Carfilzomib and pomalidomide in patients with relapsed and/or refractory multiple myeloma with baseline risk factors

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While survival times have increased over the last decade, most patients with multiple myeloma (MM) eventually relapse and become refractory to therapy. The treatment of patients with relapsed and/or refractory MM is frequently further complicated by the presence of pre-existing comorbidities that arise from an advanced disease state and of toxicities stemming from prior antimyeloma treatment. Carfilzomib and pomalidomide have recently been approved for the treatment of patients with relapsed and refractory MM. While these agents represent important additions to the available treatment options, the identification of patients who may best benefit from the use of each of therapy is still being investigated. A number of patient-related and disease-related factors may impact treatment efficacy and/or tolerability, and the clinical presentation and medical history of each patient must be carefully considered to optimize treatment. Here, we review results from carfilzomib and pomalidomide clinical trials in patients with relapsed and/or refractory MM who also have baseline comorbidities or treatment-induced or disease-induced complications (including the presence of renal impairment, cardiac risk factors, peripheral neuropathy, or high-risk chromosomal abnormalities) to evaluate the safety and efficacy of the two agents in these difficult-to-treat patients and to provide treatment recommendations specific to each scenario.

Key words: carfilzomib, multiple myeloma, pomalidomide

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy [1]. Following the increased use of novel therapeutics in the last decade, such as the immunomodulatory agents lenalidomide and thalidomide and the proteasome inhibitor bortezomib, survival times have improved for patients with MM [2]. Most patients, however, inevitably relapse and develop treatment-refractory disease [3]. Recently, two new agents, carfilzomib and pomalidomide, have been approved in the United States (and for pomalidomide, also in Europe) to treat patients with relapsed and refractory MM [4].

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Carfilzomib is a proteasome inhibitor that binds selectively and irreversibly to its target. Carfilzomib was approved in the United States for use as a single agent in the treatment of patients with MM who have failed at least two prior regimens (including an immunomodulatory agent and bortezomib) and have progressed within 60 days of last treatment. The approval of carfilzomib was based on efficacy and safety results from a phase II study (PX-171-003-A1 [NCT00511238]) and the safety results from three other phase II studies (PX-171-003-A0, PX-171-004, and PX-171-005 [NCT00511238, NCT00530816, NCT00721734]) [5–8]. The recommended dose and schedule for carfilzomib is 20 mg/m² during cycle 1, followed by escalation to a target dose of 27 mg/m² during cycle 2, and beyond, administered i.v. on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle [9].

Pomalidomide is an immunomodulatory agent that was developed to improve on the efficacy and safety of thalidomide; it was approved for use in combination with dexamethasone in the United States and Europe to treat patients with MM who have failed at least two prior regimens (including lenalidomide and bortezomib) and have progressed on last treatment (Europe) or within 60 days of last treatment (United States).

The approval of pomalidomide was based on the phase I/II study MM-002 (NCT00833833), which demonstrated that pomalidomide plus low-dose dexamethasone was more effective than single-agent pomalidomide in patients with relapsed and refractory MM [10], and on the phase III study MM-003 (NCT01311687), which demonstrated that pomalidomide plus low-dose dexamethasone was more effective than high-dose dexamethasone in patients with primary refractory or relapsed and refractory MM [11]. The recommended dose and schedule for pomalidomide is 4 mg orally once daily on days 1–21 of a 28-day cycle. When pomalidomide is combined with dexamethasone, the recommended dexamethasone dose is 40 mg orally once weekly [12].

While these agents have shown significant promise in treating patients with relapsed and/or refractory MM, identification of the patient populations that may best benefit from treatment with these agents is ongoing. A number of patient-related and disease-related factors may impact treatment efficacy and/or tolerability. Therefore, balancing clinical efficacy and safety is important when treating these patients.

