

Ixazomib (Ninlaro®) National Drug Monograph July 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Ixazomib is a reversible proteasome inhibitor that has synergistic cytotoxic effects with lenalidomide.
Indication(s) Under Review	Indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy
Dosage Form(s) Under Review	Dosage Form(s), Strength(s) Capsules in 2.3 mg, 3 mg and 4 mg strengths
REMS	<input type="checkbox"/> REMS <input type="checkbox"/> No REMS <i>See Other Considerations for additional REMS information</i>
Pregnancy Rating	Can cause embryo-fetal toxicity

Executive Summary

Efficacy	<ul style="list-style-type: none"> • Ixazomib + lenalidomide/dexamethasone (Rd) improved Progression Free Survival (PFS) compared to placebo + Rd (20.7 vs. 14.7 months, respectively) • PFS benefit was consistent among all pre-specified subgroups, including those with high-risk cytogenetics • At 23 months, the median Overall Survival (OS) had not been reached in either group • Similar patient-reported quality of life scores were noted between ixazomib and placebo groups. 								
Safety	<ul style="list-style-type: none"> • Serious adverse events (Grade 3 or 4) occurred in 74 vs. 69% of ixazomib vs. placebo-treated patients, respectively • Most common adverse events include: thrombocytopenia, rash and gastrointestinal events (nausea, vomiting, diarrhea, constipation) • Patients received ixazomib for a median of 17 cycles (range, 1-34) compared with placebo, which was given for a median of 15 cycles (range, 1-34) 								
Other Considerations	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="background-color: #e0e0e0;">Outcome in clinically significant area</td> <td>Ixazomib + Rd vs. placebo + Rd PFS 20.6 vs. 14.7 months OS not reached</td> </tr> <tr> <td style="background-color: #e0e0e0;">Effect Size</td> <td>HR 0.74(0.59-0.94); p=0.01</td> </tr> <tr> <td style="background-color: #e0e0e0;">Potential Harms (Gr 3 or 4)</td> <td>Thrombocytopenia 26 vs. 11%; Neutropenia 26 vs. 30%</td> </tr> <tr> <td style="background-color: #e0e0e0;">Net Clinical Benefit</td> <td>Moderate</td> </tr> </table>	Outcome in clinically significant area	Ixazomib + Rd vs. placebo + Rd PFS 20.6 vs. 14.7 months OS not reached	Effect Size	HR 0.74(0.59-0.94); p=0.01	Potential Harms (Gr 3 or 4)	Thrombocytopenia 26 vs. 11%; Neutropenia 26 vs. 30%	Net Clinical Benefit	Moderate
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Potential Harms (Gr 3 or 4)	Thrombocytopenia 26 vs. 11%; Neutropenia 26 vs. 30%								
Net Clinical Benefit	Moderate								
Potential Impact	<p>Projected place in therapy.</p> <ul style="list-style-type: none"> • Ixazomib + Rd is an all-oral therapeutic option in relapsed/refractory MM with improved PFS compared to placebo + Rd <p>Patient convenience.</p> <ul style="list-style-type: none"> • The all oral regimen of ixazomib + Rd represents a therapeutic option in the relapsed/refractory myeloma setting. • Adherence to the ixazomib + Rd regimen appears to be high • Toxicities can be managed with no significant impact on patient-reported QoL for up to 23 months 								

Background**Purpose for review**

Recent FDA approval

Issues to be determined:

- ✓ Evidence of need
- ✓ Does ixazomib offer advantages to currently available alternatives?
- ✓ Does ixazomib offer advantages over current VANF agents?
- ✓ What safety issues need to be considered?
- ✓ Does ixazomib have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options

Refer to **Appendix 2. Therapeutic Options in R/R Multiple Myeloma by Drug Class**

Efficacy (FDA Approved Indications)**Literature Search Summary**

A literature search was performed on PubMed/Medline (1966 to July 2016) using the search terms ixazomib and Ninlaro®. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

