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1 **Role of Proteasome Inhibitors in Relapsed and/or Refractory Multiple Myeloma**

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13 **Competing Interests**

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16 honoraria and membership and membership on an entity's Board of Directors or advisory committees
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24 **ABSTRACT**

25 Proteasome inhibition is an established treatment strategy for patients with multiple myeloma as
26 proteasome inhibitors selectively target and disrupt the protein metabolism of aberrant plasma cells.
27 Since the introduction of the first-in-class proteasome inhibitor bortezomib, the therapeutic landscape
28 for multiple myeloma has shifted with the development of next-generation proteasome inhibitors
29 (carfilzomib and ixazomib) and new classes of agents. Treatment with modern combination therapies
30 has been shown to result in deep responses and improved outcomes, and these potent regimens are
31 increasingly used as frontline therapy. As patients continue to live longer with modern frontline therapy,
32 there will be an increased need for effective regimens after initial treatment failure. Several recent
33 studies have shown that treatment with combination therapy incorporating proteasome inhibitors
34 induces deep and durable responses in patients with relapsed and/or refractory multiple myeloma. In
35 this review, we review pivotal data and discuss the role of proteasome inhibitor-based doublet and
36 triplet regimens for the management of relapsed/refractory multiple myeloma in the era of modern
37 combination therapy.

38

39 Keywords: carfilzomib, bortezomib, ixazomib, efficacy, safety

40 **INTRODUCTION**

41 Multiple myeloma is a plasma cell dyscrasia characterized by uncontrolled proliferation and bone
42 marrow infiltration of aberrant plasma cells and the presence of abnormal monoclonal protein secreted
43 by these cells in the serum and/or urine.¹ It is the second most common hematologic malignancy in the
44 United States (30 280 estimated new cases in 2017)^{1,2} and constitutes 0.8% of all new cancer cases
45 worldwide.³

46 Multiple myeloma is an aggressive and incurable disease for most patients, characterized by periods of
47 remission and relapse. Patients with relapsed multiple myeloma have been defined by Dimopoulos et al
48 as those with active disease who have received at least one prior therapy and are not refractory to the
49 last therapy; patients with relapsed/refractory multiple myeloma are defined as those with disease
50 relapse who have previously achieved at least a minimal response or those with disease progression on
51 salvage therapy or within 60 days of discontinuation of last therapy.⁴ With each relapse, patients face
52 increasingly worse outcomes and each subsequent line of therapy tends to result in a shorter duration
53 of response than previous lines. Each line of therapy is associated with an increased risk of treatment-
54 and disease-related complications.⁵ The poor prognosis also reflects the genomic complexity of relapsed
55 multiple myeloma, with tumors acquiring multiple genetic and epigenetic alterations that promote
56 treatment resistance and refractory disease.^{1,4} The introduction of new classes of drugs, such as
57 proteasome inhibitors, has improved survival outcomes in these difficult-to-treat populations.⁶⁻⁸

58 The ubiquitin-proteasome pathway regulates cellular homeostasis through protein catabolism
59 (proteolysis).⁹⁻¹² Inhibition of proteasome function disrupts several important cellular pathways and
60 affects malignant plasma cells to a greater extent than normal cells. Proteasome inhibition as a
61 treatment strategy for multiple myeloma was clinically validated with the accelerated approval of the
62 first-in-class proteasome inhibitor bortezomib in 2003 for relapsed/refractory multiple myeloma. Since

63 this approval, 2 next-generation proteasome inhibitors, carfilzomib and ixazomib, have also been
64 approved for patients with relapsed/refractory multiple myeloma.¹³

65 With the availability of several distinct proteasome inhibitors and other new drug classes (eg, histone
66 deacetylase inhibitors, monoclonal antibodies) with established efficacy, the potential options for
67 multidrug regimens based on proteasome inhibitors have increased. In addition, the treatment
68 paradigm for multiple myeloma has shifted to a more aggressive approach emphasizing the early use of
69 potent combination therapies to achieve deep responses and prolonged survival.¹⁴ More than half of
70 patients who are treated with modern multidrug regimens along with transplantation and maintenance
71 achieve a complete response,¹⁵ which has been associated with improved survival outcomes.¹⁶ Based on
72 these observations, frontline therapy with 3-drug regimens is currently considered a standard of care.¹⁷

73 Importantly, recent data from the SWOG S0777 study showed that treatment with the 3-drug
74 combination of bortezomib, lenalidomide, and dexamethasone significantly improved progression-free
75 survival (PFS) and overall survival (OS) compared with lenalidomide and dexamethasone alone in
76 patients with newly diagnosed multiple myeloma.¹⁸ Thus, as frontline triplet therapy becomes more
77 established and patients continue to live longer, there will be greater need for potent regimens after
78 initial treatment failure. In a study of Medicare patients with multiple myeloma diagnosed between
79 2008 and 2011, it was found that among patients who received frontline doublets, 58% continued
80 doublets as second-line therapy.¹⁹ Among patients receiving frontline triplets, 26% continued triplets,
81 47% switched to doublets, and 27% switched to monotherapy as second-line therapy.¹⁹ These treatment
82 patterns underscore the ongoing need for effective doublet and triplet therapy at first relapse. Modern
83 combination regimens, including those based on proteasome inhibitors, have been found to result in
84 deep responses, even in patients with relapsed/refractory disease.^{14,20}

85 Although not every modern combination regimen includes a proteasome inhibitor, proteasome
86 inhibition is an important treatment strategy for patients with multiple myeloma. Given the essential

87 role of proteasome inhibition in multiple myeloma and the availability of several potential treatment
88 options for patients with relapsed/refractory disease, it is important to assess the role of proteasome
89 inhibitors in this setting to aid in the selection of optimal treatment strategies. Here, we review pivotal
90 data and discuss the role of proteasome inhibitor-based doublet and triplet regimens for the
91 management of relapsed/refractory multiple myeloma in the era of modern combination therapy.

92 **DISCUSSION**

93 **The Proteasome and Proteasome Inhibitors**

94 The proteasome, first observed in 1968 and characterized in the late 1980's,⁹⁻¹² is a multicatalytic
95 protease complex located in the nucleus and cytoplasm of eukaryotic cells. Each catalytic subunit (β 1,
96 β 2, β 5) of the proteasome is named after an enzyme with similar proteolytic activity as the
97 corresponding subunit: caspase-like, trypsin-like, and chymotrypsin-like, respectively.²¹ The proteasome
98 is a key component of the ubiquitin-proteasome pathway, which is a central platform for recycling
99 proteins involved in important cellular processes including cell cycle progression, DNA repair, and
100 transcription.²² The scientists responsible for the discovery of ubiquitin-mediated protein degradation
101 were awarded the Nobel Prize in Chemistry in 2004.²³ Timely proteolysis through the ubiquitin-
102 proteasome pathway is an important regulator of homeostasis in normal cells.²² Malignant plasma cells
103 almost always secrete a greater amount of immunoglobulins (ie, proteins) than normal plasma cells and
104 are consequently more dependent on the ubiquitin-proteasome pathway for survival.²¹ Therefore, the
105 proteasome is a rational target for antimyeloma therapies. Preclinical studies have demonstrated that
106 proteasome inhibition results in the build-up of proteins within malignant plasma cells leading to
107 activation of the unfolded protein stress response and decreased NF- κ B activity, both of which induce
108 apoptosis.²¹

109 Three proteasome inhibitors have been approved for the treatment of patients with multiple myeloma:
110 bortezomib, carfilzomib, and ixazomib. Structurally, bortezomib is a dipeptide boranate.²¹ Functionally,
111 it is a slowly reversible inhibitor targeting primarily the $\beta 5$ subunit of the proteasome, with less potent
112 inhibition effects on the $\beta 1$ and $\beta 2$ subunits.²¹ Since the introduction of bortezomib, 2 new proteasome
113 inhibitors have entered the clinic for patients with relapsed/refractory multiple myeloma, carfilzomib
114 (first approved in 2012) and ixazomib (first approved in 2015). Carfilzomib, bortezomib, and ixazomib
115 have unique structural and mechanistic properties, resulting in differential proteasome inhibition
116 profiles. Carfilzomib, a tetrapeptide epoxyketone, selectively targets and irreversibly inhibits the
117 proteasome. Compared with bortezomib, carfilzomib has greater selectivity for the $\beta 5$ subunit²¹ of the
118 proteasome and less off-target activity against nonproteasomal proteases.²⁴ In patients with relapsed or
119 refractory multiple myeloma, carfilzomib has been shown to induce deeper and more sustained
120 proteasome inhibition compared with bortezomib.²⁵ Ixazomib is structurally similar to bortezomib and is
121 a citrate ester of boronic acid.¹³ After aqueous exposure, ixazomib hydrolyzes to the free boric acid
122 MLN2238, which is the pharmacologically active metabolite.¹³ Ixazomib reversibly inhibits the
123 proteasome with selectivity for the $\beta 5$ subunit. Ixazomib is orally bioavailable and has a shorter 20S
124 proteasome disassociation half-life than bortezomib.²⁶ In preclinical studies, ixazomib demonstrated
125 more favorable pharmacokinetic, pharmacodynamic, and antitumor activity profiles compared with
126 bortezomib.²⁶

