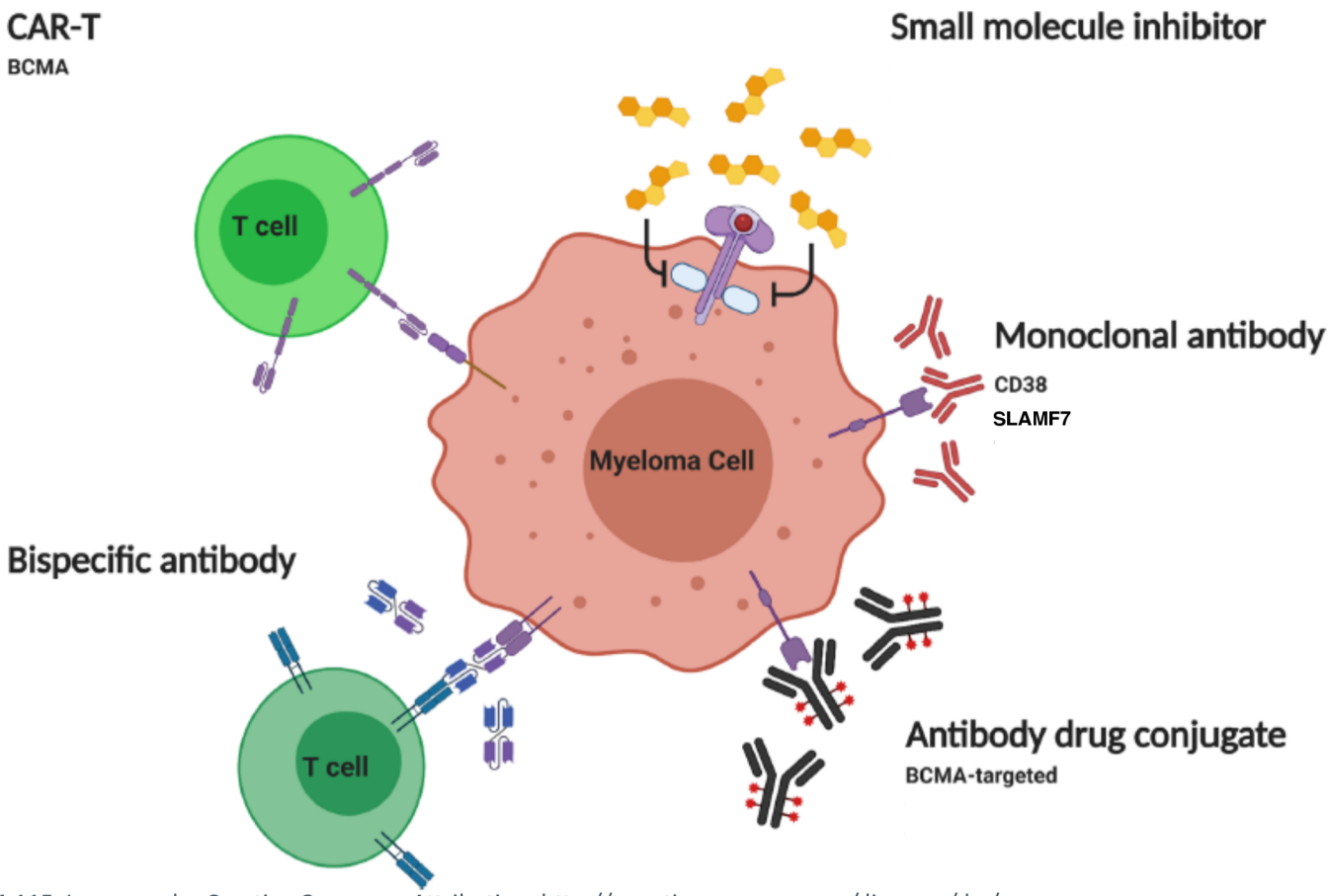
Navigating the MM Drug Arsenal



Rajkumar. Am J Hematol. 2020;95:548. Su. J Hematol Onco. 2021;14:115.

Slide credit: ProCE.com and clinicaloptions.com

Emerging Targetable Modalities for MM Treatment



Su. J Hematol Onco. 2021;14:115. Image under Creative Commons Attribution: http:// creativecommons.org/ licenses/ by/ 4.0/. (Edited to remove/add text)

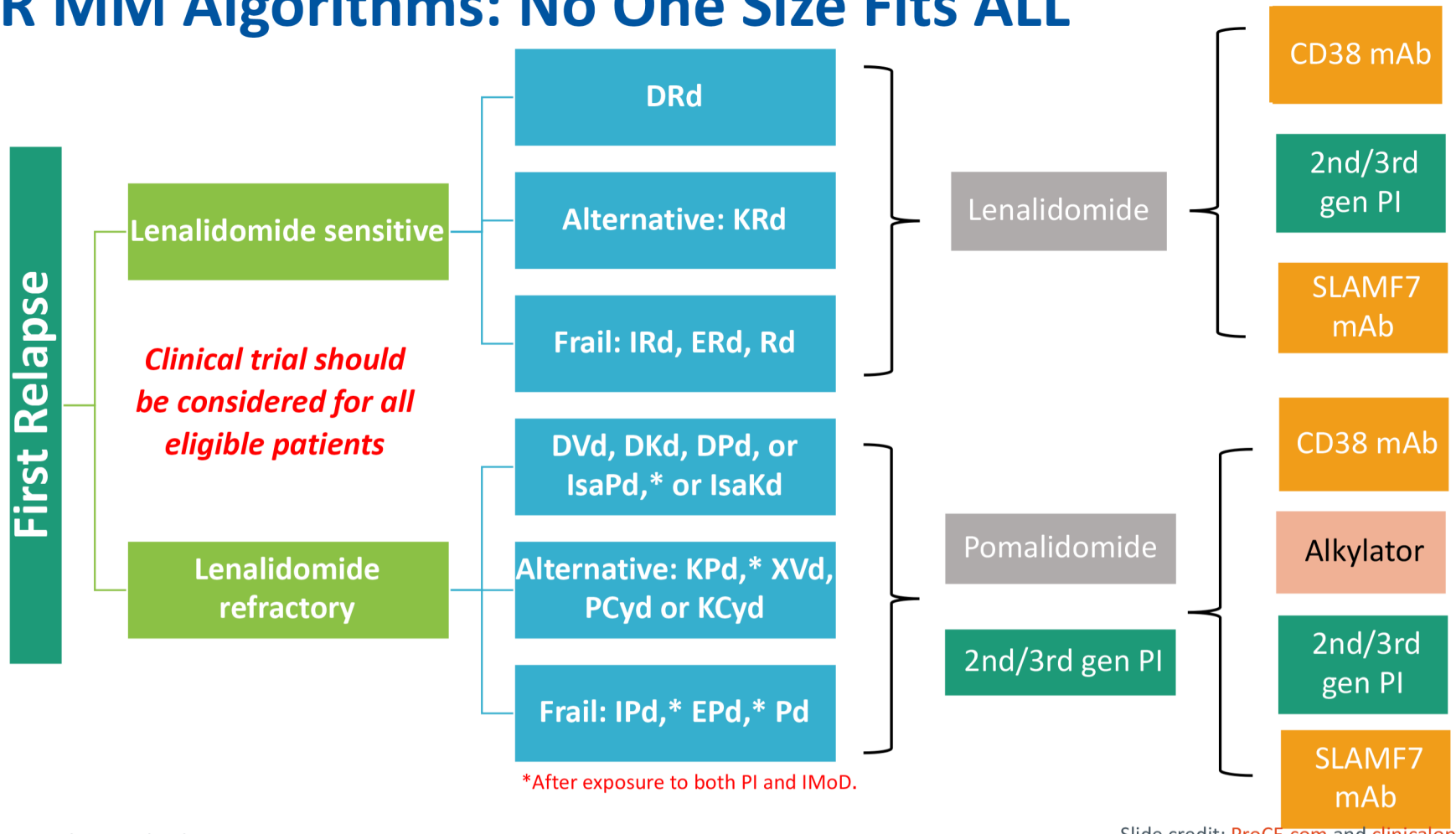
Slide credit: ProCE.com and clinicaloptions.com

General Considerations for R/R MM Treatment

- **Disease related**
  - Duration of response from initial therapy
    - Early relapse (1-3 prior lines)
    - Late relapse (>3 prior lines)
  - Cytogenetic risk
  - Indolent vs aggressive relapse rate
  - Active vs biochemical relapse
- **Patient related**
  - Age
  - Performance status
  - Comorbidities (cardiac, renal, etc)
  - Pre-existing toxicity (neuropathy, cytopenia)
- **Regimen related**
  - Prior drug exposure
    - IMiD-based
    - PI-based
  - Triple class exposed (Quad)
    - Anti-CD38 mAbs
  - Toxicity (infections, cytopenias, neuropathy, etc)
  - Administration route/cost
    - Outpatient vs inpatient
    - Location convenience
  - Prior aHCT

Hernandez-Rivas. Biomarker Research 2022; 10:1. Sonneveld. Haematologica. 2016;101:396.

R/R MM Algorithms: No One Size Fits ALL

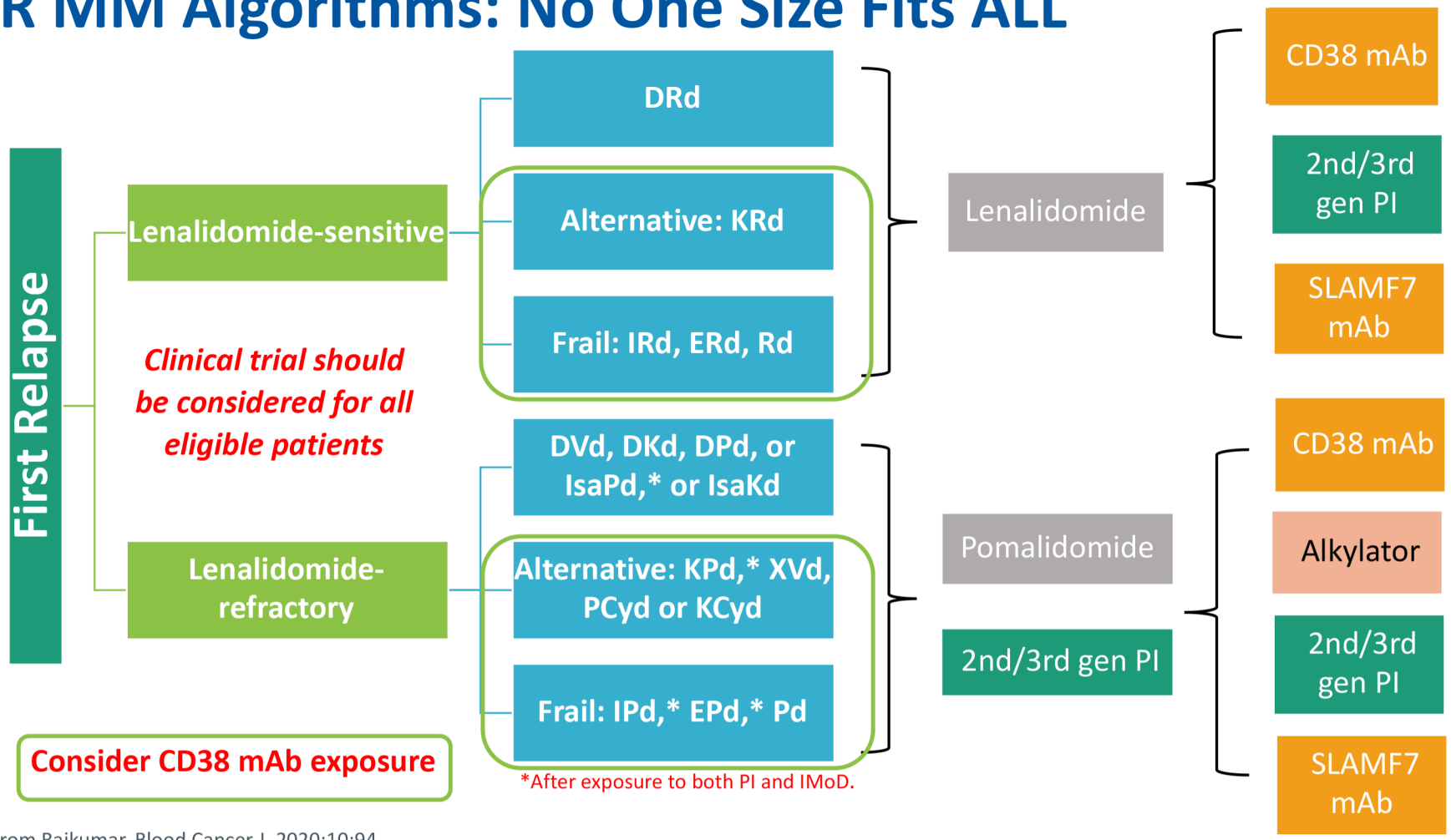


*After exposure to both PI and IMoD.

Adapted from Rajkumar. Blood Cancer J. 2020;10:94.

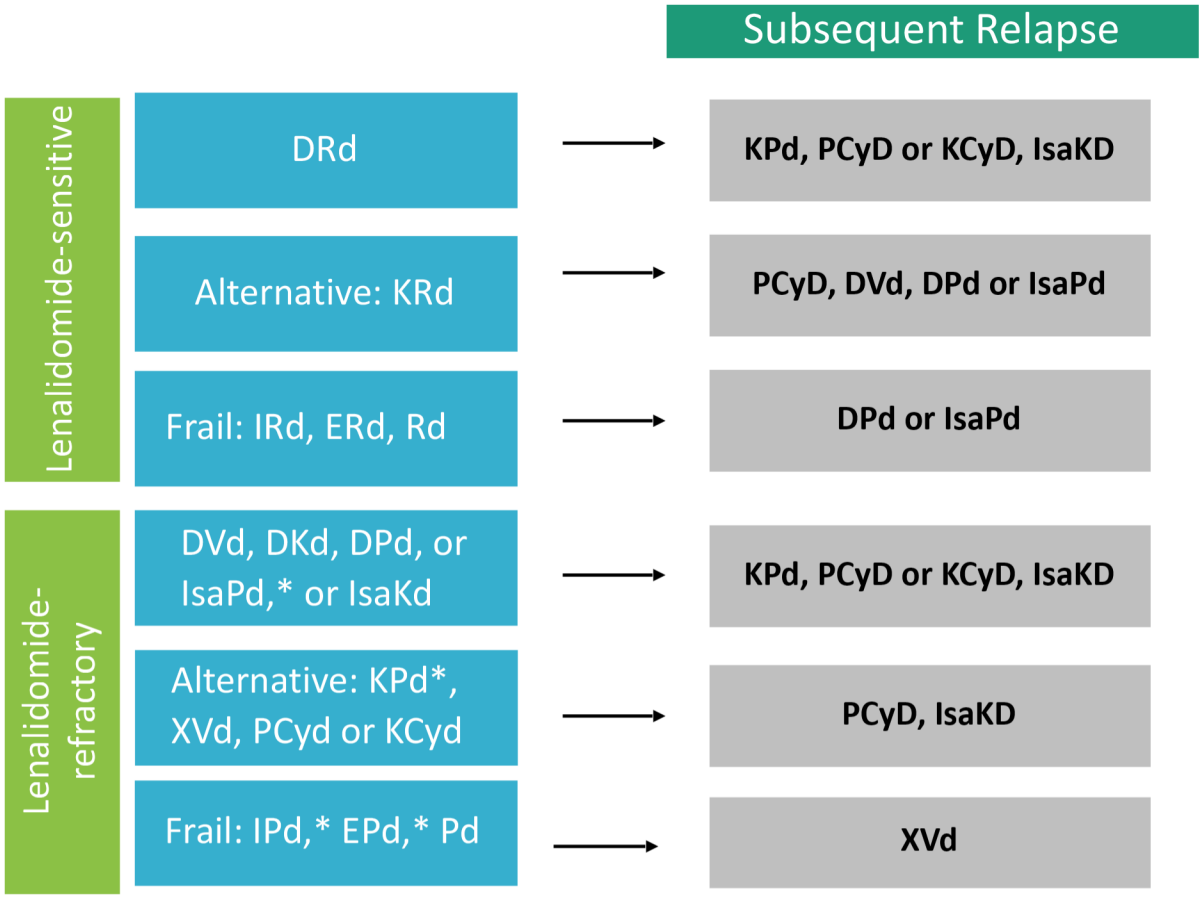
Slide credit: ProCE.com and clinicaloptions.com

R/R MM Algorithms: No One Size Fits ALL



Adapted from Rajkumar. Blood Cancer J. 2020;10:94.

