BiTEs, CARs, and Much More: Updates in Multiple Myeloma

Dennis Marjoncu, PharmD, BCOP
Clinical Pharmacy Specialist – Hematology/Oncology
Methodist University Hospital
Memphis, TN

TOPA

1

Disclosures

- Dr. Marjoncu has no relevant financial relationships with ineligible companies to disclose.
- I will discuss investigational drugs and notify you of off-label uses.

TOPA

2

Objectives

- Describe the pathophysiology of multiple myeloma
- Summarize the recent literature updates for agents in multiple myeloma
- Apply evidence-based recommendations to patient cases

TOPA

3

Incidence

~35,730 new cases	1.8% of all new cancers	59.8% relative 5-year survival
12,590 deaths	2.1% of all cancer deaths	Median age 69

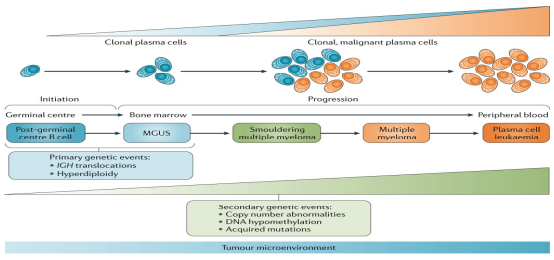
Incidence per 100,000

Incidence per 100k	Male	Female
African American	7.3	5
White	3.7	2.2

SEER Cancer Stat Facts: Multiple Myeloma. National Cancer Institute. Bethesda, MD.

4

Pathophysiology



https://media.springernature.com/full/springer-static/image/art%3A10.1038%2Fnrdp.2017.46/MediaObjects/41572_2017_Article_BFnrdp201746_Fig1_HTML.jpg

5

Monoclonal Gammopathy of Undetermined Significance (MGUS)

- Precursor to multiple myeloma (MM)

Incidence	• 3-5% of those >65 years • 10% of those >80 years
Progression	• 1-2% annual progression to symptomatic MM • 18% 20-year progression to MM

Cowan AJ, et al. *JAMA*. 2022; 327(5):464-477.

6

Where There is Smoke There Is Fire

- Smoldering Multiple Myeloma (SMM)
  - More advanced disorder
  - 10% annual progression to MM
  - Historical treatment included serial monitoring of labs
  - High-risk patients may benefit from lenalidomide

Cowan Aj, et al. *JAMA*. 2022; 327(5):464-477.
National Comprehensive Cancer Network. Multiple Myeloma. Version 3.2023

7

Risk Factors

Cowan Aj, et al. *JAMA*. 2022; 327(5):464-477.

8

Signs and Symptoms

Criteria	Definition	Incidence
Ca^{+2}	Corrected calcium >11 mg/dL	13%
Renal	Serum creatinine (SCr) >2 mg/dL Creatinine clearance (CrCl) <40 mL/min/1.73 m^2	19%
Anemia	Hemoglobin (Hgb) <10 mg/dL Hgb <2 g/dL below lower limit of normal (LLN)	73%
Bone	Lytic lesions (+)	79%

Fatigue
Increased serum proteins
Pathologic fractures
Lymphadenopathy
Cytopenias

Cowan Aj, et al. *JAMA*. 2022; 327(5):464-477.

9

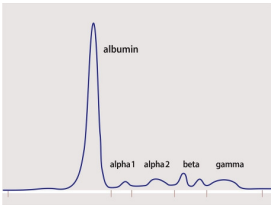
Diagnosis

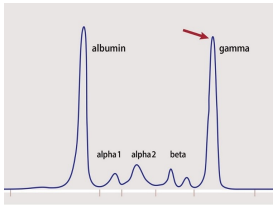
- Complete Blood Count (CBC)
- Complete Metabolic Panel (CMP)
- B_2 Microglobulin, Albumin, Lactate Dehydrogenase (LDH)
- Serum Protein Electropheresis (SPEP) with Immunofixation
- Serum Free Light Chains (FLC)
- 24-hour Urine Protein Electropheresis and Immunofixation
- Bone Marrow (BM) Biopsy (Bx)
- Low-Dose CT or PET/CT

Cowan Aj, et al. *JAMA*. 2022; 327(5):464-477.
National Comprehensive Cancer Network. Multiple Myeloma. Version 3.2023

10

SPEP





https://s3.us-west-1.wasabisys.com/imf-d8-prod/2019-04/SPEP2.jpg
https://s3.us-west-1.wasabisys.com/imf-d8-prod/2019-04/SPEP1.jpg

11

Risk Stratification

- Revised International Staging System (R-ISS)

	RISS 1	R-ISS 2	R-ISS 3
B_2 macroglobulin, mg/dL	<3.5	≤5.5	>5.5
Albumin, g/dL	≥3.5	<3.5	Any
LDH	WNL	Any	>ULN
High Risk Genetics	Absent	Present or Absent	Present
5-year overall survival	77%	62%	47%

WNL = within normal limits
ULN = upper limit of normal

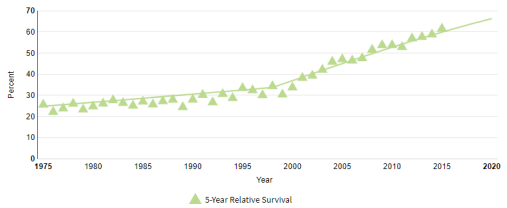
Standard Risk	High Risk
t(11;**14**)	t(4;**14**) Del(17p) = tp53 mutation T(**14**;16) T(**14**:20) 1q+
Trisomies • 3,5,7,9,11,15,19,21	

Cowan Aj, et al. *JAMA*. 2022; 327(5):464-477.
National Comprehensive Cancer Network. Multiple Myeloma. Version 3.2023

12

Prognosis

- 15th leading cause of cancer death
- Median age at death = 75



SEER Cancer Stat Facts: Multiple Myeloma. National Cancer Institute. Bethesda, MD.

