APSHO Regional Lecture Series

Accredited Educational Activities for Advanced Practitioners in Oncology

Collaborative Practice in the Management of Patients With Cancer

Management of Multiple Myeloma Patients Treated With Immunotherapy

Program Chair

Sandra Kurtin, RN, MS, AOCN®, ANP-C
The University of Arizona Cancer Center
Clinical Assistant Professor of Medicine
Adjunct Clinical Assistant
Professor of Nursing
The University of Arizona

APSHO Regional Lecture Series

Disclosures

Faculty

Ms. Kurtin has served as consultant for Amgen, BMS, Celgene, Genentech, Incyte, Janssen, Novartis, Takeda, and Pharmacyclics.

Planning Committee

Moshe C. Ornstein, MD, MA, Cleveland Clinic Taussig Cancer Institute (Reviewer) has nothing to disclose. Alana Brody, Terry Logan, Lynn Rubin, and Wendy Smith (MEI) have nothing to disclose. Sandy Leatherman, Annamarie Luccarelli, and Jessica Tamasi (APSHO) have nothing to disclose. Claudine Kiffer and Annie Yueh (Harborside Press) have nothing to disclose.

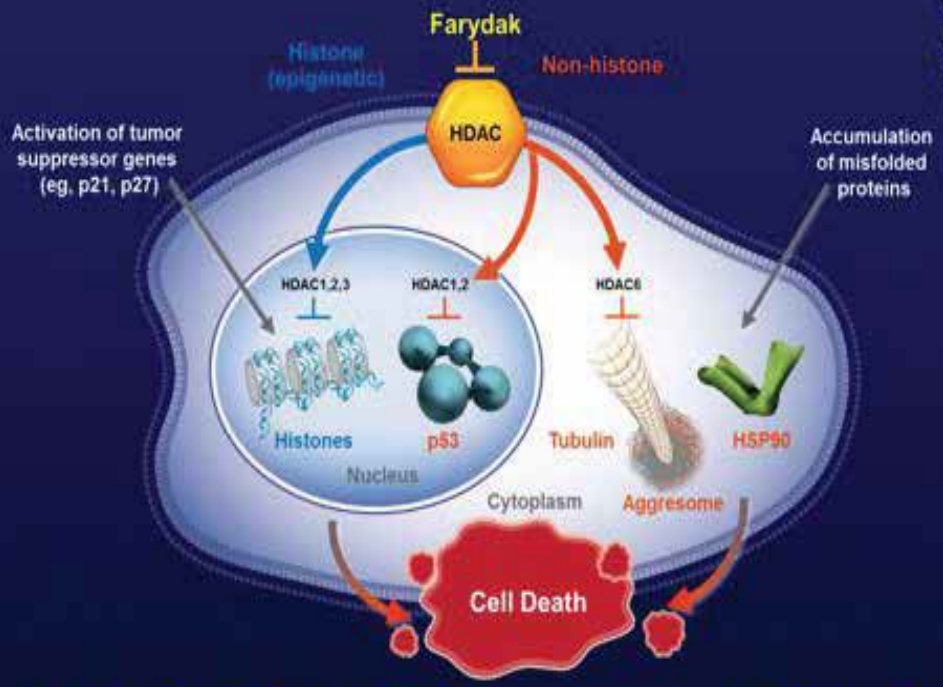
Learning Objectives

- Describe the various mechanisms of action of agents used to treat multiple myeloma (MM)
- Apply the principles of risk-adapted treatment using case-based scenarios to illustrate the impact of patient attributes and disease-specific attributes in MM
- Manage toxicities associated with newer agents used to treat MM
- Apply the principles of adjunctive supportive care in the treatment of patients with MM

Newly Approved Agents: Immunotherapy, HDAC Inhibitors, and Oral Proteasome Inhibitors

Panobinostat

- Panobinostat is a pan-deacetylase inhibitor that inhibits a broad range of deacetylase enzymes, which target both histone and non-histone proteins involved in oncogenesis[1]



Panobinostat inhibits growth and promotes death of myeloma cells through inhibition of HDAC enzymes:

- **Histone proteins,** which are implicated in epigenetic dysregulation, resulting in activation of tumor suppressor genes[1-5]
- **Non-histone proteins,** which promote toxic accumulation of misfolded proteins, leading to cell stress[1,6-8]

1. Atadja P. *Cancer Lett.* 2009; 280:233-241
2. Bolden JE, et al. *Nat Rev Drug Discov.* 2006; 5:769-784
3. De Bruyne E, et al. *Blood.* 2010; 115:2430-2440
4. Mannava S, et al. *Blood.* 2012;119:1450-1458
5. Kalushkova A et al. *PloS One.* 2010;5:e11483
6. Catley L, et al. *Blood.* 2006 ;108:3441-3449
7. Hideshima T, et al. *Mol Cancer Ther.* 2011; 10:2034-2034
8. Hipp MS, et al. *Trends Cell Biol.* 2014;24:506-514

Panobinostat in Combination With Bortezomib and Dexamethasone (Pan/Btz/Dex)

Registration trial: Phase III PANORAMA1 trial

Primary objective: PFS with PAN-BTZ-Dex vs. Pbo-BTZ-Dex in RMM or RRMM

Efficacy

- PFS benefit of 7.8 months with PAN-BTZ-Dex among patients who received ≥2 prior regimens including bortezomib and an IMiD
- Prior IMiD (12.3 vs. 7.4 months; hazard ratio [HR], 0.54; 95% CI, 0.43-0.68)
- Prior bortezomib plus IMiD (10.6 vs. 5.8 months; HR, 0.52;95%CI, 0.36-0.76),
- ≥2 prior regimens including bortezomib and an IMiD (12.5 vs. 4.7 months; HR, 0.47; 95% CI, 0.31-0.72)

Safety

Common grade 3/4 adverse events:

- Thrombocytopenia, lymphopenia, neutropenia, diarrhea, and asthenia/fatigue
- Minimal peripheral neuropathy
- Incidence of on-treatment deaths among patients who received prior bortezomib and an IMiD (regardless of number of prior regimens) was similar between treatment arms.