R/R MM Algorithms: No One Size Fits ALL



*After exposure to both PI and IMoD.

Adapted from Rajkumar. Blood Cancer J. 2020;10:94.

Clinical trial should be considered for eligible patients

Key: consider 2 new agents that patient is not refractory to or novel agents

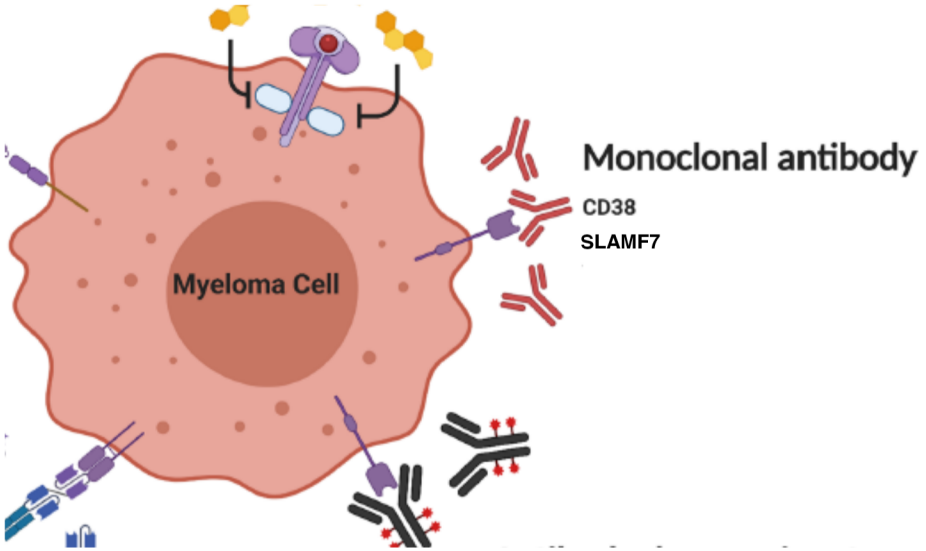
4+ prior lines

- **Belantamab mafodotin†‡**
- **Idecabtagene vicleucel†**
- **Ciltacabtagene autoleucel†**

†After exposure to ≥1 PI, IMiD, and anti-CD38 mAb.
‡4+ prior therapies.

Monoclonal Antibodies in MM

- Monoclonal antibodies (mAbs)
  - Daratumumab (D)
  - Isatuxumab-irfc (Isa)
  - Elotuzumab (E)
- **Future directions**
  - **4- vs 3-drug regimens in first-line therapy and subsequent relapse options**

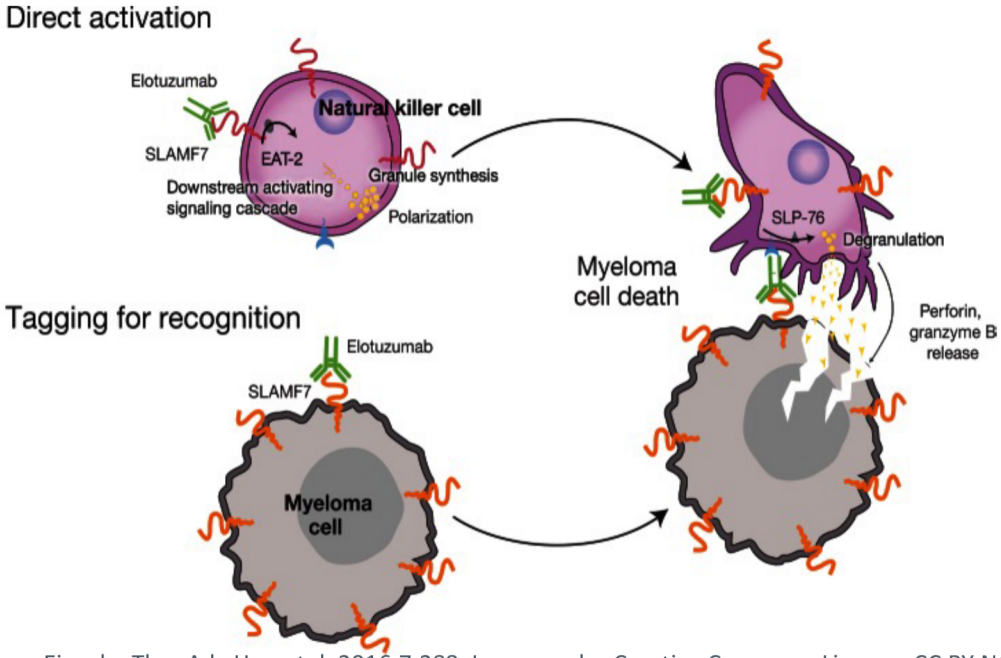


Su. J Hematol Onco. 2021;14:115. Image under Creative Commons Attribution: http:// creativecommons.org/ licenses/ by/ 4.0/. (Edited to remove/add text)

Slide credit: ProCE.com and clinicaloptions.com

Elotuzumab (Elo)

- Mechanism of action: Anti-SLAMF7 mAb
  - NK cell–mediated ADCC and NK activation via SLAMF7 and macrophage-mediated ADCP



Key Administration Aspects in R/R MM Setting (28-Day Cycle)	
Dosing	▪ Cycle 1-2: 10 mg/kg IV on D1, 8, 15, and 22 ▪ Cycle 3+: 10 mg/kg IV on D1 and 15 (ERd), or 20 mg/kg IV on D1 only (EPd)
Renal/liver dosing	▪ Hold treatment for grade ≥3 transaminitis ▪ No renal adjustments
Adverse events	▪ **Fatigue**, pyrexia, cough, **infections**, **PNA**, cardiotoxicity, hyperglycemia, hepatotoxicity
Pearls	▪ Cardiotoxicity: increased HR, altered BP, peripheral edema ▪ **Premedicate** with dexamethasone, an H_1,-and H_2 antagonist, and APAP ▪ HSV prophylaxis
FDA-approved combinations	▪ Elotuzumab 10 mg/kg with Q2W regimen: + lenalidomide/dex (ERd) [1-3 prior therapies] ▪ Elotuzumab 20mg/kg with Q4W regimen: + pomalidomide/dex (EPd) [≥2 prior therapies]

Einsele. Ther Adv Hematol. 2016;7:288. Image under Creative Commons License: CC BY-NC 3.0. Elotuzumab PI.

Slide credit: ProCE.com and clinicaloptions.com

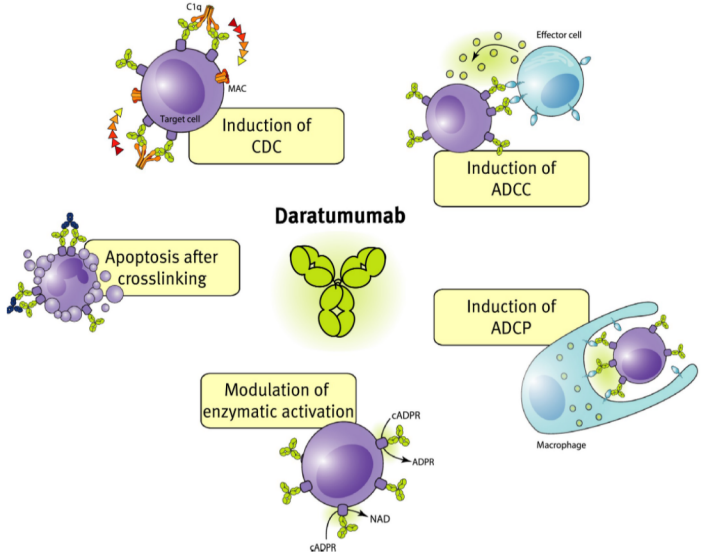
Elotuzumab Combinations

	ELOQUENT-2 (ERd vs Rd)	ELOQUENT-3 (EPd vs Pd)
Study population	**1-3 lines of therapy** (N = 646), CrCl ≥30 mL/min	**≥2 lines of therapy** (N = 117); excluded pts with prior pomalidomide exposure; CrCl <45 mL/min
Study design	Phase III trial ▪ Randomized 1:1: **ERd** (n = 321) vs Rd (n = 325) – Stratified by β_2M, no. of tx lines, prior IMiD	Phase II trial ▪ Randomized 1:1: **EPd** (n = 60) vs Pd (n = 57) – Stratified by no. of tx lines, ISS stage
Patient characteristics	▪ 52% 2-3 prior lines tx; 6% IMiD-/ 70% PI-exposed ▪ 32% high-risk cytogenetics, 20% ≥75 yr old	▪ Median of 3 prior lines tx; 68% IMiD and PI-refractory ▪ 24% high-risk cytogenetics, 22% ≥75 yr old
Outcomes	Median f/u: 70.6 mo ▪ **PFS: 19.4 vs 14.9 mo**; *P* <.001 ▪ **OS: 48.3 vs 39.6 mo**; *P* = .0408 – OS prolonged by 17.4 mo in ERd vs Rd in pts with 2-3 prior lines of therapy	Minimal f/u: 9.1 mo ▪ **PFS: 10.3 vs 4.7 mo** (*P* = .008) ▪ **ORR: 53 vs 26%** – ≥CR 8 vs 2%
Safety	▪ TEAEs: diarrhea 50 vs 39%, anemia 44 vs 38%, pyrexia 41 vs 26%, neutropenia: 36 vs 43% ▪ Infections: 84 vs 75%, pneumonia 22 vs 16% ▪ Serious AEs: 75 vs 61%	▪ TEAEs: neutropenia: 23 vs 31%, anemia 25 vs 36%, hyperglycemia 20 vs 15% with similar infections 65% ▪ Similar G3/4 AEs
Key takeaway	ERd had a significant relative reduction of 30% in the risk of PD or death with similar toxicities	EPd has activity in advanced IMiD and PI-ref patients with tolerable toxicities

Dimopoulos. Blood Cancer Journal. 2020;10:91. Lonial. NEJM. 2015;373:621. Dimopoulos. NEJM. 2018;379:1811.

Daratumumab

- Mechanism of action: anti-CD38 mAb
  - Direct tumor activity: ADCC, ADCP, CDC, and apoptosis
  - Immunomodulatory actions



Key Administration Aspects in R/R MM Setting (28-Day Cycle)	
Dosing (IV)	▪ Cycle 1-2: 16 mg/kg IV weekly x 8 doses; can split Day 1 dose ▪ Cycle 3-6: 16 mg/kg Days 1 and 15 x 8 doses ▪ Cycle 7+: 16 mg/kg IV monthly
Dosing (SC) [prefilled syringe]	▪ Flat dose: 1,800 mg daratumumab and 30,000 units hyaluronidase-fihj (↑ SC tissue permeability); frequency same as IV ▪ Administer over 3-5 min
Renal/liver dosing	▪ None
Adverse events	▪ **Cytopenia, IRR, fatigue,** fever, URTI, cough, nausea, back pain
Pearls	▪ Pre-meds 1-hr: APAP + anti-histamine, H2RA ± montelukast along with corticosteroid ▪ Monitor: fever, chills, rigors, bronchospasm, angina, edema, hypotension, nausea (interrupt infusion for reactions) ▪ When using combination with PI: give corticosteroid 1st, followed by daratumumab then PI ▪ Dose/frequency may differ with combined therapy
FDA-approved combinations	▪ **PI-based**: bortezomib 1.3mg/m^2 (DVd)/carfilzomib 20mg/m^2, then 70mg/m^2 (DKd) ▪ **IMiD-based:** lenalidomide (DRd)/pomalidomide (DPd) ▪ Can be given as monotherapy

Daratumumab PI. Daratumumab hyaluronidase-fihj PI. Van de Donk. Immunological Reviews 2016;270:95.

Slide credit: ProCE.com and clinicaloptions.com

IMiD-Based Combinations: Daratumumab

	POLLUX (DRd vs Rd)	APOLLO (DPd vs Pd)
Study population	**≥1 line** of tx including PI/IMiD, CrCl >30mL/min, and not R-ref (N = 569)	**≥1 line** of tx including PI/ IMiD, CrCl >30 mL/min, ref to R in first line only, (N = 304)
Study design	Phase III trial ▪ Randomized 1:1: **DRd** (n = 286) vs Rd (n = 283) – Stratified by no. of prior tx lines and ISS stage, R-exposed	Phase III trial ▪ Randomized 1:1: **D (SC or IV) + Pd** (n = 151) vs Pd (n = 153) – Stratified by no. of prior tx lines and ISS stage
Patient characteristics	▪ 44% prior PI and IMiD, 21% ref to bortezomib ▪ **32% high-risk** cytogenetics, 21.5% ≥75 yr old	▪ 75% 2-3 prior lines tx; 42% ref to PI and IMiD ▪ **24% high-risk** cytogenetics, 18.5% ≥75 yr old
Outcomes	Median follow-up of 44.3 mo ▪ **PFS ITT: 44.5 vs 17.5 mo*** – High risk: 26.8 vs 8.3 mo, V-ref: 34.3 vs 11.3 ▪ sCR: 29.2 vs 10.5%* ▪ **MRD negativity rate: 30.4 vs 5.3%*** ▪ Median time to next tx: **50.6 vs 23.1 mo***	Median follow-up of 16.9 mo ▪ **PFS: 12.4 vs 6.9 mo**; *P* = .0018 ▪ **≥VGPR 51 vs 20%*,** sCR or better: 9 vs 1% ▪ MRD negativity rate: 9 vs 2%; *P* = .01 ▪ Median time to next tx: 23.2 vs 11 .8 mo
Safety	▪ All-grade neutropenia: 63.3 vs 48% ▪ Similar TEAEs including rate of primary malignancies	▪ Grade 3/4 TEAEs: neutropenia (68% vs 51%); anemia (17% vs 21%), similar thrombocytopenia ▪ All-grade pneumonia: 15 vs 8%
Key takeaway **P* <.0001	DRd demonstrated benefit in patients with 1-3 prior tx lines, including patients with high-risk cytogenetics, refractory to last line of tx, or age ≥65	DPd reduced the risk of disease progression or death (37%) with similar rates of infections and hematologic toxicity

Bahlis. Leukemia. 2020;34:1875. Kaufman. Blood Cancer J. 2020; 10:111. Dimopoulos. Lancet Oncol. 2021;22:801.

PI-Based Combinations: Daratumumab

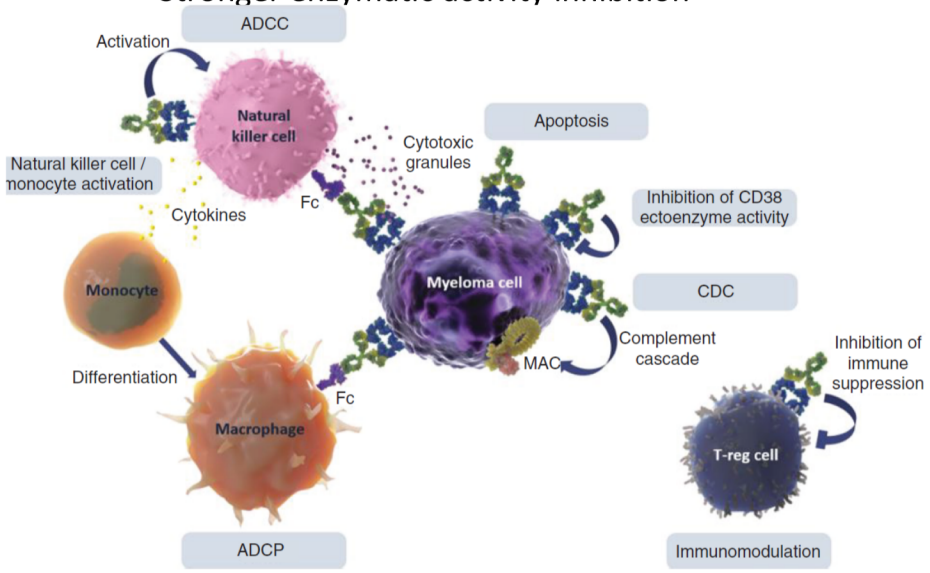
	CASTOR (DVd vs Vd)	CANDOR (DKd vs Kd)
Study population	**≥1 line** of tx including PI/IMiD (N = 498)	**1-3 lines** of tx, prior anti-CD38 (n = 1)/ K-exposure allowed (>6 mo prior), CrCl >20mL/min, (N = 466)
Study design	Phase III trial ▪ Randomized 1:1: **DVd** (n = 251) vs Vd (n = 247) – Stratified by ISS stage, prior PI, no. of prior tx lines	Phase III trial ▪ Randomized 2:1: **DKd** (n = 312) vs Kd (n = 154) (twice weekly K) – Stratified by ISS stage, prior PI/CD38 mAb, no. of prior tx lines
Patient characteristics	▪ 47% 1 prior line of tx, 69% prior PI, 28.5% ref IMiD ▪ 11.5% ≥75 yr old	▪ ~55% 2-3 prior lines tx; 12% ref to PI and IMiD ▪ 16% high-risk cytogenetics, 11.5% ≥75 yr old
Outcomes	Median follow-up: 40 mo ▪ PFS: **16.7 vs 7.1 mo*** ▪ ≥CR: 30 vs 10%* ▪ **MRD negativity rate: 14 vs 2%,** 20% vs 3% (1 prior line tx)* ▪ Median time to next tx: **25.4 vs 9.7 mo***	Median follow-up: 27.8 mo ▪ PFS: **28.6 vs 15.2 mo*** ▪ CR or better: 33 vs 13% ▪ Subsequent tx: **34 vs 54%**
Safety	▪ G3/4 TEAEs: thrombocytopenia(46% vs 33%) anemia (16%), and pneumonia (10%) ▪ Higher rates of G3/4 infection with DVd (29% vs 19%)	▪ G3/4 TEAEs (87 vs 76%): thrombocytopenia (25 vs 16%), HTN (21 vs 15), pneumonia (18 vs 9%), anemia (17 vs 15%) ▪ All-grade respiratory infections: 78 vs 58%
Key takeaway	DVd demonstrated significant PFS/ORR benefit regardless of prior tx with PI or IMiD with manageable toxicity profile	Significant PFS improvement with DKd including IMiD-ref subgroups with similar hematologic/infectious toxicities and discontinuation rates due to AE's (20%)

*P <.0001

Mateos. Clin Lymphoma Myeloma Leuk. 2020;20:509. Usmani. Lancet Oncol. 2022;23:65.