- Refer to **Appendix 1. Table 1. International Myeloma Working Group Uniform Response Criteria** for approval endpoints.
- The TOURMALINE-MM1 Study Group conducted a double-blind, placebo-controlled, phase 3 trial in which 722 patients (147 sites in 26 countries) with relapsed, refractory or relapsed and refractory multiple myeloma were included.
- Patients were randomized 1:1 to receive ixazomib + lenalidomide/dexamethasone or placebo + lenalidomide/dexamethasone.
 - Ixazomib 4 mg PO on days 1, 8 and 15 of a 28-day cycle or matching placebo
 - Lenalidomide 25 mg PO on days 1-21 of a 28-day cycle
 - Dexamethasone 40 mg PO on days 1, 8, 15 and 22
- Thromboprophylaxis was required by all patients
- Stratification was performed by number of prior therapies, previous exposure to proteasome inhibitors and International Staging System disease stage
- Treatment was continued until disease progression or toxicity. Response assessments were performed every cycle.
- Primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS) in the ITT population and OS in those with del(17p), health-related quality of life, and others.
- Results at first pre-specified median follow up at 15 months showed improvement in PFS; second pre-specified analysis at 23 months conducted to assess survival.

Table 1. Efficacy Results

Variable	Ixazomib + Rd (360)	Placebo + Rd (362)	
PFS (mo)	20.6	14.7	HR 0.74(0.59-0.94); p=0.01
High risk cytogenetics	Ixazomib + Rd (75)	Placebo + Rd (62)	
	21.4	9.7	HR 0.54(0.32-0.92); p=0.02
ORR (%)	78 (74-83)	72 (67-76)	P=0.04
≥ VGPR (%)	48 (43-53)	39 (34-44)	P=0.01
CR (%)	12 (9-15)	7 (4-10)	P=0.02
VGPR	36 (31-42)	32 (28-37)	-
SD (%)	11 (8-15)	16 (13-21)	-
Time to response (mo)	1.1	1.9	P=0.009
Duration of response (mo)	20.5	15	-
Time to PD (mo)	21.4	15.7	P=0.007

- The benefit of improvement in PFS was consistent among pre-specified patient subgroups, including those with high risk cytogenetics, who are considered a poor prognostic group, and those with prior exposure to proteasome inhibitor therapy.
- Responses deepened with increasing duration of treatment.
- An analysis at 23 months indicated that the median overall survival had not yet been reached in either group; a total of 171 deaths occurred (81 ixazomib vs. 90 placebo group)
- Study regimen was discontinued in 62 vs. 63% of ixazomib vs. placebo-treated patients. Progressive disease was the reason in 34 vs. 40% of patients, respectively.
- At 23-months, similar patient-reported quality of life scores were noted between ixazomib and placebo groups. Nausea and vomiting symptoms were similar between the groups; diarrhea appeared to worsen with ixazomib in later cycles.

Potential Off-Label Use

According to www.clinicaltrials.gov, ixazomib is under investigation in the following settings:

- Newly diagnosed MM in combination or as monotherapy
- Relapsed/refractory MM in combination with other agents
- Maintenance therapy post autologous stem cell transplant
- In combination with interferon for metastatic renal cell carcinoma
- In combination with rituximab for indolent B-cell Non Hodgkin Lymphoma
- Relapsed/refractory Follicular Lymphoma
- Treatment of chronic Graft Vs. Host Disease

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	<ul style="list-style-type: none"> • None
Contraindications	<ul style="list-style-type: none"> • None
Warnings/Precautions (all Grades)	<ul style="list-style-type: none"> • Thrombocytopenia • GI toxicities: diarrhea (42%), constipation (34%), nausea (26%), vomiting (22%) • Peripheral neuropathy (28%) • Peripheral edema (25%) • Cutaneous reactions (19%): typically maculo-papular and macular rash • Hepatotoxicity (6%) • Embryo-fetal toxicity