127 **Activity of Approved Proteasome Inhibitor-Based Combination Therapies in Relapsed/Refractory** 128 **Multiple Myeloma**

129 To date, a total of 7 proteasome inhibitor-based combination therapies have been approved for the
130 treatment of patients with relapsed/refractory multiple myeloma (doublet, $n=3$; triplet, $n=4$). The
131 approved doublets are bortezomib plus dexamethasone, bortezomib plus pegylated doxorubicin, and
132 carfilzomib plus dexamethasone. The approved triplets are bortezomib plus panobinostat and

133 dexamethasone, bortezomib plus daratumumab and dexamethasone, carfilzomib plus lenalidomide and
134 dexamethasone, and ixazomib plus lenalidomide and dexamethasone. Pivotal data supporting the
135 approval of these therapies are summarized in Tables 1 and 2. Results from these pivotal studies and
136 studies supporting other combination therapies recommended by the National Comprehensive Care
137 Network are described below. The current National Comprehensive Care Network Guidelines evaluate
138 treatments with categories of evidence and consensus (eg, category 1: based upon high-level evidence
139 and there is uniform consensus the intervention is appropriate; category 2A: based upon lower-level
140 evidence and there is uniform consensus the intervention is appropriate) and categories of preference
141 (eg, preferred intervention: based on superior evidence; other recommended intervention:
142 interventions may be somewhat less effective, more toxic, or based on less mature data).¹⁷ These
143 categories of evidence and consensus from the National Comprehensive Care Network guidelines are
144 included in the descriptions of the proteasome inhibitor-based therapies in this review. All proteasome
145 inhibitor-based doublets recommended by the National Comprehensive Care Network guidelines were
146 included in the review. Because there are a large number of recommended proteasome inhibitor-based
147 triplets in these guidelines, only triplets based on a proteasome inhibitor plus an immunomodulatory
148 agent or monoclonal antibody were included, as these were deemed to be the most clinically relevant
149 based on the authors' judgment.

150 *Approved Bortezomib-Based Regimens*

151 Doublets

152 Bortezomib plus dexamethasone has been a standard of care in relapsed/refractory multiple myeloma
153 and was approved in the United States in 2014 when used as re-treatment (see Re-treatment with
154 Proteasome Inhibitors) and in the European Union in 2014 for patients with progressive multiple
155 myeloma who have received at least one prior therapy. The broader European Union approval was

156 based on a retrospective matched-pairs analysis of the MMY-2045, APEX, and DOXIL-MMY-3001 clinical
157 trials. The analysis demonstrated improved overall response rate (75% vs. 41%; odds ratio, 3.467;
158 $P<0.001$), time to progression (median, 13.6 vs. 7.0 months; hazard ratio [HR], 0.394; $P=0.003$), and PFS
159 (median, 11.9 vs. 6.4 months, HR, 0.595; $P=0.051$) after second-line treatment with bortezomib and
160 dexamethasone versus bortezomib alone.³⁹ The National Comprehensive Care Network considers
161 bortezomib plus dexamethasone a treatment option under “other recommended regimens” (category 1;
162 not preferred) for patients with relapsed/refractory multiple myeloma.¹⁷

163 Bortezomib plus liposomal doxorubicin was approved in 2007 for the treatment of patients with
164 relapsed or refractory multiple myeloma who have not previously received bortezomib and have
165 received at least one prior therapy. This approval was based on the DOXIL-MMY-3001 study, which was
166 a randomized, phase 3 trial comparing bortezomib plus liposomal doxorubicin with bortezomib
167 monotherapy in patients with relapsed or refractory multiple myeloma. At the interim analysis, time to
168 progression was longer for combination treatment compared with monotherapy (median, 9.3 vs. 6.5
169 months; HR, 1.82 [monotherapy vs. combination]; $P<0.0001$).²⁷ The results from the final OS analysis of
170 this study showed that OS was similar between the treatment arms (median, 33.0 vs. 30.8 months; HR,
171 1.05; $P=0.61$).²⁸ The National Comprehensive Care Network considers bortezomib plus doxorubicin (with
172 dexamethasone) a category 1 option (not preferred) for patients with relapsed/refractory multiple
173 myeloma.¹⁷

174 Triplets

175 Bortezomib has been evaluated as part of triplets combining a proteasome inhibitor with new classes of
176 drugs, as demonstrated in the CASTOR and PANORAMA1 studies. The randomized, phase 3 CASTOR
177 study showed that treatment with daratumumab in combination with bortezomib and dexamethasone
178 resulted in significantly longer PFS compared with bortezomib and dexamethasone alone (median, 16.7

179 vs. 7.1 months; HR, 0.31; $P < 0.0001$).³⁸ Based on results from the CASTOR trial, this combination was
180 approved in 2016 for the treatment of patients with multiple myeloma who have received at least one
181 prior therapy. This combination is also considered a preferred regimen (category 1) for the treatment of
182 patients with relapsed/refractory multiple myeloma.¹⁷

183 The panobinostat plus bortezomib and dexamethasone regimen was approved in 2015 for patients with
184 multiple myeloma who have received at least 2 prior regimens, including bortezomib and an
185 immunomodulatory drug. The pivotal trial supporting this approval was PANORAMA-1, which evaluated
186 panobinostat or placebo plus bortezomib and dexamethasone in patients with relapsed or
187 relapsed/refractory multiple myeloma. The primary analysis of this trial demonstrated that treatment
188 with panobinostat plus bortezomib and dexamethasone resulted in significantly longer PFS compared
189 with placebo plus bortezomib and dexamethasone (median, 11.99 vs. 8.08 months; HR, 0.63;
190 $P < 0.0001$).³⁰ The final OS analysis for this trial showed a trend toward OS benefit for panobinostat over
191 placebo, but the difference was not found to be statistically significant (median, 40.3 vs. 35.8 months;
192 HR, 0.94; $P = 0.54$).³¹ The National Comprehensive Care Network has included this combination as a
193 category 1 option for patients with at least 2 prior therapies, including an immunomodulatory drug and
194 bortezomib.¹⁷

195 *Approved Carfilzomib-Based Regimens*

196 Doublets

197 In a head-to-head study of 2 proteasome inhibitors (carfilzomib vs. bortezomib), the randomized, phase
198 3 ENDEAVOR trial compared carfilzomib (56 mg/m² infused over 30 minutes) and dexamethasone with
199 bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (1 to 3 prior
200 lines of therapy). This carfilzomib regimen was based on results from a phase 1 study, which established
201 the maximum tolerated dose of carfilzomib to be 56 mg/m² when administered as a 30-minute

202 infusion.⁴⁰ The first interim analysis of ENDEAVOR showed that there was a statistically significant
203 increase in PFS for the carfilzomib group compared with the bortezomib group (median, 18.7 vs. 9.4
204 months; HR, 0.53, $P<0.0001$).³² The second interim analysis of ENDEAVOR showed that carfilzomib also
205 provided a significant and clinically meaningful OS improvement compared with bortezomib, prolonging
206 median OS by 7.6 months (47.6 vs. 40.0 months; HR, 0.79; 1-sided $P=0.010$).³⁶ Use of bisphosphonates
207 was balanced between treatment arms and did not confound the OS analysis.⁴¹ Notably, ENDEAVOR is
208 the first and currently the only phase 3 study to demonstrate a significant OS advantage in the relapsed
209 or refractory multiple myeloma setting in a head-to-head comparison of 2 different proteasome
210 inhibitors.³⁶

211 The results of the ENDEAVOR study established the combination of carfilzomib with dexamethasone as a
212 new treatment option for patients with relapsed or refractory multiple myeloma who are being
213 considered for doublet therapy.³⁶ The carfilzomib (56 mg/m²) and dexamethasone combination was
214 approved in 2016 for the treatment of patients with relapsed or refractory multiple myeloma (with 1 to
215 3 prior lines of therapy), and this combination is the only doublet that is recognized as a preferred
216 treatment option (category 1) for previously treated multiple myeloma by the National Comprehensive
217 Care Network.¹⁷

