2020 NCODA Fall Summit

Multiple Myeloma: Exploring the Rapidly Evolving Treatment Landscape for Relapsed or Refractory Disease

Kathryn Maples, PharmD, BCOP
Clinical Pharmacy Specialist, Multiple Myeloma
Winship Cancer Institute, Emory Healthcare
Atlanta, Georgia

#NCODASummit20

Pharmacist, Nurse, and Physician Educational Objectives

After completion of this activity, participants will be able to:

- Recognize approved and pipeline medications used for the treatment of relapsed or refractory multiple myeloma based on mechanisms of action
- Discuss the rationale behind the use of combination therapies for the treatment of patients with relapsed or refractory multiple myeloma
- Describe ways the oncology care team can assist in the supportive care of patients with relapsed or refractory multiple myeloma

Pharmacy Technician Educational Objectives

After completion of this activity, participants will be able to:

- Recognize approved and pipeline medications used for the treatment of relapsed or refractory multiple myeloma based on mechanisms of action
- Discuss the rationale for use of combination therapies in the treatment of patients with relapsed or refractory multiple myeloma
- Describe ways members of the oncology care team can assist in the supportive care of patients with relapsed or refractory multiple myeloma

Multiple Myeloma Background

Overview of Multiple Myeloma (MM)

- Malignancy of plasma cells
- Proliferation of monoclonal plasma cells in the bone marrow
  - Leads to bone destruction and bone marrow failure
- Abnormal plasma cells secrete proteins
  - Heavy chains: IgG, IgA, IgM; IgE/D at low levels
  - Light chains: kappa or lambda
  - None (non-secretors)

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Multiple Myeloma (Version 2.2021).
Palumbo A, Anderson K. *N Engl J Med*. 2011;364(11):1046-1060.

Epidemiology

- 32,270 new cases in 2020
  - 1.8% of all new cancer diagnoses
- 12,830 deaths in 2019
  - 2.1% of all cancer deaths
- Median age at diagnosis: 69 years
- 5-year relative survival: 53.9%
- Risk factors:
  - Male sex, African American race, monoclonal gammopathy of undetermined significance (MGUS), chemical exposure

Siegel RL, et al. *CA Cancer J Clin*. 2019;69 (1):7-34.
SEER Stat Fact Sheets: Myeloma. Accessed August 24, 2020. seer.cancer.gov/statfacts/html/mulmy.html

Revised IMWG Diagnostic Criteria

MGUS	Smoldering Myeloma	Multiple Myeloma
• M-protein <3 g/dL (serum) • Clonal plasma cells in marrow <10% • No SLiM-CRAB criteria	• M-protein ≥3 g/dL (serum) or ≥500 mg/24 h (urine) • Clonal plasma cells in marrow 10%-60% • No SLiM-CRAB criteria	• Clonal marrow plasma cells ≥10% or ≥1 biopsy-proven bony or extramedullary plasmacytoma • SLiM-CRAB criteria

SLiM	CRAB
S Clonal plasma cells in BM ≥60% Li Serum FLC ratio ≥100 M >1 focal lesion ≥5 mm on MRI	C Calcium elevation (>11 mg/dL or >1 mg/dL higher than ULN) R Renal insufficiency (CrCL <40 mL/min or SCr >2 mg/dL) A Anemia (Hgb <10 g/dL or 2 g/dL < normal) B Bone disease (≥1 lytic lesions on skeletal radiography, CT, or PET/CT)

Rajkumar SV, et al. *Lancet Oncol*. 2014;15(12):e538-e554. IMWG, International Myeloma Working Group.

Revised International Staging System (R-ISS)

Stage	Criteria	Genetics	5-year Overall Survival
I	B_2-microglobulin <3.5 mg/L and serum albumin ≥3.5 g/dL	No del (17p) No t(4;14) No t(14;16) Normal LDH	82%
II	Not stage I or III		62%
III	B_2-microglobulin ≥5.5 mg/L	Del(17p) t(4;14) t(14;16) High LDH	40%

Palumbo A, et al. *J Clin Oncol*. 2015;33(26):2863-2869.