Safety Considerations^{1,2}

- Diarrhea, constipation, nausea and vomiting occasionally require the use of antidiarrheal and antiemetic medications as well as supportive care. Doses should be adjusted for Grade 3 or 4 symptoms. GI symptoms were most notable during the first 3 months of therapy, considered low grade and manageable with supportive therapy.
- Eye disorders were reported in 26% of ixazomib-treated patients (vs. 16% in the placebo regimen); most common reactions were blurred vision, dry eye and conjunctivitis.
- Thrombocytopenia. Platelet nadirs typically occur between days 14-21 of each 28-day cycle with recovery by the start of the next cycle. Monitor platelet counts at least monthly during treatment. Consider more frequent monitoring during the first 3 cycles. Manage thrombocytopenia with dose modifications and platelet transfusions.
- Monitor patients for symptoms of neuropathy; those with new or worsening peripheral neuropathy may require dose modification. Grade 3 events were similar in the TOURMALINE-MM1 study groups at 2% each.
- Evaluate for underlying causes should peripheral edema occur; provide supportive care, consider dose adjustment of dexamethasone or ixazomib for Grade 3 or 4 symptoms.
- Manage rash with supportive care or dose modification if Grade 2 or higher. Rash events were most notable during the first 3 months of therapy and were often self-limiting. Medical management included antihistamines, topical glucocorticoids and dose adjustment.
- Monitor hepatic enzymes regularly; adjust dosing for Grade 3 or 4 symptoms.
- Rates of Grade 3 peripheral neuropathy was 2% in both treatment groups. Ixazomib had slightly more Grade 1, 2 events at 27% vs. 22% in the placebo group.
- Median relative dose intensity was 97.4 vs. 98.8% for ixazomib vs. placebo, respectively.
- Patients received ixazomib for a median of 17 cycles (range, 1-34) compared with placebo, which was given for a median of 15 cycles (range, 1-34)

Adverse Reactions^{1,2}

Common adverse reactions	Most common adverse reactions ($\geq 20\%$) are diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting and back pain.
Death/Serious adverse reactions	Thrombocytopenia 26 vs. 11% and neutropenia 26 vs. 30% (ixazomib vs. placebo, respectively) Any Grade ≥ 3 adverse event: 74 vs. 69% (ixazomib vs. placebo, respectively)
Discontinuations due to adverse reactions	17% vs. 14% (ixazomib vs. placebo)

Drug Interactions

Drug-Drug Interactions

- Strong CYP3A Inducers. Avoid concomitant administration of ixazomib with strong inducers such as rifampin, phenytoin, carbamazepine and St. John's Wort

Risk Evaluation

As of July 22, 2016

Comments																
Sentinel event advisories	<ul style="list-style-type: none"> None Sources: ISMP, FDA, TJC 															
Look-alike/sound-alike error potentials	<table border="1"> <thead> <tr> <th>NME Drug Name</th> <th>Lexi-Comp</th> <th>First DataBank</th> <th>ISMP</th> <th>Clinical Judgment</th> </tr> </thead> <tbody> <tr> <td>ixazomib</td> <td>Bortezomib Carfilzomib Idelalisib</td> <td>None</td> <td>None</td> <td>Ixabepilone Ixekizumab Ibrutinib</td> </tr> <tr> <td>Ninlaro®</td> <td>None</td> <td>None</td> <td>None</td> <td>Neoral Nilandron Nelarabine Teflaro</td> </tr> </tbody> </table> <ul style="list-style-type: none"> (Lexi-Comp, First Databank, and ISMP Confused Drug Name List) 	NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment	ixazomib	Bortezomib Carfilzomib Idelalisib	None	None	Ixabepilone Ixekizumab Ibrutinib	Ninlaro®	None	None	None	Neoral Nilandron Nelarabine Teflaro
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Other Considerations