Here, we review data from recent clinical trials that examined the safety and efficacy of carfilzomib or pomalidomide in select patient populations. It should be noted, however, that patients in clinical trials are subject to eligibility criteria and may not be completely representative of patients with MM in a real-world population.

renal impairment

It is estimated that 20%–60% of patients with MM develop renal insufficiency or progressive renal failure during the course of their disease [13, 14]. The development of renal failure is an important negative prognostic factor for patient survival [15–17]. The dose of agents that are eliminated via the kidneys or that have a pharmacokinetic profile that is influenced by renal dysfunction may need to be reduced in patients with renal failure, which can impact treatment efficacy [12, 18–21].

Carfilzomib

Carfilzomib is well tolerated in patients with relapsed and/or refractory MM and concomitant renal insufficiency, including patients on chronic hemodialysis [22]. The PX-171-005 study examined the safety of carfilzomib in patients with relapsed and/or refractory MM and varying degrees of renal impairment, ranging from chronic hemodialysis to normal renal function (Table 1) [22]. Patients received 15 mg/m² carfilzomib in cycle 1; if the dose was tolerated, it was increased to 20 mg/m² in cycle 2 and 27 mg/m² for cycle 3 and beyond, as tolerated.

In the PX-171-005 study, carfilzomib was found to be cleared predominantly through extrarenal pathways [22], and carfilzomib pharmacokinetics did not appear appreciably different in patients with renal impairment (including those on dialysis) compared with those with normal renal function. Importantly, the safety profile of carfilzomib was similar across all groups of renal function. There were no appreciable differences in the type, frequency, or severity of adverse events (AEs) in the PX-171-005 study when compared with the other phase II studies of single-agent carfilzomib, where patients had a creatinine clearance (CrCl) ≥30 ml/min [5–8]. Carfilzomib was safely escalated to 27 mg/m² in patients with renal impairment and did not appear to be associated with nephrotoxicity, suggesting that carfilzomib does not require dose or schedule modifications for use in patients with MM and concomitant renal insufficiency.

A cross-trial safety analysis of data from the four key phase II studies of single-agent carfilzomib (PX-171-003-A0, PX-171-003-A1, PX-171-004, and PX-171-005; N = 526) found that carfilzomib has an acceptable tolerability profile in patients with renal dysfunction (patients were required to have a CrCl ≥30 ml/min, with the exception of PX-171-005) [23]. Across all four studies, 24% of patients had moderate-to-severe renal dysfunction (CrCl <50 ml/min), and 39% had mild renal dysfunction (CrCl ≥50 to <80 ml/min). Although the majority of patients entered into the phase II studies with some degree of renal dysfunction at baseline, grade 3/4 renal AEs were uncommon (reported in 7% of patients; n = 38) and were predominantly grade 3 (82%; 31/38 patients). In addition, 48% of renal AEs were associated with disease progression.

Of the 515 patients assessable for creatinine values, 87% did not have worsening of renal function during the course of treatment. Among those who had worsening renal function, it was transient in 46% (31/68 patients).

Efficacy in patients with baseline renal impairment was also similar to that of patients with normal baseline renal function. The pivotal phase II trial PX-171-003-A1 examined overall response rates (ORRs) in patients with normal renal function compared with patients with mild or moderate impairment of renal function when treated with a target dose of 27 mg/m² carfilzomib [6]. The investigators found that response rates were similar across groups, suggesting that renal impairment does not impact carfilzomib efficacy: the ORR for response-evaluable patients (n = 257) was 24% [95% confidence interval (CI) 19–29], and ORR for patients with CrCl of 30 to <50 ml/min (n = 57) was 25% (95% CI 14–38); 50 to <80 ml/min (n = 100) was 28% (95% CI 20–38); and ≥80 ml/min (n = 92) was 20% (95% CI 12–29).
pomalidomide