Class: Histone deacetylase inhibitor

FDA-Approved Indication (2/25/2015):

In combination with bortezomib and dexamethasone for the treatment of MM in patients who have received at least two prior chemotherapy regimens

dex = dexamethasone; len = lenalidomide; PR = partial response; VGPR = very good partial response; IMID = immumodulatory agent; HR = hazard ratio; CI = confidence interval.

Richardson, Hungria et al, *Blood*. 2016;127(6):713-721; www.clinicaltrials.gov #NCT01023308

PAN-BTZ-Dex: Clinical Management

Patient management

- Severe diarrhea in 25% of patients
- At first sign of abdominal cramping, loose stools, or onset of diarrhea, patients should be treated with anti-diarrheal medication (e.g., loperamide)
- Consider and administer prophylactic anti-emetics as clinically indicated
- Cardiac toxicities, including ischemic events and severe arrhythmias
- Hematologic toxicities: thrombocytopenia and myelosuppression
- Hepatotoxicity
- Embryo-fetal toxicity
- Management of adverse drug reactions may require treatment interruption and/or dose reductions

Dosing Considerations

- Hepatic impairment
  - Mild: starting dose 15 mg
  - Moderate: starting dose 10 mg
  - Severe: avoid panobinostat use
- Renal impairment
  - Mild to severe renal impairment did not impact plasma exposure of panobinostat; not studied in patients on dialysis
- Co-administration with CYP3A inhibitors: starting dose 10 mg
- Dose modifications for the following toxicities detailed in package insert:
  - Thrombocytopenia
  - Neutropenia
  - Anemia
  - Diarrhea

dex = dexamethasone; len = lenalidomide; PR = partial response; VGPR = very good partial response.

Richardson, Hungria et al, Blood. 2016;127(6):713-721

Table 1. Panobinostat Recommended Schedule

21-day cycle

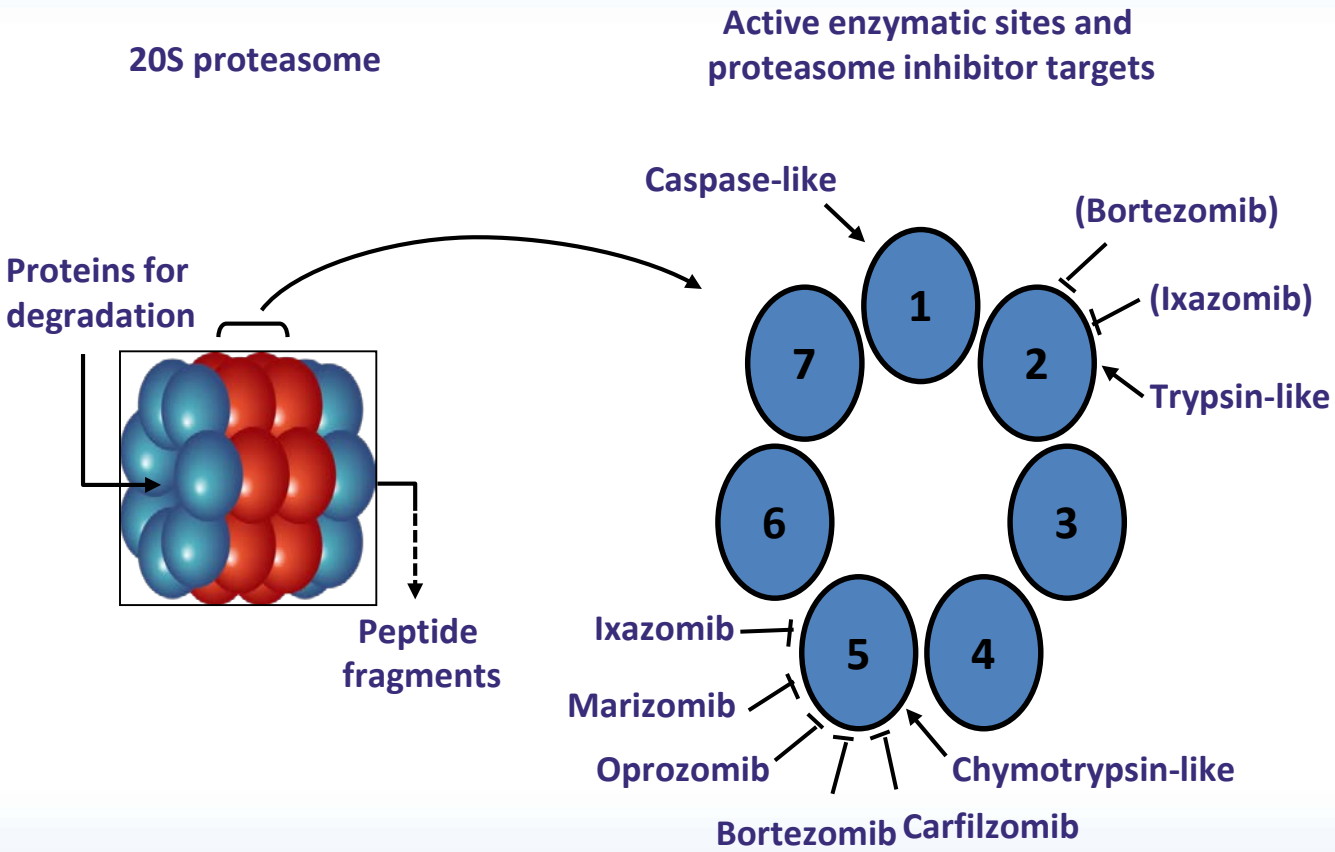
Cycles 1 to 8	Week 1 Days	Week 2 Days	Week 3
Panobinostat	1 3 5	8 10 12	Rest period
Bortezomib	1 4	8 11	Rest period
Dexamethasone	1 2 4 5	8 9 11 12	Rest period

Note. Recommended dosing schedule for panobinostat in combination with bortezomib and dexamethasone during cycles 1 to 8. Panobinostat is dosed orally at 20 mg, bortezomib is dosed at 1.3 mg/m^2, and dexamethasone is recommended at a dose of 20 mg. Information from Novartis Pharmaceuticals (2015).