Isatuximab-irfc

- Mechanism of action: multimodal anti-CD38 mAb
  - Similar mechanism to daratumumab
  - Direct tumor effect: CDC, ADCC, ADCP
  - Direct apoptosis without cross-linking and is independent of effector cells
  - Stronger enzymatic activity inhibition



Key Administration Aspects in R/R MM Setting (28-Day Cycle)	
Dosing	▪ Cycle 1: 10 mg/kg IV on D1, 8, 15, and 22 ▪ Cycle 2+: 10 mg/kg IV on D1 and 15
Renal/liver dosing	▪ None
Adverse events	**Neutropenia**, **IRRs, pneumonia, URTI, diarrhea**, secondary malignancies, hypertension
Pearls	▪ Same pre-meds as daratumumab ▪ When using combination with PI: give corticosteroid 1st, followed by isatuximab then PI ▪ Withhold treatment for excision of skin cancer; resume isatuximab treatment after resection
FDA-approved combinations	▪ **IMiD based**: pomalidomide (IsaPd) ▪ **PI based**: carfilzomib 20mg/m^2, then 70mg/m^2 (IsaKd)

Moreau. Future Oncol. 2020;16:4347. Image under Creative Commons Attribution 4.0 International (CC BY NC ND 4.0). Isatuximab-irfc PI.

Slide credit: ProCE.com and clinicaloptions.com

Isatuximab-irfc: R/R MM Literature

	ICARIA-MM (IsaPd vs Pd)	IKEMA (IsaKd vs Kd)
Study population	**≥2 prior lines of tx**, including R and a PI (N = 307)	**1-3 prior lines** of tx, no prior K and not CD38 mAb ref, CrCl >15mL/min (N = 302)
Study design	Phase III trial ▪ Randomized 1:1: **IsaPd** (n = 154) vs Pd (n = 153) – Stratified by age, no. of prior tx lines	Phase III trial ▪ Randomized 3:2: **IsaKd** (n = 179) vs Kd (n = 123), K twice weekly – Stratified by R-ISS stage, no. of tx lines
Patient characteristics	Median 3 prior lines of tx, 93% R-ref, 71% ref IMiD/PI ▪ 20% high-risk cytogenetics, 20% ≥75 yr old	Median 2 prior lines of tx, 33% ref (R or PI), 21% ref IMiD/PI ▪ 24% high-risk cytogenetics, 9% ≥75 yr old
Outcomes *P <.0001	Median follow: 35.3 mo ▪ **PFS: 11.1 vs 5.9 mo*,** MRD neg: 7 vs 0% ▪ ORR: 63 vs 33%; **≥VGPR 38% vs 11%** ▪ TTNT: 15.5 vs 8.9 mo*	Median follow-up: 20.7 mo ▪ **PFS: NR IsaKd** vs 19.15 mo, P = .0007 ▪ ORR: 87 vs 83%; ≥VGPR: 73% vs 56%, P = .0011 ▪ MRD neg: 30 vs 13% (P = .004)
Safety	▪ TEAEs: IRRs: 36 vs 3%, pneumonia: 33 vs 30%, similar rates of thrombocytopenia ▪ G3/4 neutropenia higher in IsaPd (50% vs 35%) ▪ AE related death → 9 vs 10%	▪ TEAEs: IRRs: 46 vs 3%, URTI: 36 vs 24%, HTN: 37 vs 31%, diarrhea 36 vs 29% ▪ ≥G3 neutropenia higher in IsaKd (19% vs 7%) ▪ AE related death: 3% both groups
Key takeaway	The addition of Isa to Pd significantly improves PFS and OS by ~7 mo with manageable toxicity	Significant PFS improvement with IsaKd including difficult subgroups with similar hematologic/infectious toxicities

Richardson. Lancet Oncol. 2022;23:416. Moreau. Lancet. 2021;397:2361. Moreau. EMJ Hematol. 2022;10 (suppl 1):2.

Anti-CD38 mAbs: Changing R/R MM Playing Field

- Introduction of anti-CD38+ mAbs have impacted the management of patients with MM
- Limited literature on therapies following CD38+ tx and TCE patients in real-world
- MAMMOTH study: retrospective review (n = 275 R/R MM) refractory to CD38 mAb tx
  - Median time between diagnosis and CD38+ refractory diseased: 50.1 mo
    - Median of 4-prior lines tx (1-16), 25% penta-ref, 54% triple/quad-ref
  - Median OS of entire cohort: 8.6 mo; 5.6 mo (penta-ref)
  - Best achieved PFS was with combinations of carfilzomib and alkylating agents
- LocoMMotion: Prospective on real-world SOC after ≥3 prior lines or double-ref disease
  - 1st interim analysis of 225 patients with a median follow-up of 3.7 mo
  - 73.8% were triple-class refractory, median of 4.0 (range: 2–13) prior lines of tx
  - ORR of salvage tx was 20.1%
- **Key Takeaway:** TCE MM patients have a poor prognosis (OS 1-4 mo) and new therapies to be tested in this population

Gandhi. Leukemia. 2019;33:2266. Mateos. ASCO 2021. Abstr 8041. Moreau. EMJ Hematol. 2022;10(suppl1):2.

Key mAbs Infusion Considerations

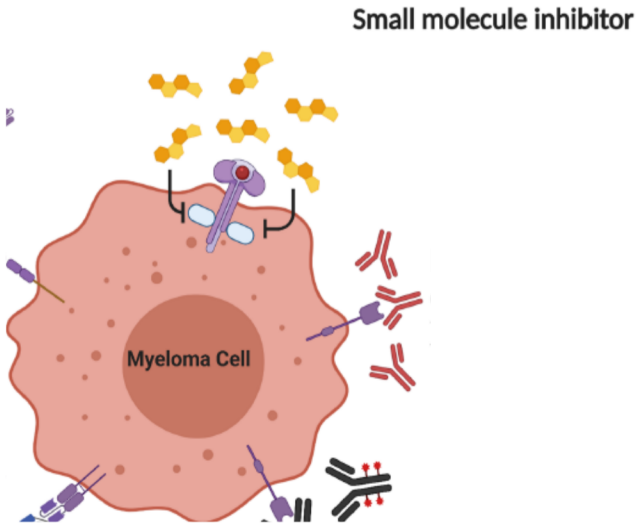
	Daratumumab IV	Daratumumab Hyaluronidase SC	Isatuximab IV	Elotuzumab IV
Infusion Duration	Variable: initial ~ .5-8 hr Rapid infusion (if tolerated)	SC push over 3-5 min	Variable: 1.25 to 3.5 hr Fixed infusion 250mL Max rate of 200mL/hr	Variable; concentration dependent dilution- 0.5-5 mL/min
Clinical Pearls	▪ HBV testing ▪ Herpes zoster prophylaxis ▪ Interference with serological testing (obtain baseline type and screen) ▪ Pre-, post-meds for IRR ▪ Can split dose 8mg/kg Days 1 and 2	▪ Same as IV formulation + ▪ Requires monitoring after first dose (institutional) for delayed IRR	▪ HSV prophylaxis ▪ Approved regimens excluded previous CD38 mAbs ▪ Real-word data suggest activity ▪ Interference with serological testing (obtain baseline type and screen) ▪ Premeds for IRR	▪ Not used as single agent ▪ Premeds for IRR ▪ HSV prophylaxis

Daratumumab PI. Daratumumab hyaluronidase-fihj PI. Elotuzumab PI. Isatuximab PI. Djebbari. ASH 20201. Abstr 1963.

Slide credit: ProCE.com and clinicaloptions.com

Small Molecule Inhibitors

- Small molecule inhibitors
  - Selinexor (XPO-1 Inhibitor)
  - Venetoclax (BCL-2 Inhibitor)



Su. J Hematol Onco. 2021;14:115. Image under Creative Commons Attribution: http:// creativecommons.org/ licenses/ by/ 4.0/. (Edited to remove/add text)

Slide credit: ProCE.com and clinicaloptions.com

Selinexor (X)

- XPO1 is an essential nuclear exporter of >200 TSPs
  - XPO1 is overexpressed in myeloma cells
- Mechanism of action: binds to the cargo binding pocket of XPO1
  - Restores activity of TSP in the nucleus
  - Selective apoptosis of malignant cells (TP53-independent)

IMAGE NOT AVAILABLE

Key Administration Aspects in R/R MM Setting (28-Day Cycle)	
Dosing	▪ 80 mg PO twice weekly in combination with 20 mg of dexamethasone ▪ **100 mg PO (five 20-mg tablets) once weekly with Vd**
Renal/liver dosing	▪ None
Adverse events	▪ **GI: nausea/vomiting/diarrhea,** decreased appetite, electrolyte abnormalities, hyperglycemia ▪ Hematologic: **thrombocytopenia** >**anemia** >>neutropenia ▪ CNS: **fatigue,** altered mental state, dizziness
Pearls	▪ Optimize hydration, caloric intake, blood counts, and concomitant medications and give with antiemetics
FDA-approved combinations	▪ PI-based after ≥1 line of tx: selinexor + Vd ▪ Selinexor + dexamethasone after ≥4 lines of therapy

Richard. Future Oncol. 2020;16:1331. Selinexor PI. Parikh. Hematol Oncol. 2014;7:78.
Chari. NEJM. 2019;381:727. Tai. Leukemia. 2013;28:155.

Selinexor: Toxicity Considerations

	Selinexor	
Select AEs to Assess	Thrombocytopenia, neutropenia (consider TPO/growth factor support) **Considered highly emetogenic** ▪ Consider longer acting antiemetic (ie, olanzapine or rolapitant) as standing with 5-HT3 for breakthrough Hyponatremia Infections	
Recommended Monitoring	Monitor patients at baseline and during treatment for cytopenia, neutropenia, hyponatremia, infections Monitor patients' body weight and potential for dehydration **Provide antiemetic (and anti-diarrheal) prophylaxis;** consider IV hydration for patients at risk of dehydration **Consider starting selinexor therapy at reduced dose of 80 mg once weekly**	
Recommended Dose Reductions	Starting dose (XVd): 100 mg once weekly ▪ First: 80 mg once weekly ▪ Second: 60 mg once weekly ▪ Third: 40 mg once weekly ▪ Discontinue after third reduction	Starting dose (Xd): 80 mg Days 1 and 3 ▪ First: 100 mg once weekly ▪ Second: 80 mg once weekly ▪ Third: 60 mg once weekly ▪ Discontinue after third reduction

Selinexor PI. Gavriatopoulou. Leukemia. 2020;34:2430.

Slide credit: ProCE.com and clinicaloptions.com

Selinexor: Combined Options for R/R MM*

Regimen	+ Dexamethasone (20 mg)	+ Bortezomib + Dexamethasone (40 mg)	+ Pomalidomide + Dexamethasone (40 mg)	+ Daratumumab + Dexamethasone (4 0mg)
FDA approval[1]	≥4 prior tx and refractory to 2 PI, 2 IMiD and anti-CD38 mAb	Adults previous treated with ≥1 prior therapy	N/A	N/A
Dosing	80 mg PO days twice weekly	100 mg PO weekly	RP2D: 60 mg PO weekly XPd (P: 4mg)	RP2D: 100 mg PO weekly DXd (D: 16 mg/kg)
Clinical trial	**STORM Trial** (N = 122)[2] Phase II, single arm	**BOSTON Trial** (N = 402)[3] Phase III	**STOMP trial** (N = 72)[4] Phase IB/II	**STOMP trial** (n = 34)[6] Phase IB/II
Comparator	N/A	XVd vs Vd (V: 1.3mg/m^2)	N/A (2+ lines of tx)	N/A (≥3 lines of tx)
Outcomes	▪ ORR: 26%, DoR: 4.4 mo ▪ PFS: 3.7 mo, OS: 8.6 mo After median 7 tx lines	▪ ORR: 76.4 vs 62.3% ▪ PFS: 13.9 vs 9.5 mo	▪ ORR: 65 vs 31% for Pd[5] ▪ PFS (P naive/non ref): 12.2 mo	▪ ORR 73% ▪ PFS: 12.5 mo ▪ (CD38 mAb naive)
Safety	All-grade: thrombocytopenia (73%), anemia (67%), neutropenia (40%), nausea (72%)	All-grade: thrombocytopenia (60%), anemia (36%), neutropenia (15%), nausea (50%)	Neutropenia, anemia, thrombocytopenia, leukopenia, fatigue	Thrombocytopenia, nausea, fatigue, anemia, neutropenia

*Several other combinations in phase IB/II: carfilzomib, lenalidomide and ixazomib

1. Selinexor PI. 2. Chari. NEJM. 2019;381:727. 3. Grosicki. Lancet. 2020;396:1563. 4. White. ASCO 2021. Abstr 8018. 5. San-Miguel. Lancet Oncol. 2013;14:1055. 6. Gasparetto. eJHaem. 2021;5:56.

Venetoclax (Ven)

- Mechanism of action: selective oral inhibitor of BCL-2
  - Binds directly to the BCL-2 protein
  - Displaces pro-apoptotic proteins and restores the apoptotic process

IMAGE NOT AVAILABLE

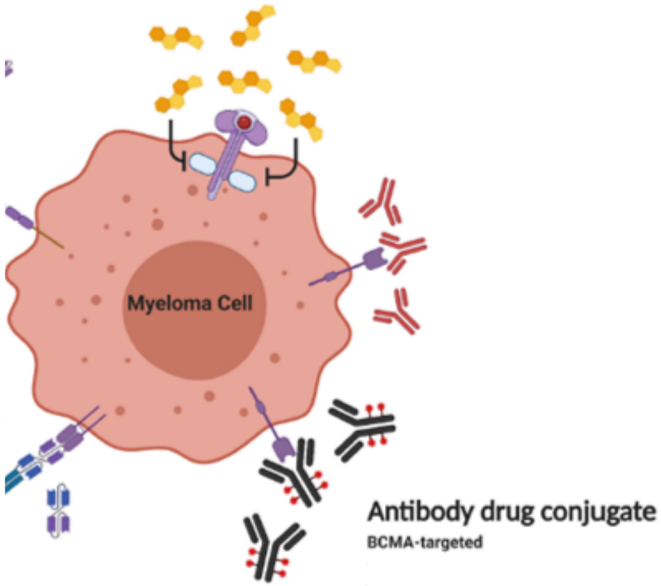
Key Administration Aspects in R/R MM Setting	
Dosing	▪ 800 mg PO daily in 21-day cycles x 8 cycles, then 35-day cycles until progression
Renal / Liver Dosing	▪ Reduce by 50% for Child-Pugh Class C
Adverse events	**Diarrhea, nausea**, **infections**, thrombocytopenia, anemia, TLS neutropenia, **pneumonia**, edema, hyperglycemia, electrolyte abnormalities
Pearls	▪ Dose reductions for CYP3A4 inhibitors ▪ Herpes zoster/PJP prophylaxis ▪ Monitor TLS risk ▪ Consider dose-escalation 400 mg daily (first wk), then increase to 800 mg daily
Not FDA Approved	Off label use in R/R MM **w/ t(11:14) only**
BELLINI Trial Phase III **Ven+ Vd** vs **Placebo+ Vd**	Median follow-up of 18.7 mo ▪ PFS: **22.4 vs 11.5 mo**; *P* = .01, ORR 85% vs 70% ▪ PFS improvement at the cost of higher rate of fatal infections. OS favors placebo. Higher CR rates in R/R MM with t(11;14)

Kaufman, et al. **Ven + d** after 1+ line of Tx (n = 31) in patients with t(11;14): demonstrated **single-agent activity** in for who are **refractory to CD38 mAb**

Salvaris. Future Oncol. 2021;174:371. Kaufman. Lancet Oncol. 2020;21:1630. Kaufman. Am J Hematol. 2021;96:418. Venetoclax PI.