218 Triplets

219 Results from the interim analysis of the randomized, phase 3 ASPIRE study showed that treatment with
220 carfilzomib (27 mg/m² infused over 10 minutes), lenalidomide, and dexamethasone significantly
221 improved PFS compared with lenalidomide and dexamethasone alone (median, 26.3 vs. 17.6 months;
222 HR, 0.69; $P=0.0001$) in patients with relapsed or refractory multiple myeloma (1 to 3 prior lines of
223 therapy). The median PFS duration of 26 months in the carfilzomib arm was noted to be the longest
224 observed to date in the relapsed setting.²⁰ In the ASPIRE regimen, carfilzomib was given for 18 cycles

225 and then patients continued on lenalidomide and dexamethasone alone, similar to the control arm. The
226 current standard of care is to use antimyeloma therapies until disease progression, which is the case for
227 the active arms of other phase 3 trials in relapsed/refractory multiple myeloma reviewed here. A post-
228 hoc analysis of ASPIRE showed that the HR for PFS at 18 months was 0.58.⁴² Recently, results from a
229 prespecified final analysis of OS in ASPIRE showed that carfilzomib plus lenalidomide and
230 dexamethasone reduced the risk of death compared with lenalidomide and dexamethasone, prolonging
231 median OS by 7.9 months (48.3 vs. 40.4 months; HR, 0.79; 95% CI, 0.67–0.95).³⁷ Notably, this is the first
232 and currently the only study in patients with relapsed or refractory multiple myeloma to demonstrate an
233 OS advantage for a triplet regimen against lenalidomide and dexamethasone.

234 Based on results from the ASPIRE study, the combination of carfilzomib with lenalidomide and
235 dexamethasone was approved in 2015 for the treatment of patients with relapsed or refractory multiple
236 myeloma (1 to 3 prior lines of therapy in the United States and 1 or more prior line in the European
237 Union). This regimen is also considered a category 1 preferred treatment option for patients with
238 previously treated multiple myeloma by the National Comprehensive Care Network.¹⁷

239 *Approved Ixazomib-Based Regimens*

240 Doublets

241 Ixazomib is currently not approved by the US Food and Drug Administration to be used as part of a
242 doublet for the treatment of relapsed and/or refractory multiple myeloma.

243 Triplets

244 Interim results from the randomized, phase 3 TOURMALINE-MM1 study demonstrated that the addition
245 of ixazomib (versus placebo) to lenalidomide and dexamethasone significantly prolonged PFS in patients
246 with relapsed and/or refractory multiple myeloma (median 20.6 vs. 14.7 months; HR 0.74; $P=0.01$).³⁵
247 These data supported the approval (2015) of ixazomib plus lenalidomide and dexamethasone for the

248 treatment of patients with multiple myeloma who have received at least one prior therapy. In addition,
249 this regimen is a category 1 preferred treatment option for patients with previously treated multiple
250 myeloma.¹⁷ Notably, this regimen is the only approved all-oral triplet based on a proteasome inhibitor.
251 Longer follow-up results from TOURMALINE-MM1 demonstrated a smaller improvement in PFS
252 compared with the interim results (median, 20.0 vs. 15.9 months; $P=0.05$).⁴³

253 **Activity of Other Proteasome Inhibitor-Based Combination Therapies in Relapsed/Refractory Multiple** 254 **Myeloma**

255 Several other proteasome-inhibitor based combination regimens are recommended by clinical
256 guidelines, but have not yet been approved by regulatory agencies. This section summarizes the data
257 supporting treatment recommendations from the National Comprehensive Care Network, with a focus
258 on doublets and triplets containing a proteasome inhibitor and dexamethasone with either an
259 immunomodulatory drug or a monoclonal antibody.

260 *Doublets*

261 The combination of once-weekly carfilzomib plus dexamethasone for patients with relapsed or
262 refractory multiple myeloma was evaluated in the phase 1/2 CHAMPION-1 study. The phase 1 portion of
263 this trial established the maximum tolerated dose of carfilzomib administered once weekly (30-minute
264 infusion) as 70 mg/m².⁴⁴ Among patients treated at this dose in the phase 1 and 2 portions of the study
265 ($n=104$), the overall response rate was 77% and median PFS was 12.6 months, demonstrating the
266 activity of this regimen.⁴⁴ Once-weekly administration of carfilzomib may be more convenient for
267 patients compared with twice-weekly administration. The carfilzomib regimen used in CHAMPION-1 is
268 included in the National Comprehensive Care Network guidelines as a recommended regimen (category
269 2A).¹⁷ This regimen is being investigated in the phase 3 ARROW study (NCT02412878), which compares
270 once-weekly carfilzomib (70 mg/m²) versus twice-weekly carfilzomib (27 mg/m²). At the interim analysis,

271 this trial met its primary endpoint. Patients who received the once-weekly carfilzomib had significantly
272 longer PFS compared with those who received the twice-weekly carfilzomib regimen (median, 11.2 vs.
273 7.6 months; HR, 0.69; 95% CI, 0.54–0.88).⁴⁵

274 Ixazomib is currently not approved in any doublet regimen, but the combination of ixazomib and
275 dexamethasone has shown promising activity in 2 phase 2 studies. In 1 study ($N=33$), patients with
276 relapsed multiple myeloma with limited prior exposure to bortezomib received weekly ixazomib with
277 dexamethasone added for suboptimal responses (lack of a minor response by cycle 2, partial response
278 by cycle 4, or disease progression at any time). Dexamethasone was added for 22 (67%) patients, 4 of
279 whom achieved a partial response or better after suboptimal response. With or without the addition of
280 dexamethasone, the overall response rate was 34%, and the median event-free survival was 11.5
281 months.⁴⁶ In the other study ($N=70$), patients with relapsed multiple myeloma (who were proteasome
282 inhibitor-naïve or received fewer than 6 cycles of therapy with bortezomib and had a partial response or
283 better with no progression at the time of discontinuation) were randomized to receive ixazomib 4 or 5.5
284 mg in combination with dexamethasone. Overall response rates were 31% in the 4 mg arm and 51% in
285 the 5.5 mg arm.⁴⁷ Median event-free survival was similar for both arms (8.4 and 8.2 months,
286 respectively). Patients receiving the 5.5-mg dose had higher rates of grade ≥ 3 adverse events considered
287 possibly related to treatment (54% vs. 21%) and adverse events requiring dose reductions (43% vs. 17%)
288 compared with patients receiving the 4-mg dose. Based on these data, the ixazomib plus
289 dexamethasone regimen is recognized as a category 2A treatment option for patients with
290 relapsed/refractory multiple myeloma (at least one prior therapy) by the National Comprehensive Care
291 Network.¹⁷

292 In addition to proteasome inhibitor-dexamethasone doublet regimens, the pairing of a proteasome
293 inhibitor with a histone deacetylase inhibitor has also been evaluated.⁴⁸ In a phase 1/2 study of
294 carfilzomib plus panobinostat ($N=42$), the overall response rate was 67% and median PFS was 7.7

295 months in patients with relapsed/refractory multiple myeloma.⁴⁹ Based on this promising phase 1/2
296 data, carfilzomib plus panobinostat is a recommended treatment option (category 2A) for patients with
297 previously treated multiple myeloma.¹⁷

298 *Triplets Containing a Proteasome Inhibitor and an Immunomodulatory Drug*

299 Although not yet approved by regulatory agencies, the combination of bortezomib, lenalidomide, and
300 dexamethasone is considered a preferred regimen (category 1) for the treatment of patients with
301 relapsed/refractory multiple myeloma by the National Comprehensive Care Network.¹⁷ This
302 recommendation is based on results from a phase 2 study of 64 patients with relapsed or
303 relapsed/refractory multiple myeloma. In this study, the overall response rate was 64%, median PFS was
304 9.5 months, and median OS was 30 months.⁵⁰ Notably, the SWOG S0777 study showed that treatment
305 with this triplet improved PFS and OS compared with lenalidomide and dexamethasone in patients with
306 newly diagnosed multiple myeloma.¹⁸

