# Carfilzomib (Kyprolis®)

## National Drug Monograph

## August 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 Documents will be placed in the Archive section when the information is deemed to be no longer current.*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** | Carfilzomib is an epoxyketone proteasome inhibitor that binds irreversibly to the 20S proteasome |
| **Indication(s) Under Review** | • In combination with dexamethasone or lenalidomide + dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received 1-3 lines of therapy<br>• As a single agent for the treatment of patients with relapsed/refractory myeloma who have received one or more lines of treatment |
| **Dosage Form(s) Under Review** | Dosage Form(s), Strength(s)<br>Injectable: 60 mg lyophilized powder in single-dose vial for reconstitution |
| **REMS** | ☐ REMS ☒ No REMs |
| **Pregnancy Rating** | Can cause fetal harm |

## Executive Summary

**Efficacy**

- Carfilzomib was initially FDA-approved in 2012 as monotherapy in myeloma patients who received at least 2 prior regimens, including bortezomib and an immunomodulatory agent. This approval was based upon ORR in a heavily pre-treated population.
- The indication for carfilzomib was expanded in 2015 based upon results from the ASPIRE trial in the relapsed/refractory population in which carfilzomib-lenalidomide-dexamethasone were compared to lenalidomide-dexamethasone alone. PFS was 26.3 vs. 17.6 months, respectively.
- The support for the latest indication in 2016 is from the ENDEAVOR trial in which carfilzomib-dexamethasone was compared to bortezomib-dexamethasone. PFS was 18.7 vs. 9.4 months, respectively.

**Safety**

- Most common adverse reactions (≥ 20%) in the monotherapy trials are: anemia, fatigue, thrombocytopenia, nausea, pyrexia, dyspnea, diarrhea, headache, cough, peripheral edema
- Most common adverse reactions (≥20%) in the combination trials are: anemia, neutropenia, diarrhea, dyspnea, fatigue, thrombocytopenia, pyrexia, insomnia, muscle spasm, cough, upper respiratory tract infection, hypokalemia
- Peripheral neuropathy is much less common with carfilzomib, compared to bortezomib (Kd vs. Vd: ≥ Gr 2 PN 6 vs. 32%).
- Cardiac toxicity is a concern with carfilzomib, and requires ongoing monitoring throughout the duration of therapy.

**Other Considerations**

| **Outcome in clinically significant area** | PFS, ORR |
|---|---|
| **Effect Size** | KRd vs. Rd<br>PFS 26.3 vs. 17.6 mos<br>HR 0.69(95% CI 0.57-0.83); p=0.0001<br>Kd vs. Vd<br>PFS 18.7 vs. 9.4 mos<br>HR 0.53 (95% CI 8.4-10.4); p<0.0001<br>Carfilzomib monotherapy<br>ORR 23.7% |
| **Potential Harms (Gr 3 or 4)** | KRd: Neutropenia 27%, thrombocytopenia 15%, |

| | | |
|---|---|---|
| | | hypokalemia 6%, hypophosphatemia 31% , pneumonia 9%<br>Kd: anemia 12%, thrombocytopenia 10%, dyspnea 5%, HTN 6%<br>Carfilzomib monotherapy: pneumonia 8%, ARF 5%, pyrexia 3%, hypercalcemia 3%, CHF 3%, anemia 24%, dyspnea 2%, thrombocytopenia 25%, lymphopenia 12% |
| | **Net Clinical Benefit** | Moderate |
| Potential Impact | Projected place in therapy<br>• Carfilzomib, either as monotherapy or in combination with dexamethasone or lenalidomide/dexamethasone are therapeutic options in relapsed/refractory multiple myeloma<br>Patient convenience<br>• Carfilzomib is given via intravenous route on two consecutive days per week, depending on the cycle of therapy, so access to an infusion clinic is necessary.<br>• Components lenalidomide and dexamethasone are both oral, yet only taken on certain days of the treatment cycle, which may be confusing for some patients. | |

## Background

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|---|---|
| **Purpose for review** | FDA approval<br><br>**Issues to be determined:**<br>✔ Evidence of need<br>✔ Does carfilzomib offer advantages to currently available alternatives?<br>✔ Does carfilzomib offer advantages over current VANF agents?<br>✔ What safety issues need to be considered?<br>✔ Does carfilzomib have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use? |
| **Other therapeutic options** | Refer to **Appendix 2.**<br>**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 carfilzomib and Kyprolis®. 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.

**Review of Efficacy**
- Refer to **Appendix 1. Table 1. International Myeloma Working Group Uniform Response Criteria** for approval endpoints.
- Carfilzomib was initially FDA-approved in 2012 as monotherapy in myeloma patients who received at least 2 prior regimens, including bortezomib and an immunomodulatory agent. This approval was based upon ORR.
- In 2015, the indication for carfilzomib expanded to include use in combination with lenalidomide and dexamethasone in the relapsed myeloma setting after 1-3 prior regimens. This indication is based upon results from the ASPIRE trial in which carfilzomib-lenalidomide-dexamethasone were compared to lenalidomide-dexamethasone alone.
- In 2016, another indication is approved that includes carfilzomib in combination with dexamethasone in the relapsed or refractory setting in those who received 1-3 prior lines of therapy. The support for this latest indication is from the ENDEAVOR trial in which carfilzomib-dexamethasone was compared to bortezomib-dexamethasone.