Setting the Stage: Available and Emerging Therapies in Relapsed/Refractory Multiple Myeloma

Criteria for Relapse

Biochemical relapse	• Increase in serum/urine M protein • Increase in involved free light chain levels • Increase in bone marrow plasma cell percentage
Clinical relapse	• Presence/worsening of CRAB criteria • Development of new bone lesions or soft tissue plasmacytoma • Hyperviscosity related to serum paraprotein

NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma (Version 2.2021).

Management of R/R MM

- Currently no universal standard for optimal therapy sequence in relapsed/refractory (R/R) disease
- Factors impacting treatment selection
  - Patient age and comorbidities
  - Disease cytogenetics
  - Timing and aggressiveness of relapse
  - Response to prior treatments, adverse affects
  - Drug cost/access

Moreau P. *Blood*. 2017;130(13):1507-1513.

NCCN-Recommended First-Line Therapies

Transplant-eligible	Transplant-ineligible
Bortezomib/lenalidomide/dexamethasone **(category 1)**	Bortezomib/lenalidomide/dexamethasone **(category 1)**
Bortezomib/cyclophosphamide/dexamethasone	Daratumumab/lenalidomide/dexamethasone **(category 1)**
Carfilzomib/lenalidomide/dexamethasone	Lenalidomide/low-dose dexamethasone **(category 1)**
Ixazomib/lenalidomide/dexamethasone (category 2B)	Bortezomib/cyclophosphamide/dexamethasone
Bortezomib/thalidomide/dexamethasone **(category 1)**	Daratumumab/bortezomib/melphalan/prednisone **(category 1)**
Others: Daratumumab-VTD, Daratumumab-RVD, KCd	Others: IRD, KRD, Vd, KCd

Maintenance Therapy
Lenalidomide **(category 1)** Ixazomib **(category 1)** Bortezomib

NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma (Version 2.2021).

Treatment Options for R/R MM Overview

Immunomodulatory agents (IMiDs)	Proteasome inhibitors (PIs)	Monoclonal antibodies (mAbs)	Novel mechanisms	Corticosteroids
•Lenalidomide •Pomalidomide •Thalidomide	•Bortezomib •Carfilzomib •Ixazomib	•Daratumumab •Elotuzumab •Isatuximab-irfc	• Belantamab mafodotin-blmf Anti-BCMA mAb • Panobinostat HDAC inhibitor • Selinexor Nuclear export inhibitor • Venetoclax* BCL-2 inhibitor	•Dexamethasone •Prednisone

Kumar S, et al. *J Clin Oncol*. 2020;38(suppl):8509; NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma (Version 2.2021); Blenrep. Prescribing information. GlaxoSmithKline; August 2020. Accessed August 20, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2020/761158s000lbl.pdf

*Not FDA approved for MM.

First Relapse Treatment Options

Carfilzomib-Based Regimens

Study/ Patient Population	Median Follow-up (months)	Median PFS (months)	ORR	≥ VGPR	Adverse Effects (grades 3-4)
ASPIRE: Carfilzomib lenalidomide dexamethasone (KRd) v. Rd **1-3 prior lines of therapy** **KRd (n = 396) vs Rd (n = 396)**	32.3 vs 31.5	26.3 vs 17.6	87.1% vs 66.7%	69.9% vs 40.4%	• Neutropenia (29.6% vs 26.5%) • Anemia (17.9% vs 17.2%) • Thrombocytopenia (16.6% vs 12.3%) • Diarrhea (3.8% vs 4.1%) • Hypertension (4.3% vs 1.8%) • Cardiac failure (3.8% vs 1.8%)
Phase 1: Carfilzomib Pomalidomide Dexamethasone (KPd) **≥1 prior line of therapy & lenalidomide refractory (n = 32)**	26.3	7.2	50%	16%	• Neutropenia (44%) • Thrombocytopenia (22%) • Anemia (19%) • Pneumonia (9%)

Stewart AK, et al. *N Engl J Med*. 2015;372:142-152; Shah JJ, et al. *Blood*. 2015;126(20):2284-2290.