307 Combination regimens consisting of pomalidomide and dexamethasone with bortezomib, carfilzomib, or
308 ixazomib are considered recommended therapeutic options (category 2A) by the National
309 Comprehensive Care Network for patients who have received at least 2 prior therapies, including an
310 immunomodulatory drug and a proteasome inhibitor (specifically bortezomib for the bortezomib- and
311 carfilzomib-based triplets), and have demonstrated disease progression on or within 60 days of
312 completion of the last therapy.¹⁷ Phase 1 studies have demonstrated promising activity for bortezomib
313 with pomalidomide and dexamethasone;¹⁷ the randomized phase 3 OPTIMISMM trial (NCT01734928)
314 recently showed that bortezomib with pomalidomide and dexamethasone improved PFS compared with
315 bortezomib and dexamethasone alone in patients with relapsed or refractory multiple myeloma.⁵¹ In
316 phase 1 and 2 studies, treatment with carfilzomib plus pomalidomide and dexamethasone was found to
317 be highly active in both heavily pretreated patients with relapsed or refractory multiple myeloma

318 (median of 6 prior regimens; $N=72$), with an overall response rate of 64%,⁵² and less pretreated,
319 proteasome inhibitor naïve/sensitive patients ($n=64$), with an overall response rate of 84%.⁵³ In phase
320 1/2 studies, ixazomib plus pomalidomide and dexamethasone has shown early promising activity in
321 patients with double-refractory disease (partial response or better in 8 of 13 patients)⁵⁴ and in patients
322 with relapsed/refractory multiple myeloma who received at least one prior therapy ($n=25$, overall
323 response rate of 48%).⁵⁵

324 *Triplets Containing a Proteasome Inhibitor and a Monoclonal Antibody*

325 A randomized, phase 2 study compared elotuzumab plus bortezomib and dexamethasone versus
326 bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma ($N=152$). At the
327 time of the primary analysis, the addition of elotuzumab to bortezomib and dexamethasone resulted in
328 statistically significantly longer PFS compared with bortezomib and dexamethasone alone (median, 9.7
329 vs. 6.9 months; HR, 0.72; $P=0.09$ [statistical significance threshold of 2-sided $P\leq 0.05$ was used]).⁵⁶ In an
330 updated analysis, the 2-year PFS rates were 18% for bortezomib plus elotuzumab and dexamethasone
331 and 11% for bortezomib and dexamethasone.⁵⁶ This triplet combination is considered a recommended
332 regimen (category 2A; not preferred) for patients with relapsed/refractory multiple myeloma who have
333 received at least one therapy by the National Comprehensive Care Network.¹⁷

334 **Activity of Proteasome Inhibitor-Based Regimens at First Relapse**

335 The first relapse is a critical juncture on the myeloma disease continuum. Each subsequent relapse is
336 associated with increased genomic complexity and drug resistance, resulting in increasingly shorter
337 response durations.^{57,58} Furthermore, data suggest that achievement of deep responses at first relapse
338 versus subsequent relapses is more strongly associated with improved survival outcomes.⁵⁹ Thus, early
339 treatment with highly effective therapy at first relapse, when the disease is still at a sensitive stage, is
340 critical for maximizing OS for patients with relapsed/refractory multiple myeloma.^{57,60} Consistent data

341 from pivotal trials show that proteasome inhibitor-based combination therapies are highly effective
342 treatment options for first relapse (Table 3).

343 *Doublets*

344 The matched-pairs analysis, described previously, compared bortezomib and dexamethasone with
345 single-agent bortezomib. This analysis showed that bortezomib and dexamethasone resulted in greater
346 response and delayed disease progression compared with bortezomib monotherapy when used as
347 second-line treatment.³⁹

348 A secondary analysis of the ENDEAVOR study established the benefit of carfilzomib and dexamethasone
349 when used at first relapse, and demonstrated that it is more effective than bortezomib and
350 dexamethasone in this setting. Results from this analysis showed that in the subgroup of patients who
351 had received 1 prior line of therapy, there was a clinically meaningful improvement in PFS for patients
352 treated with carfilzomib plus dexamethasone versus bortezomib and dexamethasone (median, 22.2 vs.
353 10.1 months; HR, 0.447; $P<0.0001$).⁶¹ Additionally, the final OS analysis of ENDEAVOR showed that
354 patients at first relapse had a 17% lower risk of death if treated with carfilzomib plus dexamethasone
355 versus bortezomib plus dexamethasone (median OS was not estimable in either arm).⁶²

356 *Triplets*

357 The ASPIRE study established the benefit of adding carfilzomib to the immunomodulatory backbone of
358 lenalidomide and dexamethasone for the treatment of patients at first relapse. A secondary analysis of
359 the ASPIRE study demonstrated that the addition of carfilzomib to lenalidomide and dexamethasone led
360 to a 12-month improvement in median PFS compared with lenalidomide and dexamethasone alone
361 (29.6 vs. 17.6 months; HR, 0.71; $P=0.0118$) in patients with 1 prior line of therapy.⁶⁴ Importantly, the
362 final analysis of OS in ASPIRE showed that the OS benefit for the carfilzomib group compared with the

363 control group was most pronounced at first relapse, with an 11-month prolongation of median OS (47.3
364 vs. 35.9 months; HR, 0.81).³⁷

365 A subgroup analysis of the TOURMALINE-MM1 study demonstrated a trend for improvement in PFS with
366 ixazomib, lenalidomide, and dexamethasone compared with lenalidomide and dexamethasone alone for
367 patients at first relapse (median, 20.6 vs. 16.6 months; HR, 0.88; 95% CI, 0.65–1.20).⁶⁵ However, the
368 magnitude of benefit (HR, 0.88) appeared to be lower than that in the overall population (HR, 0.74). It
369 was noted that patients with 1 prior therapy without transplant had greater benefit with ixazomib,
370 lenalidomide, and dexamethasone than patients with 1 prior therapy and transplant (HR 1.232 vs. 0.604)
371 and further investigation into this effect is ongoing.⁶⁵

372 Another pivotal study demonstrated the benefit of adding a novel agent to the proteasome inhibitor
373 backbone of bortezomib and dexamethasone for patients at first relapse. In a subgroup analysis of
374 CASTOR, it was found that the addition of daratumumab to bortezomib and dexamethasone led to
375 significantly improved PFS for patients with 1 prior line of therapy (median, not reached vs. 7.9 months;
376 HR, 0.19; $P < 0.0001$).³⁸

377 **Re-treatment with Proteasome Inhibitors in Proteasome Inhibitor-Sensitive Patients**

378 The choice of salvage therapy at relapse is an important decision that depends on several factors,
379 including the type of previous treatment and duration of response to previous treatment. As
380 bortezomib-based regimens are among the most commonly used frontline therapies,⁶⁶ it is important
381 that treatments used at relapse retain efficacy and tolerability in patients with previous bortezomib
382 exposure. Several proteasome inhibitor-based doublets and triplets have demonstrated activity in
383 patients with prior bortezomib exposure.

384 *Doublets*

385 Guidelines from the National Comprehensive Care Network state that if relapse occurs more than 6
386 months after treatment completion, re-treatment with the same therapy may be considered.¹⁷ In
387 concordance with these guidelines, the phase 2 RETRIEVE trial ($n=126$) showed that re-treatment with
388 bortezomib (with or without dexamethasone) was effective (overall response rate of 40%) in patients
389 with multiple myeloma who had achieved a partial response or better upon completion of prior
390 bortezomib therapy and relapsed more than 6 months after prior bortezomib therapy.²⁹ These data
391 supported approval of bortezomib re-treatment (as a single agent or with dexamethasone) for patients
392 with relapsed multiple myeloma.

393 The ENDEAVOR study included a large group of patients ($n=502$) who were previously exposed to
394 bortezomib but were not bortezomib refractory (similar to the RETRIEVE population), which allowed for
395 a robust comparison of carfilzomib and dexamethasone versus bortezomib and dexamethasone among
396 patients with prior bortezomib exposure (Table 4). Median PFS was 7.5 months longer in the carfilzomib
397 group compared with the bortezomib group among patients with previous bortezomib exposure
398 (median, 15.6 vs. 8.1 months; HR, 0.56; $P<0.0001$).^{32,61} Treatment with carfilzomib also extended OS by
399 14.8 months versus re-treatment with bortezomib in this subgroup (median, 47.6 vs. 32.8 months; HR,
400 0.84; 95% CI, 0.65–1.08).⁶² Although bortezomib re-treatment has been a common therapeutic
401 strategy,⁶⁶ these head-to-head results suggest that treatment with carfilzomib at relapse is more
402 effective (complete response rates, PFS, and OS) than re-treatment with bortezomib for patients with
403 prior bortezomib exposure.