**Table 1. Relapsed/Refractory Myeloma**

| | DESIGN | POPULATION | ARMS | OUTCOMES |
|---|---|---|---|---|
| Siegel, et al. | P2, open-label, single-arm, multicenter | N=257<br>Median age 63 yrs<br>Median 5 prior regimens<br>82% rec'd ≥ 4 prior lines<br>95% refractory to last line<br>73% refractory to bortezomib<br>74% ≥ 1 SCT<br>ISS Stage II or III 69%<br>High risk 28% (n=75)<br>Baseline PN Gr 1 or 2 – 77% | Carfilzomib 20mg/m2 IV<br>C#1, days 1, 2, 8, 9, 15, 16<br>Of a 28-day cycle<br>Carfilzomib 27 mg/m2 IV<br>C#2-12 | Primary endpoint ORR, which included sCR, CR, VGPR, PR<br>ORR 23.7%<br>ORR 29.6% (high risk pts)<br><br>Median DoR 7.8 months<br>Median OS 15.6 months<br>Median duration of treatment 3 months (range, 0.03-17)<br><br>Tx-related PN 12.4% overall |
| Stewart, et al. for ASPIRE | P3, R/R<br>Median 2 prior regimens<br>60% bortezomib<br>20% lenalidomide | N=792<br>Median age 64 yrs<br>ECOG 2 - 9.5%<br>ISS Stage III 20%<br>Prev SCT 57%<br>High risk 12.6% | KRd vs. Rd<br>Carfilzomib-len-dex vs. len-dex<br><br>Carfilzomib 20mg/m2 IV<br>C#1, days 1 and 2<br>Carfilzomib 27mg/m2 IV<br>C#1, days 8, 9 and 15, 16<br>Carfilzomib 27mg/m2 IV<br>C#2-12, days 1, 2, 8, 9, 15, 16<br>C#13-18, days 1, 2, 15, 16<br><br>Len 25mg PO daily, day 1-21<br>Dex 40, days 1, 8, 15, 22 | PFS 26.3 vs. 17.6 mos<br>HR 0.69(95% CI 0.57-0.83); p=0.0001<br><br>Median OS not reached<br>24-mo OS 73 vs. 65%<br>HR 0.79 (95% CI 0.63-0.99); p=0.04<br><br>CR or better 31.8 vs. 9.3% (p<0.001)<br><br>ORR 87 vs. 67% (p<0.001)<br><br>Mean time to response 1.6 vs. 2.3 months<br>Median DoR 28.6 vs. 21.2 months<br>Median duration of treatment 88 vs. 57 weeks<br><br>Tx-related PN 17.1 vs. 17% |
| Dimopoulous, et al for ENDEAVOR | P3, R/R<br>Median 2 prior regimens<br>54% bortezomib<br>38% lenalidomide | N=929<br>Median age 65 yrs<br>ECOG 2 – 7%<br>ISS Stage II-III 56%<br>High risk 21% | Kd vs. Vd<br>Carfilzomib-dex vs. bortezomib-dex<br><br>Carfilzomib 20mg/m2 IV<br>C#1, days 1 and 2<br>Carfilzomib 56mg/m2 IV<br>C#2+, days 1, 2, 8, 9, 15, 16<br><br>Bor 1.3mg/m2 IV or SC<br>Days 1, 4, 8, 11<br><br>Dex 20mg PO or IV<br>Days 1, 2, 4, 5, 8, 9, 11, 12<br><br>Disease status assessed every 4 weeks | PFS 18.7 vs. 9.4 mos<br>HR 0.53 (95% CI 8.4-10.4); p<0.0001<br><br>Median OS not reached<br><br>CR or better 13 vs. 6%<br><br>ORR 77 vs. 63%<br>OR 2.03[95% CI 1.52-2.72]; p<0.0001<br><br>Median time to response 1.1 vs. 1.1 months<br>Median DoR 21.3 vs. 10.4 months<br>Median duration of treatment 40 vs. 27 weeks<br><br>Tx-related PN 8 vs. 21% |

Other findings:

- In ASPIRE, Health-related Quality of Life (HR-QoL) improvement was noted in the KRd arm at cycle #12 (5.6 points). The minimal clinically important difference for between-group differences in the QLQ-C30 Global Health Status and Quality of Life scale is 5.0 points.
- The ASPIRE subgroup analysis of PFS indicates that the point estimate favors carfilzomib in all prespecified subgroups, including those with high cytogenetic risk disease, previous treatment with bortezomib and previous treatment with lenalidomide. The confidence intervals of each subgroup analyses cross the value of 1 in those: with high risk disease, peripheral neuropathy at baseline, prior treatment with lenalidomide, disease

nonresponsive to prior bortezomib and disease nonresponsive to bortezomib and refractory to immunomodulatory agents.

- Note regarding ENDEAVOR dosing : Higher carfilzomib dose studied was based upon results from a phase 1b/2 study that showed a higher response compared to the standard 27mg/m2 dose with a comparable safety profile.
- The ENDEAVOR subgroup analysis of PFS indicates that the point estimate favors carfilzomib in all prespecified subgroups pertaining to previous treatment, including previous stem cell transplant, previous bortezomib and immunomodulatory agents. The confidence intervals of each subgroup analyses cross the value of 1 in those: refractory to bortezomib and refractory to lenalidomide.
- Further prospective evaluation of the impact of cytogenetic abnormalities in the trial by Siegel, et al. indicates that overall response rates between those with high-risk vs. standard-risk cytogenetics were comparable (25.8 vs. 24.6%, respectively). The duration of response was shorter in high-risk patients (5.6 vs. 8.3 months, respectively), as was overall survival (9.3 vs. 19 months; p=0.0003).