Although both pomalidomide and its metabolites are primarily excreted through the kidneys, pomalidomide is extensively metabolized before excretion; thus only 2% of the parent drug is renally excreted before excretion; thus only 2% of the parent drug is renally excreted [27]. It is therefore hypothesized that renal function will not have a major effect on pomalidomide exposure in patients. There has been limited research published to date, however, on the use of pomalidomide in patients with renal impairment (RI), as pomalidomide has been primarily studied in patients with a CrCl ≥ 60 ml/min; patients with CrCl <45 ml/min were excluded from the study [25]. Median progression-free survival (PFS) and overall survival (OS) were significantly longer in both groups for patients treated with pomalidomide plus low-dose dexamethasone versus patients treated with high-dose dexamethasone.

Among patients in the phase III STRATUS study (NCT01712789), tolerability was similar for patients with relapsed and/or refractory MM who received pomalidomide plus low-dose dexamethasone regardless of whether they had moderate renal impairment (CrCl <60 ml/min; n = 162) or did not have moderate renal impairment (CrCl ≥60 ml/min; n = 290); as in the MM-003 study, patients with CrCl <45 ml/min were excluded from the study [26]. Responses rates were also similar irrespective of renal function (35% and 34%, respectively).

The ongoing phase I MM-008 study (NCT01575925) and phase II MM-013 study (NCT02045017) are prospectively evaluating the pharmacokinetics and safety of pomalidomide plus low-dose dexamethasone in patients with relapsed and/or refractory MM and severe renal impairment [28, 29]. Because patients with severe renal impairment were excluded from the pivotal MM-002 and MM-003 trials, results from these studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Percent of patients with RI at baseline</th>
<th>Safety</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carfilzomib</td>
<td></td>
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<tr>
<td>PX-171-005 [22]</td>
<td>50</td>
<td>16% on chronic dialysis 16% with CrCl &lt;30 ml/min 20% with CrCl 30–&lt;50 ml/min 24% with CrCl 50–80 ml/min 24% with CrCl &gt;80 ml/min</td>
<td>12% of patients with pre-existing RI experienced worsening RI</td>
<td>ORRs Chronic dialysis: 38% CrCl &lt;30 ml/min: 25% CrCl 30–&lt;50 ml/min: 22% CrCl 50–80 ml/min: 27% CrCl &gt;80 ml/min: 18% Efficacy not reported in patients with baseline RI</td>
</tr>
<tr>
<td>PX-171-003-A0, PX-171-003-A1, PX-171-004, PX-171-005 [23]</td>
<td>526</td>
<td>24% with CrCl &lt;50 ml/min 39% with CrCl ≥50–&lt;80 ml/min</td>
<td>13% reported worsening renal function Grade 3/4 renal AEs reported in 7% of patients overall</td>
<td>Safety not reported in patients with baseline RI ORRs CrCl 30–&lt;50 ml/min: 25%; CrCl 50–&lt;80 ml/min: 28%; CrCl ≥80 ml/min: 20%</td>
</tr>
<tr>
<td>PX-171-003-A1 [6]</td>
<td>266</td>
<td>22% with CrCl 30–&lt;50 ml/min 39% with CrCl 50–&lt;80 ml/min 36% with CrCl ≥80 ml/min</td>
<td>Safety not reported in patients with baseline RI</td>
<td>Efficacy not reported in patients with baseline RI</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MM-002 [24]</td>
<td>113 (P + D)</td>
<td>23% with CrCl &lt;45 ml/min 12% with CrCl 45–60 ml/min 62% with CrCl &gt;60 ml/min</td>
<td>AEs were generally comparable, regardless of baseline renal function</td>
<td>Efficacy not reported in patients with baseline RI</td>
</tr>
<tr>
<td>MM-003 [25]</td>
<td>302 (P + D)</td>
<td>31% with CrCl 45–60 ml/min</td>
<td>Safety not reported in patients with baseline RI</td>
<td>Median PFS: 3 months Median OS: 10 months</td>
</tr>
<tr>
<td>STRATUS (MM-010) [26]</td>
<td>456</td>
<td>36% with CrCl 45–60 ml/min 64% with CrCl ≥60 ml/min</td>
<td>AEs were generally consistent across renal function subgroups Grade 3/4 acute renal failure reported in 3% of patients with and 2% of patients without moderate RI Grade 3/4 blood creatinine increased reported in 2% of patients with and 1% of patients without moderate RI</td>
<td>In patients with moderate RI versus without moderate RI: ORR: 35% versus 34% DOR: 6 versus 7 months PFS: 4 versus 5 months OS: 9 months versus not reached</td>
</tr>
</tbody>
</table>