404 *Triplets*

405 Triplet regimens that combine proteasome inhibitors with a lenalidomide-dexamethasone backbone
406 have also improved outcomes compared with lenalidomide-dexamethasone alone in patients with
407 previous bortezomib exposure. In the ASPIRE study, the addition of carfilzomib to lenalidomide and

408 dexamethasone resulted in an approximate 8-month improvement in median PFS in bortezomib-
409 exposed patients (median, 24.4 vs. 16.6 months; HR, 0.699) and for patients treated at first relapse after
410 bortezomib-containing therapy, carfilzomib plus lenalidomide and dexamethasone resulted in 13.4
411 months of improvement (median, 29.3 vs. 15.9 months; HR, 0.577).^{64,67} Further, the addition of
412 carfilzomib to lenalidomide and dexamethasone prolonged median OS by 12 months (median, 45.9 vs.
413 33.9 months; HR, 0.82; 95% CI, 0.56–1.19) among patients treated at first relapse after prior
414 bortezomib.³⁷

415 A subgroup analysis of the TOURMALINE-MM1 study showed a consistent PFS benefit for ixazomib,
416 lenalidomide, and dexamethasone versus lenalidomide and dexamethasone, regardless of prior
417 bortezomib exposure (bortezomib-exposed: median, 18.5 vs. 13.6 months; HR, 0.746; bortezomib-naïve:
418 median, not estimable vs. 15.9 months; HR, 0.747).⁶⁵

419 Results from subgroup analyses of the CASTOR and PANORAMA-1 trials suggest that treatment with
420 potent triplet combinations based on the bortezomib-dexamethasone backbone may be more effective
421 than treatment with this backbone alone in patients with prior bortezomib exposure. In the CASTOR
422 study, PFS was improved with daratumumab plus bortezomib and dexamethasone compared with
423 bortezomib and dexamethasone alone, regardless of prior bortezomib exposure (bortezomib-exposed:
424 median, 12.3 vs. 6.7 months; HR, 0.46).³³ Among prior treatment subgroups examined in the
425 PANORAMA-1 study (group 1: prior immunomodulatory drug; group 2: prior bortezomib and
426 immunomodulatory drug; group 3: 2 or more prior regimens including bortezomib and an
427 immunomodulatory drug), the PFS benefit for panobinostat plus bortezomib and dexamethasone versus
428 bortezomib and dexamethasone alone was most pronounced in patients who had received at least 2
429 prior therapies, including bortezomib and an immunomodulatory drug, with a 7.8-month prolongation
430 in median PFS (median, 12.5 vs. 4.7 months; HR, 0.47).³⁴

431 **Re-treatment with Proteasome Inhibitors in Proteasome Inhibitor-Refractory Patients**

432 As bortezomib is a commonly used frontline antimyeloma agent, there is a need for therapies that can
433 recapture responses in patients who become bortezomib-refractory. Proteasome inhibitor-based
434 combinations have demonstrated activity in this setting (Table 5), and several general approaches have
435 been used. The first is the addition of a novel agent with a unique mechanism of action to a bortezomib-
436 based backbone. This was tested in the phase 2 PANORAMA trial where the histone deacetylase
437 inhibitor panobinostat was added to bortezomib and dexamethasone. Treatment with this combination
438 resulted in an overall response rate of 35% in bortezomib-refractory patients (n=55).⁵⁰ More recent
439 studies have evaluated the addition of venetoclax (a BCL-2 inhibitor) or selinexor (a selective exportin 1
440 inhibitor) to bortezomib and dexamethasone with promising activity; however, these combinations are
441 not yet endorsed by regulatory agencies or the National Comprehensive Care Network. Another
442 approach for proteasome inhibitor-based treatment of bortezomib-refractory patients is the use of a
443 different proteasome inhibitor, ie carfilzomib or ixazomib. Preclinically, carfilzomib and ixazomib are
444 able to overcome bortezomib resistance in multiple myeloma cell lines and patient samples.^{71,72} Building
445 on this preclinical rationale, several carfilzomib or ixazomib-based combinations have demonstrated
446 activity in bortezomib-refractory patients (Table 5). Notably, ASPIRE is the only pivotal phase 3 trial of
447 proteasome inhibitor-based combination therapy to have reported efficacy data for bortezomib-
448 refractory patients. Among these patients in ASPIRE, median PFS was extended 3 months with the
449 addition of carfilzomib to lenalidomide and dexamethasone (22.3 vs. 19.4 months; HR, 0.80), and the HR
450 for OS (0.73) also favored the carfilzomib group.^{37,64}

451 The addition of novel agents (eg, panobinostat, venetoclax, or selinexor) to a carfilzomib-based regimen
452 has also been investigated recently, and has generally shown promising activity in patients refractory to
453 a proteasome inhibitor. With the exception of carfilzomib plus panobinostat, regimens based on this
454 approach have not yet been endorsed by the National Comprehensive Care Network.

455 **Safety of Proteasome Inhibitor-Based Combination Therapies in Relapsed/Refractory Multiple**

456 **Myeloma**

457 Bortezomib, carfilzomib, and ixazomib each have their own unique safety profiles, which reflects their
458 distinct structural and mechanistic properties. In the ENDEAVOR study, rates of grade ≥ 3 adverse events
459 and serious adverse events were slightly more common with carfilzomib versus bortezomib. Grade ≥ 3
460 adverse events that were more common ($\geq 2\%$) with carfilzomib were anemia, hypertension, dyspnea,
461 decreased lymphocyte count, pyrexia, and cardiac failure whereas those that were more common in the
462 bortezomib group were diarrhea and peripheral neuropathy.³⁶

463 The safety profiles of bortezomib and carfilzomib are affected by the route of administration and/or
464 dosing schedule used. Subcutaneous administration has been shown to result in a lower rate of
465 peripheral neuropathy compared with intravenous bortezomib administration.⁷³ For carfilzomib, a
466 longer infusion time (ie, 30 vs. 10 minutes) permits safe administration of higher doses of carfilzomib
467 compared with the originally approved dose of 27 mg/m².^{32,44} The CHAMPION-1 study showed that
468 once-weekly administration of carfilzomib (70 mg/m²; 30-minute infusion) in combination with
469 dexamethasone was generally well tolerated in patients with relapsed or refractory multiple myeloma,
470 with only 12% of patients discontinuing treatment due to adverse events.⁴⁴

471 In randomized studies comparing a triplet versus a doublet, adverse event rates tended to be slightly
472 higher in the triplet arm than in the doublet arm, as expected (Table 6). In the PANORAMA-1 study, the
473 addition of panobinostat to bortezomib and dexamethasone was associated with an increased incidence
474 of grade 3 or 4 thrombocytopenia, lymphopenia, neutropenia, diarrhea, and asthenia or fatigue.³⁰ In the
475 ASPIRE study, the addition of carfilzomib to lenalidomide and dexamethasone was associated with an
476 increased incidence of diarrhea, cough, fever, and hypertension.²⁰ In the TOURMALINE-MM1 study, the
477 addition of ixazomib to lenalidomide and dexamethasone was associated with an increased incidence of

478 thrombocytopenia, rash, gastrointestinal events, and peripheral neuropathy.³⁵ In the CASTOR study, the
479 addition of daratumumab to bortezomib and dexamethasone led to an increased incidence of
480 thrombocytopenia and infusion-related reactions.³³

481 **Factors to Consider When Selecting Proteasome Inhibitor Therapy**

482 Several disease-, treatment-, and patient-related factors should be considered when selecting therapy.
483 These factors have been reviewed in detail elsewhere.⁷⁴ We briefly highlight some of these factors and
484 how they apply to selection of proteasome inhibitor-based therapy.

485 The presence of high-risk cytogenetic features is associated with a poor prognosis and there is a need
486 for therapies that can overcome (or partly overcome) this adverse prognosis. Subgroup analyses of the
487 ASPIRE, ENDEAVOR, TOURMALINE-MM1, and CASTOR studies have shown that modern proteasome
488 inhibitor-based combination therapy improves outcomes regardless of cytogenetic risk status, including
489 in patients with high-risk cytogenetics.⁷⁵⁻⁷⁸ Safety and tolerability should also be considered when
490 selecting therapy. As peripheral neuropathy is associated with bortezomib, regimens with other
491 proteasome inhibitors (ie, carfilzomib or ixazomib) may be preferred in patients for whom this toxicity is
492 a concern. Similarly, the potential for cardiac toxicity should be considered when evaluating carfilzomib-
493 based therapy.⁷⁹ Safety and efficacy should be considered together and the overall benefit-risk profile
494 assessed. Another factor to consider is convenience. For patients who cannot easily travel to the clinic,
495 an oral proteasome inhibitor such as ixazomib may be preferred. Once-weekly administrations of
496 carfilzomib and bortezomib have been evaluated,^{44,80} and these may be more convenient than the
497 currently approved twice-weekly administrations.