A.R.R.O.W. – Carfilzomib

478 patients randomized 1:1 to once-weekly (n=240) or twice-weekly (n=238) dosing

↓

Once weekly: 70 mg/m² Days 1, 8, 15
Twice weekly: 27 mg/m² Days 1, 2, 8, 9, 15, 16

↓

Primary end point: PFS

Phase 3 Study	
Objective	To compare PFS for once- vs twice-weekly carfilzomib in patients with R/R MM after 2-3 treatments, including PI and IMiD
Results	Median PFS: 11.2 months with once-weekly versus 7.6 months with twice weekly (HR, 0.69; 95% CI, 0.54-0.83) **Adverse effects** • ≥Grade 3 higher with once weekly (68%) vs twice weekly (62%) • Anemia: 18% vs 18% • Pneumonia: 10% vs 7% • Thrombocytopenia: 7% vs 7% • Grade 3 or worse cardiac failure: 3% vs 4%
Conclusion	Once-weekly dosing yielded higher PFS with similar adverse effect profile

Moreau P, et al. *Lancet Oncol*. 2018;19:953-964.

Daratumumab-Based Regimens

Study/Patient Population	Therapy	Median Follow-up (months)	Median PFS (months)	ORR	≥ VGPR	SAEs (grades 3-4)
POLLUX 1+ prior lines of therapy	DaraRd (n = 286) vs Rd (n = 283)	44.3	44.5 vs 17.5	92.9% vs 76.4%	75.8% vs 44.2%	**Neutropenia** (51.9% vs 37.0%), anemia (12.4% vs 19.6%), thrombocytopenia (12.7% vs 13.5%), **fatigue** (6.4% vs 2.5%), diarrhea (5.3% vs 3.2%)
CASTOR 1+ prior lines of therapy	DaraVd (n = 251) vs Vd (n = 247)	40.0	16.7 vs 7.1	82.9% vs 63.2%	59.2% vs 29.1%	**Thrombocytopenia** (45.3% vs 32.9%), anemia (14.4% vs 16.0%), **neutropenia** (12.8% vs 4.2%), neuropathy (4.5% vs 6.8%), all-grade infusion reactions 45.3% (dara)
Phase 1b 2+ prior lines of therapy	DaraPd (n = 103)	13.1	8.8	60%	42%	**Neutropenia** (77%), anemia (28%), thrombocytopenia (19%), fatigue (12%)
CANDOR 1+ prior lines of therapy	DaraKd (n = 312) vs Kd (n = 154)	17	NR vs 15.8	84.3% vs 74.7%	-	Serious AEs (56.2% vs 45.8%), grade ≥ 3 cardiac failure (3.9% vs 8.5%)

Dimopoulos MA, et al. *N Engl J Med*. 2016;375:1319-1331; Bahlis NJ, et al. *Leukemia*. 2020;34:1875-1884; Palumbo A, et al. *N Engl J Med*. 2016;375:754-766; Mateos MV, et al. *Clin Lymphoma Myeloma Leuk*. 2019;20(8):509-518. Chari A, et al. *Blood*. 2017;130:974-81.; Dimopoulos MA et al. *Lancet*. 2020;396:186-197.

Daratumumab-Pomalidomide-Dexamethasone

Cohorts	ORR	Median PFS
Daratumumab + pomalidomide naive	91.7%	Not reached at median follow-up of 41 months
Daratumumab or pomalidomide refractory	40.9%	3.2 months
Daratumumab and pomalidomide refractory	33.3%	Not reported

Conclusion: Earlier use of daratumumab + pomalidomide warranted due to significantly improved median PFS and ORR

Nooka AK, et al. *Cancer*. 2019;125:2991-3000.

Subcutaneous Daratumumab: Phase 3 Trial

522 patients randomized 1:1 to SC (n=263) or IV (n=259)

↓

SC: 1800 mg flat dose
IV: 16 mg/kg

↓

ORR and maximum trough concentration (Cycle 3, day 1 pre-dose)

Objective	Noninferiority study of subcutaneous (SC) versus intravenous (IV) daratumumab
Results	At a median follow-up of 7.5 months: • ORR 41% with SC vs 37% with IV (RR 1.11, 95% CI 0.89-1.37) • C_{trough} 593 ug/mL with SC vs 522 ug/mL with IV Most common adverse effects, SC vs IV: • Anemia (grade 3/4): 13% vs 14% • Neutropenia (grade 3/4): 13% vs 8% • Pneumonia (grade 3/4): 3% vs 4% • Infusion-related reactions (all grade): 13% vs 34%
Conclusion	SC daratumumab noninferior to IV in ORR, pharmacokinetics, and safety

Mateos MV, et al. *Lancet Haematol*. 2020;7:e370-e380.