AE, adverse events; CrCl, creatinine clearance; D, dexamethasone; DOR, duration of response; ORR, overall response rate; P, pomalidomide; PFS, progression-free survival; OS, overall survival.
will help clarify the safety and efficacy of pomalidomide in this patient subgroup [29]. Preliminary data from 16 patients in the MM-008 study suggest that, when normalized by the pomalidomide dose received, exposure to pomalidomide in patients with severe renal impairment is similar to that in patients with normal or mildly impaired renal function [29].

**scenario-based treatment recommendation**

While pomalidomide and its metabolites are excreted primarily through the kidney, carfilzomib is cleared predominantly extra-renally. Based on available data, however, we conclude that patients with moderate renal impairment can be treated with either carfilzomib or pomalidomide (Table 2). In patients with severe renal impairment, carfilzomib may be preferred, given the evidence demonstrating its safety and efficacy in this setting and the lack of published data on pomalidomide. Results from the ongoing pomalidomide MM-008 and MM-013 studies will facilitate future treatment recommendations for patients with severe renal impairment.

**cardiovascular history or risk factors**

Cardiovascular events are commonly reported in patients with MM [30] and may be associated with certain classes of anti-MM agents, including anthracyclines and alkylating agents [31–34]. Thus, an understanding of the tolerability of agents in patients with pre-existing cardiovascular comorbidities is an important consideration in the treatment of MM.

**carfilzomib**

In the four key phase II trials, patients who had New York Heart Association class III or IV congestive heart failure, symptomatic cardiac ischemia, conduction abnormalities uncontrolled by conventional intervention, or myocardial infarction within the previous 6 months (or previous 3 months for the PX-171-005 study) were excluded [5–8, 22]. Despite these exclusion criteria, 74% of patients had a history of cardiovascular events (Table 3) [23]. In addition, 70% had baseline cardiovascular risk factors, defined as the use of at least one cardiovascular or antidiabetic medication before study entry.

Overall, grade 3/4 cardiac events occurred in 10% of patients treated with carfilzomib; the majority (60%) were cardiac failure [35]. Thirty-eight patients (7%) reported cardiac failure events, regardless of causality, and 18 patients (3%) reported ischemic heart disease [35]. Notably, among patients with any cardiac failure event, 87% had a history of a cardiac comorbidity, and among patients with any ischemic heart disease event, 89% had a history of cardiac disease [35]. Hypertension (mainly grade 1/2) was reported in 14% of patients, and more than half of these patients had a history of hypertension [23]. In the phase II studies, overall mortality was the same (7%) for patients with and without baseline cardiac risk factors [23].

In the randomized phase III study ASPIRE, which compared carfilzomib, lenalidomide, and dexamethasone (KRd) with lenalidomide and dexamethasone (Rd) in patients with relapsed MM (NCT01080391), 6% of patients in the KRd group and 4% of patients in the Rd group reported cardiac failure of any grade.

### Table 2. Scenario-based treatment recommendations

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Carfilzomib</th>
<th>Pomalidomide</th>
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</thead>
<tbody>
<tr>
<td>Renal impairment</td>
<td></td>
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<tr>
<td>Moderate renal impairment</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Severe renal impairment</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Pre-existing cardiac disease</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>History of venous thromboembolism or risk factors for thromboembolic complications</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Pre-existing peripheral neuropathy</td>
<td>+</td>
<td>+</td>
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<tr>
<td>High-risk cytogenetics</td>
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<td></td>
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<tr>
<td>Del17p</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>+</td>
<td>–</td>
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</tbody>
</table>

+ indicates treatment may be a good option; – indicates that another treatment option may be preferred.