13

Response Criteria

Response	Criteria
sCR	CR + Normal FLC + (-) clonal cells in BMBx
CR	(-)Immunofixation in serum & urine Disappearance of any soft tissue plasmacytomas <5% plasma cells in BM aspirates
VGPR	Serum/Urine M-protein detectable on immunofixation but NOT electrophoresis or ≥90% reduction in serum M-protein + urine M-protein <100 mg/24 hr
PR	≥50% serum M-protein decrease AND ≥90% urine M-protein decrease
SD	Does not meet any other response criteria
PD	Worsening of disease

sCR = stringent complete response
CR = complete response
VGPR = very good partial response
PR = partial response
SD = stable disease
PD = progressive disease

Kumar S, et al. *Lancet Oncol.* 2014; 15:e538-548.
National Comprehensive Cancer Network. Multiple Myeloma. Version 3.2023

14

Which of the following is considered standard-risk?

t(4;14) 0%

t(11;14) 0%

t(14;16) 0%

t(14;20) 0%

Start the presentation to see live content. For screen share software, share the entire screen. Get help at **pollev.com/app**

16

New Updates In Multiple Myeloma

17

Brief Review of Daratumumab

NDMM (autoHCT eligible)	CASSIOPEIA	Daratumumab-VTD improved RR, MRD(-), and PFS
	GRIFFIN	Daratumumab-VRD improved RR, MRD(-), and PFS
NDMM (autoHCT ineligible)	ALCYONE	Daratumumab-VMP improved RR, MRD(-), PFS, and OS
	MAIA	Daratumumab-RD improved RR, MRD(-), PFS, and OS

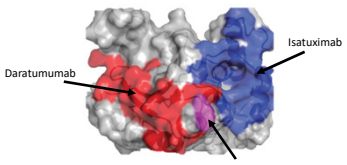
NDMM = newly-diagnosed MM
autoHCT = autologous hematopoietic cell transplant
VTD = bortezomib/thalidomide/dexamethasone
VRD = bortezomib/lenalidomide/dexamethasone
VMP = bortezomib/melphalan/prednisone
RD = lenalidomide/dexamethasone
RR = response rates
MRD = minimal residual disease
PFS = progression-free survival
OS = overall survival

Moreau P, et al. *Lancet.* 2019; 394:29-38.
Voorhees P, et al. *Blood.* 2020; 136(8):936-945.
Mateos MV, et al. *Lancet.* 2020; 395(10218):132-141.
Facon T, et al. *Lancet Oncol.* 2021; 22(11):1582-1596.

18

Daratumumab vs Isatuximab

	Daratumumab	Isatuximab
Dose	16 mg/kg	10 mg/kg
Frequency	C1-2: Days 1, 8, 15, 22 C3-6: Days 1, 15 C7+: Day 1	C1: Day 1, 8, 15, 22 C2+: Day 1, 15



Darzalex (daratumumab) [prescribing information]. Horsham, PA: Janssen Biotech Inc; January 2023.
Sarclisa (isatuximab) [prescribing information]. Bridgewater, NJ: Sanofi-Aventis US LLC; July 2022.
https://www.researchgate.net/publication/337557845_Therapeutic_Opportunities_with_Pharmacological_Inhibition_of_CD38_with_Isatuximab/figures?lo=1

19

Repeating Anti-CD38

N=59	
Median age	66
Prior autoHCT	47 (80%)
Prior lines of therapy, median	6
Time to isatuximab after daratumumab discontinuation Median (months) >6 months	 13.2 38 (64%)
Combined with pomalidomide/dexamethasone (Pd)	55 (93%)

Mohan M, et al. *Am J Hematol.* 2022; 97(7):e276-e280.

20

Repeating Anti-CD38

N=59	N (%)	P-value
CBR (ORR + SD) PR SD	26 (44%) 15 (25%) 15 (25%)	N/A
PD	18 (31%)	N/A
CBR based on time since daratumumab >6 months ≤6 months	 57.9% 19%	0.004
Augmentation of response ≥VGPR on daratumumab <VGPR on daratumumab	25 (42.4%) 18.8% 81.3%	0.025

CBR = clinical benefit rate
ORR = overall response rate

Mohan M, et al. *Am J Hematol.* 2022; 97(7):e276-e280.

21

IV or SubQ Daratumumab

	Daratumumab	Daratumumab-Hyaluronidase
Route	IV	SubQ
Dose	16 mg/kg	1800 mg – 30,000 units
Frequency	Weekly x8; every other week x8; monthly thereafter	
Cost/dose*	Dose = 1280 mg (round to 1200 mg) $7947.72	Dose = 1800 mg – 30,000 units $9027.42
Cost Δ/dose	$1079.70	
Chair Time Initial Subsequent Rapid	 ~6-8 hours ~3-4 hours 90 minutes	3-5 minutes
Net Loss in Chair Revenue¥	$1095 - $5840	---

¥$730/hr gained when streamlining administration times
*Assume 80 kg patient; wholesale acquisition cost (WAC)

Sugalski JM, et al. *J Oncol Pract.* 2019; 15(5):e458-e466.
Mateos MV, et al. *Lancet Haematol.* 2020; 7(5):e370-e380.