- Capsules should not be opened, broken, or chewed
- Continue up to 8 cycles for patients with clinical benefit who do not experience unacceptable toxicity
- Advise patients to avoid star fruit, pomegranate, grapefruit or their juices because they can affect panobinostat pharmacology
- If dose reduction is required, dose of panobinostat should be reduced in increments of 5 mg (i.e., from 20 to 15 mg, or from 15 to 10 mg)

Novartis Pharmaceuticals, 2015; Noonan et al. (2016). *J Adv Pract Oncol*. 7(Suppl).

Molecular Targets of Proteasome Inhibitors



Adapted from McBride A, Ryan PY. *Expert Rev Anticancer Ther* 2013;13:339-358

Ixazomib Citrate

Class: Proteasome inhibitor
Registration Trial: TOURMALINE-MM1
ClinicalTrials.gov Identifier: NCT01850524

- International, randomized, double-blind, placebo-controlled clinical trial of 722 patients
  - Ixazomib, lenalidomide and dexamethasone compared to placebo, lenalidomide and dexamethasone in relapsed and/or refractory multiple myeloma
- Approval based on a 6 month improvement in median PFS: 20.6 months vs. 14.7 months (placebo regimen) HR = 0.74 (95% CI, 0.587, 0.939); P=0.012.
- Median time to response 1.1 mo in the ixazomib arm and 1.9 mo in the placebo arm

FDA Approved Indication (11/20/2015): In combination with Lenalidomide + Dexamethasone in patients who have received at least 1 prior therapy

Adverse events (AEs)

- No grade 4 non-hematological toxicity
- Grade 3 occurring in $\geq$ 5% of pts with a $\geq$ 5% difference in the two arms:
  - Thrombocytopenia: 3% of patients on Ixazomib and 1% on the placebo arm had a platelet count of $\leq$ 10,000 during treatment
  - Diarrhea (42% vs. 36%), constipation (34% vs. 25%)

Other AEs

- Neutropenia, peripheral edema, backache
- Disorder of the eye
- Rash: generally self-limiting
- Neuropathy: majority were grade 1/2 with incidence similar in both arms

dex = dexamethasone; len = lenalidomide

Ninlaro prescribing information, 2016

Ixazomib Citrate: Clinical Management

Patient Management

- Baseline CBC
  - ANC > 1,000/mm^3
  - Platelet count > 75,000/mm^3
- Monitor CBC at least monthly or more frequently if indicated
  - Platelet nadir, days 14-21 of each cycle
- All patients should receive shingles prophylaxis (Acyclovir)
- Treatment should be continued until disease progression or unacceptable toxicity
- Oral adherence

Dosing Considerations

- Avoid concomitant use with strong CYP3A inducers
- After oral administration median time to peak plasma concentration = 1 hour
- Should be taken at least 1 hour before or at least 2 hours after food
- Hepatic impairment
  - reduce the starting dose to 3 mg in patients with moderate or severe hepatic impairment
- Renal impairment
  - reduce the starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis
- Dose modification must be balanced for all drugs in the regimen

Ninlaro prescribing information, 2016.