Antibody–Drug Conjugates

- Antibody–drug conjugates
  - Belantamab mafodotin-blmf

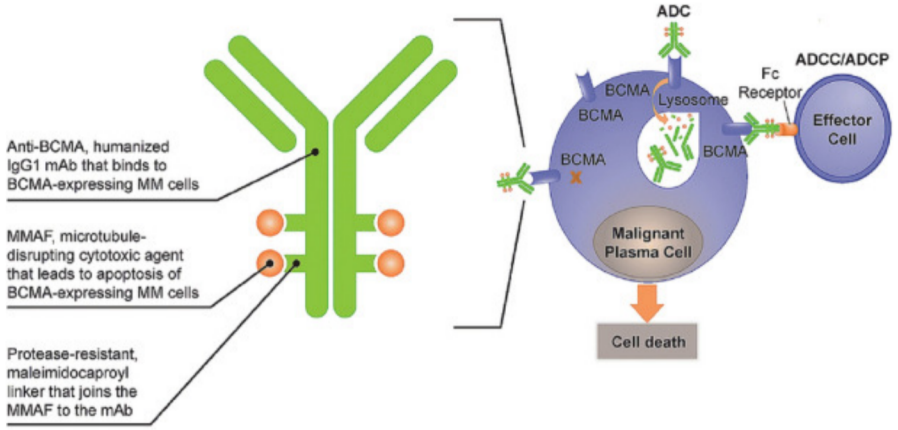


Su. J Hematol Onco. 2021;14:115. Image under Creative Commons Attribution: http:// creativecommons.org/ licenses/ by/ 4.0/. (Edited to remove/add text)

Slide credit: ProCE.com and clinicaloptions.com

Belantamab Mafodotin-blmf

- Mechanism of action: ADC targeting BCMA found primarily on MM cells
  - Belantamab mafodotin-blmf (Belamaf) is internalized
    - MMAF is released via proteolytic cleavage and disrupts microtubule network leading to cell cycle arrest and apoptosis
  - ADCC and ADCP



Key Administration Aspects in R/R MM Setting	
Dosing	▪ 2.5 mg/kg IV over 30 min every 3 wk ▪ ≥4 therapies including an anti-CD38 monoclonal antibody, PI, and IMiD
Renal/liver dosing	▪ None
Adverse events	**Ocular toxicity: keratopathy (76%), decreased visual acuity (55%)**, **blurred vision (27%), dry eye (19%)**, IRRs (18%: G1/2), nausea, pyrexia, increased serum glucose, fatigue, **thrombocytopenia (69%; 17% G4)**
Pearls	▪ Ophthalmic exams: baseline, prior to each dose, and promptly for any worsening symptoms ▪ Preservative-free lubricant eye drops (4x/day)/avoid contact lenses ▪ Dose adjustments based on corneal adverse reaction (Keratopathy and Visual Acuity Scale) ▪ May impair fertility

REMS

Farooq. Ophthalmol Ther. 2020;9:889. Image under Creative Commons Attribution 4.0 International (CC BY NC 4.0).
Belantamab mafodotin-blmf PI. Tai. Blood. 2014;123:3128. Lonial. Lancet Oncol. 2020;21:207.

Belantamab Mafodotin-blmf DREAMM-2

	DREAMM-2
Study population	≥3 lines of tx including PI/IMiD/anti-CD38 mAb (N = 196)
Study design	2-arm, phase II trial Study arms (1:1) ▪ **2.5 mg/kg belamaf (n = 97)** ▪ 3.4 mg/kg belamaf (n = 99) – prior dose in DREAMM-1
Patient characteristics	▪ Median age: 65 (60-70), ▪ Median no. of prior lines of tx: 7 (3-21) ▪ 42% had high-risk cytogenetics
Outcomes (2.5 mg/kg arm)	Median follow-up of 13 mo • **ORR: 32%; ≥VGPR 19%; DoR 11 mo** • PFS: 2.8 mo, OS: 13.7mo
Key takeaway	Single-agent belantamab mafodotin shows anti-myeloma activity with a manageable safety profile in patients with R/R MM

Adverse Events	2.5 mg/kg (n = 95)	
Events leading to dose delays	54%	
Events leading to dose reductions	35%	
Events leading to discontinuation	9%	
	Gr 1-2	**Gr 3-4**
Keratopathy	43%	27%
Thrombocytopenia	15%	20%
Anemia	4%	20%
IRR	17%	3%

Lonial. Lancet Oncol. 2020;21:207. Lonial. Cancer. 2021;127:4198.

Managing Belantamab Mafodotin Toxicity

Keratopathy

- Conduct ophthalmic exams at baseline, prior to each dose, and promptly if symptoms (dry eye, blurred vision) occur
- Counsel patients to use preservative-free lubricant eye drops and avoid contact lenses unless directed by an ophthalmologist
  - However, prophylactic steroid eye drops DO NOT prevent or reduce risk of keratopathy
- Hold belamaf until improvement; resume or permanently discontinue based on severity

Dose Modifications
(see package insert for detailed instructions)

Starting dose: 2.5 mg/kg IV every 3 wk

↳ Dose reduction: 1.9 mg/kg IV every 3 wk

Discontinue if unable to tolerate 1.9 mg/kg dosing

Grade	Description	Dose Modifications
1	**Exam findings**: mild superficial keratopathy **Change in BCVA**: decline of 1 line on Snellen Visual Acuity	Continue at current dose
2	**Exam findings**: moderate superficial keratopathy **Change in BCVA**: decline of 2-3 lines on Snellen Visual Acuity, not worse than 20/200	Hold until improvement in exam and BCVA to grade 1, then resume at current dose
3	**Exam findings:** severe superficial keratopathy **Change in BCVA:** decline of >3 lines on Snellen Visual Acuity, not worse than 20/200	Hold until improvement in exam and BCVA to grade 1, then resume at reduced dose
4	**Exam findings:** corneal epithelial defect **Change in BCVA:** Snellen Visual Acuity worse than 20/200	**Consider permanent discontinuation** If continuing, follow grade 3 recommendations

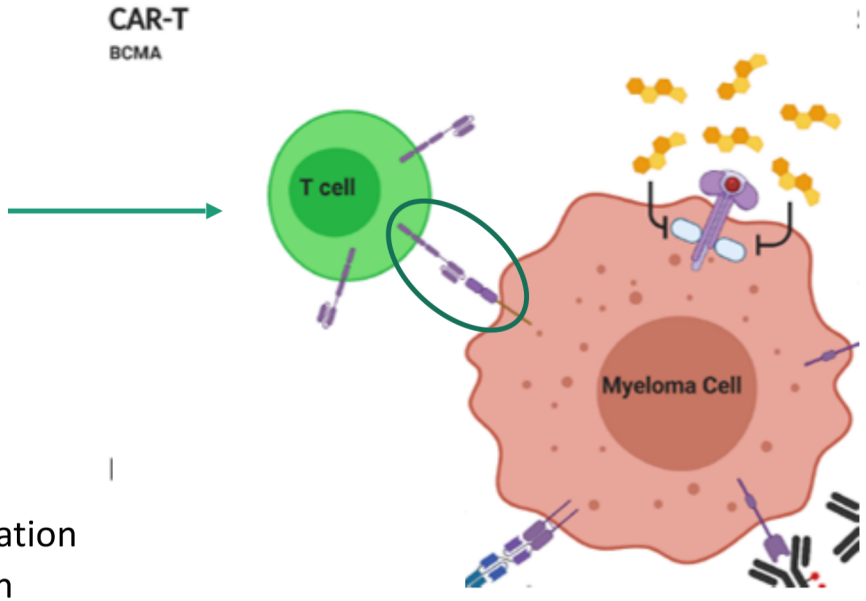
Belantamab mafodotin is only available through REMS program

Belantamab mafodotin PI. Wahab. Front Oncol. 2021;11:678634.

Chimeric Antigen Receptor Therapy: BCMA Targeting in R/R MM

Modified autologous T-cell immunotherapy product

- Consists of a patient's own T-cells that are harvested
- Undergoes further manufacturing to provide genetic modification targeting BCMA found on MM cells



Mechanism of Action: Antigen-specific activation

- CAR T-cell proliferation, cytokine secretion
- Subsequent cytolytic killing of BCMA-expressing MM cells

Su. J Hematol Onco. 2021;14:115. Image under Creative Commons Attribution: http:// creativecommons.org/ licenses/ by/4.0/. (Edited to remove/add text)

Approved Autologous CART R/R MM Products

	Idecabtagene Vicleucel (Ide-cel)	Ciltacabtagene Autoleucel (Cilta-cel)
CAR type	**BCMA/CD137 (4-1BB)/CD3z**	2-BCMA epitope binding domains/**CD137 (4-1BB)/CD3z**
Costimulatory domain	4-1BB	
Vector	lentivirus	
LD (3 days)	Cyclophosphamide IV 300mg/m^2 daily + fludarabine 30mg/m^2 IV daily	
Pivotal trial	**KarMMA-2 (R/R MM)**	**CARTITUDE-1 (R/R MM)**
Median time from apheresis to delivery	33 days	29 days

IMAGE NOT AVAILABLE

Role in R/R MM: FDA approved for the treatment of adult patients with **R/R MM after 4 or more prior lines of therapy, including an IMiD, PI, and an anti-CD38 mAb**

Idecabtagene vicleucel PI. Ciltacabtagene autoleucel PI.

Slide credit: ProCE.com and clinicaloptions.com

CART-Related Toxicities: CRS and ICANS

	CRS	ICANS
Definition	▪ Supraphysiologic response after any immune therapy ▪ Results in activation of infused T-cells and/or other IECs	▪ Pathologic process involving the CNS after any immune therapy ▪ Results in activation of infused T-cells and/or other IECs
Signs/ Symptoms	▪ Fever ▪ Hypotension ▪ Hypoxia ▪ Organ dysfunction	▪ Aphasia ▪ Confusion, delirium ▪ Cognitive impairment ▪ Motor weakness ▪ Seizures ▪ Cerebral edema
Management*	▪ Supportive care ▪ Tocilizumab ▪ Steroids	▪ Supportive care ▪ Steroids

*In order of increase treatment intensity.

Toxicity	Ide-Cel	Cilta-Cel
CRS	All grade: 84% Grade 3-4: 5% Grade 5: 1%	All grade: 95% Grade 3-4: 4% Grade 5: 1% (+HLH)
Median onset or duration, days (range)	**Onset: 1 (1-12) days** Duration: 5 (1-63) days	**Onset: 7 (5-8) days** Duration: 4 (3-6) days
NT (ICANS)	All grade: 18% Grade 3-4: 3%	All grade: 17% Grade 3-4: 2%
Median onset or duration, days (range)	**Onset: 2 (1-10) days** Duration: 3 (1-26) days	**Onset: 8 (6-8) days** Duration: 4 (3-6.5) days

Recommended Monitoring:

- Remain inpatient for ≥7 days after CAR T-cell infusion at certified healthcare facility to monitor for CRS and NT
- Post discharge: remain close to certified healthcare facility for at least 30 days. No driving/hazardous activities for at least 2 mo

Idecabtagene vicleucel PI. Ciltacabtagene autoleucel PI. Berdeja. Lancet. 2021;398:10297. Munshi. NEJM. 2021;384:705. Lee. Biol Blood Marrow Transplant. 2019;25:625.

CAR T-Cell Therapy–Associated TOXicity (CARTOX) Working Group

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	≥100.4°F/38°C	≥100.4°F/38°C	≥100.4°F/38°C	≥100.4°F/38°C
With either:				
Hypotension	None	Responsive to fluids	Requiring 1 vasopressor (with or without vasopressin)	Requiring multiple vasopressors (excluding vasopressin)
And/or **Hypoxia**	None	Low-flow nasal cannula or blow-by	High-flow nasal canula, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (CPAP, BiPAP Intubation and mechanical ventilation)
Organ toxicity	Gr 1 organ toxicity	Gr 2 organ toxicity	Gr 3 organ toxicity or Gr 4 transaminitis	Gr 4 organ toxicity (minus Gr 4 transaminitis)

*Fever not attributable to any other cause. In patients who have CRS then receive antipyretics or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

Lee. Biol Blood Marrow Transplant. 2019;25:625. Neelapu. Nat Rev Clin Oncol. 2018;15;47.

Slide credit: ProCE.com and clinicaloptions.com

Pharmacy Practice Points for Immune Effector Cell–Associated Neurotoxicity

- Prophylaxis for seizures with levetiracetam (typically begins during LD chemotherapy)
- 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 neurologic toxicities include (depending on nature/severity):
  - Seizure control (eg, benzodiazepines ± phenobarbital and/or lacosamide)
  - Corticosteroids (eg, dexamethasone, methylprednisolone)
  - Hyperventilation and hyperosmolar therapy (eg, for higher grade cerebral edema)

Idecabtagene vicleucel PI. Neelapu. Hematol Oncol. 2019;37 suppl 1:48. MDACC. IEC therapy toxicity assessment and management (also known as CARTOX) – adult. Approved September 15, 2020.

CART-related Toxicities: Other Supportive Care

- TLS prophylaxis
  - Fluids with cyclophosphamide LD, allopurinol if high risk (institutional specific)
- Neutropenia (avoid during CRS)
  - Consider G-CSF use for prolonged, severe neutropenia
    - Some utility in starting >7 days post-cell infusion
- Hypogammaglobulinemia
  - Administer IVIG for IgG <400 mg/dL and/or persistent respiratory illnesses
  - Utility of prophylactic infusions is unknown

Recommended Monitoring:

- Monitor blood counts and immunoglobulin levels after infusion
- Can support neutropenia with growth factor and/or transfusion support for other cytopenias

Ciltacabtagene autoleucel PI. Idecabtagene vicleucel PI. Miao. Front. Immunol. 2021;12:663201.
Yanez. Hemasphere. 2019;3:e186.

CART-related Toxicities: Other Supportive Care

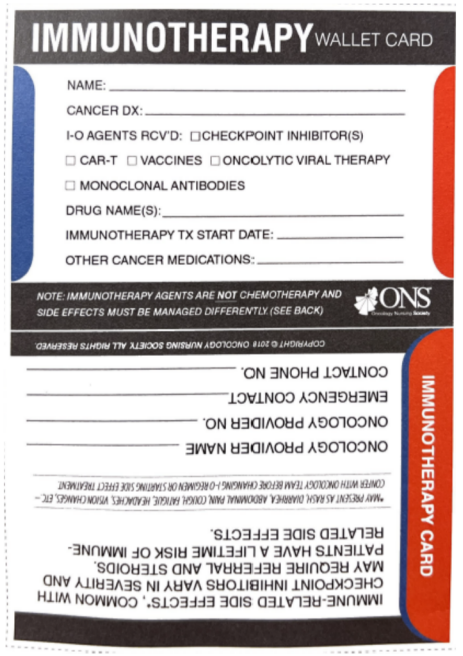
- Infection prophylaxis/vaccinations
  - HSV active agent x 1-yr post CART, anti-fungal and fluroquinolone during neutropenic period
  - PJP prophylaxis starting D+30
  - Complete any outstanding vaccinations at least 2 wk prior to CAR-T (e.g. influenza, pneumococcal, COVID)
  - Delay post-infusion vaccinations for at least 3-6 mo (1 yr for live)
  - Consider checking antibody titers

Toxicity	Ide-Cel	Cilta-Cel
Infections (bacterial, viral, fungal), %	69	58
Hypogammaglobulinemia, %	21	12
Gr 3/4 neutropenia/thrombocytopenia >1 mo, %	41/48	10

Ciltacabtagene autoleucel PI. Idecabtagene vicleucel PI. Munshi. NEJM. 2021;384:705. Anderson. ASCO 2021. Abstr 8016. Berdeja. Lancet. 2021;398:10297. Hill. Blood. 2020;136:925.