- Drug is commercially provided in single blister packs that can be dispensed as a one-pack (weekly dosing) or three-pack (per cycle dosing). Store at room temperature.
- Capsules are cytotoxic and should not be opened or crushed.
- In previously treated multiple myeloma, the combination of ixazomib/lenalidomide/dexamethasone are considered a Category 1 recommendation in the NCCN Multiple Myeloma Guidelines Version 3.2016; ixazomib monotherapy and ixazomib/dexamethasone are given Category 2A recommendations.
- NICE guidelines are currently in development.
- ICER considers OS and PFS benefit of an additional 3-5 months as the range for minimum clinically meaningful improvement. The predictive power of PFS in relapsed and/or refractory disease is controversial, yet it is a standard for regulatory submission to the FDA and other key MM trials used PFS as their primary endpoint. As such, ICER assigns the evidence on the comparative clinical effectiveness of ixazomib/len/dex vs. len/dex a B+ rating in the second- and third-line therapy settings. The incremental cost-effective ratio was estimated to be \$434,000 per QALY in the second-line setting and \$485,000 per QALY in the third-line setting for ixazomib/len/dex.

Outcome in clinically significant area	Ixazomib + Rd vs. placebo + Rd PFS 20.6 vs.14.7 months OS not reached
Effect Size	HR 0.74(0.59-0.94); p=0.01
Potential Harms (Gr 3 or 4)	Thrombocytopenia 26 vs. 11%; Neutropenia 26 vs. 30%
Net Clinical Benefit	Moderate

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life

Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio

Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)

Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Dosing and Administration

- Recommended starting doses are as follows:
 - Ixazomib 4 mg orally once a week on days 1, 8 and 15 of a 28-day cycle
 - Lenalidomide 25 mg PO daily on days 1 through 21 of a 28-day cycle
 - Dexamethasone 40 mg PO on days 1, 8, 15 and 22 of a 28-day cycle
- Ixazomib should be taken on the same day at approximately the same time for the first 3 weeks of a 4-week cycle; Take at least one hour before or at least two hours after food; Swallow the capsule whole with water; It should not be crushed, chewed or opened.
- Refer to the package insert for full dosing information.

Special Populations (Adults)

	Comments
Elderly	<ul style="list-style-type: none"> • No differences in safety or effectiveness were noted between younger and older patients
Pregnancy	<ul style="list-style-type: none"> • Embryo-fetal toxicity was noted in pregnant rabbits and rats. Women should avoid becoming pregnant while receiving treatment. Male and female patients of childbearing potential must use effective contraception during treatment and for 90 days following.
Lactation	<ul style="list-style-type: none"> • There is a potential for adverse events in nursing infants, therefore women should be advised to discontinue nursing.
Renal Impairment	<ul style="list-style-type: none"> • Mean AUC increased by 39% in severe renal impairment or ESRD requiring dialysis. Reduce the starting dose in these patients.
Hepatic Impairment	<ul style="list-style-type: none"> • Mean AUC increased by 20% in moderate or severe hepatic impairment. Reduce the starting dose in these patients.
Pharmacogenetics/genomics	<ul style="list-style-type: none"> • No data identified

Projected Place in Therapy

- The addition of ixazomib to Rd resulted in an improvement in PFS by ~ 6 months. Improvement in PFS was also noted among the high risk disease population, who is considered a poor prognostic subgroup, as well as those with exposure to prior proteasome inhibitor therapy.
- An all-oral proteasome inhibitor-based regimen, such as ixazomib + Rd can be advantageous to patients with travel limitations. There is no need for outpatient oncology clinic chair time and associated expenses.
- Although not directly compared, in the relapsed/refractory study population, the ixazomib/len/dex (IRd) combination appears to be associated with less Grade 3, 4 toxicity and SAEs than carfilzomib/len/dex (KRd) or carfilzomib/dex (Kd).
- The evidence supporting use of the ixazomib combination was based upon a double-blind, placebo-controlled, phase 3 trial involving 722 patients.