Ixazomib Citrate: Dosing

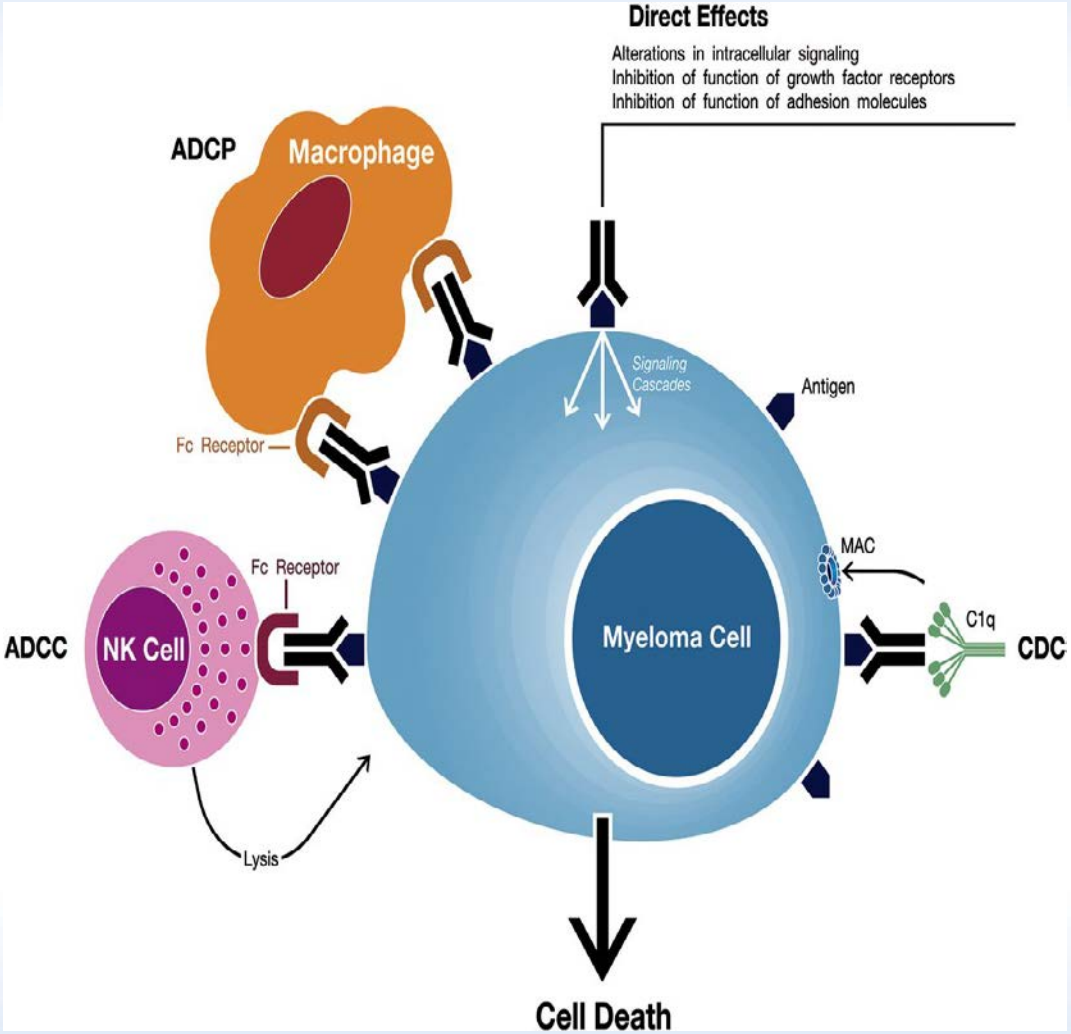
Dosing Schedule for Ixazomib

	Week 1		Week 2		Week 3		Week 4	
	Day 1	Days 2-7	Day 8	Days 9-14	Day 15	Days 16-21	Day 22	Days 23-28
Ixazomib	√		√		√			
Lenalidomide	√	√ daily	√	√ daily	√	√ daily	√	
Dexamethasone	√		√		√		√	

- Should be taken at least 1 hour before or at least 2 hours after food
- Missed doses or emesis:
  - Missed dose should not be taken with 72 hours of the next scheduled dose
  - Do not repeat the dose if vomiting occurs
- Swallow pill whole, do not crush or chew

Ninalro prescribing information, 2016.

Mechanisms of Action of Monoclonal Antibodies Targeting Surface Antigens on MM Cells

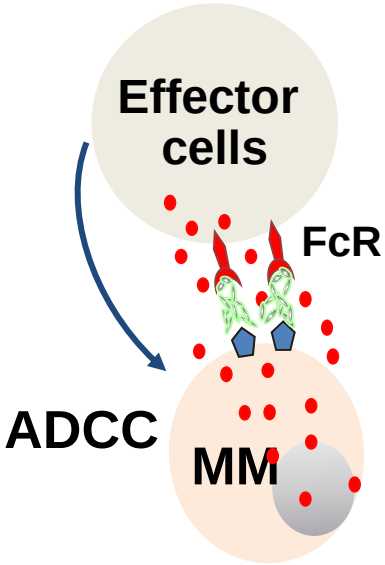


blood

Niels WC, et al. *Blood* 2016;127:681-695

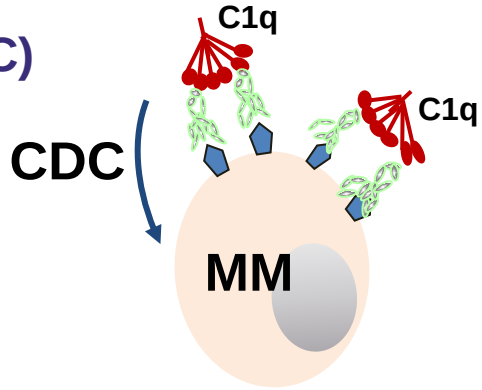
MAb-Based Targeting of Myeloma

Antibody-dependent cellular cytotoxicity (ADCC)



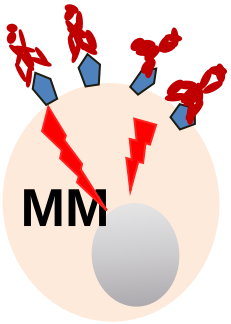
Lucatumumab or Dacetuzumab (CD40)
Elotuzumab (SLAMF7)
Daratumumab (CD38)
XmAb 5592 (HM1.24)
SAR650984 (CD38)

Complement-dependent cytotoxicity (CDC)



Daratumumab (CD38)
SAR650984 (CD38)