22

COLUMBA

	SubQ (N=263)	IV (N=259)	Odds Ratio
ORR ≥CR ≥VGPR	108 (41%) 5 (2%) 50 (19%)	96 (37%) 7 (3%) 44 (17%)	1.11 (0.89 – 1.37) 0.71 (0.22 – 2.27) 1.16 (0.73 – 1.85)
C_{trough}, ug/mL	593	522	
Geometric Mean Ratio (GMR)	107.93% (95.74% - 121.67%)		
PFS, median (mo)	5.6	6.1	0.99 (0.78 – 1.26)
OS 6-month 24-month	 88% 55.8%	 83% 51.6%	 0.90 (0.59 – 1.35) 0.92 (0.72 – 1.17)

Usmani SZ, et al. *Haematologica.* 2022; 107(10):2408-2417.
Mateos MV, et al. *Lancet Haematol.* 2020; 7(5):e370-e380.

23

COLUMBA

	SubQ (N=263)	IV (N=259)
Serious ADE Pneumonia	68 (26%) 7 (3%)	76 (29%) 11 (4%)
Grade 3 Anemia Neutropenia Thrombocytopenia	 34 (13%) 34 (13%) 36 (14%)	 36 (14%) 20 (8%) 35 (14%)
Infusion reactions	33 (12.7%)	89 (34.5%)
Package Insert	**SubQ**	**IV**
Infusion reactions	9%	37%
Time to reaction, hour (range)	3.2 (4 minutes – 84 hours)	1.5 (0 – 73 hours)

ADE = adverse drug event

Usmani SZ, et al. *Haemotologica.* 2022; 107(10):2408-2417.
Mateos MV, et al. *Lancet Haematol.* 2020; 7(5):e370-e380.
Darzalex (daratumumab) [prescribing information]. Horsham, PA: Janssen Biotech Inc; January 2023.
Darzalex Faspro (daratumumab/hyaluronidase) [prescribing information]. Horsham, PA: Janssen Biotech Inc; December 2022.

24

NCCN Statement

"Daratumumab IV infusion or daratumumab and hyaluronidase-fihj, subcutaneous injection may be used in all daratumumab-containing regimens"

National Comprehensive Cancer Network. Multiple Myeloma. Version 3.2023

25

Audience Survey

- Does your institution preferentially use IV or SubQ daratumumab?

26

Venetoclax (Venclexta®)

27

Venetoclax

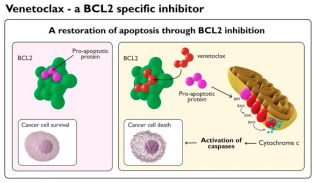
Indication	• Not currently indicated in MM (chronic lymphocytic leukemia (CLL) and Acute myeloid leukemia (AML only))
Dose	• 800 mg once daily
Supportive Care	• Tumor lysis syndrome (TLS) prophylaxis

Venclexta (venetoclax) [prescribing information]. North Chicago, IL: AbbVie Inc; June 2022.

28

Venetoclax

- Displaces BCL-2, which displaces the proteins, activating capsases that lead to cell death via apoptosis



https://ars.els-cdn.com/content/image/1-s2.0-S0301472X18300420-exphem3611-fig-0001.jpg
Venclexta (venetoclax) [prescribing information]. North Chicago, IL: AbbVie Inc; June 2022.

29

BELLINI

≥18 years
RRMM
1-3 prior therapies

Venetoclax 800 mg qday + Vd (N=194)

Placebo + Vd (N=97)

C1-8 (21 days)
Bortezomib day 1,4,8,11
Dexamethasone day 1-2,4-5,8-9,11-21

C9+ (35 days)
Bortezomib day 1,8,15,22
Dexamethasone day 1-2,8-9,15-16,22-23

Vd = bortezomib/dexamethasone
Bortezomib = 1.3 mg/m^2 day 1,4,8,11
Dexamethasone = 20 mg day 1-2, 4-5, 8-9, 11-12

1° Endpoint:
PFS by independent review committee (IRC)

2° Endpoint:
ORR and each individual response
OS
Patient-reported quality-of-life (QoL)
MRD(-)

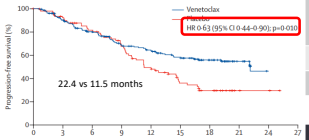
	Venetoclax (N=194)	Placebo (N=97)
Age, median (years)	66	65
Prior therapy 1 2 or 3	 91 (47%) 103 (53%)	 44 (45%) 53 (55%)
Prior autoHCT	116 (60%)	57 (59%)
High risk	31 (16%)	18 (19%)
t(11;14) (+)	20 (10%)	15 (15%)

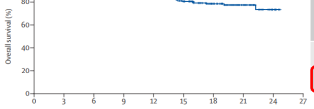
Kuma SJ, et al. *Lancet Oncol.* 2020; 21(12):1630-1642.