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Appendix 1: Approval Endpoints

Table 1. International Myeloma Working Group Uniform Response Criteria

Disease Response	Criteria
Stringent Complete Response (sCR)	CR as defined below, plus: <ul style="list-style-type: none"> • Normal free light chain ratio, and • Absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry
Complete Response (CR)	<ul style="list-style-type: none"> • Negative immunofixation of serum and urine, and • Disappearance of any soft tissue plasmacytomas, and • < 5% plasma cells in bone marrow Additional criterion in patients with measurable disease by serum free light chain levels only: <ul style="list-style-type: none"> • Normal free light chain ratio of 0.26 to 1.65
Very good partial response (VGPR)	<ul style="list-style-type: none"> • Serum and urine M-component detectable by immunofixation but not on electrophoresis, or • $\geq 90\%$ reduction in serum M-component plus urine M-component < 100 mg/24 h Additional criterion in patients with measurable disease by serum free light chain levels only: <ul style="list-style-type: none"> • > 90% decrease in difference between involved and uninvolved free light chain levels
Partial Response (PR)	<ul style="list-style-type: none"> • $\geq 50\%$ reduction of serum M-protein and reduction in 24-hour urinary M-protein by $\geq 90\%$ or to < 200 mg/24 h If serum and urine M-protein are not measurable: <ul style="list-style-type: none"> • Decrease of $\geq 50\%$ in difference between involved and uninvolved free light chain levels If serum and urine M-protein and serum free light assay are not measurable: <ul style="list-style-type: none"> • $\geq 50\%$ reduction in bone marrow plasma cells, provided baseline percentage was $\geq 30\%$ In addition to the above criteria, if present at baseline: <ul style="list-style-type: none"> • $\geq 50\%$ reduction in size of soft tissue plasmacytomas
Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR or PD
Progressive disease (PD)/relapse	Any one or more of the following: <ul style="list-style-type: none"> • Increase of 25% from lowest response value in any of: <ul style="list-style-type: none"> ○ Serum M-component (absolute increase ≥ 0.5 g/dL), and/or ○ Urine M-component (absolute increase ≥ 200 mg/24 h), and/or ○ Difference between involved and uninvolved free light chain levels (absolute increase > 10 mg/dL) (only in patients without measurable serum and urine M-protein levels), and/or ○ Bone marrow plasma cell percentage (absolute percentage $\geq 10\%$) (only in patients without measurable serum and urine M-protein levels and without measurable disease by free light chain levels) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

All response categories and relapse require 2 consecutive assessments made at any time before the institution of any new therapy. If radiographic studies were performed, sCR, CR, VGPR, PR and SD require no known evidence of progressive or new bone lesions. CR and VGPR require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of ≥ 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL. For PD, definite increase of plasmacytoma defined as a 50% (at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion). Rajkumar SV, et al. Blood 2011; 117: 4691-4695. Durie BG, et al. Leukemia 2006; 20: 1467-1473.

APPENDIX 2. Considerations of Therapeutic Options in Relapsed/Refractory Multiple Myeloma by Drug Class

	Therapeutic Alternative	Other Considerations			
	Therapy	Status (F, NF)	Population studied	Outcomes	Toxicity/Notes
IMMUNOMODULATORY DERIVATIVES (IMiDS)	Lenalidomide/dex (Rd) Rd vs. dex (MM-009, MM-010)	F	P3, R/R	ORR 60 vs. 20-30% CR 15 vs. 1-3% OS 30 vs. 20 months	Gr 3,4 neutropenia 30-40 vs. 2-4%; VTE 11 vs. 4% Caution with use in renal impairment
	Pomalidomide/dex (Pd vs. P HIdex) [NIMBUS] <hr/> Pom/dex vs. Pom/Cy/dex [Baz 2016]	NF	P3, RR (median 5 prior, 100% prior len & bor, 75% ref to len & bor) Median age 65 yrs ECOG 2-3 (18%) ISS Stage III (32%) Previous SCT (70%) <hr/> P2, R/R (>2 prior, len-refractory)	Pd (n=302) vs. P HIdex (n=153) Median f/u 10 mos Median PFS 4 vs. 1.9 mos PFS HR 0.48 (95% CI 0.39-0.60); p<0.0001 OS HR 0.74 (95% CI 0.56-0.97); p=0.285 ORR 31 vs. 10%; p<0.0001 <hr/> ORR 39 vs. 65% PFS 4.4 vs. 9.5 mos (NS)	DC due to AEs: 9% SAEs 61% Tx-related deaths: 4%