Apoptosis/growth arrest via targeting signaling pathways

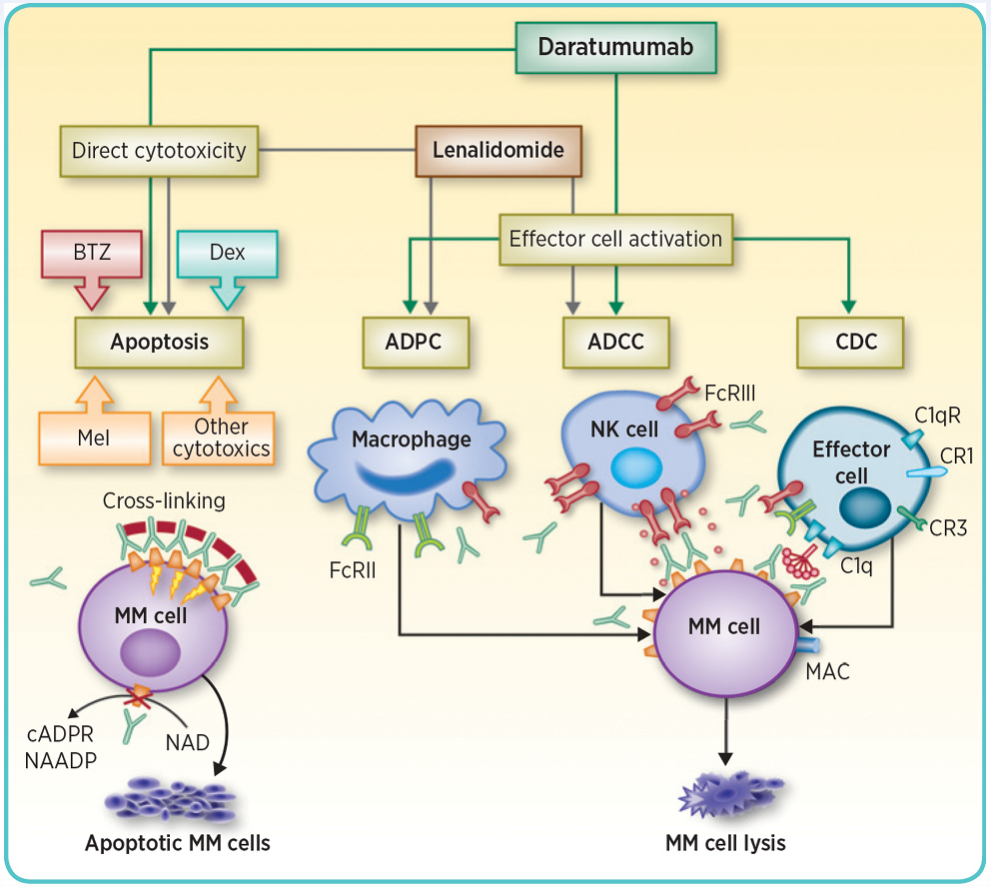


huN901-DM1* (CD56)
nBT062-maytansinoid/ DM4* (CD138)
1339 (IL-6) BHQ880 (DKK) RAP-011 (Activin A)
Daratumumab (CD38)
SAR650984 (CD38)
J6M0-MMAF* (BCMA)

Tai YT, et al. *Bone Marrow Res*. 2011;2011:924058; Balasa B, et al. *Cancer Immunol Immunother*. 2015;64:61-73

Daratumumab

- Humanized monoclonal antibody
- Target: CD38
  - Responsible for receptor mediated adhesion, signal transduction, and regulation of intracellular calcium
- Dara eliminates tumor cells expressing the CD38 antigen
- Mechanism: Antibody-dependent cellular cytotoxicity (ADCC)
  - Major mechanism of cell death
  - Complement-dependent cytotoxicity (CDC)
  - Apoptosis
- Results in decline in M protein and bone marrow plasma cells



dex = dexamethasone; len = lenalidomide.

Daratumumab

FDA Approval: November 16, 2015
Registration Trial: MMY2002 (SIRIUS) study
ClinicalTrials.gov Identifier: NCT01985126

- Approval was based on a multi-center, open-label study evaluating response rates in 106 patients with relapsed or refractory multiple myeloma treated with daratumumab monotherapy.
- Median of 5 prior lines of therapy
- The objective response rate was 29% (95% CI: 21-39%) with a median response duration of 7.4 mo (range: 1.2 to 13.1+ mo)

FDA Approved Indication (11/16/15)
Treatment of patients with multiple myeloma who have received at least 3 lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, or who are double-refractory to a proteasome inhibitor and an immunomodulatory agent

- **Updated approval: 7/26/16** The FDA granted daratumumab (Darzalex) a breakthrough therapy designation for use in combination with len/dex or Vel/dex as a treatment for patients with multiple myeloma following at least 1 prior therapy -

Adverse events

- The most frequently reported adverse reactions (incidence ≥20%) were infusion reactions, fatigue, nausea, back pain, pyrexia, cough, and upper respiratory tract infection
- Interference with cross-matching and red blood cell antibody screening

FDA News Release, 2015; Darzalex prescribing information, 2015.

Daratumumab

Administration: IV

The recommended dose for daratumumab is 16 mg/kg

Pre-medicate with corticosteroids, antipyretics, and antihistamines

Schedule	Weeks
Weekly	Weeks 1-8
Every 2 weeks	Weeks 9-24
Every 4 weeks	Weeks 25 until disease progression

Infusion rates for daratumumab administration

	Dilution volume	Initial rate (first hour)	Rate increment	Maximum rate
First infusion	1000 mL	50 mL/hr	50 mL/hr every hour	200 mL/hr
Second infusion	**500 mL**	50 mL/hr	50 mL/hr every hour	200 mL/hr
Subsequent infusions	500 mL	**100 mL/hr**	50 mL/hr every hour	200 mL/hr

FDA News Release, 2015; Darzalex prescribing information, 2015.

Special Considerations for Daratumumab

For patients treated with CD38-targeting antibodies with higher risk of respiratory complications (e.g., FEV1, 80%), post-infusion medication should be considered (e.g., antihistamines, b-2 adrenergic receptor agonist by inhalation, or control medication for patients with asthma and COPD such as inhalation corticosteroids.

Prophylactic treatment with the oral leukotriene antagonist montelukast 10 mg the day before and again on the morning of infusion may be considered prior to daratumumab.

For daratumumab: Patients with known COPD with a FEV1, 50% of the predicted normal value, with moderate or severe persistent asthma within the past 2 years, or with uncontrolled asthma, were excluded from trials with daratumumab.