RRMM = relapsed/refractory multiple myeloma

30

BELLINI





Overall Population	Venetoclax (N=194)	Placebo (N=97)
ORR¶	159 (82%)	66 (68%)
sCR*	15 (8%)	2 (2%)
CR¶	36 (19%)	3 (3%)
VGPR*	63 (32%)	30 (31%)
DoR, median (month)	NR	12.8
MRD(-), 10^{-4}¶	37 (19%)	3 (3%)

t(11;14) Population	Venetoclax (N=20)	Placebo (N=15)
ORR¥	18 (90%)	7 (47%)
sCR*	4 (20%)	0
CR*	5 (25%)	1 (7%)
VGPR*	5 (25%)	3 (20%)
DoR, median (month)	NR	12.2
MRD(-), 10^{-4}	8 (40%)	0

*P=not significant
¥P<0.01
¶P<0.001

DoR = duration of response

Kuma SJ, et al. *Lancet Oncol.* 2020; 21(12):1630-1642.

31

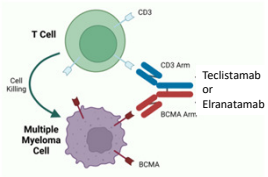
Bi-Specifics

Teclistamab-cqyv (Tecvayli®)
Elranatamab-bcmm (Elrexfio®)
Talquetamab-tgvs (Talvey®)

32

Teclistamab-cqyv & Elranatamb-bcmm

- Bi-specific T-cell engager (BiTE) with CD3 and B-cell maturation antigen (BCMA) binding arms
- Binding to CD3 on T-cells and BCMA on MM cells activated T-cells, releasing pro-inflammatory cytokines and lysis of BCMA(+) cells

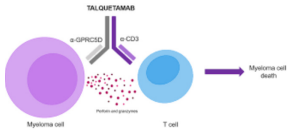


Elrexfio (elranatamab) [prescribing information]. New York, NY: Pfizer, Inc; August 2023.
Tecvayli (teclistamab) [prescribing information]. Horsham, PA: Janssen Biotech Inc; October 2022.

33

Talquetamab-tgvs

- BiTE that binds to CD3 on T-cells and G protein-coupled receptor class C group 5 member D (GPRC5D)
- GPRC5D expressed on plasma cells and hard keratinized tissue. Binding causes lysis of malignant cells



Talvey (talquetamab) [prescribing information]. Horsham, PA: Janssen Biotech Inc; 2023

34

Comparing BiTEs

	Teclistamab	Elranatamab	Talquetamab
Indication	RRMM ≥4 prior therapies		
Administration	SubQ		
Mechanism	CD3 - BCMA		CD3 – GPRC5D
Dosing	D1: 0.06 mg/kg D4: 0.3 mg/kg D7: 1.5 mg/kg then weekly	D1: 12 mg D4: 32 mg D8: 76 mg then weekly until week 24, then Q2 weeks	D1: 0.01 mg/kg D4: 0.06 mg/kg D7: 0.4 mg/kg D10: 0.8 mg/kg then Q2 weeks or 0.4 mg/kg q1 week
CRS, n (%) Grade ≥3 Onset (days) Duration (days)	72.1% 0.6% 2 2	56.3% 0 2 2	76% 1.5% 27 hours from last dose 17 hours
ICANS, n (%) Grade ≥3 Onset (days) Duration (days)	14.5% 0.6% 4 3	3.4% 0 3 2	9% 0 2.5 2

Elrexfio (elranatamab) [prescribing information]. New York, NY: Pfizer, Inc; August 2023.
Tecvayli (teclistamab) [prescribing information]. Horsham, PA: Janssen Biotech Inc; October 2022.
Talvey (talquetamab) [prescribing information]. Horsham, PA: Janssen Biotech Inc; 2023

CRS = cytokine release syndrome
ICANS = immune effector cell-associated neurotoxicity syndrome

35

Comparing BiTEs

	Teclistamab	Elranatamab	Talquetamab	
Trial	MajesTEC-1	MagnetisMM-3	MonumenTAL-1	
Design	Single-arm, open-label	Single-arm, open-label	Open-label	
Inclusion	≥18 years ≥3 prior lines No prior BCMA therapy	≥18 years ≥3 prior lines No prior BCMA therapy	≥18 years ≥3 prior lines	
			Weekly (N = 100)	Q2 week (N = 87)
N	165	123	100	87
Age, median (years) White, n (%) Prior therapy, median Prior autoHCT, n (%) High-risk, n (%) Penta-refractory, n (%)	64 134 (81.2) 5 (2 – 14) 135 (81.8) 38 (25.7) 116 (70.3)	68 72 (58.5) 5 (2 – 22) 87 (70.7) 31 (25.2) 87 (70.7)	67 168 (90) 5 (4 – 13) 146 (78) 54 (29) NR	
ORR, n (%) ≥CR ≥VGPR	104 (63) 65 (39.4) 97 (58.8)	75 (61) 43 (35) 69 (56.1)	73 (73) 35 (35) 57 (57)	65 (73.6) 29 (33) 51 (58)

Moreau M, et al. *N Engl J Med.* 2022; 387(6):495-505.
Lesokhin AM, et al. *Nat Med.* 2023; Online ahead of print
Chari A, et al. *N Engl J Med.* 2022; 387(24):2232-2244.