	Therapeutic Alternative	Other Considerations			
	Therapy	Status (F, NF)	Population studied	Outcomes	Toxicity/Notes
PROTEASOME INHIBITORS (PI)	Bortezomib monotherapy or Bortezomib combo with lenalidomide, dex [Richardson, et. al., 2014]	F	P2, R/R	ORR ~ 30% monotherapy ORR ~ 65% combination	<ul style="list-style-type: none"> FDA: treatment of MM Given IV or SC; SC preferred d/t ↓ risk neuropathy Thrombocytopenia 43% Peripheral neuropathy 40% with twice weekly dosing ~20% with once weekly dosing Prior neurotoxic tx, pre-existing neuropathy may worsen Safe in renal impairment [APEX trial] Antiviral prophylaxis needed
	Rd + Carfilzomib vs. Rd [ASPIRE 2015, n=792]	NF	P3, R/R (median 2 prior regimens: 60% prior bortezomib; 20% prior len) Median age 64 yrs ECOG 2 (9.5%) ISS Stage III (20%) Previous SCT (57%) High risk (12.6%)	PFS 26.3 vs. 17.6 mos (p=0.0001) 24-mo OS 73 vs. 65% (NS) ORR 87 vs. 67% (p<0.001)	<ul style="list-style-type: none"> FDA: Monotherapy of R/R MM in those who received ≥ 1 prior therapy AND in combo with Rd or dex in those who received 1-3 prior therapies Grade 3, 4: 84 vs. 81% 15 vs. 18% discontinued due to AEs ↑ QoL with carfilzomib (5.6 pt difference) Antiviral prophylaxis needed <hr/> <ul style="list-style-type: none"> SAEs 48 vs. 36% Anemia 14 vs. 10%; HTN 9 vs. 3%; thrombocytopenia 8 vs. 9%, pna 7 vs. 8% Note: carfilzomib dose higher than other studies (56 mg/m2 vs. 27 mg/m2) Antiviral prophylaxis needed
	Kd vs. Vd [ENDEAVOR 2016, N=929]		P3, R/R (1-3 prior)	Median f/u 12 mos (1 st interim) PFS 18.7 vs. 9.4 mos [HR 0.53; p<0.001]	
	Ixazomib/len/dex (IRd) vs. Rd [TOURMALINE-MM1 2016, N=722]	NF	P3, R/R (median 1 prior, NOT refractory to len or PI-based therapy) Median age: 66 yrs ECOG 2 (6%) ISS Stage III (12%) Previous SCT (57%) High risk (19%) Prior bortez 69% Prior len 12%	IRd (n=360) vs. Rd (n=362) Median f/u 15 mos (1 st interim) ORR 78 vs. 72%; p=0.04 PFS 21 vs. 15 mos [HR 0.74 (95% CI 0.59-0.94) p=0.01]; OS not mature	<ul style="list-style-type: none"> FDA: In combo with Rd in those who received ≥ 1 prior tx Gr 3, 4 thrombocytopenia 19 vs. 9% Diarrhea 45%, constipation 35%, nausea 29%, peripheral neuropathy 27%, peripheral edema 28%, rash 36% Antiviral prophylaxis needed