SC versus IV Daratumumab

	SC Daratumumab	IV Daratumumab
FDA-Approved Indications	**Newly diagnosed MM:** • DaraRd, Dara-VMP **R/R MM:** • Dara monotherapy, DaraVd, DaraRd	**Newly diagnosed MM:** • Dara-VMP, DaraRd, Dara-VTD **R/R MM:** • Dara monotherapy, DaraVd, DaraRd, DaraPd, DaraKd
Dosing	1800 mg flat dose (15 mL)	16 mg/kg in 1000 mL (dose 1), then 500 mL
Administration	SC push over 3-5 minutes	Infusion rates vary based on dose; range from ≈1.5 to 8 hours
Pre-medications	Corticosteroid, antipyretic, antihistamine, montelukast (dose 1 only)	
Post-medications (often only given for high-risk)	Methylprednisone 20 mg (or equivalent) x 2 days after administration of dose, inhaled corticosteroids/bronchodilators in select patients	
Pearls	Observe after cycle 1, day 1; length of time will be institution specific	Can consider split dose for cycle 1 and give 8 mg/kg over days 1 and 2

Darzalex IV. Prescribing information. Janssen Biotech Inc; June 2020. Accessed August 24, 2020. janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX-pi.pdf; Darzalex Faspro SC. Prescribing information. Janssen Biotech Inc; May 2020. Accessed August 24, 2020. janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX+Faspro-pi.pdf

Alternative PI + IMiD Combinations

Study/ Patient Population	Therapy	Median Follow-up (months)	Median PFS (months)	ORR	≥ VGPR	Adverse Effects (Grades 3-4)	Pearls
OPTIMISSM 1-3 prior therapies, including lenalidomide for 2+ cycles	Bortezomib, pomalidomide, dexamethasone (n=281) vs VD (n=278)	15.9	11.2 vs 7.1	82.2% vs 50.0%	52.7% vs 18.3%	• Neutropenia (42% vs 9%) • Infection (31% vs 18%), • Thrombocytopenia (27% vs 29%) • Peripheral neuropathy (8% vs 4%)	Alternative to KPD for a patient who cannot tolerate or has contraindication to carfilzomib
TOURMALINE -MM1 1-3 prior therapies	Ixazomib, lenalidomide, dexamethasone (n=360) vs Rd (n=362)	14.7	20.6 vs 14.7	78% vs 72%	48% vs 39%	• Neutropenia (23% vs 24%) • Thrombocytopenia (19% vs 9%) • Anemia (9% vs 13%), • Diarrhea (6% vs 3%) • Rash (5% vs 2%)	• All oral regimen • May not be ideal for a patient who progresses on ixazomib maintenance

Richardson PG, et al. *Lancet Oncol*. 2019;20:781-794; Moreau P, et al. *N Engl J Med*. 2016;374:1621-1634.

Elotuzumab + IMiD

Study/Patient Population	Therapy	Median Follow-up (months)	Median PFS (months)	ORR	≥ VGPR	Adverse Effects (Grades 3-4)	Pearls
ELOQUENT-2 1-3 prior therapies	EloRd (n=321) vs Rd (n=325)	48	19.4 vs 14.9	79% vs 66%	35% vs 29%	**Lymphopenia** (77% vs 49%), anemia (19% vs 21%), thrombocytopenia (19% vs 20%), neutropenia (34% vs 44%)	**Dosing:** 10 mg/kg IV weekly cycles 1-2, then every other week for cycles 3+
ELOQUENT-3 At least 2 prior therapies, including lenalidomide and a PI	EloPd (n=60) vs Pd (n=57)	9.1	10.3 vs 4.7	53% vs 26%	20% vs 9%	Anemia (10% vs 20%), neutropenia (13% vs 27%), thrombocytopenia (8% vs 5%), infections (13% vs 22%)	**Dosing:** 10 mg/kg IV weekly cycles 1-2, then 20 mg/kg monthly for cycles 3+

• Infusion less time than IV daratumumab
• Not to be used as monotherapy

Lonial S, et al. *N Engl J Med*. 2015;373:621-631; Dimopoulos MA, et al. *Cancer*. 2018;124:4032-4043; Dimopoulos MA, et al. *N Engl J Med*. 2018;379:1811-1822.