36

Comparing BiTEs

	Teclistamab	Elranatamab	Talquetamab	
Trial	MajesTEC-1	MagnetisMM-3	MonumenTAL-1	
N	165	123	187	
			Weekly (N=100)	Q2 week (N=87)
DoR, median (months)	18.4	Not reached	9.5	Not estimable
TTR, median (months) Time to CR	1.2 (0.2 – 5.5) Not reported	1.05 (0.89 – 15.67) 6.1 (1.2 – 14.3)	1.2 (0.2-10.9)	1.3 (0.2-9.2)
MRD(-), n (%)	30 (46)*	110 (89.7)*	NR	NR
PFS, median (months) 15-month (all) 15-month (≥CR)	11.3 (8.8 – 17.1) Not reported Not reported	13.4 (9.2 – not estimable) 50.9% 89.5%	NR	NR
OS, median (months) 15-month (all) 15-month (≥CR)	18.3 (15.1 – not estimable) Not reported Not reported	Not reached 56.7% 92.6%	NR	NR

Moreau M, et al. *N Engl J Med.* 2022; 387(6):495-505.
Lesokhin AM, et al. *Nat Med.* 2023; Online ahead of print
Chari A, et al. *N Engl J Med.* 2022; 387(24):2232-2244.

*in patients with ≥CR
TTR = time to response

37

Managing BiTE CRS

Grade	Definition	Management
1	Fever	Hold dose until resolve Premed next dose
2	+fluid-responsive hypotension OR low-flow O_2 needed	As above PLUS Hospitalize x48 hours next dose
3	1 pressor or high-flow O_2 needed	As above PLUS Supportive therapy Permanently stop if repeat
4	Multiple pressors or positive pressure needed	Permanently stop Supportive therapy

Tecvayli (teclistamab) [prescribing information]. Horsham, PA: Janssen Biotech Inc; October 2022.

38

Managing BiTE ICANS

Grade	Definition	Management
1	ICE score 7-9 Awaken spontaneously	Hold until resolution Consider prophylactic anti-epileptics
2	ICE score 3-6 Awaken to voice	As above PLUS Dexamethasone 10 mg IV q6 hr Hospitalize x48 hours next dose
3	ICE score 0-2 Awaken to tactile stimuli Non-status epilepticus seizures Increased intracranial pressure (ICP)	As above PLUS Anti-epileptics
4	Cannot do ICE score Status epilepticus Diffuse ICP	As above PLUS Consider methylprednisolone 1000 mg qday

Tecvayli (teclistamab) [prescribing information]. Horsham, PA: Janssen Biotech Inc; October 2022.

ICE = immune effector cell encephalopathy

39

Ciltacabtagene Autoleucel (Carvykti®)

40

Ciltacabtagene Autoleucel

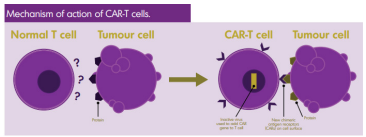
Indication	• RRMM after ≥4 prior therapies
Dose	• 0.5 – 1 x10^6 cells/kg
Supportive Care	• Fludarabine/cyclophosphamide lymphodepletion • Premedicate with acetaminophen and H1RA

Carvykti (ciltacabtagene autoleucel) [prescribing information]. Horsham, PA: Janssen Biotech Inc; February 2023.

41

Ciltacabtagene Autoleucel (Cilta-cel)

- Genetically modified T-cells.
- Anti-BCMA receptor added via lentiviral vectors with 4-1BB costimulatory domain
- Once reinfused, T-cells target BCMA(+) cells



https://z9a2f9c2.rocketcdn.me/wp-content/uploads/2020/06/CAR-T-Mechanism.png
Carvykti (ciltacabtagene autoleucel) [prescribing information]. Horsham, PA: Janssen Biotech Inc; February 2023.

42

CARTITUDE-1

≥18 years
≥3 prior lines
Progression ≤12 months from last therapy
No prior BCMA therapy

→ Lymphodepletion followed by cilta-cel (N=97) → Follow-up

1º Endpoint:
ORR

2º Endpoint:
DoR
MRD(-)
PFS
OS

	Cilta-cel (N=97)
Age, median (years)	61
White	69 (71%)
Prior therapy, median (range)	6 (4-8)
≥60% plasma cells in marrow	21 (22%)
Prior autoHCT	87 (90%)
Prior alloHCT	8 (8%)
High risk	23 (24%)
Triple-class refractory	85 (88%)
Penta refractory	41 (42%)

Berdeja JG, et al. *Lancet*. 2021; 398(10297):314-324.

43

CARTITUDE-1

N=97	
ORR sCR CR VGPR	94 (96.9%) 65 (67%) 0 25 (26%)
MRD(-) (N=57 evaluable) MRD(-) ≥CR	53 (93%) 33 (34%)
TTR, median (months)	1 (0.9 – 1)
DoR, median (months)	Not reached (15.9 – not estimable)

N=97	
PFS, median (months)	Not reached (16.8 – not estimable)
12-month PFS CR	77% 85%
12-month OS	89%

Berdeja JG, et al. *Lancet*. 2021; 398(10297):314-324.

44

CARTITUDE-1

N=97	
CRS Grade ≥3	92 (95%) 4 (4%)
Onset, median (days) After day 3	7 (5 – 8) 82 (89%)
Duration, median (days)	4 (3 – 6)
Tocilizumab ≥3 doses	67 (69%) 4 (5.9%)
Steroids	21 (22%)
Anakinra	18 (19%)

N=97	
ICANS Grade ≥3	20 (21%) 9 (9%)
Onset, median (days)	8 (6 – 8)
Duration, median (days)	4 (3 – 6.5)
Tocilizumab	4 (4%)
Steroids	9 (9%)
Anakinra	3 (3%)

Berdeja JG, et al. *Lancet*. 2021; 398(10297):314-324.

45

Based on the trials discussed, which would be appropriate for a 66 year old male with RRMM that has received 5 prior therapies, and relapse 15 months from last therapy?