MONOCLONAL ANTIBODIES AND HISTONE DEACETYLASE INHIBITORS	Therapy vs. Comparator	Status (F, NF)	Population studied/ Patient characteristics	Outcomes	Toxicity/Notes
	Daratumumab alone (no comparator) [SIRIUS, 2016] MOA: Mab against CD38	NF	P2, R/R (5 prior) N=106 Median age 63.5 yrs ECOG 2 (8%) ISS Stage III (38%) Previous SCT (80%) Del(17p): 17% Refractory to len and bortez (82%)	Median f/u: 9.3 mos Median PFS 3.7 mos Median OS 17.5 mos ORR 29% (3 CR, 10 VGPR, 18 PR) Time to response 1 mo.	<ul style="list-style-type: none"> • FDA: MM who received at least 3 prior lines of tx, including PI and IMiD or who are double-refractory to PI and an IMiD • Fatigue 40%, anemia 33%, nausea 29%, thrombocytopenia 25%, neutropenia 23% • DC due to AEs: 5% • SAEs: 30% • IRR (1st) 37%, subsequent 6% • Premeds: steroid, APAP, antihistamine • Antiviral prophylaxis • Interferes with cross-matching and RBC Ab screening • May confuse IgG kappa myeloma responses
	Elotuzumab + Rd vs. Rd [ELOQUENT-2, 2015, N=646] MOA: Mab against SLAMF7	NF	P3, R/R (median 2 prior) Median age: 66 yrs ECOG 2 (9%) ISS Stage III (21%) Previous SCT (54%) Del(17p): 32% Prior bortez 70% Prior len 6%	ERd (n=321) vs. Rd (n=325) Median f/u: 24.5 mos At 24 mos. ORR 79 vs. 66% (p<0.001) PFS 19 vs. 15 mos [HR 0.70(95% CI 0.57-0.85)p<0.001] OS data not mature	<ul style="list-style-type: none"> • FDA: In combo with Rd who have received 1-3 prior tx • Similar benefit across all ages and risk groups • Gr 3, 4: 65 vs. 57% • Lymphocytopenia 77 vs. 49% • Second primary malignancy 9 vs. 6% • DC due to AEs: 13% • SAEs 65% • Treatment-related deaths 2% • Premeds: H1-blocker, H2-blocker, APAP for IRR • May confuse IgG kappa myeloma responses
	Panobinostat + Vd vs. Placebo + Vd [PANORAMA1, 2014, N=768] MOA: HDAC inhibitor	NF	P3, R/R (51% 1 prior) Median age: 63 yrs ECOG 2 (5%) ISS Stage III (22%) Previous SCT (58%) Prior bortez 38% Prior len 21%	Pan + Vd (n=387) vs. Placebo + Vd (n=381) Median f/u: 6.4 vs. 5.9 mos Median PFS 12 vs. 8 mos; ORR 60.7 vs. 54.6% (p=0.09) OS data not mature	<ul style="list-style-type: none"> • FDA: MM who received at least 2 prior lines of tx, including bortezomib and an IMiD • Boxed warning: risk serious, potentially fatal diarrhea, cardiac ischemic events, severe arrhythmias • SAEs: 60 vs. 24%, include BMS, diarrhea, fatigue, peripheral neuropathy • DC due to AEs: 9% • Treatment-related deaths: 4% • Avoid in recent MI, unstable angina, ↑ QT interval, etc. • Gr 3, 4: diarrhea 25%

ALKYLATING AGENT-BASED REGIMENS & MISC	Therapeutic Alternative	Other Considerations			
	Therapy	Status (F, NF)	Population studied	Outcomes	Toxicity/Notes
	VAD (vincristine/doxorubicin/dexamethasone) [Anderson, et al., 1995]	F	P2, R/R	ORR 60% (CR 3%)	<ul style="list-style-type: none"> Vincristine, doxorubicin given via CIVI over 4 days No longer used by myeloma centers
	MP (melphalan/prednisone) or Cyclophosphamide/prednisone	F			<ul style="list-style-type: none"> May provide response in relapse s/p autologous SCT
	Bortezomib/bendamustine/dex [Ludwig, et al., 2014]	NF	P2, R/R (1-6 prior)	ORR 60.8% Time to response 31 days PFS 9.7 mos; OS 25.6 mos	<ul style="list-style-type: none"> Gr 3, 4: thrombocytopenia 38%, infections 23%, anemia 15%, neuropathy 7%
	Bortezomib/vorinostat vs. bortezomib/placebo [VANTAGE 088, N=637]	NF	P3, Relapsed/non-refractory (1-3 prior) Excluded bortezomib-resistant	ORR 56 vs. 41% PFS 7.73 vs. 7.03 mos	<ul style="list-style-type: none"> Gr 3, 4: thrombocytopenia 45 vs. 24%, neutropenia 28 vs. 25%, anemia 17 vs. 13%