### Table 3. Key safety and efficacy results in carfilzomib and pomalidomide trials for patients with cardiovascular history

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Percent of patients with cardiovascular history at baseline</th>
<th>Safety</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carfilzomib</td>
<td></td>
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<tr>
<td>PX-171-003-A0, PX-171-003-A1, PX-171-004, PX-171-005 [23, 35]</td>
<td>526</td>
<td>74% with a medical history of cardiovascular events</td>
<td>7% of patients overall reported cardiac failure, of which 87% had a history of a cardiac comorbidity</td>
<td>Efficacy not reported in patients with cardiovascular history</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70% with baseline cardiovascular risk factors</td>
<td>3% of patients overall reported an ischemic heart disease event, among which 89% had a history of cardiac disease</td>
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<td></td>
<td>14% of patients overall reported hypertension, among which more than half had a history of hypertension</td>
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<td></td>
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<td></td>
<td>Overall mortality was the same (7%) for patients with and without baseline cardiac risk factors</td>
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<tr>
<td>Pomalidomide</td>
<td></td>
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<tr>
<td>MM-002 [36]</td>
<td>55% of patients had ‘abnormal not clinically significant’ values at baseline</td>
<td>Safety not reported in patients with cardiovascular history</td>
<td>Efficacy not reported in patients with cardiovascular history</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Scenario-based treatment recommendations

Table 3. Key safety and efficacy results in carfilzomib and pomalidomide trials for patients with cardiovascular history
while 6% and 5% of patients, respectively, reported ischemic heart disease [37].

The rates of cardiac failure reported in the phase II (6%–8%) and phase III studies (5%–6%) were similar to the rate reported with bortezomib (8%) [38]. Most cardiac events were reported in patients with baseline risk factors, including patients with pre-existing cardiac comorbidities or prior treatment with an agent with known cardiotoxicity.

There has been little information published on the use of carfilzomib in patients with a history of thromboembolic events or other risk factors for venous thromboembolism, but low incidence rates have been reported in patients who received single-agent carfilzomib treatment (1%) [39]. In the ASPIRE trial, 7% of patients who received KRd and 4% of patients who received Rd reported deep vein thrombosis of any grade [37].

**pomalidomide**

There have been few reports on the efficacy or safety of pomalidomide in patients with baseline cardiovascular risk factors. In the MM-002 study, most shifts in electrocardiographic results in patients receiving pomalidomide or pomalidomide with dexamethasone were from normal baseline to ‘abnormal not clinically significant,’ and there were similar incidence rates reported in both treatment groups [36]. Overall, the effect of pomalidomide on electrocardiogram parameters has not yet been fully established [40].

In a phase I study in which thromboprophylaxis was not required (N = 24), four patients (13%) with relapsed or refractory MM reported thrombosis following pomalidomide treatment [41]. Later trials required aspirin or equivalent thromboprophylaxis, resulting in lower rates of thromboembolic complications. In the MM-002 (N = 221) and MM-003 trials (N = 450), the rate of deep vein thrombosis or pulmonary embolism was 2% in patients who received pomalidomide or pomalidomide with dexamethasone; rates were not reported in patients with a history of thromboembolic events [10, 11].

**scenario-based treatment recommendation**

Based on available data, patients with pre-existing cardiac disease may be treated with pomalidomide or carfilzomib. In patients with a history of venous thromboembolism or other risk factors for thromboembolic complications, it may be preferable to administer carfilzomib (or other alternative treatment options) instead of pomalidomide, although pomalidomide is considered safe with adequate thromboprophylaxis.