Anti-BCMA CART REMS Program and Boxed Warnings

- Both products are available under a Risk Evaluation and Mitigation Strategy (REMS)
  - Healthcare providers who prescribe, dispense or administer must be trained in management of CRS and neurological toxicities and complete the knowledge assessment
  - Requires immediate access to 2 doses of tocilizumab for each patient within 2 hr of the infusion if needed
  - Patient wallet card
- Additional Warnings
  - Hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS)
    - Can occur with CRS or NT/ICANS
  - Prolonged and/or recurrent cytopenias with bleeding and infection risk
  - Cilta-Cel specifically: Parkinsonism and Guillain-Barré syndrome and associated complications (fatal or life-threatening reactions have occurred)



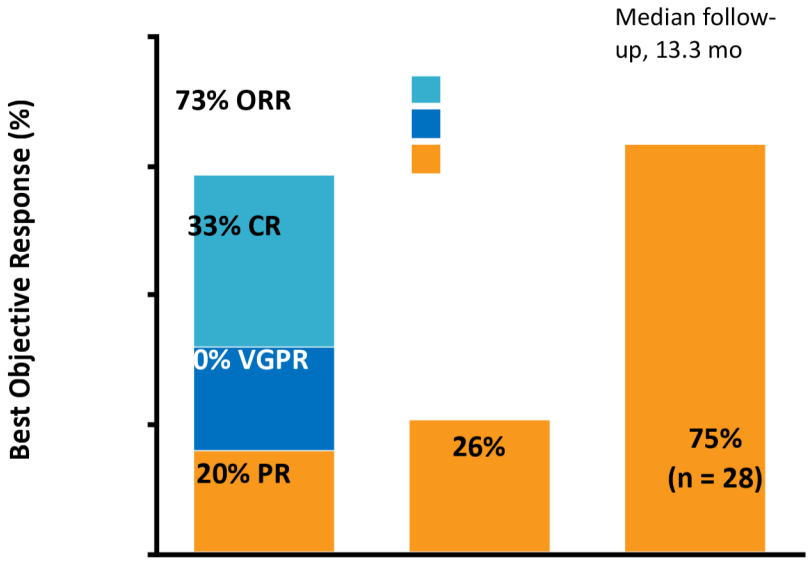
Ciltacabtagene autoleucel PI. Idecabtagene vicleucel PI.

Slide credit: ProCE.com and clinicaloptions.com

Ide-cel in R/R MM: KarMMa-1

	KarMMa-1
Study population	**≥3 previous lines tx**, including IMiD, PI, and anti-CD38 mAb and refractory to their last regimen (N = 140 apheresed/ n= 128 treated)
Study design	Open-label, multicenter, phase II trial ▪ Target cell dose: 150-450 x 10^6 CAR T-cells ▪ 88% received bridging Tx
Patient characteristics	▪ Median no. of prior lines: 6 (3-16) ▪ Median age: 61 (33-78) yr old ▪ 94% prior aHCT ▪ 94% ref to anti-CD38 mAb ▪ 84% triple class ref ▪ **26% penta-ref** (2 PIs, 2 IMiDs, and anti-CD38 mAb) ▪ 35% high-risk cytogenetics
Outcomes	Median follow-up of 24.8 mo ▪ DoR: (PR or better): 10.9 mo (all pts), 21.5 mo (patients with sCR) ▪ PFS: 8.6 mo; OS: 24.8 mo (*continue to mature*) ▪ OS >20 mo in high-risk disease progression
Safety	Cytopenias (97%) and CRS (84%) most common any-grade toxicities

Munshi. NEJM. 2021;384:705. Anderson. ASCO 2021. Abstr 8016.

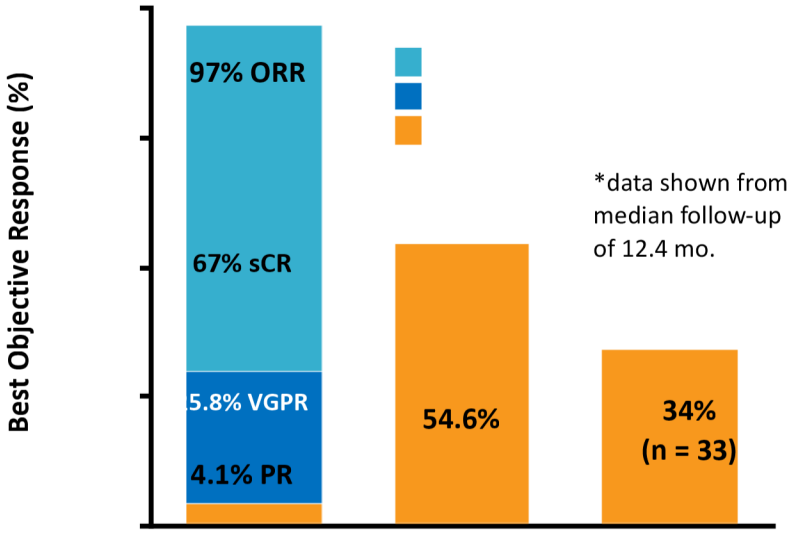


FDA approval March 26, 2021, based on KarMMa-1 results

Slide credit: ProCE.com and clinicaloptions.com

Cilta-cel in R/R MM: CARTITUDE-1

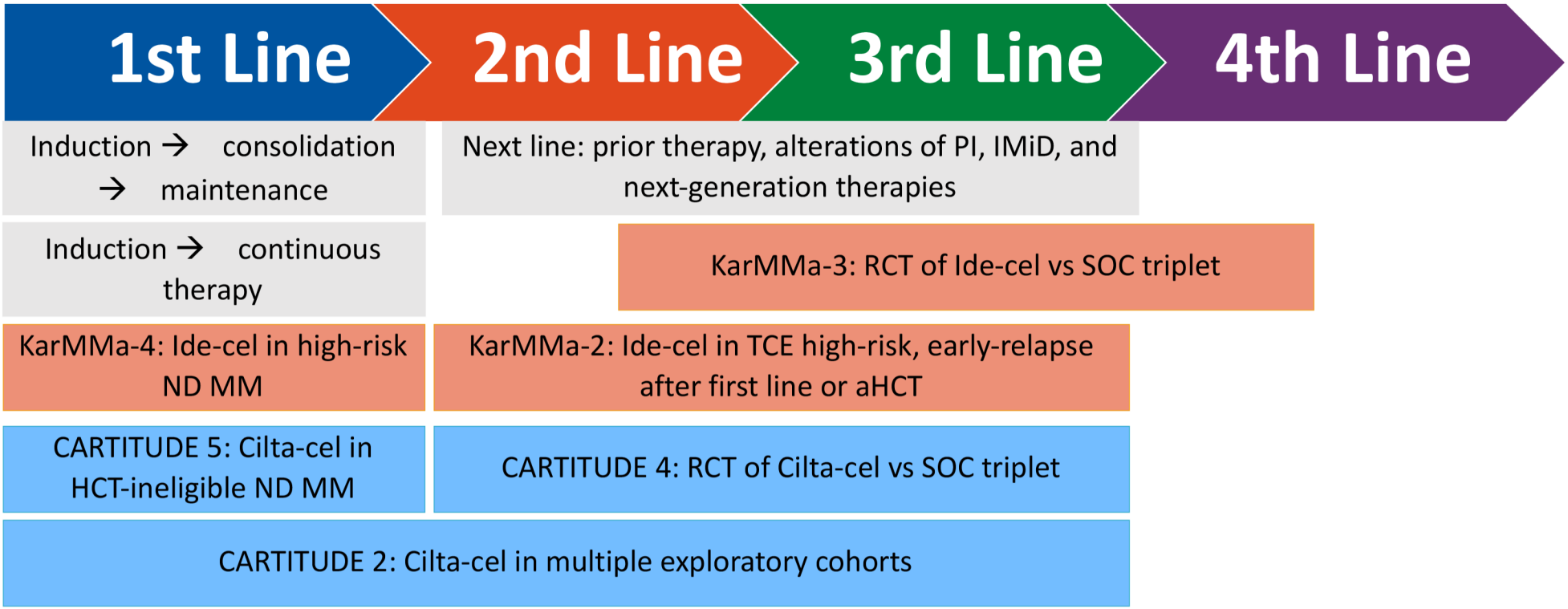
	CARTITUDE-1
Study population	**≥3 previous lines tx**, including IMiD, PI, and anti-CD38 mAb and ref to their last tx (n = 113 apheresed; n= 97 treated)
Study design	Open-label, multicenter, phase IB/II trial ▪ Target cell dose: 0.75×10^6 CAR-positive T-cells/kg ▪ 75% received bridging Tx
Patient characteristics	▪ Median no. of prior lines: 6 (4-8) ▪ Median age: 61 (56-68) yr old ▪ 90% prior aHCT ▪ 97% ref to anti-CD38 mAb, 88% triple class ref ▪ **42% penta-ref** (2 PIs, 2 IMiD, and anti-CD38 mAb) ▪ 24% high-risk cytogenetics
Outcomes	Median 2-yr follow-up ▪ 97.9% ORR with 82.5% sCR ▪ MRD (-) 92% (n = 61) ▪ 2-yr PFS 60.5% and OS 74%
Safety	Cytopenia (96%) and CRS (95%) most common any-grade toxicities. One Gr 5 CRS and one HLH-related death. ▪ 5% experienced cluster of movement and neurocognitive TEAEs



FDA approval February 28, 2022, based on CARTITUDE-1 results

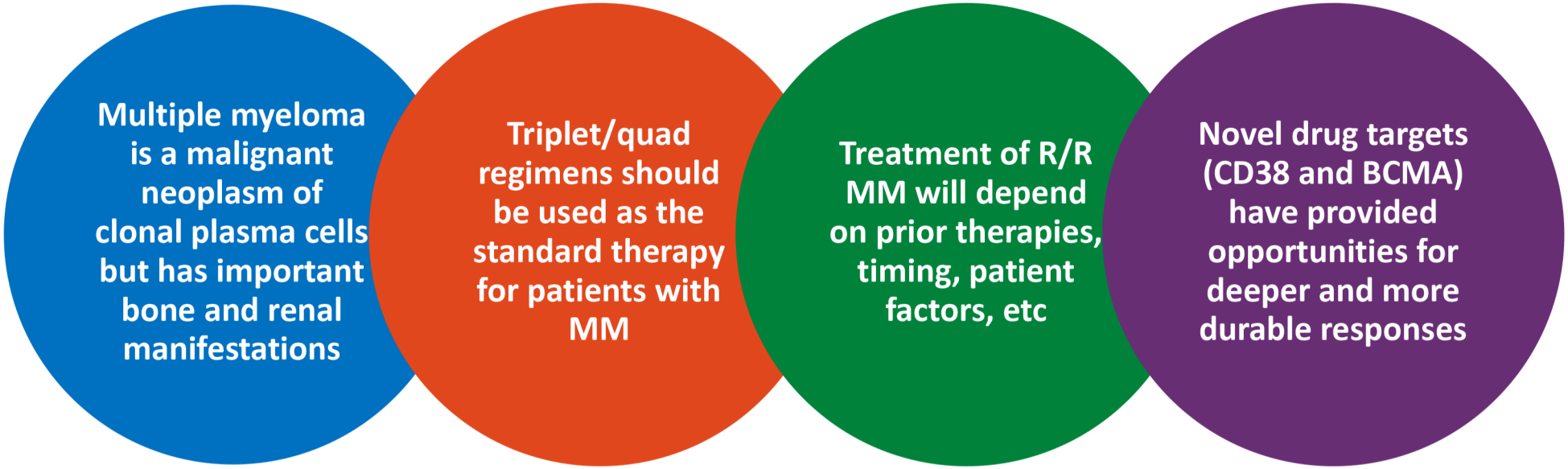
Berdeja. Lancet. 2021;398:314. Usmani. ASCO 2021. Abstr 8005. Martin. ASCO 2021. Abstr 8045. Jakubowiak. ASH 2021. Abstr 3938. Martin. 2021 ASH. Abstr 549.

Emerging CART Therapies: Moving Closer to the Starting Line



Slide credit: ProCE.com and clinicaloptions.com

Summary and Final Thoughts



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Emerging Therapies for Multiple Myeloma and Managed Care Considerations

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Supported by educational grants from Bristol-Myers Squibb and Karyopharm Therapeutics Inc.

Promising CD38-Targeted Myeloma Therapies in Clinical Trials (March 2022)

Trial	Regimen and MM Setting	Current Status
Phase III CEPHEUS (NCT03652064)	Frontline **daratumumab** + VRd vs VRd alone in transplant ineligible	▪ Recruiting (N = 395) ▪ Primary completion: 4/2022
Phase III PERSEUS (NCT03710603)	Frontline **daratumumab** + VRd vs VRd alone in transplant eligible	▪ Active, not recruiting (N = 690) ▪ Primary completion: 5/2025
Phase Ib study (NCT04045794)	**Isatuximab** (subcutaneous) + pomalidomide/dex in relapsed/refractory	▪ Recruiting (N = 56) ▪ Primary completion: 4/2024
Phase I/II study (NCT03215030)	**Modakafusp** (TAK-573)/dex in relapsed/refractory	▪ Recruiting (N = 151) ▪ Primary completion: 2/2022
Phase I study (NCT04017130)	**MT-0169** in relapsed/refractory (MM and NHL)	▪ Recruiting (N = 144) ▪ Primary completion: 1/2024
Phase I/II study (NCT03439280)	**Mezagitamab** (TAK-079) in relapsed/refractory	▪ Active, not recruiting (N = 100) ▪ Primary completion: 2/2022

ClinicalTrials.gov.

Slide credit: ProCE.com and clinicaloptions.com

Promising Cereblon Degraders in Clinical Trials for Myeloma: Iberdomide and Mezigdomide

Agent	Clinical Trials	Context
Iberdomide (CC-220)	▪ Completed: Phase Ib/IIa, 4th line Tx ▪ Ongoing: Phase III EXCALIBUR study of **iberdomide, daratumumab, dex vs DVd** as 2nd line+ Tx (N = 730) (NCT04975997) ▪ Not yet recruiting: Phase III MIDAS study of post-Isa-KRd maint w/**iberdomide vs lenalidomide** (N = 716) (NCT04934475)	▪ Iberdomide has the potential to replace lenalidomide in frontline therapy of myeloma
Mezigdomide (CC-92480)	▪ Completed: Phase I/II, 4th line Tx ▪ Ongoing: Phase I/II study of **mezigdomide ± dex** in R/R myeloma and ≥3 prior lines (N = 201) (NCT03374085) ▪ Ongoing: Phase I/II study of triplets with **mezigdomide + SOC** in R/R and newly diagnosed myeloma (N = 408) (NCT03989414)	▪ Potent cereblon E3 ligase ▪ Mezigdomide has the potential to replace pomalidomide in treatment of relapsed/refractory myeloma

ClinicalTrials.gov.

Slide credit: ProCE.com and clinicaloptions.com

BCMA in Multiple Myeloma

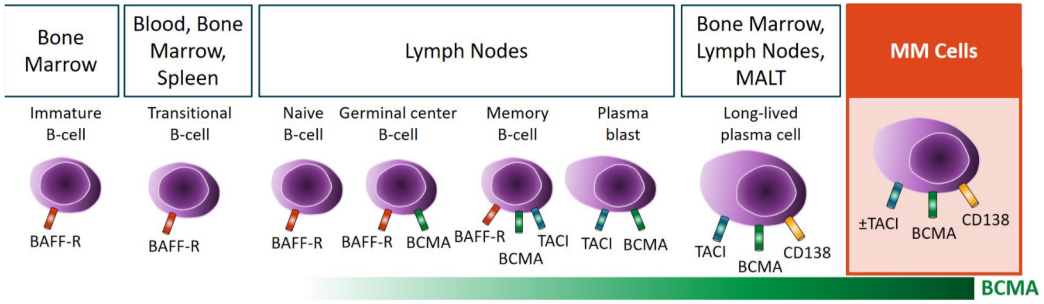


IMAGE NOT AVAILABLE

- 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

Cho. Front Immunol. 2018;10:1821.