## Potential Off-Label Use

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

- Use in mantle cell lymphoma, T-cell lymphoma, diffuse large B-cell lymphoma
- Relapsed Waldenstrom's Macroglobulinemia
- In combination with rituximab, ifosfamide, etoposide for relapsed/refractory diffuse large B-cell lymphoma
- In combination with ibrutinib in relapsed/refractory mantle cell lymphoma
- Antibody-mediated lung transplant rejection
- In combination with panobinostat for relapsed/refractory multiple myeloma
- Refractory renal cell carcinoma
- Amyloidosis
- Consolidation post autologous transplant for high risk patients
- Newly diagnosed multiple myeloma

**Table 2. Select Trials in Newly Diagnosed Multiple Myeloma**

| | DESIGN | ARMS | RESULTS |
|---|---|---|---|
| Jakubowiak AJ, et al. | P1/2, N=53 | Carfilzomib-len-dex (CRd)<br>C 20, 27 or 36 mg/m2, days 1, 2, 8, 9, 15, 16 and days 1, 2, 15, 16 after cycle #8<br>+ Len 25mg/day, days 1-21<br>+ Dex 40mg/wk, C#1-4, then 20mg/wk, C# 5-8 | After median 12 cycles,<br>Near-CR 62%; sCR 42%<br>If completed ≥ 8 cycles,<br>near-CR 78%; sCR 61%<br>24-mos PFS 92% |
| Korde N, et al. | P2, N=25 | Carfilzomib-len-dex (CRd)<br>C 20 mg/m2, days 1, 2 of C#1<br>C 36 mg/m2, days 1, 2, 8, 9, 15, 16<br>+Len 25mg/day, d1-21, then<br>Len 10mg/day, after C#8<br>+Dex 20mg, C#1-4, then Dex 10mg, C#5-8 | After median 10 months<br>CR or sCR 56%<br>nCR 62%<br>VGPR 89%<br>PFS 83.3%<br>Responses ↑ with # cycles |
| Bringhen S, et al. | P2, N=58<br>Age ≥ 65 yrs | Carfilzomib-cyclophosphamide-dex (CCyd) | After median 18 months<br>≥ PR 95%<br>≥ VGPR 71%<br>≥ nCR 49%<br>≥ CR 33%<br>sCR 20%<br>2-yr PFS 76%; 2-yr OS 87% |

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

| | Comments |
|---|---|
| **Boxed Warning** | • None |
| **Contraindications** | • None |
| **Warnings/Precautions (all Grades)** | • Cardiac toxicity. Patients with normal baseline ventricular function, as well as those with pre-existing cardiac conditions have experienced cardiac failure, restrictive cardiomyopathy, myocardial ischemia and infarction, including fatalities, throughout the course of carfilzomib therapy. A death due to cardiac arrest was reported within one day of administration. Rates of cardiac failure were higher in the carfilzomib-containing arms of studies evaluating KRd vs. Rd (6 vs. 4%) and Kd vs. Vd (8 vs. 3%).<br>• Acute renal failure. AEs involving renal insufficiency have occurred in ~ 10% of patients treated with carfilzomib. Acute renal failure occurred more often in those with advanced relapsed and refractory myeloma who received carfilzomib monotherapy. Risk was greater in those with reduced baseline estimated creatinine clearance.<br>• Tumor lysis syndrome (TLS). Cases of TLS, including fatalities, have been reported. Those with a high tumor burden should be considered at greatest risk.<br>• Pulmonary toxicity. Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in less than 1% of those receiving carfilzomib. Some cases have been fatal.<br>• Pulmonary hypertension. Pulmonary arterial hypertension (PAH) has been reported in ~ 1% of treated patients. Grade 3 or greater PAH has been noted in < 1%.<br>• Dyspnea. Dyspnea was reported in 28% of patients treated with carfilzomib (Grade 3 or greater in 4%). Evaluate to exclude cardiopulmonary conditions.<br>• Hypertension including hypertensive crisis and hypertensive emergency. Serious hypertensive episodes have been observed with carfilzomib and some cases have been fatal. |

| | **KRd** | **Rd** |
|---|---|---|
| HTN events (%) | 16 | 8 |
| | **Kd** | **Vd** |
| HTN events (%) | 26 | 10 |

| | | |
|---|---|---|
| • Venous thrombosis. VTE (including DVT and PE) has been observed with carfilzomib. The incidence of VTE was 2% with carfilzomib monotherapy. | | |

| | **KRd** | **Rd** |
|---|---|---|
| VTE (%) in first 12 cycles | 13 | 6 |
| | **Kd** | **Vd** |
| VTE events (%) in first 6 months | 9 | 2 |

| | |
|---|---|
| | • Infusion reactions. Reactions can occur immediately following or up to 24 hours after administration of carfilzomib. Symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness or angina. Some reactions have been life-threatening.<br>• Thrombocytopenia. Platelet nadirs are typically observed between Day 8 and 15 of each 28-day cycle with recovery usually by the start of the next cycle. Thrombocytopenia was reported in ~ 40% of patients in clinical trials.<br>• Hepatic toxicity and failure. Cases of hepatic failure have been reported (<1%) during treatment. Serum transaminases can also be increased by carfilzomib therapy.<br>• Thrombotic microangiopathy. Cases of thrombotic microangiopathy, |

| | |
|---|---|
| | including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) have been reported; some events have been fatal.<br>• Posterior reversible encephalopathy syndrome (PRES). PRES has been reported. Patients may present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual/neurologic disturbances, alone with HTN. Diagnosis is confirmed by neuroradiological imagining. Discontinue carfilzomib if PRES is suspected and evaluate.<br>• Embryo-fetal toxicity. Based upon its mechanism of action and findings in animals, it is suspected that carfilzomib can cause fetal harm when administered to a pregnant woman. |