Isatuximab-irfc + IMiD

Study/Patient Population	Therapy	Median Follow-up (months)	Median PFS (months)	ORR	≥ VGPR	Adverse Effects (Grades 3-4)	Pearls
ICARIA-MM ≥2 prior therapies, including lenalidomide and a PI	IsaPd (n=154) vs Pd (n=153)	11.6	11.5 vs 6.5	60% vs 35%	32% vs 9%	**Infusion reactions** (38% vs 0%), upper respiratory tract infections (28% vs 17%), diarrhea (26% vs 20%)	• No data in patients who previously received daratumumab • Dosing: 10 mg/kg IV weekly for cycle 1, then other week for cycles 2+ • Infusion time less than IV daratumumab

Lonial S, et al. *N Engl J Med*. 2015;373:621-631; Dimopoulos MA, et al. *N Engl J Med*. 2018;379:1811-1822; Attal M, et al. *Lancet*. 2019;394:2096-2107.

Later Relapse Treatment Options

Selinexor: XPO Inhibitor

- First-in-class, oral, selective inhibitor of nuclear export compound exportin 1 (XPO1)
  - XPO1 overexpressed in myeloma cells
  - Inhibition of XPO1 leads to accumulation of tumor suppressor proteins, cell cycle arrest, and apoptosis
  - FDA approved with dexamethasone for R/R MM in patients previously treated with 2 PIs, 2 IMiDs, and a CD38-monoclonal antibody (triple-class refractory)
  - NCCN recommendation for "useful in certain circumstances"
- **STORM trial** (phase 2b)
  - Selinexor 80 mg PO twice weekly + dexamethasone 20 mg twice weekly
  - Outcomes: median PFS 3.7 months, median OS 8.6 months, ORR 26%
  - Most common grade 3/4 adverse effects: anemia (44%), thrombocytopenia (58%), fatigue (25%)
    - Nausea and decreased appetite occurred in 72% and 56% of patients, respectively

Chari A, et al. *N Engl J Med*. 2019;381:727-738.

Selinexor: Combination Therapy

- **BOSTON:** phase 3 study of patients exposed to 1 to 3 prior lines of therapy
  - Once-weekly selinexor 100 mg PO + bortezomib 1.3 mg/m^2 + dexamethasone 40 mg (SVd); n = 195 versus twice weekly VD; n = 207
  - Outcomes
    - SVd resulted in significantly longer median PFS: 13.9 months and 9.5 months
    - Median OS NR with SVd versus 25 months with Vd alone (P = 0.28)
  - ≥Grade 3 adverse effects: thrombocytopenia (35.9% vs 15.2%), fatigue (11.3% vs 0.5%), nausea (7.7% vs 0%)
- **STOMP**: phase 1b/2 study
  - Selinexor in combination with carfilzomib, lenalidomide, or pomalidomide
  - Ongoing

Dimopoulos MA, et al. *J Clin Oncol*. 2020;38:8501; Gasparetto C, et al. *J Clin Oncol*. 2020;38:8510; Gasparetto C, et al. *J Clin Oncol*. 2020;38:8530.

Panobinostat: Histone Deacetylase Inhibitor

- Oral agent blocking aggresome pathway
  - Dosed every other day for 3 doses/week weeks 1 and 2 of a 21-day cycle
- **PANORAMA-1**: phase 3 randomized trial of panobinostat + Vd (PanoVd) vs Vd
  - Patients received at least 2 prior lines of therapy, including bortezomib and IMiD
  - Outcomes: PanoVd vs Vd
    - Median PFS: 11.99 months vs 8.08 months
    - Median OS: 40.3 months vs 35.8 months
  - Adverse effects: PanoVd vs Vd
    - Thrombocytopenia (67% vs 31%), lymphopenia (53% vs 40%)
    - Diarrhea (26% vs 8%)
    - Fatigue (24% vs 12%)
  - Led to FDA approval in combination with bortezomib + dexamethasone
  - Recommended in NCCN guidelines; adverse effects may limit use