Venetoclax + Vd 0%

Teclistamab-cqyv 0%

Ciltacabtagene autoleucel 0%

Belantamab mafodotin 0%

Start the presentation to see live content. For screen share software, share the entire screen. Get help at **pollev.com/app**

47

BiTEs, CARs, & not Much More: Updates in Multiple Myeloma

Dennis Marjoncu, PharmD, BCOP
Clinical Pharmacy Specialist – Hematology/Oncology
Methodist University Hospital
Memphis, TN

TOPA

48

49

Carfilzomib/Lenalidomide/ Dexamethasone (KRD) vs VRD

50

ENDURANCE

≥18 years
NDMM
No intention for autoHCT

KRD (N=545)
VRD (N=542)

36-weeks induction

Lenalidomide maintenance

KRD (28-day cycles)
- Carfilzomib 36 mg/m² days 1-2, 8-9, 15-16
- Lenalidomide 25 mg qday days 1-21
- Dexamethasone 40 mg days 1, 8, 15, 22

VRD (21-day cycles)
- Bortezomib 1.3 mg/m²
  - C1-8: Days 1, 4, 8, 11
  - C9-12: Days 1 & 8
- Lenalidomide 25 mg qday days 1-21
- Dexamethasone 40 mg days 1, 8, 15, 22

1º Endpoint:
PFS
OS in maintenance phase

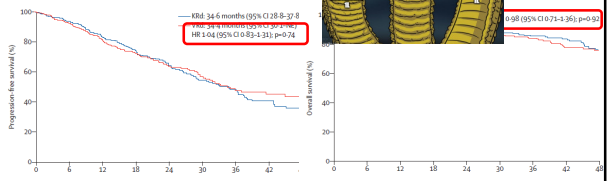
2º Endpoint:
ORR
Time to progression (TTP)
DoR

	KRD (N=545)	VRD (N=542)
Age, median (years)	65	64
White	448 (86%)	443 (85%)
High risk	127 (28%)	128 (28%)
Intent to autoHCT at progression	398 (73%)	396 (73%)

Kumar SK, et al. *Lancet Oncol.* 2020; 21(10):1317-1330.

51

ENDURANCE



	KRD (N=545)	VRD (N=542)	HR; p-value
PFS, median (months)	34.6	34.4	1.04 (0.83 – 1.31); p=0.74
36-month OS	86%	84%	0.98 (0.71 – 1.36); p=0.92
TTP, median (months)	44.6	36.3	0.97 (0.75 – 1.24); p=0.79
ORR	87%	84%	0.26

Kumar SK, et al. *Lancet Oncol.* 2020; 21(10):1317-1330.

TTP = time to progression

52

Elotuzumab (Empliciti®)

53

Elotuzumab

Indication
- RRMM in combination with Rd (≥3 prior therapies) or Progressive disease (Pd[illegible] prior therapies)

Dose (28-day cycles)
- [illegible] then Q2 weeks (C3+) [illegible]-2) then 20 mg/kg Q4

Supportive Care
- [illegible] medicate with ste[illegible] H2RA, and acetaminophen

Empliciti (elotuzumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; March 2022.

54

ELOQUENT-1

≥18 years
NDMM
Not eligible for autoHCT

Elotuzumab + Rd (N=374)
Placebo + Rd (N=374)

Treat until progression or toxicity

1º Endpoint:
PFS

2º Endpoint:
ORR
OS

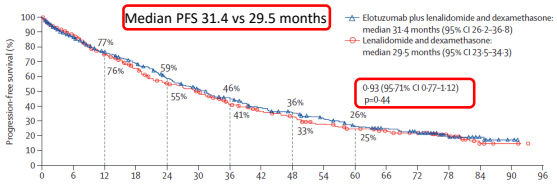
Lenalidomide = 25 mg daily days 1-21
Dexamethasone = 40 mg days 1,8,15,22
Elotuzumab:
- C1-2: 10 mg/kg days 1,8,15,22
- C3-18: 10 mg/kg days 1,15
- C19+: 20 mg/kg day 1

	Elotuzumab (N=374)	Placebo (N=374)
Age, median (years)	73	73
White	360 (96%)	351 (94%)
High risk	31 (8%)	35 (9%)
ISS		
I	114 (30%)	101 (27%)
II	155 (41%)	170 (45%)
III	105 (28%)	103 (28%)

Dimopoulos MA, et al. *Lancet Haematol.* 2022; 9(6):e403-e414.

55

ELOQUENT-1



	Elotuzumab (N=374)	Placebo (N=374)
ORR	310 (83%)	297 (79%)
sCR	32 (9%)	32 (9%)
CR	35 (9%)	38 (10%)
VGPR	130 (35%)	114 (30%

Dimopoulos MA, et al. *Lancet Haematol.* 2022; 9(6):e403-e414.

56

57

Melphalan Flufenamide (Melflufen)

Indication	• RRMM after ≥4 prior the
Dose	-day cycle)
Supportiv Care	• N/A

Pepaxto (melphalan flufenamide) [prescribing information]. Waltham, MA: Oncopeptides Inc; February 2021.