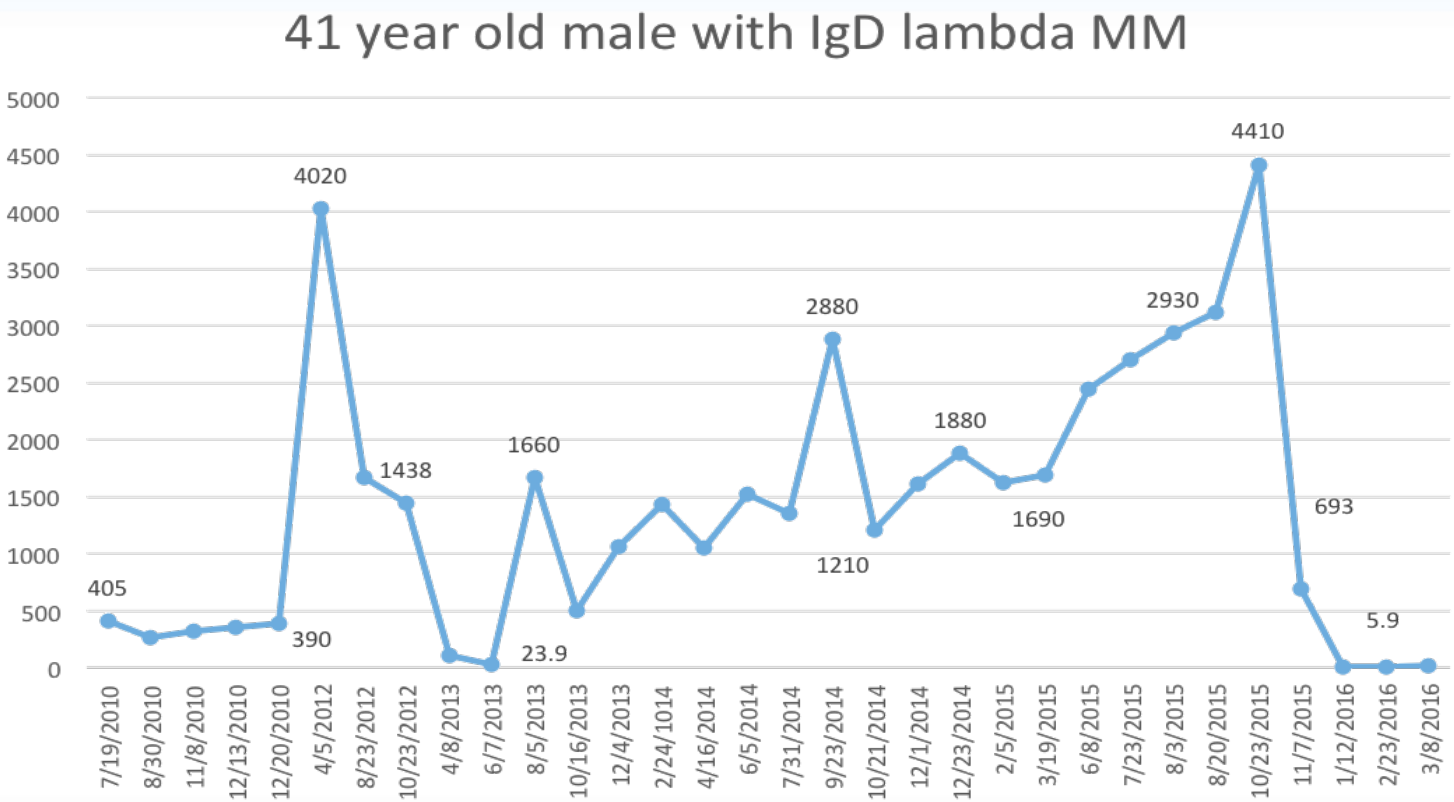
Recommendations

FEV1 testing for patients with suspicion of having COPD, and it should be considered to exclude patients from daratumumab treatment if FEV1, 50% of predicted.

van de Donk, NW, et al. (2016). *Blood* 127(6): 681-695.

Daratumumab in a Patient With Multiple Relapses, Refractory to IMIDs and Proteasome Inhibitors

IgD levels 2010-2016 (normal: ≤ 15.3 mg/dL)



Thal/Dex VTD CVDD | **Auto-PBSCT Rev/Dex** | **Auto-PBSCT** | **Velcade/Pom/Dex** | **Car/Pom/Dex** | **Velcade/Pom/Dex** | **Daratumumab**

Courtesy of Sandra Kurtin, University of Arizona Cancer Center

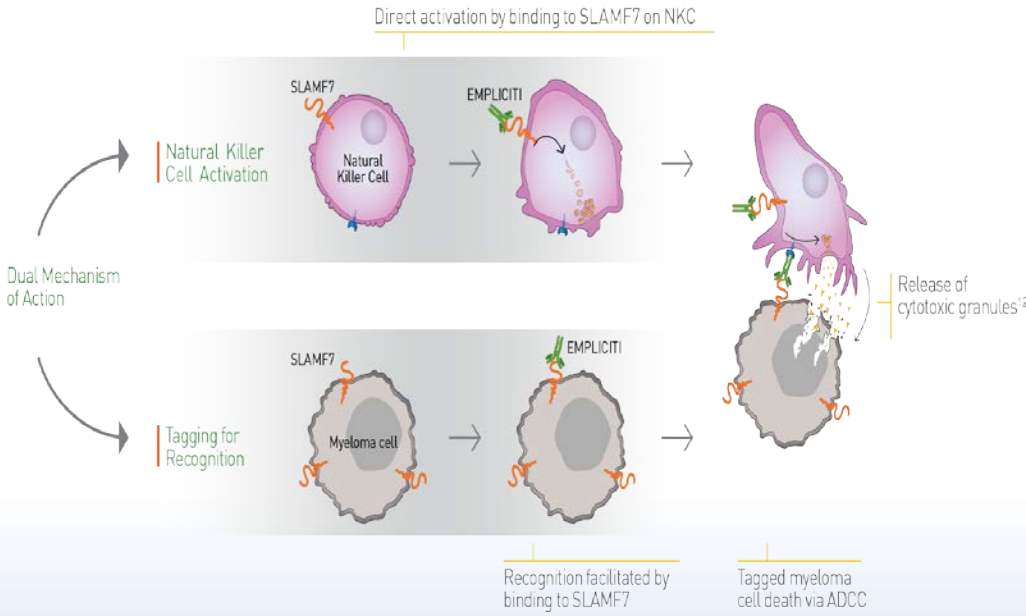
Elotuzumab

Humanized monoclonal antibody

Target: myeloma cells expressing signaling lymphocyte activation family 7 (SLAMF-7, also called CS1)