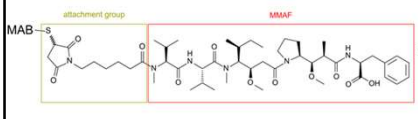
San-Miguel JF, et al. *Lancet Oncol*. 2014;15:1195-1206; San-Miguel JF, et al. *Blood*. 2015;126(23):3026; Farydak. Prescribing information. Secura Bio. September 2019. Accessed August 18, 2020. us.farydak.com/assets/pdf/Farydak-SBI-USPI-201909.pdf

Venetoclax: BCL-2 Inhibitor

- Oral agent indicated in relapsed disease in patients with t(11;14)
  - 400 mg by mouth daily x 1 month, 800 mg by mouth daily thereafter + dexamethasone weekly
- **Phase 1 data**:
  - ORR with venetoclax monotherapy and in combination with Vd were 21% and 67%, respectively
  - ORR increased to 40% with venetoclax monotherapy and 65% with Vd in patients with t(11;14)
- **BELLINI trial**: Venetoclax + Vd (VenVd) vs Vd alone in patients with R/R MM with 1-3 prior lines of therapy; phase 3 trial
  - Median follow-up of 28.6 months
    - ORR 82% vs 68%
    - Minimal residual disease negativity rates were 13% vs 1%
  - Median PFS not reached for patients with t(11;14) (13% of total population) in the combination arm vs 9.3 months for Vd alone

Kumar S, et al. *Blood*. 2017;130:2401-2409; Moreau P, et al. *Blood*. 2017;130(22):2392-2400; Kaufman JL, et al. *Blood*. 2019;134(suppl_1):926. Kumar S, et al. *J Clin Oncol*. 2020:38(suppl):8509; Harrison S, et al. *Blood*. 2019;134(suppl_1):142.

B-Cell Maturation Antigen (BCMA) Target



- BCMA is expressed on normal plasma cells and MM cells
  - Normal cells:
    - Supports survival of plasma cells
    - Produces antibodies
    - Class switch of immunoglobulin
  - MM cells:
    - Promotes proliferation and survival of MM cells
    - Associated with immunosuppressive bone marrow microenvironment
    - Increased sBCMA level is associated with disease progression and worse outcomes

Cho SF, et al. *Front Immunol*. 2018;9:1821. Image entered into the public domain on March 16, 2014.

Belantamab mafodotin-blmf: DREAMM-2

- Fully humanized antibody-drug conjugate against BCMA conjugated to the microtubule-disrupting agent MMAF (monomethyl auristatin-F)

Open-label, phase 2, multinational study	
Patients	• Disease progression after 3 or more prior lines of therapy (IMiDs, PI, CD38 mAb) • 2.5 mg/kg (n=97) or 3.4 mg/kg (n=99) belantamab mafodotin-blmf IV day 1 every 3 weeks

Results	• ORR: 31% of patients in 2.5 mg/kg cohort and 34% in 3.4 mg/kg cohort
	• Grade 3/4 adverse effects 2.5 mg/kg versus 3.4 mg/kg:
	  • Keratopathy: 27% vs 21%
	  • Thrombocytopenia: 20% vs 33%
	  • Anemia: 20% vs 25%

Conclusion	• Single-agent belantamab mafodotin shows anti-myeloma activity with a manageable safety profile • Led to priority review with FDA August 2020 at 2.5 mg/kg dose

Lonial S, et al. *Lancet Oncol*. 2020;21:207-221. Blenrep. Prescribing information. GlaxoSmithKline; August 2020. Accessed August 20, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2020/761158s000lbl.pdf

Belantamab mafodotin-blmf Supportive Care

- Baseline and subsequent ophthalmic exams required prior to each dose
- Eyecare
  - Preservative-free artificial tears: 2-4 drops in each eye 4 times daily
  - Cooling eye mask may be applied during infusion
  - Avoid contact lenses
- Platelet transfusions may be needed for thrombocytopenia

Lonial S, et al. *Lancet Oncol*. 2020;21:207-221. Blenrep. Prescribing information. GlaxoSmithKline; August 2020. Accessed August 20, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2020/761158s000lbl.pdf