58

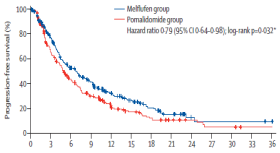
OCEAN

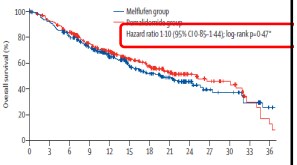
≥18 years old
RRMM (2-4 prior lines)
Refractory to lenalidomide within 18 months of randomization

Melflufen 40 mg day 1 + dexamethasone (Md) (N=249)

Pd (N=249)

Treat until progression or toxicity





Median OS 19.8 (Md) vs 25 (Pd) months

Schjesvold FH, et al. *Lancet Haematol*. 2022; 9:e98-e110

59

Food and Drug Administration (.gov)
https://www.fda.gov › drugs › fda-...

FDA grants accelerated approval to melphalan flufenamide for relapsed or ...

Mar 1, 2021 — The recommended dose of melphalan flufenamide is 40 mg intravenously over 30 minutes on day 1 of each 28-day treatment cycle, in combination ...

Cancer Network
https://www.cancernetwork.com › ...

Melphalan Flufenamide Withdrawn From US Market Following Discourse With FDA

Oct 25, 2021 — Melphalan flufenamide was granted an accelerated approval in February 2021. Advertisement. References. Oncopeptides withdraws Pepaxto® in US, ...

60

Belantamab Mafodotin (Bela-maf)

Indication	• RRMM after ≥4 prior the
Dose	eks
Supportiv Care	• Opthalmic exams requ aseline and before each dose

Blenrep (belantamab mafodotin) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; February 2022.

61

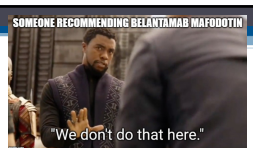
DREAMM-3

Enrollment	RRMM (≥2 prior therapies)
Randomization	Belantamab mafodotin 2.5 mg/kg day 1 Pd

	Bela-maf	Pd	HR; p-value
PFS, median (months)	11.2	7	1.03 (0.72 – 1.47)
ORR ≥VGPR	41% 25%	36% 8%	
DoR, median (months) 12-month DoR	Not reached 76.8%	8.5 48.4%	
OS, median (months)	21.2	21.1	1.14 (0.77 – 1.68)

https://clinicaltrials.gov/ct2/show/NCT04162210
https://www.gsk.com/en-gb/media/press-releases/gsk-provides-update-on-dreamm-3-phase-iii-trial-for-blenrep/

62



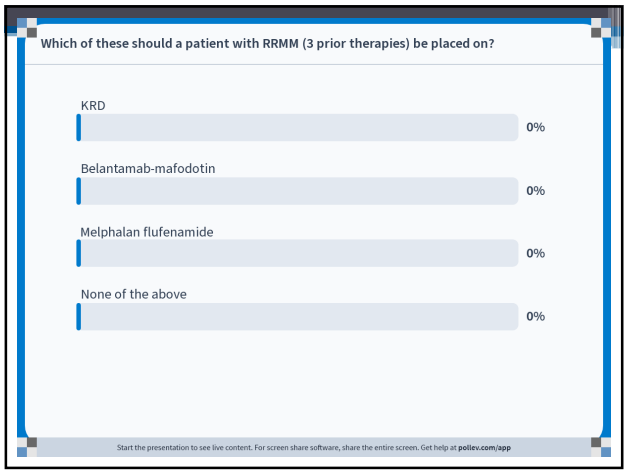
IMPORTANT PRESCRIBING INFORMATION

Subject: Initiation of the Process of Voluntary Withdrawal of the Biologic License Application for BLENREP® (belantamab mafodotin-blmf) for treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

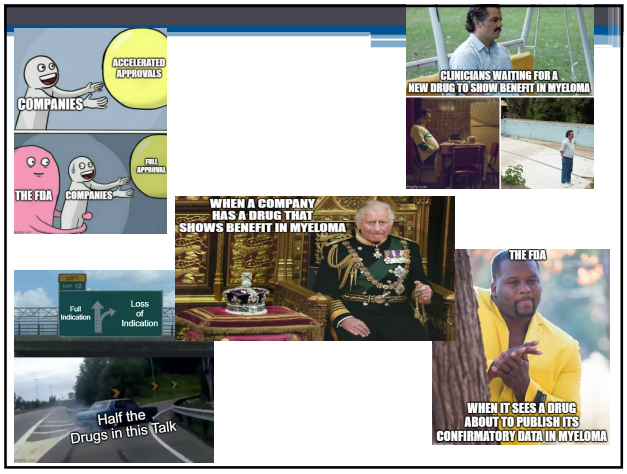
Trial	
DREAMM-7	Bela-maf + bortezomib/dexamethasone in RRMM
DREAMM-8	Bela-maf + pomalidomide/dexamethasone in RRMM

https://www.blenrep.com/content/dam/cf-pharma/dsa-blenrepv3/en_US/pdf/Blenrep-(belantamab-mafodotin-blmf)DearHCPLetterNov2022.pdf