**Safety Considerations**[1, 2]

- Monitor for signs and symptoms of cardiac failure or ischemia and evaluate promptly if toxicity is suspected. Withhold carfilzomib for Grade 3,4 cardiac AEs until recovery, then consider whether to restart at 1 dose level reduction based upon risk/benefit assessment
- Monitor for evidence of volume overload, especially in those at risk for cardiac failure.
- Risk of cardiac failure increases in those ≥ age 75 years, compared to younger patients; those with NYHA Class III and IV heart failure, recent MI, conduction abnormalities, angina or arrhythmias uncontrolled by medications were not eligible for clinical trials and may be at greater risk for cardiac complications.
- Incidence of peripheral neuropathy in the monotherapy trial (Siegel, et al.) was 12.4% overall. The ASPIRE investigators report the incidence of peripheral neuropathy 17.1% vs 17% (KRd vs. Rd, respectively), while the ENDEAVOR investigators report PN in 8 vs. 21% (Kd vs. Vd, respectively). These PN rates with carfilzomib are much lower than those reported with studies evaluating subcutaneous bortezomib, where PN incidence is 38%.
- Monitor renal function with regular measurement of SCr and/or estimated CrCl. Reduce or withhold dose as appropriate.
- Ensure patients at risk of TLS are well-hydrated before Cycle #1 and subsequent cycles as needed. Consider uric acid-lowering drugs in those at risk. Monitor for evidence of TLS during treatment and manage promptly, including interruption of carfilzomib until resolved.
- Discontinue carfilzomib if suspect pulmonary toxicity has occurred.
- If suspect PAH, evaluate with cardiac imaging and/or other tests, as indicated. Withhold carfilzomib for pulmonary HTN until resolved or returned to baseline. Consider risk/benefit assessment before restarting carfilzomib.
- Stop carfilzomib for Grade 3 or 4 dyspnea until resolved or returned to baseline. Consider risk/benefit assessment before restarting carfilzomib.
- Monitor blood pressure regularly in all patients. If HTN cannot be adequately controlled, withhold carfilzomib and evaluate. Consider risk/benefit assessment before restarting carfilzomib.
- Thromboprophylaxis is recommended for patients being treated with the combination of carfilzomib + dexamethasone or with lenalidomide + dexamethasone. The regimen should be based upon an assessment of the patient's underlying risks.
- Patients using oral contraceptives or hormonal contraceptive methods associated with an increased risk of thrombosis should consider an alternative method of effective contraception while receiving treatment with carfilzomib in combination with dexamethasone or lenalidomide + dexamethasone
- To reduce the incidence and severity of infusion reactions, administer dexamethasone as a premedication. Inform patients of the risk and of symptoms they might experience, and instruct them to contact a physician immediately should an infusion-reaction symptom occur.
- Monitor platelet counts frequently during treatment. Reduce or withhold carfilzomib dose, as appropriate.
- Monitor liver enzymes regularly, regardless of baseline values. Reduce or withhold dose, as appropriate.
- Monitor for signs/symptoms of TTP/HUS. If suspected, stop carfilzomib and evaluate. Carfilzomib may be restarted if TTP/HUS is excluded.

**Adverse Reactions**[1, 2]

| | |
|---|---|
| Common adverse reactions | • Most common adverse reactions (≥ 20%) in the monotherapy trials are: anemia, fatigue, thrombocytopenia, nausea, pyrexia, dyspnea, diarrhea, headache, cough, peripheral edema<br>• Most common adverse reactions (≥20%) in the combination trials are: anemia, neutropenia, diarrhea, dyspnea, fatigue, thrombocytopenia, pyrexia, insomnia, muscle spasm, cough, upper respiratory tract infection, hypokalemia<br>• Kd vs. Vd: ≥ Gr 2 PN 6 vs. 32% |
| Death/Serious adverse reactions | • KRd: Neutropenia, thrombocytopenia, hypokalemia, hypophosphatemia, pneumonia<br>• Kd: anemia, thrombocytopenia, dyspnea, HTN<br>• Carfilzomib monotherapy: pneumonia, ARF, pyrexia, hypercalcemia, CHF, anemia, dyspnea |
| Discontinuations due to adverse reactions | • KRd vs. Rd: 15 vs. 18%<br>• Kd vs. Vd: 20 vs. 21% |

**Drug Interactions**

**Drug-Drug Interactions**

- Carfilzomib is metabolized by peptidase and epoxide hydrolase activities, therefore it is unlikely to be affected by concomitant CYP P450 inhibitors and inducers.

## Risk Evaluation

As of July 22, 2016

| | **Comments** |
|---|---|
| Sentinel event advisories | • None<br>• Sources: ISMP, FDA, TJC |
| Look-alike/sound-alike error potentials | See nested table below |

| NME Drug Name | Lexi-Comp | First DataBank | ISMP | Clinical Judgment |
|---|---|---|---|---|
| !Carfilzomib 60mg inj | Bortezomib<br>Ixazomib | None | None | Carmustine<br>Certolizumab<br>Ceritinib<br>Cobimetinib |
| Kyprolis | None | None | None | Kynamro |

- !**High alert medication:** The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error
- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

## Other Considerations

- NCCN Multiple Myeloma Guidelines Version 3.2016 lists carfilzomib/lenalidomide/dexamethasone as a category 2A recommendation as primary therapy for transplant candidates.
- NCCN Multiple Myeloma Guidelines Version 3.2016 lists carfilzomib/lenalidomide/dexamethasone as a category 1 recommendation as a preferred regimen for previously treated multiple myeloma. It also lists carfilzomib monotherapy and the combination of carfilzomib/dexamethasone, both as category 2A recommendations.
- NICE appraisal of carfilzomib/lenalidomide/dexamethasone is in progress with a scheduled publication date of April 2017.
- 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 carfilzomib/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 $200,000 per QALY in the second-line setting and $240,000 per QALY in the third-line setting for carfilzomib/len/dex.