Other Emerging Investigational Drugs

- Melphalan flufenamide (Melflufen)
  - First-in-class peptide-drug conjugate
  - Targets aminopeptidases and rapidly releases alkylating agents into tumor cells
  - Phase 2 HORIZON (NCT02963493); phase 3 OCEAN trial (NCT03151811)
- Iberdomide (CC-220)
  - Orally bioavailable cereblon modulator (CELMoD), structurally similar to pomalidomide and lenalidomide but binds with higher affinity
  - Phase 1/2 (NCT02773030)
- CC-92480
  - Novel IMiD under investigation
  - Phase 1 (NCT03803644, NCT03374085)

NIH ClinicalTrials.gov. Accessed July 6, 2020. clinicaltrials.gov

Pharmacist Role in Managing Relapsed/Refractory Multiple Myeloma

Medication-Specific Monitoring

IMiDs	• VTE prophylaxis, pregnancy risk, secondary malignancies • Lenalidomide: rash and diarrhea
PIs	• Herpes reactivation, blepharitis/conjunctivitis • Bortezomib: peripheral neuropathy • Ixazomib: nausea/vomiting • Carfilzomib: heart failure, TMA
Monoclonal antibodies	• Infusion-related reactions, hepatitis B reactivation, interference with serological testing (obtain baseline type and screen)
Selinexor	• Nausea/vomiting, weight loss, appetite suppression
Venetoclax	• Tumor lysis syndrome monitoring
Belantamab	• Keratopathy, dry eyes, blurry vision

NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma (Version 2.2021); NCCN Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections (Version 2.2020); Lonial S, et al. *Lancet Oncol*. 2020;21:207-221; Lee DW, et al. *Biol Blood Marrow Transpl*. 2019;35(4):625-638.

Supportive Care

- Bone-modifying agents
  - Zoledronic acid
  - Pamidronate
  - Denosumab
- Venous thromboembolism (VTE) prophylaxis
  - Aspirin 81 to 162 mg by mouth daily
  - Based on risk factors, consider oral rivaroxaban 10 mg daily or apixaban 2.5 mg BID
- VTE treatment
  - Enoxaparin or rivaroxaban/apixaban
- Peripheral neuropathy
  - Gabapentin, pregabalin, duloxetine

NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma (Version 2.2021); NCCN Clinical Practice Guidelines for Cancer-Associated Venous Thromboembolic Disease (Version 1.2020), NCCN Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections (Version 2.2020), Hershman DL, et al. *J Clin Oncol*. 2014;32(18):1941-1967; Anderson K, et al. *J Clin Oncol*. 2018;36(8):812-818.

Supportive Care

- Myelosuppression/Infection
  - Growth factor support and transfusions as needed
  - Erythropoietin-stimulating agents in select cases
  - Herpes simplex virus/varicella zoster prophylaxis (eg, acyclovir)
  - Bacterial prophylaxis (eg, levofloxacin) as needed for prolonged neutropenia
  - PJP prophylaxis (eg, sulfamethoxazole/trimethoprim) indicated based on steroid dose
- Endocrine monitoring
  - Thyroid-stimulating hormone (on IMiDs) and blood glucose
- Renal dysfunction
  - Renally adjustments
  - Dose after hemodialysis if needed

NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma (Version 2.2021).; NCCN Clinical Practice Guidelines for Cancer-Associated Venous Thromboembolic Disease (Version 1.2020), NCCN Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections (Version 2.2020), Hershman DL et al. *J Clin Oncol*. 2014;32(18):1941-1967. Anderson K, et al. *J Clin Oncol*. 2018;36(8):812-818.

Pharmacist-Led Communication

- Education of patients, caregivers, medical team
- Supportive care recommendations
- Chemotherapy dosing
  - Recommended dose modifications based on organ function or adverse effects
  - Management of drug–drug interactions
- Medication adherence techniques
  - Medication calendars, alarms, apps
  - Telehealth visits
  - Appropriate dosage form selection based on patient-specific factors
- Transitions of care
  - Multidisciplinary communication

Mackler E, et al. *J Oncol Pract*. 2019;15(4):e346-e355; Sweiss K, et al. *J Oncol Pract*. 2018;14(11):e674-e682; Segal E, et al. *J Oncol Pharm Pract*. 2019;25(8):1945-1967.