Promising BCMA Antibody–Drug Conjugates in Clinical Trials for Myeloma (March 2022)

Trial and Population	BCMA ADC	Cytotoxic Conjugate	Current Status
Phase I: R/R MM and other BCMA+ heme malignancies (N = 79) (NCT02064387)	Belantamab mafodotin	MMAF	▪ First-in-class approval in 2020 ▪ Phase I study recruiting ▪ Multiple phase III trials of combination regimens ongoing
Phase I/IIa: R/R MM and other plasma cell disorders (N = 78) (NCT04879043)	HDP-101	Amanitin	▪ Recruiting
Phase I: R/R MM (N = 42) (NCT02561962)	AMG 224	Mertansine (DM1)	▪ Early phase I results published[1] ▪ Study ongoing (not recruiting)
Phase I: R/R MM (N = 160) (NCT04036461)	CC-99712	Undisclosed	▪ Recruiting

1. Lee. Leukemia. 2021;35:255.

Slide credit: ProCE.com and clinicaloptions.com

BCMA Antibody–Drug Conjugates for Myeloma: Early Clinical Trial Results

Trial	Regimen	Current Status	N	ORR, %	Median PFS, Mo	Safety
Phase I DREAMM-I (NCT02064387)	Belantamab mafodotin	Completed recruitment	79	60	12	▪ Keratopathy: 69% (mostly gr 1/2) ▪ Thrombocytopenia (all gr): 63% ▪ IRRs: 29% (mostly gr 1/2)
Phase II DREAMM-2 (NCT03525678)	Belantamab mafodotin	Active, not recruiting	97 (2.5 mg/kg), 99 (3.4-mg/kg)	78	--	▪ Keratopathy, 2.5-mg/kg cohort: 44% gr 1/2, 27% gr 3 ▪ Keratopathy, 3.4-mg/kg cohort: 54% gr 1/2, 20% gr 3 ▪ Thrombocytopenia (all gr), 2.5-mg/kg cohort: 35% ▪ Thrombocytopenia (all gr), 3.4-mg cohort: 58% ▪ IRRs, 2.5-mg/kg cohort: 18% (mostly gr 1/2) ▪ IRRs, 3.4-mg/kg cohort: 15% (mostly gr 1/2)
Phase I/II DREAMM-6 (NCT03544281)	Belantamab mafodotin + Vd or Rd	Recruiting	18 (RVd 2.5-mg/kg cohort)	78	--	▪ Keratopathy: 44% gr 1/2, 56% gr 3 ▪ Thrombocytopenia: 61% (gr 3/4) ▪ IRRS: 17% (all gr 2)
Phase I AMG 224 (NCT02561962)	AMG 224	Active, not recruiting	42	23	--	▪ Keratopathy: 36% (all gr 1/2) ▪ Thrombocytopenia: 24% (gr ≥3) ▪ IRRs: 3% (gr 2)

Sanchez. Ther Adv Hematol. 2021;12:2040620721989585.

Slide credit: ProCE.com and clinicaloptions.com

Belantamab Mafodotin in MM: DREAMM Program

Trial	Population	Phase	Intervention	Est Primary Completion Date
DREAMM-3	2L+ RR MM	III	Belamaf vs Pom + Dex	6/22
DREAMM-4	3L+ RR MM	I/II	Belamaf + Pembro	7/23
DREAMM-5	3L+ RR MM	I/II	Belamaf + innovative drugs	2/28
DREAMM-6	1L+ RR MM	I/II	Belamaf + Rd vs Belamaf + Vd	8/22
DREAMM-7	1L+ RR MM	III	Belamaf + BVd vs Belamaf + DVd	8/26
DREAMM-8	1L+ RR MM	III	Belamaf + BPd vs Belamaf + PVd	1/27
DREAMM-9	NDMM	I/III	Belamaf + VRd vs VRd	2/27
DREAMM-12	2L+ RR MM	I	Belamaf varying degree of renal function	2/25
DREAMM-13	2L+ RR MM	I	Belamaf varying degree of hepatic function	5/24

DREAMM Clinical Trial Program (dreammtrials.com) accessed 3/11/22

Slide credit: ProCE.com and clinicaloptions.com

CAR T-BCMA for Myeloma: Clinical Trial Results

CAR-T Construct	Study	N	3x Class Refractory	HR CG/EMD, %	mPFS, Mo (95% CI)	mOS, Mo (95% CI)	≥CR, %	CRS, %	NT, %
Ide-cel (bb2121)	Phase I CRB-401	62	69	27/37	8.8 (5.9-11.9)	34.2 (19.2-NE)	39	76	36
	Phase II KarMMa	128	84	35/39	8.8 (5.6-11.6)	19.4 (18.2-NE)	33	84	18
Cilta-cel	Phase I/II LEGEND	57	NR	NR	20 (10-28)	Median NR 18-mo: 68% (54-79)	74	90	1
	Phase Ib/II CARTITUDE-1	97	88	24/13	22.8 (22.8-NE)	Median NR 18-mo: 80.9% (71.4-87.6)	80	95	21
Orva-cel	Phase I/II EVOLVE	62	94	41/23	300 x 10^6: 9.3 Others: NR	NR	36	89	13
bb21217	Phase I CRB-402	69	64	33/NR	mPFS: NR mDOR: 17.0	NR	29	70	16
NCI CAR-BCMA	Phase I	24	NR	46/NR	mPFS: NR mEFS: 31 wks	NR	8	71	NR
Penn CART BCMA	Phase I	25	72	96/28	Cohorts 1/2/3: 65/57/125 d	NR	8	88	32
P-BCMA-101	Phase I/II PRIME	55	60	NR	NR	NR	NR	17	4
Zevor-cel (CT053)	Phase I LUMMICAR Study 2	20	85	55/25	NR	NR	25	79	16
ALLO-715	Phase I UNIVERSAL	31	NR	48/23	NR	NR	≥VGPR: 40	45	0
C-CAR088	Phase I	23	NR	81/NR	mPFS: NR 6-mo: 65.1%	NR	44	91	4

Strassl. Cancers (Basel). 2021;13:4701.

Ongoing Clinical Development of Approved BCMA CAR-T Therapies

Trial	Population	Phase	Regimen	Estimated Completion
KarMMa-2 (NCT03601078)	≥3rd line RR MM	II	Idecabtagene vicleucel	08/22
KarMMa-3 (NCT03651128)	2nd-4th line RR MM	III	Idecabtagene vicleucel vs SOC	05/22
CARTITUDE-2 (NCT04133636)	1st-3rd line RR MM	II	Ciltacabtagene autoleucel	05/22
CARTITUDE-4 (NCT04181827)	1st-3rd line RR MM	III	Ciltacabtagene autoleucel vs DPd or PVd	04/26
CARTITUDE-5 (NCT04923893)	ND MM	III	VRd → ciltacabtagene autoleucel vs VRd → Rd	02/26

ClinicalTrials.gov.

Slide credit: ProCE.com and clinicaloptions.com

ALLO-715: First Allogeneic ("Off-the-shelf") CAR-T cell Therapy

Administration and Efficacy	ALLO-715 320 or 480 x 10^6 + FCA (n = 24)	Ide-Cel 300/450 x 10^6 (n = 100)
Tx w/target cell product, n (%)	43 (90)	100 (74)
Days to Tx initiation	5	33
ORR, %	71	72
▪ ≥VGPR	46	53
– MRD neg	92	75
▪ CR/sCR	25	28
Median DOR, mo	8.3	11.0

Safety	ALLO-715 Phase I (N = 43)	Ide-Cel 300/450 x 10^6 (n = 127)
CRS, any/gr 3, %	56/2	85/9
Neurotox, any/gr 3, %	14/0	28/4
Gr ≥3 infection, %	19	23
Gr ≥3 neutropenia, %	70	89
AE-associated death, %	7	6

Mailankody. ASH 2021. Abstract 651.

Slide credit: ProCE.com and clinicaloptions.com

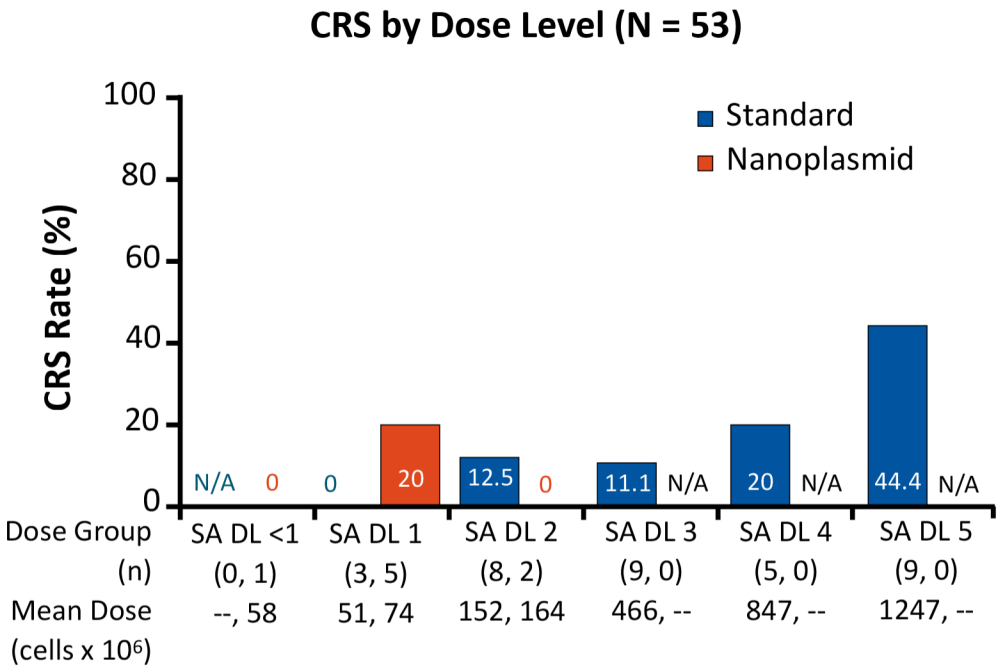
P-BCMA-101 (Autologous) and P-BCMA-ALLO-1 (Allogeneic) CAR T-Cell Therapies

- These CAR T-cell therapies comprise of high percentage of T_{SCM} cells which may provide greater response rates, longer duration of response, and increased safety[1-6]
- P-BCMA-101 (autologous): manufactured using transposons instead of viral vectors, intended to preferentially transpose T_{SCM} cells, include a safety switch to turn off CAR T-cells, and a drug resistance gene to allow for positive selection of CAR T-cells during manufacturing
  - As of October 15, 2021, 98 patients have been treated with P-BCMA-101 in 5 dose levels of single-agent P-BCMA-101[7]
  - The favorable safety profile allowed outpatient treatment in 28 (29%) patients[7]
- P-BCMA-ALLO1 CAR-T cells are generated from healthy donor T-cells using Cas-CLOVER to knockout Beta-2 microglobulin to prevent host vs graft rejection[7]
  - Currently ongoing trial with P-BCMA-ALLO-1 40 R/R MM patients

1. Spear. CAR-TCR Summit Summit. 2. Larson. AACR 2018. Abstr 960. 3. Moffit. SITC 2018. 4. Fraietta. Nature. 2018;558:307.
5. Bu. Oncotarget. 2018;9:25764. 6. Busch. Semin Immunol. 2016;28:28. 7. Costello. ASH 2021. Abstr 3858.

PRIME: P-BCMA-101 Safety

TEAE, n (%)	Patients (N = 55)	
	Any Grade	Grade ≥3
DLT	0	0
CRS ▪ Administered tocilizumab ▪ Administered steroids	9 (17.0) 4 (7.3) 3 (5.5)	0
Neurotoxicity	2 (3.8)	2 (3.8)
Infection ▪ Overall ▪ First mo	 24 (45.3) 9 (17.0)	 10 (18.9) 4 (7.5)
Neutropenia/ decreased neutrophils	41 (77.4)	40 (75.5)
Thrombocytopenia/ decreased platelets	22 (41.5)	16 (30.2)
Anemia	21 (39.6)	16 (30.2)
WBC count decreased	21 (39.6)	19 (35.8)
Fatigue	17 (32.1)	0



No patient with CRS was admitted to ICU or required safety switch use.
CRS did not occur in RIT, R, or RP cohorts.
CRS occurred in 1 of 4 patients receiving cyclic dosing (1 of 2 nanoplasmid).

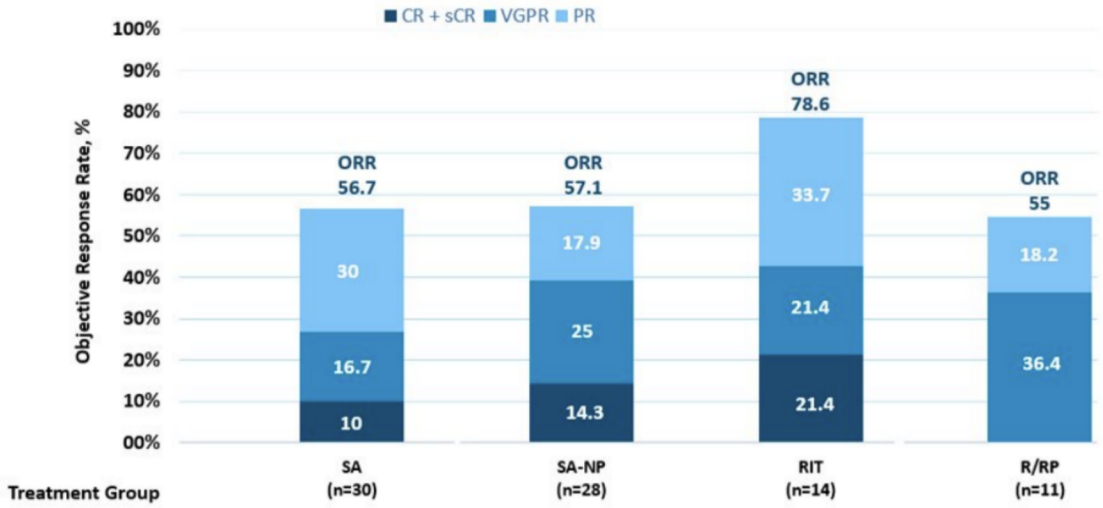
Most frequent TEAEs: infection, neutropenia, thrombocytopenia, anemia, leukopenia, fatigue.

Costello. ASH 2020. Abstr 134.

Slide credit: ProCE.com and clinicaloptions.com

PRIME: P-BCMA-101 Response by Treatment Group

Response in Evaluable Patients by Treatment Group



Data cutoff: October 15, 2021

ORR includes confirmed and unconfirmed responses, sCR, CR, VGPR, or PR

- SA: single administration with non-nanoplasmid manufacturing
- SA-NP: single administration with standard nanoplasmid manufacturing
- RIT: 375 mg/m2 IV infusion 12 and 5 days prior to P-BCM-101 then Q8W until PD
- R: Len 10 mg orally daily for 21 of each 28 day cycle starting 1 wk prior to P-BCMA-101 infusion
- RP: Len 10 mg orally daily for 7 days starting 1 wk prior to apharesis and for 21 of every 28 days starting 1 wk prior to P-BCMA-101 infusion

Costello. ASH 2021. Abstr 3858.

Slide credit: ProCE.com and clinicaloptions.com

Bispecific Antibody Constructs Targeting BCMA and CD3

Agent	Design	Phase	Status	Best ORR	CRS, % (n/N)	NCT
AMG420[1]	BiTE	I	No further development	70% at MTD (n = 10)	38 (16/42)	NCT03836053
AMG701[2]	Half-life extended BiTE	I/II	Ongoing phase I/II	83% of last tested dose expansion cohort (n = 6)	61 (46/75)	NCT03287908
Teclistamab [3-7]	Bispecific Ab, IgG4 Fc region (DuoBody)	I/II	Ongoing phase I/II studies	62% at 1.5 mg/kg dose (n = 93)	72 (118/165)	NCT04557098 NCT03145181
REGN5458[8]	Bispecific Ab, IgG4 Fc region (VelociBi)	I/II	Ongoing phase I/II	75% in 200-800 mg cohort (n = 24)	38 (28/73)	NCT03761108
TNB-383B[9]	Bispecific Ab, IgG4 Fc region, dual BCMA binding domains	I	Ongoing phase I	79% in the dose-escalation cohorts of ≥40 mg Q3W (n = 24)	52 (54/103)	NCT03933735
Elranatamab [10,11]	Bispecific Ab, IgG2A Fc region	II	Ongoing phase II (MagnetisMM-3)	83.3% at RP2D SC (n = 6); 69% at RP2D in priming cohorts	73 (22/30)	NCT04649359
CC-93269[12]	Bispecific Ab, IgG1 Fc region bivalent anti-BCMA arm	I	Ongoing phase I	89% at highest tested dose at 10 mg (n = 9)	77 (23/30)	NCT03486067

1. Topp. JCO. 2020;38:775. 2. Harrison. ASH 2021. Abstr 181. 3. Usmani. ASCO 2020. Abstr 100. 4. Usmani. Lancet. 2021;398:665. 5. Garfall. ASH 2021. Abstr 180. 6. Krishnan. ASCO 2021. Abstr 8007. 7. Moreau. ASH 2021. Abstr 896. 8. Zonder. ASH 2021. Abstr 160. 9. Kumar. ASH 2021. Abstr 900. 10. Bahlis. ASCO 2021. Abstr 8006. 11. Sebag. ASH 20201. Abstr 895. 12. Costa. EHA 2020. Abstr S205. 13. Strassl. Cancers. 2021;13:4701.