| **Outcome in clinically significant area** | PFS, ORR |
|---|---|
| **Effect Size** | KRd vs. Rd<br>PFS 26.3 vs. 17.6 mos<br>HR 0.69(95% CI 0.57-0.83); p=0.0001<br>Kd vs. Vd<br>PFS 18.7 vs. 9.4 mos<br>HR 0.53 (95% CI 8.4-10.4); p<0.0001<br>Carfilzomib monotherapy<br>ORR 23.7% |
| **Potential Harms (Gr 3 or 4)** | KRd: Neutropenia 27%, thrombocytopenia 15%, hypokalemia 6%, hypophosphatemia 31% , pneumonia 9%<br>Kd: anemia 12%, thrombocytopenia 10%, dyspnea 5%, HTN 6%<br>Carfilzomib monotherapy: pneumonia 8%, ARF 5%, pyrexia 3%, hypercalcemia 3%, CHF 3%, anemia 24%, dyspnea 2%, thrombocytopenia 25%, lymphopenia 12% |
| **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

### Administration Precautions

**Hydration.** Adequate hydration is required prior to cycle #1, especially in those at risk of tumor lysis syndrome or renal toxicity. Recommended hydration includes:

- Oral fluids (30ml/kg at least 48 hours before Cycle #1, Day #1)
- Intravenous fluids (250-500 ml prior to each dose in Cycle #1)
- If needed, give additional 250-500 ml following carfilzomib administration
- Continue oral and/or IV hydration, as needed, in subsequent cycles
- Monitor patients for evidence of volume overload and adjust hydration to individual needs, especially in those at risk for cardiac failure

**Electrolyte Monitoring.** Monitor serum potassium levels regularly during treatment with carfilzomib
**Premedication**. Administer dexamethasone orally or intravenously at least 30 minutes (but no more than 4 hours) prior to all doses during Cycle #1 to reduce incidence and severity of infusion reactions
Reinstate dexamethasone premedication if these symptoms occur during subsequent cycles.
**Administration.** Infuse over 10-30 minutes depending on the carfilzomib dose regimen. Do not administer as a bolus. Flush the IV administration line with NSS or D5W, USP immediately before and after carfilzomib administration. Do not mix carfizomib with or administer as an infusion with other medicinal products.
**Dose Calculation.** Calculate the carfilzomib dose using the patient's actual body surface area at baseline. In those with a BSA greater than 2.2 m2, calculate the dose based upon a BSA of 2.2 m2.
**Thromboprophylaxis.** Thromboprophylaxis is recommended for patients being treated with carfilzomib with dexamethasone or with lenalidomide plus dexamethasone. The chosen regimen should be based on an assessment of the patient's underlying risks.
**Infection Prophylaxis**. Consider antiviral prophylaxis for patients being treated with carfilzomb to decrease the risk of herpes zoster reactivation.

### Recommended Dosing

The following three regimens are administered until disease progression or unacceptable toxicity occurs. Refer to the lenalidomide and dexamethasone prescribing information for concomitant medications that may be required (i.e. anticoagulants, antacids).

- Carfilzomib + lenalidomide + dexamethasone (Table 3)
- Carfilzomib + dexamethasone (Table 4)
- Carfilzomib monotherapy (Tables 5, 6)

**Table 3. Carfilzomib (10-minute infusion) with lenalidomide and dexamethasone**

| | Cycle 1 | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 | |
| | Day 1 | Day 2 | Days 3-7 | Day 8 | Day 9 | Days 10-14 | Day 15 | Day 16 | Days 17-21 | Day 22 | Days 23-28 |
| Carfilzomib (mg/m2) | 20 | 20 | - | 27 | 27 | - | 27 | 27 | - | - | - |
| Dex | 40 | - | - | 40 | - | - | 40 | - | - | 40 | - |
| Len | 25 mg PO daily on Days 1-21 | | | | | | | | | - | - |

| | Cycles 2-12 | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 | |
| | Day 1 | Day 2 | Days 3-7 | Day 8 | Day 9 | Days 10-14 | Day 15 | Day 16 | Days 17-21 | Day 22 | Days 23-28 |
| Carfilzomib (mg/m2) | 27 | 27 | - | 27 | 27 | - | 27 | 27 | - | - | - |
| Dex | 40 | - | - | 40 | - | - | 40 | - | - | 40 | - |
| Len | 25 mg PO daily on Days 1-21 | | | | | | | | | - | - |

| | Cycles 13-18 (Lenalidomide/Dexamethasone continue thereafter) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 | |
| | Day 1 | Day 2 | Days 3-7 | Day 8 | Day 9 | Days 10-14 | Day 15 | Day 16 | Days 17-21 | Day 22 | Days 23-28 |
| Carfilzomib (mg/m2) | 27 | 27 | - | - | - | - | 27 | 27 | - | - | - |
| Dex | 40 | - | - | 40 | - | - | 40 | - | - | 40 | - |
| Len | 25 mg PO daily on Days 1-21 | | | | | | | | | - | - |