Conclusion

- Currently no universal standard for optimal sequencing of therapy in R/R MM
- Factors impacting treatment selection for R/R MM include patient specifics, disease cytogenetics, prior therapies, and timing of relapse
- Novel agents are emerging as treatment options for R/R disease
- Pharmacists have many opportunities to intervene with chemotherapy selection, education, dosing, and supportive care

Additional Resources

International Myeloma Foundation	www.myeloma.org
National Comprehensive Cancer Network: Multiple Myeloma Guidelines	www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf
mSMART Stratification for Myeloma and Risk-Adapted Therapy	www.msmart.org/mm-treatment-guidelines
Management of Relapsed and Refractory Multiple Myeloma	Chim CS, et al. *Leukemia*. 2018;32:252-262.
B-cell maturation antigen (BCMA) in multiple myeloma	Shah N, et al. *Leukemia*. 2020;34:985-1005.
Medication Education Materials	www.chemocare.com

Supplemental Slides

Abbreviations

- ASCT: autologous stem cell transplant
- Dara-RVD: daratumumab, lenalidomide, bortezomib, dexamethasone
- DaraKd: daratumumab, carfilzomib, dexamethasone
- DaraPd: daratumumab, pomalidomide, dexamethasone
- DaraRd: daratumumab, lenalidomide, dexamethasone
- DaraVd: daratumumab, bortezomib, dexamethasone
- Dara-VMP: daratumumab, bortezomib, melphalan, prednisone
- EloPd: elotuzumab, pomalidomide, dexamethasone
- EloRd: elotuzumab, lenalidomide, dexamethasone
- HDT: high-dose therapy
- HSV: herpes simplex virus
- IRD: ixazomib, lenalidomide, dexamethasone
- IsaPd: isatuximab, pomalidomide, dexamethasone
- Kd: carfilzomib and dexamethasone
- KPD: carfilzomib, pomalidomide, dexamethasone
- KRD: carfilzomib, lenalidomide, dexamethasone
- MOA: mechanism of action
- ORR: overall response rate
- OS: overall survival
- PFS: progression-free survival
- Pd: pomalidomide and dexamethasone
- PIP: *Pneumocystis jirovecі* pneumonia
- Rd: lenalidomide and dexamethasone
- R/R MM: relapsed/refractory multiple myeloma
- RVD: lenalidomide, bortezomib, dexamethasone
- SAE: serious adverse effect
- TSH: thyroid-stimulating hormone
- Vd: bortezomib and dexamethasone
- VGPR: very good partial response
- VPD: bortezomib, pomalidomide, dexamethasone
- VZV: varicella zoster virus

Investigational BCMA-Targeted Therapies

Chimeric Antigen Receptor T-cell (CAR T-cell) Therapy		
Idecabtagene vicleucel (bb2121)	Genetically modified autologous T-cell immunotherapy (containing human cells modified with a lentiviral vector); patient's T cells are reprogrammed with a transgene encoding a CAR to identify and eliminate BCMA-expressing malignant and normal cells. After binding to BCMA-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of the CAR T cells	Phase 1 (NCT03274219) Phase 2 (NCT03601078) Phase 3 (NCT03651128)
Bb21217		Phase 1 (NCT03274219)
JCARH125		Phase 1/2 (NCT03430011)
LCAR-B38M		Phase 1/2 (NCT03090659) Phase 2 (NCT03758417)
P-BCMA-101		Phase 1/2 (NCT03288493)
CT053		Phase 1b (NCT03915184)
Bi-specific T-cell engagers (BiTEs)		
AMG420	Binds to BCMA expressed on MM cells and CD3 expressed on T cells; activates endogenous T cells by connecting CD3 in the T-cell receptor complex with BCMA on MM cells, which causes MM cell death and T-cell proliferation	Phase 1b (NCT03836053)
AMG701		Phase 1/2 (NCT03287908)
CC-93269		Phase 1 (NCT03486067)

NIH ClinicalTrials.gov. Accessed July 6, 2020. clinicaltrials.gov