**pre-existing peripheral neuropathy (PN)**

Peripheral neuropathy (PN) is commonly seen in patients with MM, arising from the disease itself or as a treatment-related toxicity. As many as 20% of patients with newly diagnosed MM may have electromyographic evidence of PN [42], and up to 75% of patients may experience treatment-emergent PN, particularly those treated with thalidomide- or bortezomib-based regimens [42–44]. Subcutaneous administration of bortezomib has been reported to reduce the incidence of PN relative to i.v. administration, but bortezomib was still associated with PN in 38% of patients in a phase III study [45].

**carfilzomib**

In the four phase II studies, 85% of patients had a history of PN, 43% of which were attributed to bortezomib treatment and 43% of which were attributed to thalidomide treatment (Table 4) [23]. Forty-seven percent of patients had previously discontinued treatment due to PN. Although 378 patients (72%) had active PN at baseline (all grade 1/2; patients with grade 3/4 PN or grade 2 PN with pain were excluded from enrollment), the majority of patients with baseline PN (87%) did not report PN-related AEs while on study.

Overall, PN was reported infrequently in the phase II studies (14% of patients). All grade 3 PN [seven cases (1%)] were reported in patients with grade 1/2 PN at baseline, and no grade 4 PN was reported. Most PN AEs occurred before cycle 6, which suggests a lack of cumulative toxicity.

Results from the PX-171-003-A1 study demonstrated that carfilzomib treatment in patients with grade 1/2 PN at baseline has similar efficacy as treatment of patients without baseline PN [6]. Of 266 patients, the majority (77%) had grade 1/2 PN at baseline. The ORR was 24% for patients with grade 1/2 PN at baseline compared with 24% among all response-evaluable patients (n = 257), and the clinical benefit rate was 36% in patients with grade 1/2 PN at baseline compared with 37% in the overall response-evaluable patient population.

In the PX-171-004 study, improved response rates were observed in patients previously treated with bortezomib who had baseline PN relative to patients without baseline PN [8]. Seventy percent of patients enrolled in the study (90/129) had a history of PN at baseline, and 53% (68/129) had grade 1/2 PN at baseline. The ORR was 56% (95% CI 43–68) in patients with a baseline PN of at least grade 1 (n = 66) compared with 39% (95% CI 27–53) in patients without baseline PN (n = 59).

In the ASPIRE study, 36% (n = 144) and 35% (n = 137) of patients in the KRd and Rd groups, respectively, had grade 1/2 PN at baseline [37]. The hazard ratio for PFS was 0.69 (95% CI 0.57–0.83; P < 0.0001) for KRd versus Rd in the overall population, while the PFS hazard ratio for patients with PN at baseline was 0.95 (95% CI 0.69–1.30) [37]. Overall, there was no meaningful difference in PN incidence rates between KRd and Rd patients (17% for both groups) [37].

Overall, carfilzomib does not appear to exacerbate existing PN and was not associated with an increase in the incidence of PN when administered with Rd. PN incidence rates reported with carfilzomib (14%–17%) were substantially lower than those reported with i.v. (56%) or subcutaneous (39%) bortezomib [45]. These findings may be at least partially attributable to the more selective proteasome inhibition of carfilzomib, because bortezomib is thought to induce neurodegeneration through off-target effects via a proteasome-independent mechanism [48].

**pomalidomide**

In the MM-003 study, 15% of patients treated with pomalidomide plus low-dose dexamethasone developed PN of any grade, including 1% with grade 3/4 PN [11]. At the 2013 Annual Meeting of the European Hematology Association, investigators from the study presented data showing that among patients with treatment-emergent PN, 52% (24/46) had grade 1 PN at baseline (patients with grade 2 or greater PN were excluded from enrollment) [46].
Nine patients (27%) experienced PN during treatment (all had PN at baseline (patients with grade 3/4 PN were excluded) (NCT00558896), more than half of the patients (59%; 20/34) were in patients with relapsed and lenalidomide-refractory MM patients with standard-risk cytogenetics [49].