Elranatamab MagnetisMM Ongoing and Planned Clinical Trial Landscape

Trial	Population (Planned N)	Phase	Regimen	Trial Status	Est. Primary Completion
MagnetisMM-1 (NCT03269136)	≥1st line RR MM (90)	I	Elranatamab monotherapy vs elranatamab + Rd vs elranatamab +Pd	Active, NR	04/23
MagnetisMM-3 (NCT04649359)	≥1st line RR MM (180)	II	Elranatamab monotherapy	Active, NR	09/22
MagnetisMM-4 (NCT05090566)	≥3rd line RR MM (105)	Ib/II	Elranatamab + nirogacestat vs elranatamab + Rd	Recruiting	11/25
MagnetisMM-5 (NCT05020236)	≥1st line RR MM (476)	III	Elranatamab monotherapy vs elranatamab + daratumumab vs DPd	Recruiting	11/24
MagnetisMM-9 (NCT05014412)	≥1st line RR MM (76)	I/II	Elranatamab monotherapy	Recruiting	06/23

MagnetisMM-2 and MagnetisMM-8 held in Japan and China, respectively. MagnetisMM-6 and MagnetisMM-7 are planned registrational trials.

ClinicalTrials.gov

Slide credit: ProCE.com and clinicaloptions.com

MagnetisMM-1: Investigator-Assessed Response by IMWG

Response, %	215 μg/kg (n = 4)	360 μg/kg (n = 4)	600 μg/kg (n = 6)	1000 μg/kg* (n = 6)	Total (≥215 μg/kg) (n = 20)
Confirmed ORR	2 (50.0)	3 (75.0)	4 (66.7)	5 (83.3)	14 (70.0)
▪ sCR	2 (50.0)	1 (25.0)	2 (33.3)	0	5 (25.0)
▪ CR	0	0	0	1 (16.7)	1 (5.0)
▪ VGPR	0	2 (50.0)	2 (33.0)	3 (50.0)	7 (35.0)
▪ PR	0	0	0	1 (16.7)	1 (5.0)
▪ MR	0	0	0	0	0
SD	2 (50.0)	0	1 (16.7)	0	3 (15.0)
PD	0	1 (25.0)	1 (16.7)	1 (16.7)	3 (15.0)

- Responses were observed beginning at 215 μg/kg dose
- Median time to response: 22 days (range: 21-50); median duration of response has not been reached
- Probability of responders being event-free at 6 months: 92.3% (95% CI: 56.7%-98.9%)
- Patients with prior BCMA-directed therapy achieved response: 2 VGPR and 1 sCR (n = 4)
- 3 patients assessed were MRD negative

*Randomized phase II dose (RP2D).

Bahlis. ASCO 2021. Abstr 8006.

MagnetisMM-1: TEAEs in ≥20% of Patients

TEAE, %	Grade 1	Grade 2	Grade 3	Grade 4	Total (n = 30)
Hematologic					
▪ Lymphopenia	0	0	6 (20.0)	19 (63.3)	25 (83.3)
▪ Anemia	0	3 (10.0)	15 (50.0)	0	18 (60.0)
▪ Neutropenia	0	0	7 (23.3)	9 (30.0)	16 (53.3)
▪ Thrombocytopenia	3 (10.0)	2 (6.7)	5 (16.7)	6 (20.0)	16 (53.3)
▪ Leukopenia	1 (3.3)	3 (10.0)	7 (23.3)	1 (3.3)	12 (40.0)
Nonhematologic					
▪ CRS	17 (56.7)	5 (16.7)	0	0	22 (73.3)
▪ Injection site reaction	13 (43.3)	2 (6.7)	0	0	15 (50.0)
▪ Nausea	5 (16.7)	5 (16.7)	1 (3.3)	0	11 (36.7)
▪ Increased AST	5 (16.7)	2 (6.7)	3 (10.0)	0	10 (33.3)
▪ Increased ALT	5 (16.7)	1 (3.3)	3 (10.0)	0	9 (30.0)
▪ Diarrhea	6 (20.0)	2 (6.7)	1 (3.3)	0	9 (30.0)
▪ Vomiting	7 (23.3)	1 (3.3)	0	0	8 (26.7)
▪ Decreased appetite	5 (16.7)	2 (6.7)	0	0	7 (23.3)
▪ Dry skin	5 (16.7)	2 (6.7)	0	0	7 (23.3)
▪ Hypokalemia	1 (3.3)	5 (16.7)	1 (3.3)	0	7 (23.3)
▪ Arthralgia	3 (10.0)	2 (6.7)	1 (3.3)	0	6 (20.0)
▪ ICANS	3 (10.0)	3 (10.0)	0	0	6 (20.0)
▪ Pyrexia	5 (16.7)	1 (3.3)	0	0	6 (20.0)

- No DLT was observed

Bahlis. ASCO 2021. Abstr 8006.

MagnetisMM-1: CRS

CRS, %	80 μg/kg (n = 6)	130 μg/kg (n = 4)	215 μg/kg (n = 4)	360 μg/kg (n = 4)	600 μg/kg (n = 6)	1000 μg/kg (n = 6)	Total (N = 30)
Overall	2 (33.3)	2 (50.0)	3 (75.0)	3 (75.0)	6 (100)	6 (100)	22 (73.3)
▪ Grade 1	1 (16.7)	2 (50.0)	3 (75.0)	2 (50.0)	4 (66.7)	5 (83.3)	17 (56.7)
▪ Grade 2	1 (16.7)	0	0	1 (25.0)	2 (33.3)	1 (16.7)	5 (16.7)

- No premedication or priming/step-up dosing to mitigate CRS was administered
- CRS was limited to grade 1/2 with no events grade >2
- Median time to CRS onset: 1 day (range: 1-3)
- Median duration of CRS: 3 days (range: 1-10)
- 9/30 (30%) of patients received tocilizumab; 3/30 (10%) received steroids for CRS
- No permanent treatment discontinuations, dose interruptions, or dose reductions due to CRS

Bahlis. ASCO 2021. Abstr 8006.

Slide credit: ProCE.com and clinicaloptions.com

Teclistamab an "Off-the-Shelf" BCMA x CD3 Bispecific Antibody: MajesTEC Clinical Trials Landscape

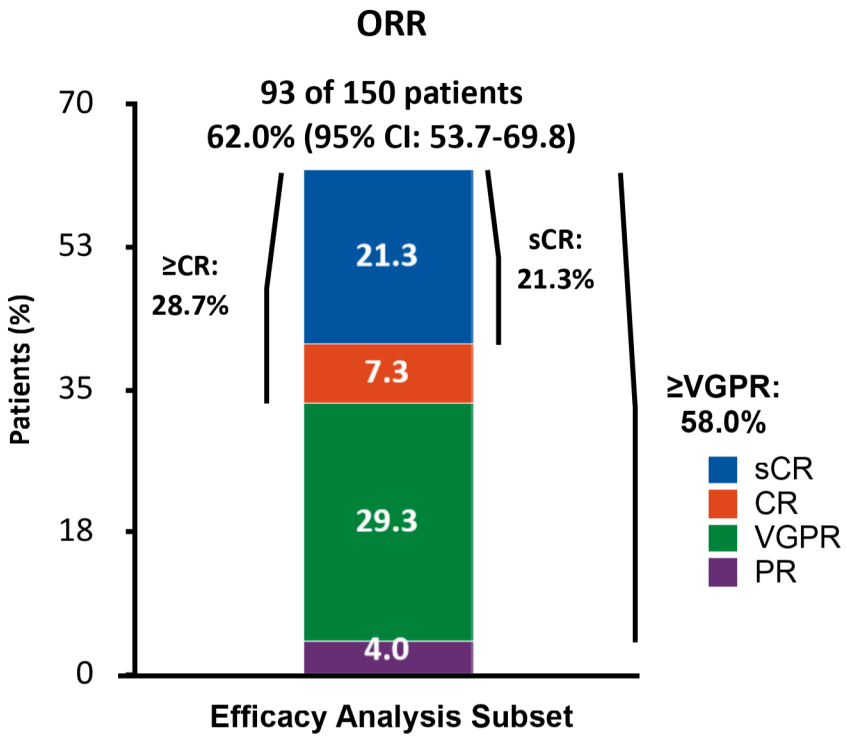
Trial	Population	Phase	Intervention	Est Primary Completion date
MajesTEC-1	RRMM, ≥3 prior lines of therapy	I/II	Teclistamab	12/24 (BLA filed 12/21)
MajesTEC-3	RRMM, 1-3 prior lines of therapy	III	Tec + Dara vs DPd vs DVd*	12/26
MajesTEC-4	NDMM	III	Tec + Len vs Len maintenance post ASCT	8/27

*Subcutaneous daratumumab.

NCT04557098. NCT05083169.

Slide credit: ProCE.com and clinicaloptions.com

MajesTEC-1: Efficacy Outcomes



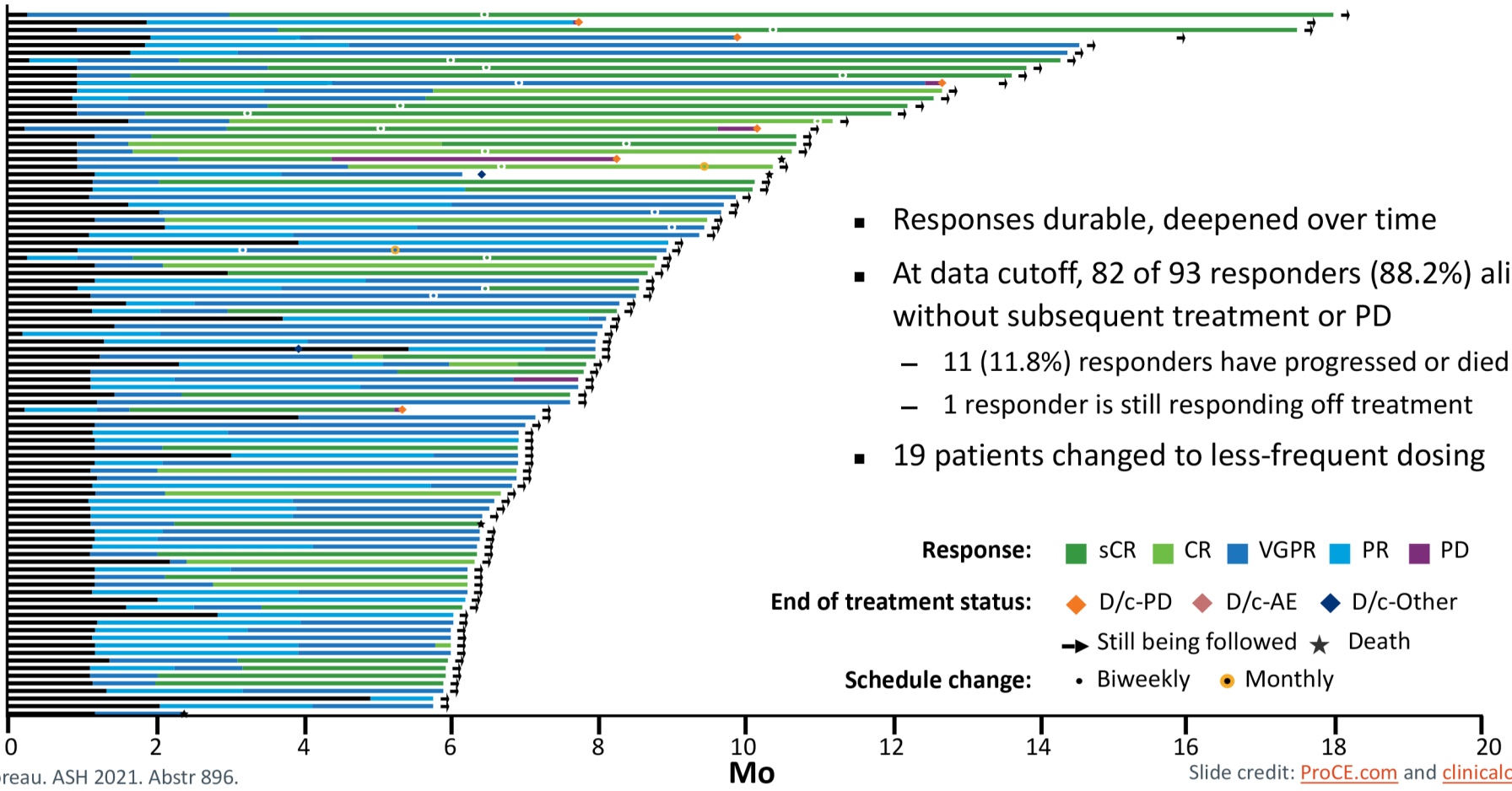
Median follow-up: 7.8 mo (range: 0.5+ to 18)

Event	All Patients (N = 165)
MRD negativity, n (%, 95% CI) ▪ At 10^{-5} ▪ At 10^{-6}	(n = 150) 37 (24.7; 18.0-32.4) 25 (16.7; 11.1-23.6)
MRD negativity with ≥CR, %	41.9
Median TTR, mo (range)	1.2 (0.2-5.5)
Median DoR, mo	Not yet reached
EFS rates, % (95% CI) ▪ 6 mo ▪ 9 mo	 92.5 (80.6-97.2) 85.9 (70.0-93.7)
PFS rates, % (95% CI) ▪ 6 mo ▪ 9 mo	64.4 (56.0-71.7) 58.5 (48.8-67.0)
Median OS	Not yet reached

Moreau. ASH 2021. Abstr 896.

Slide credit: ProCE.com and clinicaloptions.com

MajesTEC-1: Response Durability



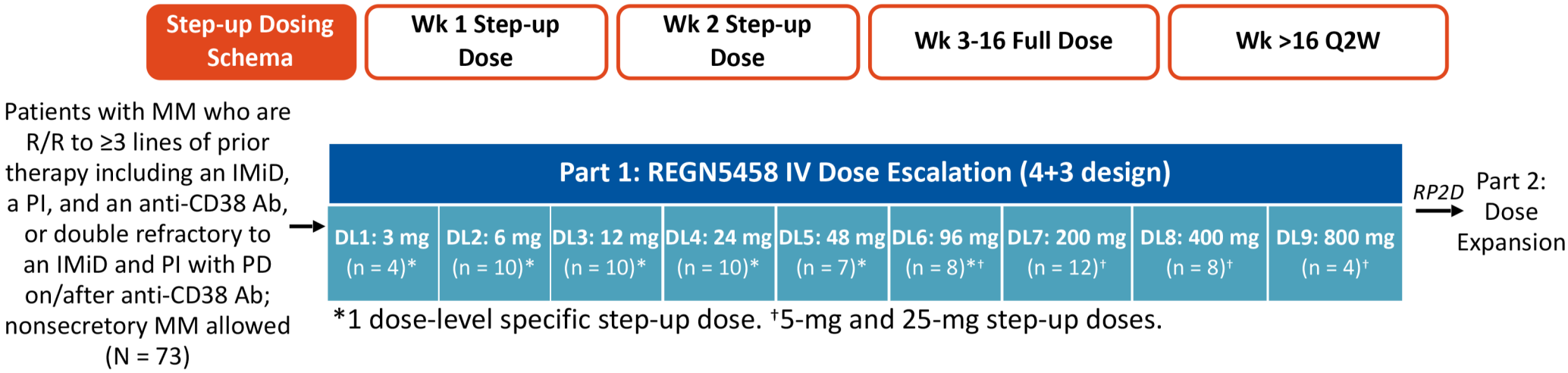
- Responses durable, deepened over time
- At data cutoff, 82 of 93 responders (88.2%) alive, without subsequent treatment or PD
  - 11 (11.8%) responders have progressed or died
  - 1 responder is still responding off treatment
- 19 patients changed to less-frequent dosing

Moreau. ASH 2021. Abstr 896.