**Table 4. Carfilzomib (30-minute infusion) with Dexamethasone**

| | Cycle 1 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 | | |
| | Day 1 | Day 2 | Days 3-7 | Day 8 | Day 9 | Days 10-14 | Day 15 | Day 16 | Days 17-21 | Day 22 | Day 23 | Days 24-28 |
| Carfilzomib (mg/m2) | 20 | 20 | - | 56 | 56 | - | 56 | 56 | - | - | - | - |
| Dex | 20 | 20 | - | 20 | 20 | - | 20 | 20 | - | 20 | 20 | - |

| | Cycles 2 and later | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 | | |
| | Day 1 | Day 2 | Days 3-7 | Day 8 | Day 9 | Days 10-14 | Day 15 | Day 16 | Days 17-21 | Day 22 | Day 23 | Days 24-28 |
| Carfilzomib (mg/m2) | 56 | 56 | - | 56 | 56 | - | 56 | 56 | - | - | - | - |
| Dex | 20 | 20 | - | 20 | 20 | - | 20 | 20 | - | 20 | 20 | - |

**Table 5. Carfilzomib (10-minute infusion) Monotherapy**

| | Cycle 1 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 |
| | Day 1 | Day 2 | Days 3-7 | Day 8 | Day 9 | Days 10-14 | Day 15 | Day 16 | Days 17-21 | Days 22-28 |
| Carfilzomib (mg/m2) | 20 | 20 | - | 27 | 27 | - | 27 | 27 | - | - |
| Dex | 4 | 4 | - | 4 | 4 | - | 4 | 4 | - | - |

| | Cycles 2-12 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 |
| | Day 1 | Day 2 | Days 3-7 | Day 8 | Day 9 | Days 10-14 | Day 15 | Day 16 | Days 17-21 | Days 22-28 |
| Carfilzomib (mg/m2) | 27 | 27 | - | 27 | 27 | - | 27 | 27 | - | - |
| Dex | prn | prn | - | prn | prn | - | prn | prn | - | - |

| | Cycles 13 and later | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 |
| | Day 1 | Day 2 | Days 3-7 | Day 8 | Day 9 | Days 10-14 | Day 15 | Day 16 | Days 17-21 | Days 22-28 |
| Carfilzomib (mg/m2) | 27 | 27 | - | - | - | - | 27 | 27 | - | - |
| Dex | prn | prn | - | - | - | - | prn | prn | - | - |

**Table 6. Carfilzomib (30-minute infusion) Monotherapy**

| | Cycle 1 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 |
| | Day 1 | Day 2 | Days 3-7 | Day 8 | Day 9 | Days 10-14 | Day 15 | Day 16 | Days 17-21 | Days 22-28 |
| Carfilzomib (mg/m2) | 20 | 20 | - | 56 | 56 | - | 56 | 56 | - | - |
| Dex | 8 | 8 | - | 8 | 8 | - | 8 | 8 | - | - |

| | Cycles 2-12 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 |
| | Day 1 | Day 2 | Days 3-7 | Day 8 | Day 9 | Days 10-14 | Day 15 | Day 16 | Days 17-21 | Days 22-28 |
| Carfilzomib (mg/m2) | 56 | 56 | - | 56 | 56 | - | 56 | 56 | - | - |
| Dex | prn | prn | - | prn | prn | - | prn | prn | - | - |

| | Cycles 13 and later | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 |
| | Day 1 | Day 2 | Days 3-7 | Day 8 | Day 9 | Days 10-14 | Day 15 | Day 16 | Days 17-21 | Days 22-28 |
| Carfilzomib (mg/m2) | 56 | 56 | - | - | - | - | 56 | 56 | - | - |
| Dex | prn | prn | - | - | - | - | prn | prn | - | - |

**Refer to Prescribing Information for the following sections:**

- **Dose Modifications Based on Toxicities**
- **Reconstitution and Preparation for Intravenous Administration**

## Special Populations (Adults)

| | **Comments** |
|---|---|
| **Elderly** | Despite differences in SAE's, no overall differences in effectiveness were observed between older and younger patients. |

| | Age < 65 yrs | 65-74 yrs | ≥ 75 yrs |
|---|---|---|---|
| C monotherapy SAE (%) | 44 | 55 | 56 |
| KRd SAE (%) | 50 | 70 | 74 |
| Kd SAE (%) | 44 | 50 | 57 |

| | |
|---|---|
| **Pregnancy** | Advise females of reproductive potential to avoid becoming pregnant while being treated with carfilzomib. Males should be advised to avoid fathering a child while being treated with carfilzomib. In the event of pregnancy, the patient should be alerted to the potential hazard to the fetus. |
| **Contraception** | Females should be advised to use effective contraceptive measures or abstain from sexual activity during treatment and for at least 30 days following completion of therapy.<br><br>Males should be advised to use effective contraceptive measures or abstain from sexual activity during treatment and for at least 90 days following completion of therapy. |
| **Lactation** | There is no information regarding the effects of carfilzomib on the breastfed infant or milk production. Consider developmental and health benefits of breastfeeding, along with the mother's clinical need for carfilzomib and any potential adverse effects on the infant. |

| | |
|---|---|
| **Renal Impairment** | No starting dose adjustment is needed in patients with baseline mild, moderate or severe renal impairment or patients on chronic dialysis. In a phase 2 study, the pharmacokinetics of carfilzomib was not influenced by baseline renal impairment. Since dialysis clearance has not been studied, drug should be administered after dialysis procedures. |
| **Overdose** | There is no known antidote for carfilzomib overdosage. Monitor patients for side effects and/or adverse reactions. One report of a patient who received a 200mg dose noted effects such as acute onset of chills, hypotension, renal insufficiency, thrombocytopenia and lymphopenia. |
| **Pharmacogenetics/genomics** | No known data |

## Projected Place in Therapy

- Carfilzomib, in combination with dexamethasone or in combination with lenalidomide/dexamethasone, improved PFS in the relapsed/refractory myeloma population.
- The benefit of improvement in ORR in high-risk patients was noted in the carfilzomib monotherapy trial, although this did not equate to improvement in OS.
- The reduction in peripheral neuropathy noted with carfilzomib can be of significant benefit, especially in those with pre-existing neuropathy. Note that comparisons to bortezomib should take into consideration the route in which bortezomib is given (less PN with SC, than IV) and regimen (less PN with weekly vs. twice weekly dosing).
- Pharmacokinetic data reveals that there are no differences in carfilzomib clearance or exposure among patients with impaired renal function compared to those with normal renal function.
- Evidence in the frontline setting is accumulating. Further studies are needed to clarify the optimal dosing regimen for safety and efficacy.