Lower response rates and decreased survival compared with subgroups. Patients with at least two chromosomal abnormalities were counted in multiple subgroups. Patients with two or more concurrent abnormalities had lower response rates and shorter PFS and OS compared with those with one abnormality (ORR was 16% versus 30%, median PFS was 2.1 versus 3.6 months, and median OS was 8 versus 11 months, respectively). However, in patients with isolated t(4;14) as a single abnormality, the ORR was 64% with a median PFS of 5 months and a median OS of 16 months. As comparison, in the overall patient population, the ORR was 24%, and the median OS was 16 months [6].

In the ASPIRE study, 13% of patients had high-risk disease (12% in the KRd group and 13% in the Rd group) [37]. However, 47% of enrolled patients were not evaluated for available treatment options.

**scenario-based treatment recommendation**

We conclude that patients with pre-existing PN may be treated with standard doses of either carfilzomib or pomalidomide plus low-dose dexamethasone.

**cytogenetic risk**

High-risk chromosomal aberrations in patients with MM—such as the loss of chromosome 13, the deletion of 17p13, or chromosomal translocations t(4;14), t(14;16), or t(14;20)—are associated with lower response rates and decreased survival compared with patients with standard-risk cytogenetics [49].

Treatment with bortezomib and, to a lesser extent, lenalidomide reduces the impact of certain high-risk cytogenetic markers on outcomes in the frontline setting, particularly in patients with t(4;14) [50–57], thus an understanding of the efficacy of carfilzomib and pomalidomide in such patients is important when evaluating available treatment options.

**Table 4. Key safety and efficacy results in carfilzomib and pomalidomide trials for patients with pre-existing peripheral neuropathy (PN)**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Percent of patients with PN at baseline</th>
<th>Safety</th>
<th>Efficacy</th>
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<tbody>
<tr>
<td><strong>Carfilzomib</strong></td>
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</tr>
<tr>
<td>PX-171-003-A0, PX-171-003-A1, PX-171-004, PX-171-005 [23]</td>
<td>526</td>
<td>85% with a history of PN</td>
<td>13% of patients who had baseline PN reported PN-related AEs</td>
<td>Efficacy not reported in patients with baseline PN</td>
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<tr>
<td></td>
<td></td>
<td>72% with active PN at baseline</td>
<td>1% of patients overall reported grade 3 PN (all had grade 1/2 PN at baseline)</td>
<td></td>
</tr>
<tr>
<td>PX-171-003-A1 [6]</td>
<td>266</td>
<td>77% with grade 1/2 PN at baseline</td>
<td>Safety not reported in patients with baseline PN</td>
<td>ORR: 24% in patients with grade 1/2 PN at baseline</td>
</tr>
<tr>
<td>PX-171-004 [8]</td>
<td>129</td>
<td>70% with a history of PN</td>
<td>Safety not reported in patients with baseline PN</td>
<td>ORR: 56% in patients with grade ±1 PN at baseline</td>
</tr>
<tr>
<td>ASPIRE [37]</td>
<td>792 (KRd, 396; Rd, 396)</td>
<td>35% had grade 1/2 PN at baseline (KRd, 36%; Rd, 35%)</td>
<td>Safety not reported in patients with baseline PN</td>
<td>PFS: HR 0.95 (95% CI 0.69–1.30) for KRd versus Rd in patients with PN at baseline</td>
</tr>
<tr>
<td><strong>Pomalidomide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MM-003 [46]</td>
<td>302 (P + D)</td>
<td>Not reported</td>
<td>15% of patients overall reported PN, of whom 52% had grade 1 PN at baseline</td>
<td>Efficacy not reported in patients with baseline PN</td>
</tr>
<tr>
<td>NCT00558896 [47]</td>
<td>34</td>
<td>59% had PN at baseline</td>
<td>26% of patients overall experienced PN, of whom 67% had PN at baseline</td>
<td>Efficacy not reported in patients with baseline PN</td>
</tr>
</tbody>
</table>