Key: F formulary, NF non-formulary, R/R relapsed/refractory, P1/2 phase 1/2, P2 phase 2, P3 phase 3, MM multiple myeloma, ORR overall response rate, CR complete response, OS overall survival, PFS progression-free survival, VGPR very good partial response, PR partial response, NS not significant, VTE venous thromboembolism, IV intravenous, SC subcutaneous, AEs adverse effects, SAE serious adverse effects, HTN hypertension, PI proteasome inhibitor, IMiD immunomodulatory drugs, MAb monoclonal antibody, APAP acetaminophen, RBC red blood cell, Ab antibody, IRR infusion-related reaction, BMS bone marrow suppression, HDAC histone deacetylase inhibitor, CIVI continuous intravenous infusion, SCT stem cell transplant

Appendix 3: Comparative Clinical Effectiveness & Comparative Value

Institute for Clinical and Economic Review (ICER) published Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness, Value and Value-Based Price Benchmarks on June 9, 2016. The group sought to assess comparative clinical effectiveness and comparative value of new myeloma regimens for second-line or later use in patients with relapsed and/or refractory disease.

Table 1. Key Trials

Key trials	Treatment	Comparator
TOURMALINE-MM1	Ixazomib + len-dex	Len-dex
ASPIRE	Carfilzomib + len-dex	Len-dex
SIRIUS	Daratumumab	None
ELOQUENT-2	Elotuzumab + len-dex	Len-dex
PANORAMA-1	Panobinostat + len-dex	Bortezomib-dex
NIMBUS	Pomalidomide + LoDex	HiDex

Minimum clinically meaningful improvements were defined as an additional 3-5 months of overall survival and progression-free survival. This is based upon ASCO recommendations in four cancer types (pancreatic, lung, breast and colon), as there are no recommendations specific to myeloma.

Table 2. ICER Evidence Ratings[#], by regimen and line of therapy

Regimen	Comparator	Second-line Evidence Rating	Third-line Evidence Rating
I + len-dex	Len-dex	B+	B+
CFZ + len-dex	Len-dex	B+	B+
Elo + len-dex	Len-dex	B+	B+
Pan + bor-dex	Bor-dex	I	P/I
Pom + LoDex	HiDex	I	P/I
Daratumumab	None	I	I

[#] Rating is based upon the magnitude of difference between a therapeutic agent and its comparator in “net health benefit” – the balance between clinical benefits and risks and/or AEs AND level of certainty that you have in your best point estimate of net health benefit. A= high certainty of superior net health benefit; B+ moderate certainty of incremental or better net health benefit; C+ moderate certainty of comparable or better net health benefit; D inferior net health benefit; P/I promising but inconclusive; I = insufficient

Table 3. Incremental results vs. len-dex in second-line setting

	I + len-dex	CFZ + len-dex	Elo + len-dex
ICER (vs. len-dex)	\$433,794	\$199,982	\$427,607
Total costs*	\$298,028	\$172,951	\$353,744
Total QALYs	0.69	0.86	0.83
Total life years (OS)	0.93	1.17	1.12

* Includes cost of drug, supportive care, administration, progression and adverse events.

Table 4. Incremental results vs. len-dex in third-line setting

	I + len-dex	CFZ + len-dex	Elo + len-dex	Pan + bor-dex
ICER (vs. len-dex)	\$484,582	\$238,560	\$481,244	-\$44,084
Total costs*	\$271,619	\$168,418	\$324,922	-\$62,588
Total QALYs	0.56	0.71	0.68	1.42
Total life years (OS)	0.89	1.12	1.07	2.02

* Includes cost of drug, supportive care, administration, progression and adverse events.

The authors conclude that their model results

- demonstrate that the new second- and third-line agents increase PFS, OS and quality of life
- at current WAC, estimates of long-term incremental cost effectiveness exceeds common thresholds
- discounts on drug costs of all components of a regimen will be necessary to meet reasonable cost-effectiveness thresholds