63



65



66

References

- SEER Cancer Stat Facts: Multiple Myeloma. National Cancer Institute. Bethesda, MD.
- https://media.springernature.com/full/springer-static/image/art%3A10.1038%2Fnclib.2017.46/MediaObjects/41572_2017_Article_Bir-ejb201766_Fig1_HTML.jpg
- Cowan AJ, Green DJ, Kwok M, et al. Diagnosis and management of multiple myeloma: A review. JAMA. 2022; 327(5):464-477.
- National Comprehensive Cancer Network. Multiple Myeloma. Version 3.2023
- https://s3.us-west-1.wasabisys.com/imf-dll-prod/2019-04/SPG.PJ.jpg
- https://s3.us-west-1.wasabisys.com/imf-dll-prod/2019-04/SPG.PL.jpg
- Kumar SK, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* 2014; 15(12):e538-48.
- Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly-diagnosed multiple myeloma (CASSIOPEIA): A randomized, open-label, phase 3 study. *Lancet.* 2019; 394(10192):29-38.
- Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: The GRIFFIN trial. *Blood.* 2020; 136(8):936-945.
- Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): A randomized, open-label, phase 3 trial. *Lancet.* 2020; 395(10223):132-141.
- Facon T, Kumar SJ, Plesner Tr et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): Overall survival results from a randomized, open-label, phase 3 trial. *Lancet Oncol.* 2021; 22(11):1582-1596.
- Darzalex (daratumumab) [prescribing information]. Horsham, PA: Janssen Biotech Inc; January 2023.
- Sarclisa (isatuximab) [prescribing information]. Bridgewater, NJ: Sanofi-Aventis US LLC; July 2022.
- https://www.researchgate.net/publication/337017865_Therapeutic_Opportunities_with_Pharmacological_Inhibition_of_CD38_with_Isatuximab/figure/fig1-1
- Mohan M, Baiocchi MR, Wah LH, et al. Clinical efficacy of sequencing CD38-targeting monoclonal antibodies in relapsed refractory multiple myeloma: A multi-institutional experience. *Am J Hematol.* 2022; 97(7):e276-e280.
- Sugrue JM, Kubal T, Mulkerin DL, et al. National Comprehensive Cancer Network Infusion Efficiency Workgroup Study: Optimizing patient flow in infusion centers. *J Oncol Pract.* 2019; 15(5):e658-e666.
- Moreau MJ, Nahi H, Legiec W, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): A multicenter, open-label, non-inferiority, randomized, phase 3 trial. *Lancet Haematol.* 2020; 7(5):e370-e380.
- Usmani SZ, Nahi H, Legiec W, et al. Final analysis of the phase III non-inferiority COLUMBA study of subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma. *Haematologica.* 2022; 107(10):2408-2417.
- Darzalex Faspro (daratumumab/hyaluronidase) [prescribing information]. Horsham, PA: Janssen Biotech Inc; December 2022.
- Venclexta (venetoclax) [prescribing information]. North Chicago, IL AbbVie Inc; June 2022.
- https://ars.els-cdn.com/content/image/1-s2.0-S0301472018300620-ugr4-ers3611-fig-00001.jpg
- Kumar SJ, Harrison SJ, Cavo M, et al. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): A randomized, double-blind, multicenter, phase II trial. *Lancet Oncol.* 2020; 21(12):1630-1642.
- Tecvayli (teclistamab) [prescribing information]. Horsham, PA: Janssen Biotech Inc; October 2022.
- Elrexfio (elranatamab) [prescribing information]. New York, NY: Pfizer, Inc; August 2023.
- Talvey (talquetamab) [prescribing information]. Horsham, PA: Janssen Biotech Inc; 2023
- Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med.* 2022; 387(9):495-505.
- Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. *N Engl J Med.* 2022; 387(24):2232-2244.
- Lesokhin AM, Tomasson MH, Arnulf B, et al. Elranatamab in relapsed or refractory multiple myeloma: Phase 2 MagnetisMM-3 trial results. *Nat Med.* 2023; Online ahead of print
- Carvykti (ciltacabtagene autoleucel) [prescribing information]. Horsham, PA: Janssen Biotech Inc; February 2023.
- https://ebz8fbc2.rocketcdn.me/wp-content/uploads/2020/08/CAR-T-Mechanism.png
- Berdeja JG, Madduri D, Usmani S, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): A phase 1b/2 open-label study. *Lancet.* 2021; 398(10297):314-324.
- Empliciti (elotuzumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; March 2022.
- Dimopoulos MA, Richardson PG, Bahlis N, et al. Addition of elotuzumab to lenalidomide and dexamethasone for patients with newly diagnosed, transplantation-ineligible multiple myeloma (ELOQUENT-1): An open-label, multicenter, randomized, phase 3 trial. *Lancet Haematol.* 2022; 9(12):e903-e914.
- Pepaxto (melphalan flufenamide) [prescribing information]. Waltham, MA: Oncopeptides Inc; February 2021.
- Schjesvold FH, Dimopoulos MA, Delimpasi S, et al. Melflufen or pomalidomide plus dexamethasone for patients with multiple myeloma refractory to lenalidomide (OCEANS): A randomized, head-to-head, open-label, phase II study. *Lancet Haematol.* 2022; 9(2):e98-e110.
- Blenrep (belantamab-mafodotin) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; February 2022.
- https://clinicaltrials.gov/ct2/show/NCT04162210
- GSK provides update on DREAMM-8 phase III trial for Blenrep in relapsed/refractory multiple myeloma. News release. GSK. November 7, 2022. Accessed June 8, 2023.
- https://www.blenrep.com/content/dam/cf-pharma/dsa-blenrepv3/en_US/pdf/Blenrep-(belantamab-mafodotin-blmf)DearHCPLetterNov2022.pdf

67

BiTEs, CARs, ~~and~~ Much More: Updates in Multiple Myeloma

Dennis Marjoncu, PharmD, BCOP
Clinical Pharmacy Specialist – Hematology/Oncology
Methodist University Hospital
Memphis, TN

TOPA
Tennessee Oncology Pharmacists Association

68