Elotuzumab exerts a dual effect:

- Induces NK-mediated myeloma cell death with minimal effect on normal cells
- Mediating antibody-dependent cell-mediated cytotoxicity through the CD16 pathway



ORR = overall response rate; PFS = progression-free survival.

Lonial S, et al. *J Clin Oncol.* 2013;31(suppl):abstract 8542; Facon T, et al. *Haematologica* 2013;98(s1):319.

Elotuzumab

Registration Trial: Phase III ELOQUENT-2 trial combining ELO, lenalidomide, and low-dose dexamethasone (ERd)

Clinical Trials.gov Identifier: NCT01239797

- Randomized patients with RRMM (1-3 prior therapies) who were *not* refractory to lenalidomide to receive ERd or standard lenalidomide-dexamethasone (Rd) in 28-day cycles
- Treatment was continued until disease progression or unacceptable toxicity
- The primary endpoints were progression-free survival (PFS) and ORR
- At interim analysis, 646 patients had been enrolled (321 ERd, 325 Rd)
- A number of patients in this trial had adverse disease attributes, including del(17p) in 32% and t(4;14) in 9%
- At 24 months of follow-up, patients in the ERd arm demonstrated a 30% reduction in the risk of disease progression or death compared to the Rd alone arm (HR 0.70 (95% CI = 0.57–0.85); p = .0004
- PFS favored ERd over Rd, with a median of 19.4 (16.6–22.2) months vs 14.9 (12.1–17.2) months and HR of 0.70 (95% CI = 0.57–0.85; p = .0004)
- At 2 years of follow-up, 35% (ERd) and 21% (Ld) of patients remained on therapy; discontinuation was mainly for disease progression (42% ERd, 47% Rd)

FDA Approved Indication (11/30/2015):

Indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies

EMPLICITI [package insert]. Princeton, NJ: Bristol-Myers Squibb Company.

Elotuzumab: Clinical Management
FDA Approval November 30, 2015

Interference with determination of complete response

- Elotuzumab is a humanized IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M-protein
- This interference can impact the determination of complete response and possibly relapse from complete response in patients with IgG kappa myeloma protein
- Correlation with clinical findings is recommended

Infections

- Grade 3/4 infections were 28% (ERd) and 24.3% (Rd)
- Monitor patients for development of infections and treat promptly
- Implement infection prophylaxis as indicated

Second primary malignancies (SPM)

- 9.1% (ERd) and 5.7% (Rd)
- No difference in hematologic SPM
- Slightly higher incidence for solid tumors (3.5% vs. 2.2%) and skin cancers (4.4% vs. 2.8%) in the ELO arm.
- Monitor patients for SPM

Hepatotoxicity

- Monitor liver enzymes periodically
- Stop elotuzumab upon grade 3 or higher elevation of liver enzymes
- After return to baseline values, continuation of treatment may be considered

EMPLICITI [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; Lonial S, et al. *N Engl J Med.* 2015;373(7):1-11. http://www.nejm.org/doi/full/10.1056/NEJMoa1505654; Cheng M, et al. *Cell Mol Immunol.*2013;10(3):230-252; Lonial S, et al. *N Engl J Med.*2015;373(suppl):1-18.

Elotuzumab: Administration and Dosing

Premedication

- Dexamethasone 28 mg orally 3-24 hours prior to infusion
- H1 and H2 blocker, dexamethasone 8 mg IV and acetaminophen 45-90 minutes prior to infusion