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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:<br>• Normal free light chain ratio, and<br>• Absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry |
| Complete Response (CR) | • Negative immunofixation of serum and urine, and<br>• Disappearance of any soft tissue plasmacytomas, and<br>• < 5% plasma cells in bone marrow<br>Additional criterion in patients with measurable disease by serum free light chain levels only:<br>• Normal free light chain ratio of 0.26 to 1.65 |
| Very good partial response (VGPR) | • Serum and urine M-component detectable by immunofixation but not on electrophoresis, or<br>• ≥ 90% reduction in serum M-component plus urine M-component < 100 mg/24 h<br>Additional criterion in patients with measurable disease by serum free light chain levels only:<br>• > 90% decrease in difference between involved and uninvolved free light chain levels |
| Partial Response (PR) | • ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 h<br>If serum and urine M-protein are not measurable:<br>• Decrease of ≥ 50% in difference between involved and uninvolved free light chain levels<br>If serum and urine M-protein and serum free light assay are not measurable:<br>• ≥ 50% reduction in bone marrow plasma cells, provided baseline percentage was ≥ 30%<br>In addition to the above criteria, if present at baseline:<br>• ≥ 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:<br>• Increase of 25% from lowest response value in any of:<br>  ○ Serum M-component (absolute increase ≥ 0.5 g/dL), and/or<br>  ○ Urine M-component (absolute increase ≥ 200 mg/24 h), and/or<br>  ○ 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<br>  ○ Bone marrow plasma cell percentage (absolute percentage ≥ 10%) (only in patients without measurable serum and urine M-protein levels and without measurable disease by free light chain levels)<br>• Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas<br>• 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)<br>Rd vs. dex<br>(MM-009, MM-010) | F | P3, R/R | ORR 60 vs. 20-30%<br>CR 15 vs. 1-3%<br>OS 30 vs. 20 months | Gr 3,4 neutropenia30-40 vs. 2-4%;<br>VTE 11 vs. 4%<br>Caution with use in renal impairment |
| | Pomalidomide/dex (Pd vs. P HIdex)<br>[NIMBUS]<br><br>Pom/dex vs. Pom/Cy/dex<br>[Baz 2016] | NF | P3, RR (median 5 prior, 100% prior len & bor, 75% ref to len & bor)<br><br>Median age 65 yrs<br>ECOG 2-3 (18%)<br>ISS Stage III (32%)<br>Previous SCT (70%)<br><br>P2, R/R (>2 prior, len-refractory) | Pd (n=302) vs. P HIdex (n=153)<br><br>Median f/u 10 mos<br>Median PFS 4 vs. 1.9 mos<br>PFS HR 0.48 (95% CI 0.39-0.60); p<0.0001<br>OS HR 0.74 (95% CI 0.56-0.97); p=0.285<br>ORR 31 vs. 10%; p<0.0001<br><br>ORR 39 vs. 65%<br>PFS 4.4 vs. 9.5 mos (NS) | DC due to AEs: 9%<br>SAEs 61%<br>Tx-related deaths: 4% |

| | Therapeutic Alternative | Other Considerations | | | |
|---|---|---|---|---|---|
| | Therapy | Status (F, NF) | Population studied | Outcomes | Toxicity/Notes |
| PROTEOSOME INHIBITORS (PI) | Bortezomib monotherapy or<br>Bortezomib combo with lenalidomide, dex<br>[Richardson, et. al., 2014] | F | P2, R/R | ORR ~ 30% monotherapy<br>ORR ~ 65% combination | • FDA: treatment of MM<br>• Given IV or SC; SC preferred d/t ↓ risk neuropathy<br>• Thrombocytopenia 43%<br>• Peripheral neuropathy 40% with twice weekly dosing<br>• ~20% with once weekly dosing<br>• Prior neurotoxic tx, pre-existing neuropathy may worsen<br>• Safe in renal impairment [APEX trial]<br>• Antiviral prophylaxis needed |
| | Rd + Carfilzomib vs. Rd<br>[ASPIRE 2015, n=792]<br><br>Kd vs. Vd<br>[ENDEAVOR 2016, N=929] | NF | P3, R/R (median 2 prior regimens: 60% prior bortezomib; 20% prior len)<br><br>Median age 64 yrs<br>ECOG 2 (9.5%)<br>ISS Stage III (20%)<br>Previous SCT (57%)<br>High risk (12.6%)<br><br>P3, R/R (1-3 prior) | PFS 26.3 vs. 17.6 mos (p=0.0001)<br>24-mo OS 73 vs. 65% (NS)<br>ORR 87 vs. 67% (p<0.001)<br><br>Median f/u 12 mos (1st interim)<br>PFS 18.7 vs. 9.4 mos [HR 0.53; p<0.001] | • 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<br>• Grade 3, 4: 84 vs. 81%<br>• 15 vs. 18% discontinued due to AEs<br>• ↑ QoL with carfilzomib (5.6 pt difference)<br>• Antiviral prophylaxis needed<br><br>• SAEs 48 vs. 36%<br>• Anemia 14 vs. 10%; HTN 9 vs. 3%; thrombocytopenia 8 vs. 9%, pna 7 vs. 8%<br>• Note: carfilzomib dose higher than other studies (56 mg/m2 vs. 27 mg/m2)<br>• Antiviral prophylaxis needed |
| | Ixazomib/len/dex (IRd) vs. Rd<br>[TOURMALINE-MM1 2016, N=722] | NF | P3, R/R (median 1 prior, NOT refractory to len or PI-based therapy)<br>Median age: 66 yrs<br>ECOG 2 (6%)<br>ISS Stage III (12%)<br>Previous SCT (57%)<br>High risk (19%)<br>Prior bortez 69%<br>Prior len 12% | IRd (n=360) vs. Rd (n=362)<br>Median f/u 15 mos (1st interim)<br>ORR 78 vs. 72%; p=0.04<br>PFS 21 vs. 15 mos<br>[HR 0.74 (95% CI 0.59-0.94) p=0.01]; OS not mature | • FDA: In combo with Rd in those who received ≥ 1 prior tx<br>• Gr 3, 4 thrombocytopenia 19 vs. 9%<br>• Diarrhea 45%, constipation 35%, nausea 29%, peripheral neuropathy 27%, peripheral edema 28%, rash 36%<br>• Antiviral prophylaxis needed |
| M O N | Therapeutic Alternative | Other Considerations | | | |