498 As survival times have improved for patients with multiple myeloma, quality of life considerations and
499 patient-reported outcomes have gained in importance when selecting therapy. However, until recently,
500 there were limited data regarding effect of proteasome inhibitor-based therapies on quality of life in

501 patients with relapsed/refractory multiple myeloma.⁸¹ A prespecified exploratory analysis of the phase 3
502 APEX trial showed that patients with relapsed multiple myeloma who received bortezomib had better
503 health-related quality of life (HRQoL) than those who received dexamethasone.⁸² Recent data from the
504 ENDEAVOR, ASPIRE, and TOURMALINE-MM1 studies have provided important additional information
505 regarding the effects of next-generation proteasome inhibitors on quality of life. A prespecified analysis
506 of the ENDEAVOR study showed that treatment with carfilzomib resulted in statistically significant
507 improvements in patient-reported health-related quality of life, fatigue, pain, side effects of treatment,
508 and neurotoxicity compared with bortezomib treatment.⁸³ In ASPIRE, the addition of carfilzomib to
509 lenalidomide resulted in a statistically significant and clinically meaningful improvement in health-
510 related quality life with no detrimental effect (compared with the control group) on other patient-
511 reported outcomes.⁸⁴ The addition of ixazomib to lenalidomide and dexamethasone in the
512 TOURMALINE-MM1 study did not have a statistically significant impact on health-related quality of life.⁸⁵
513 Overall, these studies show that combination regimens based on next-generation proteasome inhibitors
514 are able to improve (carfilzomib) or maintain (ixazomib) health-related quality of life compared with
515 recent standards of care in relapsed/refractory multiple myeloma.

516 **Conclusion**

517 Proteasome inhibitor-based regimens are essential components of modern therapy for patients with
518 relapsed/refractory myeloma, with demonstrated activity including in key subgroups such as patients in
519 first relapse and patients with prior proteasome inhibitor exposure. Consistent data from randomized
520 studies show that modern combination regimens incorporating proteasome inhibitors improve clinical
521 outcomes (including OS in some cases) compared with standard of care in patients with
522 relapsed/refractory multiple myeloma. Both doublet and triplet regimens are approved in this disease
523 setting and both are demonstrated to be effective. The only head-to-head study directly comparing 2
524 proteasome inhibitors in relapsed/refractory multiple myeloma, ENDEAVOR, demonstrated

525 improvements in complete responses, PFS, and OS for the carfilzomib-treated patients compared with
526 the bortezomib-treated patients. ASPIRE is the only phase 3 study in relapsed/refractory multiple
527 myeloma to date to demonstrate an improvement in OS with the addition of a proteasome inhibitor.
528 The benefit was most prominent when the carfilzomib, lenalidomide, and dexamethasone combination
529 was used at first relapse, especially in proteasome inhibitor-sensitive patients (after bortezomib-based
530 frontline therapy). Ixazomib, lenalidomide, and dexamethasone is the only approved, all-oral
531 proteasome inhibitor-based regimen and it offers a convenient choice when infusion therapy is not an
532 option. Bortezomib re-treatment can be an option in certain markets with limited access to modern
533 therapies.

534 There are currently 3 approved proteasome inhibitors, each with their own unique efficacy and safety
535 profiles. Bortezomib is rapidly active and has a defined efficacy and safety profile that is well-understood
536 by clinicians. It will remain a standard of care option in the frontline setting for the foreseeable future.
537 The duration of bortezomib treatment is limited by peripheral neuropathy and development of
538 relapsed/refractory disease. Like bortezomib, carfilzomib is also rapidly active. In our experience,
539 carfilzomib can be administered for an extended period (2 to 3 years), especially when given once
540 weekly. It is the proteasome inhibitor of choice at relapse because of its PFS and OS advantage
541 compared with other therapies (including bortezomib retreatment) and its ability to be combined with
542 many other agents. Several different dose densities (once- vs. twice- weekly) and dose intensities (twice-
543 weekly carfilzomib with lenalidomide and dexamethasone: 27 mg/m², twice-weekly carfilzomib with
544 dexamethasone: 56 mg/m², once-weekly carfilzomib with dexamethasone: 70 mg/m²) of carfilzomib
545 have been evaluated in randomized phase 3 trials, and the various doses and schedules have the
546 potential to offer greater flexibility in the administration and utility of carfilzomib. In contrast to
547 bortezomib and carfilzomib, ixazomib is an oral drug and thus a convenient option for patients who can
548 come to treatment centers.

549 The role of proteasome inhibitors as a class and the 3 currently approved agents will continue to evolve
550 as bortezomib becomes generic worldwide, the next-generation proteasome inhibitors move to the
551 frontline, and additional classes of drugs are incorporated in the therapeutic landscape. The cost-
552 effectiveness of generic bortezomib will need to be evaluated and it is likely that generic bortezomib will
553 have a prominent role in markets with limited financial resources, although a recent analysis of
554 ENDEAVOR predicted that twice-weekly carfilzomib 56 mg/m² with dexamethasone would be cost-
555 effective versus bortezomib and dexamethasone, even at an 85% price reduction for bortezomib and
556 dexamethasone.⁸⁶ As an increasing number of studies evaluate frontline carfilzomib- and ixazomib-
557 based regimens, the comparative effectiveness of the various proteasome inhibitor-based, upfront
558 combinations will need to be addressed, as well as the benefit-risk profile in specific patient populations.
559 Real-world evidence from claims data and patient registries will be important in this regard. As novel
560 agents with unique mechanisms of action (eg, venetoclax, selinexor, monoclonal antibodies) are
561 introduced and become established, the scope and potential of proteasome inhibitor-based
562 combinations will continue to expand, allowing effective therapy for heavily pretreated and refractory
563 patients as well as tailored combination therapies for distinct patient subgroups.

564 There are several key knowledge gaps that remain regarding the role of proteasome inhibitors.
565 Compared with the relapsed/refractory setting, phase 3 data in the upfront setting for carfilzomib and
566 ixazomib are limited. In addition, the evaluation of the best partners for proteasome inhibitors is still an
567 active area of study, and in the context of immunomodulation, there remains a question of whether
568 proteasome inhibitors should be combined with immunomodulatory drugs, monoclonal antibodies, or
569 both. To address an aspect of this question, a randomized phase 2 study (NCT02874742) is evaluating
570 the addition of daratumumab to the triplet of bortezomib, lenalidomide, and dexamethasone in patients
571 with newly diagnosed multiple myeloma. Several single-arm trials are also investigating carfilzomib and
572 dexamethasone in combination with daratumumab or lenalidomide plus daratumumab and are already

573 demonstrating positive results.⁸⁷ Beyond optimal combinations, there is no uniform standard of care or
574 data from randomized trials regarding how proteasome-based combination therapies should be
575 sequenced. This will become increasingly important as carfilzomib and ixazomib move to the frontline
576 and questions arise as to which proteasome inhibitor to use upfront, which to reserve for later lines, and
577 the efficacy of bortezomib salvage therapy after frontline carfilzomib or ixazomib. Overall, several
578 studies have found that switching to a different proteasome inhibitor or retreatment with the same
579 proteasome inhibitor can be effective strategies for patients progressing after prior proteasome
580 inhibitor exposure.^{29,32,64,65,88,89} Regarding specific sequences, a single-center, retrospective study found
581 that treatment with frontline carfilzomib-based therapy followed by bortezomib-based therapy (n=15)
582 resulted in higher response rates and deeper responses than the reverse sequence of bortezomib-based
583 therapy followed by carfilzomib-based therapy (n=39); however, larger prospective studies are
584 warranted.⁹⁰ Data from ENDEAVOR suggest it is more effective to switch to carfilzomib rather than
585 retreat with bortezomib. Regarding retreatment with carfilzomib, 1 phase 2 study (n=13) found that
586 retreatment with carfilzomib 56 mg/m² recaptured responses in patients who were refractory to
587 carfilzomib at a lower dose (27 mg/m²).⁹¹ Other knowledge gaps include the value of minimal residual
588 disease testing to assess response to proteasome inhibitor-based therapy, development of alternative
589 oral proteasome inhibitors, and effects of proteasome inhibitors on immune fitness and
590 immunomodulation.

591 The current treatment paradigm in multiple myeloma emphasizes use of potent combination therapy
592 capable of producing deep and sustained responses. Modern proteasome inhibitor-based regimens are
593 highly effective and are an important option for treating patients with relapsed/refractory disease.