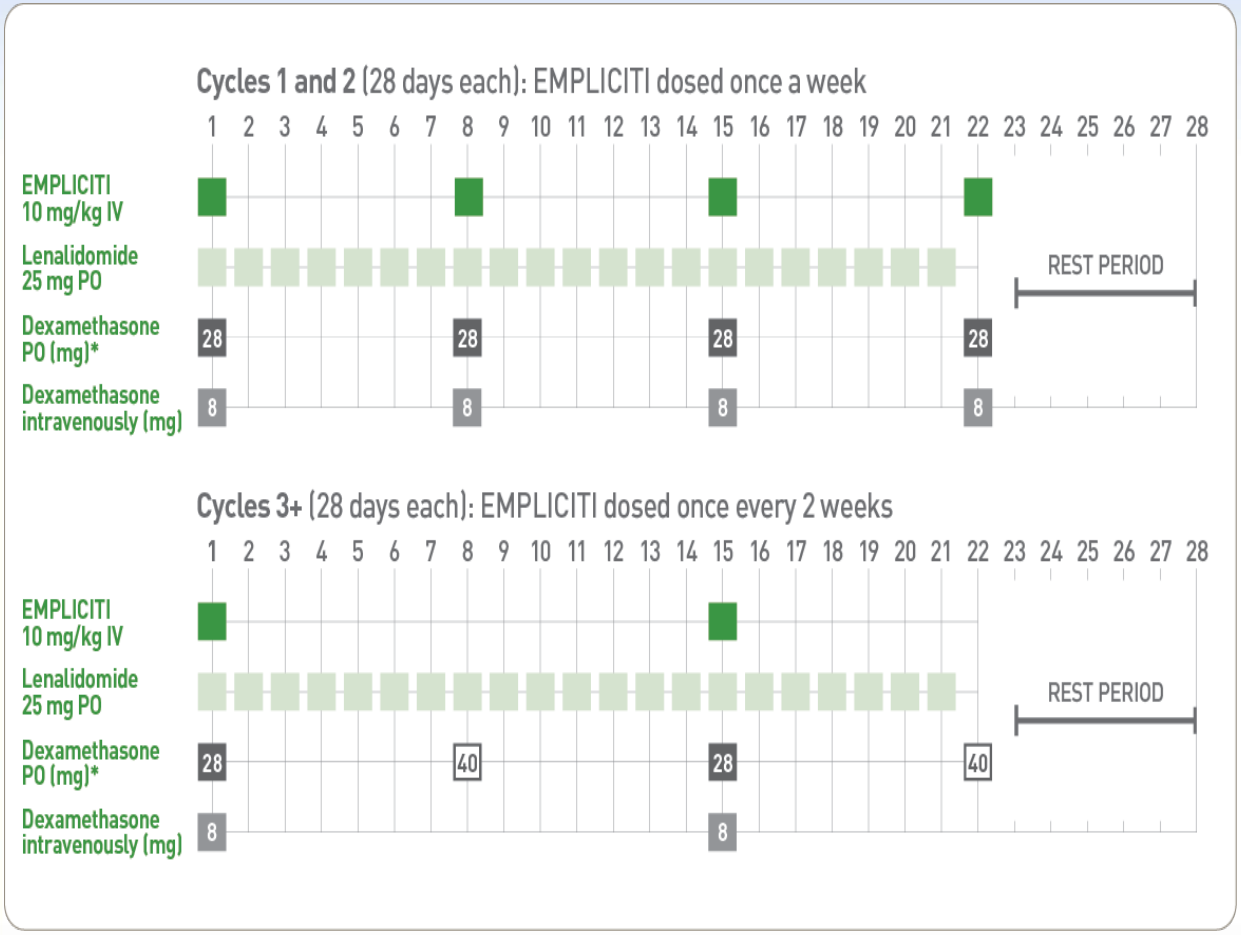
Dosing: 10 mg/kg intravenously

	Start of infusion	30 min	60 min or more
Cycle 1 dose 1	0.5 mL/min	1 mL/min	2 mL/min
Cycle 1 dose 2	1 mL/min	2 mL/min	
Cycle 1 dose 3 & 4 and all subsequent cycles	2 mL/min		

Infusion reactions

- 70% of infusion reactions occurred during the first dose
- The most common symptoms of an infusion reaction included fever, chills, and hypertension
- Bradycardia and hypotension also developed during infusions
- 5% of patients required interruption of the administration of elotuzumab for a median of 25 minutes due to infusion reaction

EMPLICITI [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; Lonial S, et al. *N Engl J Med.* 2015;373(7):1-11. http://www.nejm.org/doi/full/10.1056/NEJMoa1505654; Cheng M, et al. *Cell Mol Immunol.*2013;10(3):230-252; Lonial S, et al. *N Engl J Med.*2015;373(suppl):1-18.



The recommended dosage of elotuzumab is 10 mg/kg administered IV

Patients must be premedicated prior to each dose of elotuzumab

Treatment should continue until disease progression or unacceptable toxicity

EMPLICITI [package insert]. Princeton, NJ: Bristol-Myers Squibb Company.

Infusion Reactions vs. Hypersensitivity Reactions

- Hypersensitivity reactions are antibody-mediated and can occur only after repeated exposure to an antigen
- Anaphylactoid infusion reactions are nonantibody-mediated and often occur on the initial exposure to a drug
- Cytokine-release syndrome comprises a subset of nonantibody-mediated infusion reactions associated with the use of monoclonal antibodies and immune therapies
- Clinical symptoms of hypersensitivity reactions and nonantibody-mediated infusion reactions heavily overlap and can be difficult to distinguish in practice
- Pre-medication and having an established protocol for management is the key!

Asselin, B. (2016). *Future Oncol.* Apr 16. E-pub ahead of print. doi:10.2217/fon-2016-0005

Signs and Symptoms of Hypersensitivity Reactions

System	Clinical Findings
General	Fever, chills, flushing, rigors, sweating, fatigue, agitation, metallic taste
Cutaneous	Rash, urticaria (hives, welts, wheals) pruritus, angioedema (including face, lips or eyelids)
Respiratory	Dyspnea, wheezing, stridor, rhinitis, repetitive cough, chest tightness, throat tightness, change in voice quality (from laryngeal edema)
Cardiovascular	Tachycardia, hypotension/hypertension
Gastrointestinal	Nausea, vomiting, diarrhea, abdominal cramping
Renal	Flank pain, back pain, hematuria
Neurological	Headache, dizziness, tunnel vision, 'feeling of impending doom'

Asselin, B. (2016). *Future Oncol.* Apr 16. E-pub ahead of print. doi:10.2217/fon-2016-0005

Prevention and Treatment of Infusion Reactions in Multiple Myeloma

Prevention

- Premedication, consisting of steroids, antihistamines, and acetaminophen, 30-60 minutes prior to infusion.
- Both daratumumab and elotuzumab have specific recommendations for pre-medication, administration an post-infusion management

Treatment

- Interrupt infusion
- Activate rapid response team if available
- Activate standing orders/protocol
  - Administer antihistamines, corticosteroids, IV fluid, b-2 adrenergic receptor agonist by inhalation, oxygen if needed
- After infusion reaction is resolved, restart infusion at lower rate as described in the administration guidelines for the specific drug

van de Donk, N. W., et al. (2016). *Blood* 127(6):681-695.