| | Therapy vs. Comparator | Status (F, NF) | Population studied/ Patient characteristics | Outcomes | Toxicity/Notes |
|---|---|---|---|---|---|
| | Daratumumab alone (no comparator) [SIRIUS, 2016]<br><br>MOA: Mab against CD38 | NF | P2, R/R (5 prior)<br><br>N=106<br>Median age 63.5 yrs<br>ECOG 2 (8%)<br>ISS Stage III (38%)<br>Previous SCT (80%)<br>Del(17p): 17%<br>Refractory to len and bortez (82%) | Median f/u: 9.3 mos<br>Median PFS 3.7 mos<br>Median OS 17.5 mos<br>ORR 29%<br>(3 CR, 10 VGPR, 18 PR)<br>Time to response 1 mo. | • 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<br>• Fatigue 40%, anemia 33%, nausea 29%, thrombocytopenia 25%, neutropenia 23%<br>• DC due to AEs: 5%<br>• SAEs: 30%<br>• IRR (1st) 37%, subsequent 6%<br>• Premeds: steroid, APAP, antihistamine<br>• Antiviral prophylaxis<br>• Interferes with cross-matching and RBC Ab screening<br>• May confuse IgG kappa myeloma responses |
| | Elotuzumab + Rd vs. Rd<br>[ELOQUENT-2, 2015, N=646]<br><br>MOA: Mab against SLAMF7 | NF | P3, R/R (median 2 prior)<br><br>Median age: 66 yrs<br>ECOG 2 (9%)<br>ISS Stage III (21%)<br>Previous SCT (54%)<br>Del(17p): 32%<br>Prior bortez 70%<br>Prior len 6% | ERd (n=321) vs. Rd (n=325)<br>Median f/u: 24.5 mos<br>At 24 mos. ORR 79 vs. 66% (p<0.001)<br>PFS 19 vs. 15 mos<br>[HR 0.70(95% CI 0.57-0.85)p<0.001]<br>OS data not mature | • FDA: In combo with Rd who have received 1-3 prior tx<br>• Similar benefit across all ages and risk groups<br>• Gr 3, 4: 65 vs. 57%<br>• Lymphocytopenia 77 vs. 49%<br>• Second primary malig 9 vs. 6%<br>• DC due to AEs: 13%<br>• SAEs 65%<br>• Treatment-related deaths 2%<br>• Premeds: H1-blocker, H2-blocker, APAP for IRR<br>• May confuse IgG kappa myeloma responses |
| | Panobinostat + Vd vs.<br>Placebo + Vd<br>[PANORAMA1, 2014, N=768]<br><br>MOA: HDAC inhibitor | NF | P3, R/R (51% 1 prior)<br><br>Median age: 63 yrs<br>ECOG 2 (5%)<br>ISS Stage III (22%)<br>Previous SCT (58%)<br>Prior bortez 38%<br>Prior len 21% | Pan + Vd (n=387) vs. Placebo + Vd (n=381)<br>Median f/u: 6.4 vs. 5.9 mos<br>Median PFS 12 vs. 8 mos;<br>ORR 60.7 vs. 54.6% (p=0.09)<br>OS data not mature | • FDA: MM who received at least 2 prior lines of tx, including bortezomib and an IMiD<br>• Boxed warning: risk serious, potentially fatal diarrhea, cardiac ischemic events, severe arrhythmias<br>• SAEs: 60 vs. 24%, include BMS, diarrhea, fatigue, peripheral neuropathy<br>• DC due to AEs: 9%<br>• Treatment-related deaths: 4%<br>• Avoid in recent MI, unstable angina, ↑ QT interval, etc.<br>• Gr 3, 4: diarrhea 25% |

| | Therapeutic Alternative | Other Considerations | | | |
|---|---|---|---|---|---|
| | Therapy | Status (F, NF) | Population studied | Outcomes | Toxicity/Notes |
| ALKYLATING AGENT-BASED REGIMENS & MISC | VAD (vincristine/doxorubicin/dexamethasone) [Anderson, et al., 1995] | F | P2, R/R | ORR 60% (CR 3%) | • Vincristine, doxorubicin given via CIVI over 4 days<br>• No longer used by myeloma centers |
| | MP (melphalan/prednisone) or Cyclophosphamide/prednisone | F | | | • 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%<br>Time to response 31 days<br>PFS 9.7 mos; OS 25.6 mos | • 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%<br>PFS 7.73 vs. 7.03 mos | • 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