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Table 1. Baseline Characteristics From Pivotal Trials in RRMM

Study Name (reference)	Patient Population	Treatment Group (n)	Median (range) Age, years	ECOG PS, %	Cytogenetic Risk Status, ^a %	Median (range) Number of Prior Regimens, n
2-drug regimens						
DOXIL-MMY- 3001 ^{27,28}	RRMM, V-naive	V+PLD (324)	61 (28–85)	0: 43; 1: 57	Had cytogenetic abnormality: 43; Did not have cytogenetic abnormality: 57	NR (34% and 66% had 1 or ≥2 prior therapies, respectively)
RETRIEVE ²⁹	Patients with MM who had relapsed after achieving ≥PR with initial V-based therapy	V±DEX re- treatment (130)	67 (38–86)	NR	NR	2 (1–7)
PANORAMA ^{130,31}	Relapsed or relapsed and refractory MM, 1– 3 previous treatments	Vd (381)	63 (IQR, 56–68)	0: 43; 1: 49; 2: 8	NR	NR (52%, 28%, and 20% had 1, 2, or 3 prior lines, respectively)
ENDEAVOR ³²	RRMM, 1–3 previous treatments	Kd56 (464) Treatment	65 (35–89)	0: 48; 1: 45;	High: 25; Standard: 75	2 (IQR, 1–2)

		until PD		2: 7		
	RRMM, 1–3 previous treatments	Vd (465) Treatment until PD	65 (30–88)	0: 50; 1: 44; 2: 6	High: 28; Standard: 72	2 (IQR, 1–2)
CASTOR ³³	Relapsed or relapsed and refractory MM, ≥1 previous treatment	Vd (247) Up to 8 cycles of treatment [6 months]	64 (33–85)	NR	High: 21; Standard: 79	2 (1–10)
3-drug regimens						
PANORAMA ^{130,31,34}	Relapsed or relapsed and refractory MM, 1–3 previous treatments	PanVd (387)	63 (IQR, 56–69)	0: 45; 1: 49; 2: 5	NR	NR (51%, 32%, and 17% had 1, 2, or 3 prior lines, respectively)
ASPIRE ²⁰	RRMM, 1–3 previous treatments	KRd (396)	64 (38–87)	0 or 1: 90; 2: 10	High: 25; Standard: 75	2 (1–3)
TOURMALINE-MM1 ³⁵	Relapsed, refractory, or relapsed and refractory MM, 1–3 previous treatments	IRd (360)	66 (38–91)	0: 51; 1: 44; 2: 5	High: 27; Standard: 73	NR (62%, 27%, and 11% had 1, 2, or 3 prior therapies, respectively)
CASTOR ³³	Relapsed or relapsed and refractory MM, ≥1	DVd (251)	64 (30–88)	NR	High: 23; Standard: 77	2 (1–9)

previous treatment

^aPercentages are based on the number of patients with known cytogenetics information.

Abbreviations: DEX=dexamethasone; DVd=daratumumab, bortezomib, and dexamethasone; ECOG PS=Eastern Cooperative Oncology Group performance status; IQR=interquartile range; IRd=ixazomib, lenalidomide, and dexamethasone; Kd56=carfilzomib (56 mg/m²) and dexamethasone; KRd=carfilzomib, lenalidomide, and dexamethasone; MM=multiple myeloma; NR=not reported; PanVd=panobinostat, bortezomib and dexamethasone; PD=progressive disease; PI=proteasome inhibitor; PLD=pegylated liposomal doxorubicin; PR=partial response; Rd=lenalidomide and dexamethasone; RRMM=relapsed or refractory multiple myeloma; V=bortezomib; Vd=bortezomib and dexamethasone.

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Table 2. Activity of Approved PI-Based Combination Therapies in RRMM^a

Study Name (reference)	Patient Population	Treatment Group (n)	ORR (≥CR), %	Median	PFS Rates	Median	OS Rates
				PFS, months		OS, months	
2-drug regimens							
DOXIL-MMY-3001 ^{27,28}	RRMM, V-naive	V+PLD (324)	44 (4 ^b)	9.0	1-year: 26% ^c ; 2-year: NR	33.0	1-year: 81% ^c ; 2-year: 64% ^c
PANORAMA1 ^{30,31,34}	Relapsed or relapsed and refractory MM, 1–3 previous treatments	Vd (381)	55 (6 ^b)	8.1	1-year: 36% ^c ; 2-year: 8% ^c	35.8	1-year: 81% ^c ; 2-year: 62% ^c
	Relapsed or relapsed and refractory MM, ≥2 previous regimens including V and an immunomodulatory agent	Vd (74)	39 (≥CR not reported)	4.7	1-year: 16% ^c ; 2-year: 5% ^c	19.5	1-year: 67% ^c ; 2-year: 44% ^c
ENDEAVOR ^{32,36}	RRMM, 1–3 previous treatments	Kd56 (464) Treatment until PD	77 (13)	18.7	1-year: 63% ^c ; 2-year: 44% ^c	47.6	1-year: 83% ^c ; 2-year: 70% ^c

	RRMM, 1–3 previous treatments	Vd (465) Treatment until PD	63 (6)	9.4	1-year: 42% ^c ; 2-year: 23% ^c	40.0	1-year: 83% ^c ; 2-year: 63% ^c
CASTOR ³³	Relapsed or relapsed and refractory MM, ≥1 previous treatment	Vd (247) Up to 8 cycles of treatment [6 months]	63 (9)	7.1 ^c	1-year: 27%; 2-year: 5% ^d	NR	1-year: 82% ^c ; 2-year: NR
3-drug regimens							
ASPIRE ^{20,37}	RRMM, 1–3 previous treatments	KRd (396)	87 (32)	26.3	1-year: 77% ^c ; 2-year: 55% ^c	48.3	1-year: 89% ^c ; 2-year: 73% ^c
TOURMALINE-MM1 ³⁵	Relapsed, refractory, or relapsed and refractory MM, 1–3 previous treatments	IRd (360)	78 (14)	20.6	1-year: 67% ^c ; 2-year: NR	NR	NR
CASTOR ³³	Relapsed or relapsed and refractory MM, ≥1 previous treatment	DVd (251)	83 (19)	16.7 ^c	1-year: 61%; 2-year: 37% ^e	NR	1-year: 82% ^c ; 2-year: NR
PANORAMA1 ^{30,31,34}	Relapsed or relapsed and refractory MM, 1–3 previous treatments	PanVd (387)	61 (11 ^b)	12.0	1-year: 49% ^c ; 2-year: 21% ^c	40.3	1-year: 80% ^c ; 2-year: 67% ^c

Relapsed or relapsed and refractory MM, ≥2 previous regimens including V and an immunomodulatory agent	PanVd (73)	59 (≥CR not reported)	12.5	1-year: 51% ^c ; 2-year: 6% ^c	25.5	1-year: 74% ^c ; 2-year: 58% ^c
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^aOnly data from pivotal studies supporting regulatory approval are presented. All studies used IMWG response criteria except for DOXIL-MMY-3001 and PANORAMA1, which used EBMT criteria. ^bRate of CR. ^cEstimated from Kaplan-Meier curves. ^dValue is from an updated analysis of CASTOR.³⁸ ^ePresented at the 2017 Annual Meeting of the American Society of Hematology.³⁸

Abbreviations: CR=complete response; DVd=daratumumab, bortezomib, and dexamethasone; EBMT=European Group for Blood and Marrow Transplant; IMWG=International Myeloma Working Group; IRd=ixazomib, lenalidomide, and dexamethasone; Kd56=carfilzomib (56 mg/m²) and dexamethasone; KRd=carfilzomib, lenalidomide, and dexamethasone; MM=multiple myeloma; NR=not reported, not reached, or not estimable; ORR=overall response rate; OS=overall survival; PanVd=panobinostat, bortezomib and dexamethasone; PD=progressive disease; PFS=progression-free survival; PI=proteasome inhibitor; PLD=pegylated liposomal doxorubicin; Rd=lenalidomide and dexamethasone; RRMM=relapsed or refractory multiple myeloma; V=bortezomib; Vd=bortezomib and dexamethasone.