Slide credit: ProCE.com and clinicaloptions.com

REGN5458 in R/R MM: Study Design

- Open-label phase I study with step-up dosing followed by QW, then Q2W infusions



- **Primary objectives:** safety, tolerability, DLTs, RP2D
- **Secondary objectives:** ORR, DoR, PFS, MRD status, and OS

Zonder. ASH 2021. Abstr 160. NCT03761108.

Slide credit: ProCE.com and clinicaloptions.com

REGN5458 in R/R MM: Response

- 51% ORR for all enrolled patients
- 86% ≥VGPR and 43% ≥CR among all responders
- For patients achieving CR/sCR (with available data), 4/10 negative at MRD 10^{-5}

Response, n (%)	DL 1-3 (n = 24)	DL 4-6 (n = 25)	DL 7-9 (n = 24)
ORR	29	48	75*
▪ sCR	13	20	8
▪ CR	13	4	8
▪ VGPR	0	24	42
▪ PR	4	0	17

*Includes all patients who were evaluable for response assessment at 4 wk.

- Time to response
  - Median: <1 mo
  - 70% within first 2 mo
- Estimated median DoR not reached
  - Probability of EFS in responders at 8 mo: 90.2% (95% CI: 72.6-96.7)
- Longest responses ongoing for >19 mo at latest data cutoff (September 30, 2021)

Zonder. ASH 2021. Abstr 160.

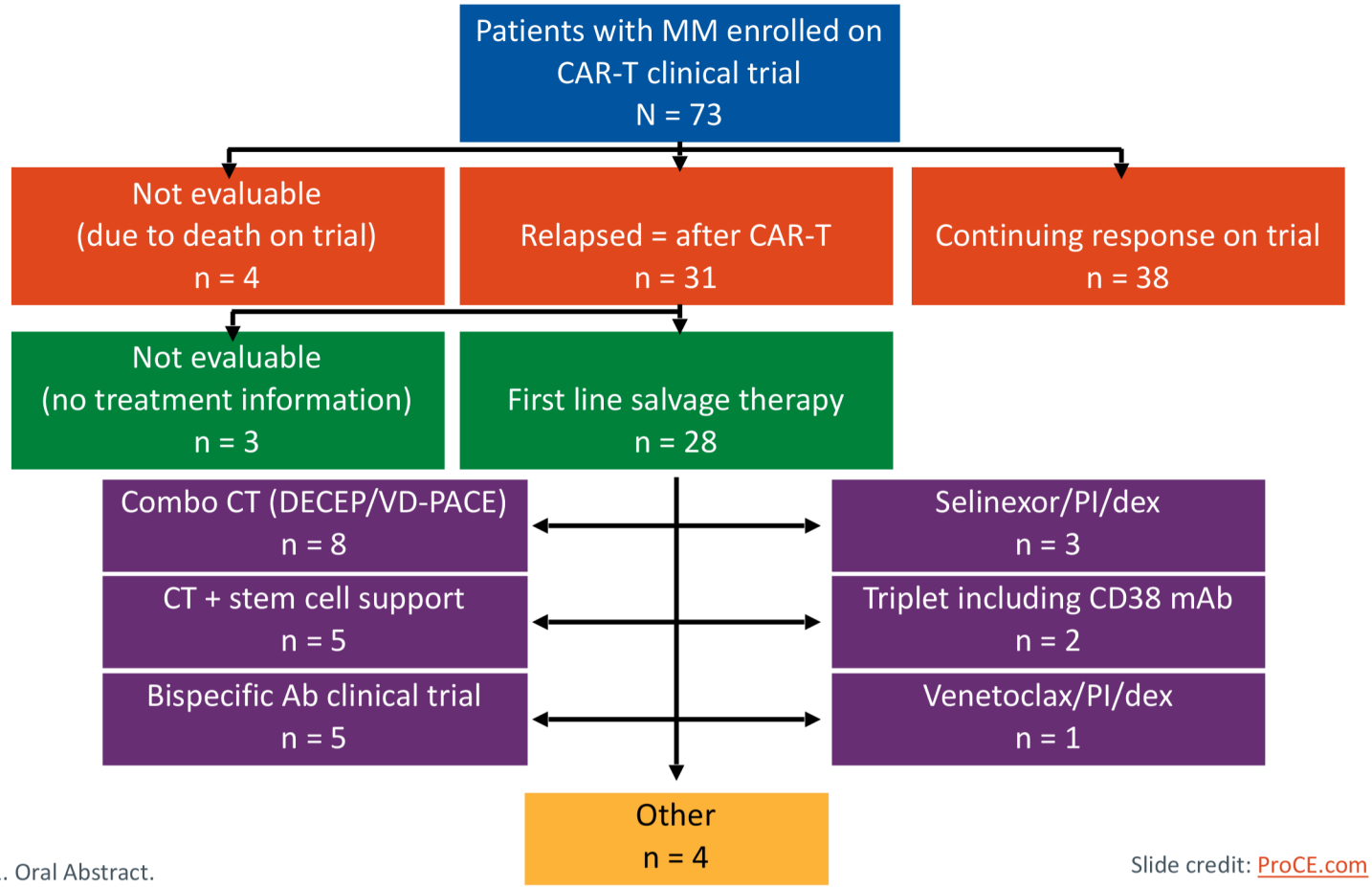
Considerations for Choosing BCMA Agents

	ADCs	Bispecific Antibody Constructs	CAR T-Cells
Production time	Off the shelf	Off the shelf	Prolonged manufacturing time
Administration	-	Challenge of continuous infusion protocols	Requires inpatient administration
Toxicities	IRR, thrombocytopenia, keratopathy	CRS, cytopenia	CRS, neurotoxicity, cytopenia, toxicities associated with lymphodepletion
Immune expansion	Do not rely on patient's endogenous effector T-cells	Rely on patient's endogenous effector T-cells, decreased capability for in vivo T-cell immune expansion and persistence	Long-term in vivo T-cell expansion and persistence

Sanchez. Ther Adv Hematol. 2021;12:2040620721989585.

Slide credit: ProCE.com and clinicaloptions.com

Considerations For Payors and Providers as BCMA CAR-T Treatments Move Upstream for MM



Van Oekelen. IMW 2021. Oral Abstract.

Slide credit: ProCE.com and clinicaloptions.com

Navigating Through Treatment Decisions and Sequencing With Current BCMA Therapeutics

- Using belantamab mafodotin as bridge therapy to CAR T-cell
- Deciding between ciltacabtagene vs idecabtagene
  - Cost, incidence, and onset of CRS, neurotoxicity, limitations with manufacturing slots, tocilizumab shortage
- Comparison between BCMA bispecific antibodies vs BCMA CAR-T
  - Cost, toxicities, route of administration, frequency, community vs academic
  - Use of BCMA-bispecific antibodies as maintenance therapy post BCMA CAR-T
- Sequencing from 1 BCMA-targeted agent to another (BCMA CAR-T ->BCMA bispecific>BCMA ADC)
- Checking BCMA expression
- New agents on the horizon to overcome BCMA resistance

Slide credit: ProCE.com and clinicaloptions.com

Managed Care Considerations

CAR T-cell Therapy: Value-Based Contracting Considerations

Idecabtagene Vicleucel[1] ($419,000)	Ciltacabtagene Autoleucel[2] ($465,000)
ORR: 82%	ORR: 98%
12 mo OS: 78%	12 mo OS: 89%
24 mo OS: 51%	24 mo OS: 74% (100% in MRD-negative patients)
Grade 3/4 CRS: 4% (median onset 1 day, median duration 7 days)	Grade 3/4 CRS: 4% (median onset 7 days, median duration 4 days)
Grade 3 neurotoxicity: 3% (median onset 2 days, median duration 5-9 days)	Grade 3 neurotoxicity: 2% (median onset 8 days, median duration 4 days)

Consider data in cross trial comparisons with caution

Munshi. NEJM. 2021;384:705. Martin. ASH 2021. Abstr 549.

Slide credit: ProCE.com and clinicaloptions.com

Proposal: A More Successful Value-Based Contract Design Would Have Dual Risk Sharing

Manufacturer provides 50% rebate up front

- 12-month and 24-month survival is assessed by payor
- Rebates tied to grade 3/4 CRS and neurotoxicity
- Based on bonus structure outlined below, bonus is paid back to manufacturer based on risk-sharing agreement for meeting outcome (survival) at defined time points:
  - Bonus structure:
    - OS: 12 mo = 50% back to manufacturer
    - OS: 24 mo = 100% back to manufacturer

Slide credit: ProCE.com and clinicaloptions.com

Upcoming Generic Agents in Myeloma

- First generic lenalidomide launched March 2022
  - May only launch limited qty, increasing volume every 12 months, then unlimited quantity beginning on January 30, 2026
- Second generic lenalidomide will be launched shortly
  - Volume increasing every 12 months (not to increase > single digit percentage) with unlimited quantity beginning January 30, 2026
- Bortezomib generic launch with numerous possible manufacturers (possibly May 2022)

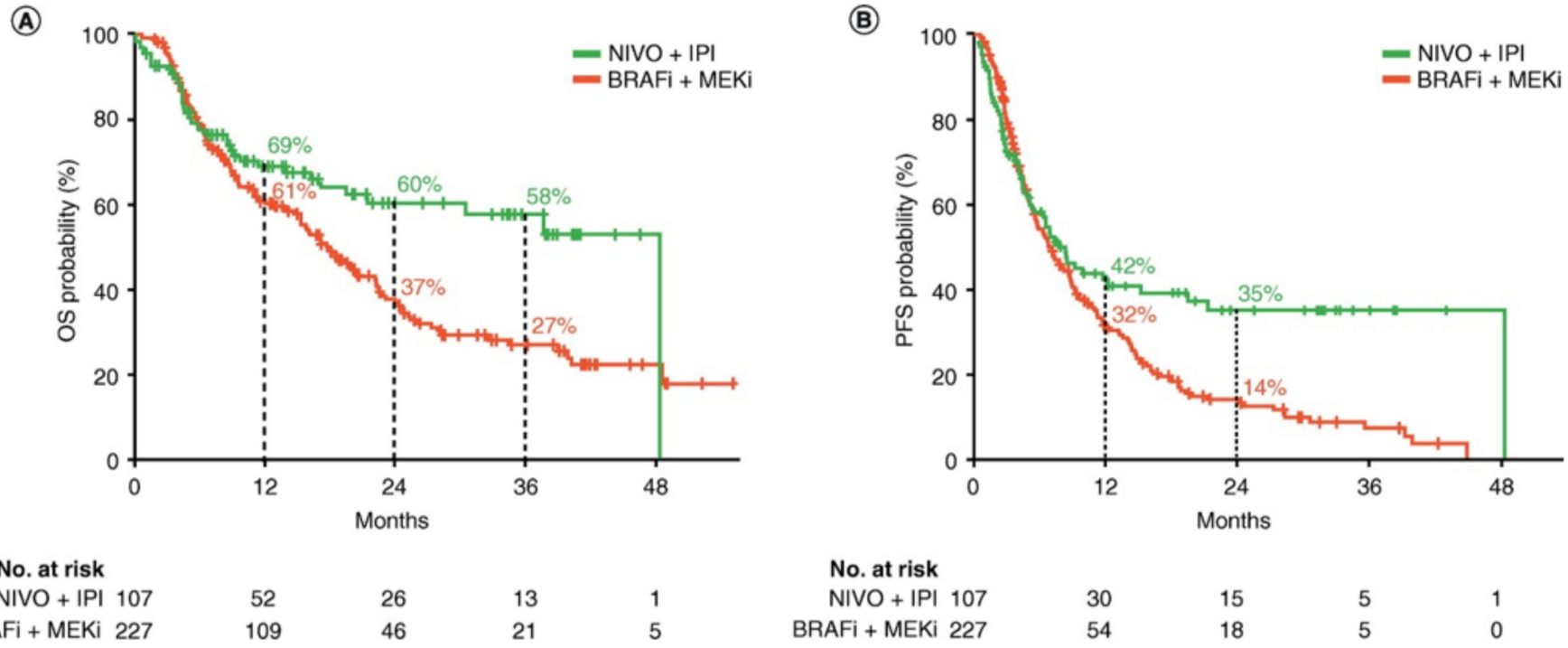
Slide credit: ProCE.com and clinicaloptions.com

Considerations for Managed Care Pharmacists, Providers

- Bortezomib launch with SubQ indication?
  - If yes, then will there be step therapy considerations for providers to prescribe carfilzomib
- Volume, pricing, access considerations for generic lenalidomide
  - Most likely very little financial impact
- Would bortezomib-based regimens be preferred over lenalidomide-based regimen through pathways?

IPD Analytics. Accessed 3/17/22.

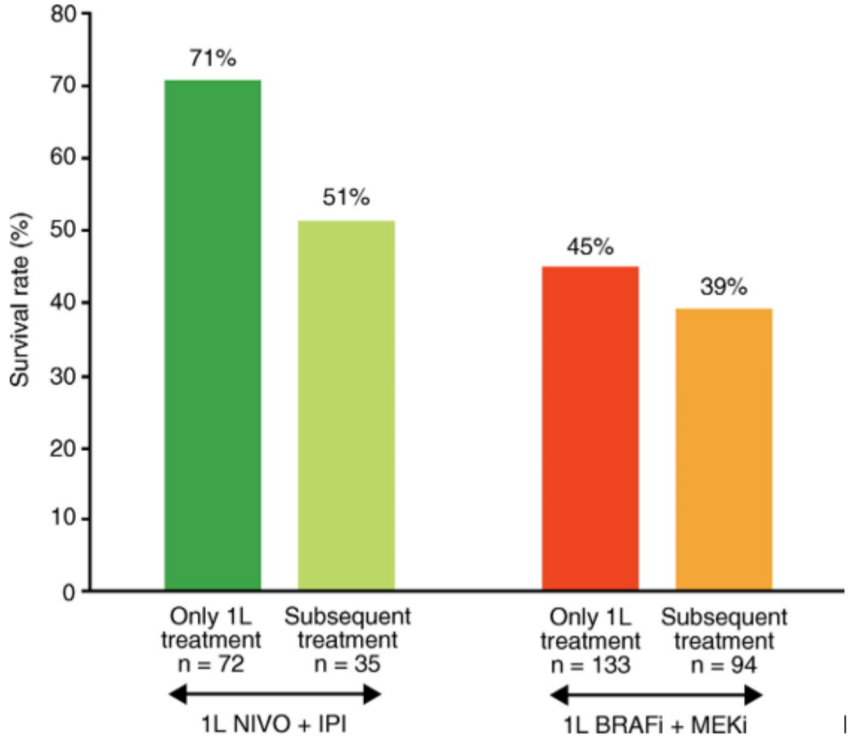
How Can We Improve Variability, Clinical, and Economic Outcomes in the Management of R/R MM? Melanoma Data



Pavlick. Future Oncology. 2020.

Slide credit: ProCE.com and clinicaloptions.com

Nivolumab + IPI vs BRAF Inhibitor + MEK Inhibitor: OS by Line of Treatment. Insights From Melanoma Data



Pavlick. Future Oncology. 2020.

Slide credit: ProCE.com and clinicaloptions.com

Managed Care Pharmacist Role With Care Coordination in Collaboration With the Healthcare Team

- BCMA CAR T-cell
  - Timely coordination of approval of BCMA CAR T-cell
  - Helping to reduce the number of cycles required for bridging therapy
  - Coordination with approval to manufacturing slot
  - Transition of care support from inpatient to ambulatory

Managed Care Pharmacist Role With Care Coordination in Collaboration With the Healthcare Team (continued)

- BCMA ADC Agent
  - Help connect patient with ophthalmologist for assessment prior to each dose
  - Adequate coverage for preservative-free ophthalmic lubricants
    - Most payors do not cover >14 days or >QID dosing
- BCMA Bispecific Agent
  - Building supportive care interventions into care plan for the approval of bispecific agents (eg, tocilizumab)
  - Transition of care support from inpatient to ambulatory

PracticePoints for Relapsed/Refractory Myeloma

- Triplet/quad regimens should be used as the standard of care for patients with relapsed/refractory myeloma
- Treatment selection for patients with R/R MM depends on multiple factors, including previous lines of treatment, cost, toxicities, patient preferences, route of administration, frequency, and community vs academic setting
- Novel drug targets (CD38 and BCMA) are providing opportunities for deeper and more durable responses
- Managed care pharmacists can help facilitate integration of BCMA-targeted therapies with timely coordination of CAR T-cell approval and manufacturing slots and building supportive care interventions into care plans for all agents

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