Table 3. Activity of Approved PI-Based Combination Therapies at First Relapse (1 previous line of therapy)

Study Name (reference)	Patient Population	Treatment Group (n)	ORR (≥CR), %	Median PFS, months	PFS Rates	Median OS, months
2-drug regimens						
ENDEAVOR ^{61,62}	Relapsed or refractory MM	Kd56 (232)	82 (12)	22.2	1-year: 71% ^a ; 2-year: 43% ^a	NR
	Relapsed or refractory MM	Vd [until PD] (232)	66 (8)	10.1	1-year: 45% ^a ; 2-year: NR	NR
CASTOR ^{38,63}	Relapsed or relapsed and refractory MM	Vd [6 months] (113)	74 (15) ^b	7.9	1-year: 29% ^a ; 2-year: 8% ^b	NR
3-drug regimens						
ASPIRE ^{37,64}	RRMM	KRd (184)	87 (34)	29.6	1-year: 80% ^a ; 2-year: 58% ^a	47.3
TOURMALINE-MM1 ⁶⁵	Relapsed, refractory, or relapsed and refractory MM	IRd (212)	77 (9)	20.6	1-year: 65% ^a ; 2-year: NR	NR
CASTOR ^{38,63}	Relapsed or relapsed and refractory MM	DVd (122)	92 (43) ^b	26.2 ^b	1-year: 78% ^a ; 2-year: 55% ^b	NR

^aEstimated from Kaplan-Meier curves. ^bPresented at the 2017 Annual Meeting of the American Society of Hematology.

Abbreviations: BTZ=bortezomib; CR=complete response; DVd=daratumumab, bortezomib, and dexamethasone; IRd=ixazomib, lenalidomide, and dexamethasone; Kd56=carfilzomib (56 mg/m²) and dexamethasone; KRd=carfilzomib, lenalidomide, and dexamethasone; MM=multiple myeloma; NR=not reported, not reached, not

estimable; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PI=proteasome inhibitor; Rd=lenalidomide and dexamethasone;
RRMM=relapsed or refractory multiple myeloma; Vd=bortezomib and dexamethasone.

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Table 4. Activity of Approved PI-Based Combination Therapies When Used After Prior PI Exposure (Re-Treatment With PIs)

Study Name (reference)	Patient Population	Treatment Group (n)	ORR (≥CR), %	Median PFS, months	PFS Rates	Median OS, months
2-drug regimens						
RETRIEVE ²⁹	Patients with MM who had relapsed after achieving ≥PR with initial V-based therapy	V±DEX re-treatment (126)	40 (1 ^a)	8.4 (TTP)	1-year TTP rate: 12% ^b ; 2-year TTP rate: NR	NR
PANORAMA1 ^{31,34}	Relapsed or refractory MM, prior exposure to V and an immunomodulatory drug	Vd (99)	41 (≥CR not reported)	5.8	1-year: 21% ^b ; 2-year: 4% ^b	24.7
ENDEAVOR ^{61,62}	Relapsed or refractory MM, prior V exposure	Kd56 (250)	71 (≥CR not reported)	15.6	1-year: 57% ^b ; 2-year: 35% ^b	47.6

	Relapsed or refractory MM, prior V exposure	Vd [until PD] (252)	60 (≥CR not reported)	8.1	1-year: 36% ^b ; 2-year: NR	32.8
CASTOR ³³	Relapsed or refractory MM, prior V exposure	Vd [6 months] (164)	NR	6.7	NR	NR
3-drug regimens						
PANORAMA1 ^{31,34}	Relapsed or relapsed and refractory MM, prior exposure to V and an immunomodulatory drug	PanVd (94)	58.5 (≥CR not reported)	10.6	1-year: 48% ^b ; 2-year: 9% ^b	27.2
ASPIRE ⁶⁴	RRMM, prior V exposure	KRd (261)	86 (30)	24.4	1-year: 75% ^b ; 2-year: 52%	NR
TOURMALINE-MM1 ⁶⁵	Relapsed, refractory, or relapsed and refractory MM, PI-	IRd (250)	77 (9)	18.4	1-year: 67% ^b ; 2-year: NR	NR

	exposed					
CASTOR ³³	Relapsed or relapsed and refractory MM	DVd (162)	NR	12.3	NR	NR

^aResults reported for CR. ^bEstimated from Kaplan-Meier curve.

Abbreviations: CR=complete response; DVd=daratumumab, bortezomib, and dexamethasone; IRd=ixazomib, lenalidomide, and dexamethasone; Kd56=carfilzomib (56 mg/m²) and dexamethasone; KRd=carfilzomib, lenalidomide, and dexamethasone; MM=multiple myeloma; NR=not reported; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PI=proteasome inhibitor; PanVd=panobinostat, bortezomib and dexamethasone; PD=progressive disease; PLD=pegylated liposomal doxorubicin; Rd=lenalidomide and dexamethasone; RRMM=relapsed or refractory multiple myeloma; TTP=time to progression; V=bortezomib; Vd=bortezomib and dexamethasone.

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Table 5. Activity of PI-Based Combination Therapies When Used in PI-Refractory Patients

Study Name or NCT#	Phase	Patient Population	Treatment Group (n)	ORR, %	Median PFS, months	Median OS, months
Approved regimens						
PX-171-003-A1 ⁶⁸	2	RRMM, refractory to V in the last prior line	Single-agent carfilzomib (45% of 266 enrolled patients)	19	NR	NR
ASPIRE ⁶⁴	3	RRMM, refractory to V in any previous regimen	KRd (60)	80	22.3	NR
NCCN-recommended regimens						
PANORAMA 2 ⁵⁰	2	RRMM, refractory to V	PanVd (55)	35	5.4	NR
CHAMPION-1 ¹⁷	1/2	RRMM, refractory to V	Once-weekly Kd (54)	63	NR	NR
NCT01496118 ⁴⁹	1/2	RRMM, refractory to V	Carfilzomib+panobinostat (15)	67	NR	NR
NCT01549431 ^{a,69}	1	RRMM, refractory to V	Carfilzomib+panobinostat (16)	44	NR	NR
NCT01464034 ⁷⁰	1	RRMM	KPd (32 ^b)	50	7.2	20.6

NCT02004275 ⁵⁴	1/2	MM, refractory to LEN and a PI	IPd (17)	62 ^c	NR	NR
NCT02119468 ⁵⁵	1/2	RRMM, refractory to LEN and V	IPd (14)	29	NR	NR

^aPresented at the 2014 ASH Annual Meeting.

^b30 of 32 patients were refractory to V.

^cORR was reported for 13 patients who received at least 1 cycle of therapy.

Abbreviations: IPd=ixazomib, pomalidomide, and dexamethasone; KRd=carfilzomib, lenalidomide, and dexamethasone; LEN=lenalidomide; MM=multiple myeloma; NCCN, National Comprehensive Care Network; NR=not reported or not reached; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PI=proteasome inhibitor; PanVd=panobinostat, bortezomib and dexamethasone; RRMM=relapsed or refractory multiple myeloma; V=bortezomib; Vd=bortezomib and dexamethasone.

Table 6. Safety of Approved PI-Based Combination Therapies in RRMM

Study Name (reference)	Treatment Group, Safety Population (n)	Median	Any AE, %	Grade ≥3 AEs, %	SAEs, %	Discontinuations Due to AEs, (%)	Dose
		Treatment Duration					Reductions Due to AEs, (%)
2-drug regimens							
DOXIL-MMY- 3001 ²⁷	V+PLD (318)	5 cycles; 105 days	98	80 ^a	36	V: 30; PLD: 36	NR
PANORAMA1 ³¹	Vd (377)	NR	NR	82 ^a	42	18	NR
ENDEAVOR ³⁶	Kd56 (463)	48.0 weeks	99	81	59	14	32
	Vd [until PD] (456)	27.0 weeks	99	71	40	16	50
CASTOR ³³	Vd [6 months] (237)	Median follow-up period was 7.4 months	95	62 ^a	NR	9	NR
3-drug regimens							
PANORAMA1 ³¹	PanVd (381)	NR	NR	96 ^a	60	34	NR
ASPIRE ³⁷	KRd (392)	72 weeks for	98	87	65	20	11 ^b

carfilzomib							
TOURMALINE-MM1 ³⁵	IRd (361)	17 cycles	98	74	47	17	56
CASTOR ³³	DVd (243)	Median follow-up period was 7.4 months	99	76 ^a	NR	7	NR

^aAny grade 3 or 4 AE. ^bReported in the primary analysis.²⁰

Abbreviations: AE=adverse event; DVd=daratumumab, bortezomib, and dexamethasone; IRd=ixazomib, lenalidomide, and dexamethasone; Kd56=carfilzomib (56 mg/m²) and dexamethasone; KRd=carfilzomib, lenalidomide, and dexamethasone; NR=not reported; PI=proteasome inhibitor; PanVd=panobinostat, bortezomib and dexamethasone; PD=progressive disease; PLD=pegylated liposomal doxorubicin; RRMM=relapsed or refractory multiple myeloma; SAE=serious AE; V=bortezomib; Vd=bortezomib and dexamethasone.