AE, adverse event; CI, confidence interval; D, dexamethasone; HR, hazard ratio; KRd, carfilzomib–lenalidomide–dexamethasone; ORR, overall response rate; P, pomalidomide; PFS, progression-free survival; Rd, lenalidomide–dexamethasone.
## Table 5. Key safety and efficacy results in carfilzomib and pomalidomide trials for patients with high-risk cytogenetics

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Percent of patients with high-risk cytogenetics at baseline</th>
<th>Safety</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carfilzomib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PX-171-003-A1 [58]</td>
<td>229 (with cytogenetics profiles available)</td>
<td>27% with high-risk cytogenetics</td>
<td>Safety not reported in patients with high-risk cytogenetics</td>
<td>ORR: 26% in high-risk patients (39% in patients with t(4;14); 17% in patients with del17p13)   Median DOR: 6 months   Median PFS: 4 months   Median OS: 9 months (12 months in patients with t(4;14); 7 months in patients with del17p13)</td>
</tr>
<tr>
<td>PX-171-004, BTZ-pretreated [7]</td>
<td>35</td>
<td>26% with unfavorable cytogenetics</td>
<td>Safety not reported in patients with high-risk cytogenetics</td>
<td>ORR: 11% in patients with unfavorable cytogenetics</td>
</tr>
<tr>
<td>PX-171-004, BTZ-naive [8]</td>
<td>122 (with cytogenetic profiles available)</td>
<td>15% with unfavorable cytogenetics</td>
<td>Safety not reported in patients with high-risk cytogenetics</td>
<td>ORR: 37% in patients with unfavorable cytogenetics</td>
</tr>
<tr>
<td>ASPIRE [37]</td>
<td>792 (KRd, 396; Rd, 396)</td>
<td></td>
<td>Safety not reported in patients with high-risk cytogenetics</td>
<td>PFS HR: 0.70 (95% CI 0.43–1.16) for KrD versus Rd in patients with high-risk cytogenetics</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MM-002 [10, 59]</td>
<td>87 (with cytogenetic profiles available)</td>
<td>27% with high-risk cytogenetics</td>
<td>Safety not reported in patients with high-risk cytogenetics</td>
<td>ORR: 23%   Median PFS: 3 months   Median OS: 13 months   Median DOR: 5 months   ORR: 28%</td>
</tr>
<tr>
<td>NCT01177735 [60]</td>
<td>71</td>
<td></td>
<td>Safety not reported in patients with high-risk cytogenetics</td>
<td></td>
</tr>
<tr>
<td>MM-003 [11, 61]</td>
<td>302 (P + D)</td>
<td></td>
<td>Safety not reported in patients with high-risk cytogenetics</td>
<td></td>
</tr>
<tr>
<td>IFM 2009-02 [62]</td>
<td>84</td>
<td></td>
<td>Safety not reported in patients with high-risk cytogenetics</td>
<td>ORR: 33% in patients with del17p; 17% in patients with t(4;14)   1-year PFS: 44%   1-year OS: 27%</td>
</tr>
<tr>
<td>IFM 2010-02 [63]</td>
<td>50</td>
<td></td>
<td>Safety not reported in patients with high-risk cytogenetics</td>
<td>Median OS: 12 months (not reached in patients with del17p; 9 months in patients with t(4;14))   8-month EFS: 59%   Median TTP: 3 months (8 months in patients with del17p; 3 months in patients with t(4;14))</td>
</tr>
</tbody>
</table>

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*aDefined as del17p13, t(4;14), or t(14;16) by interphase FISH or del13 or hypodiploidy by metaphase cytogenetics.

*Defined as t(4;14), t(14;16), or del17p in at least 60% of plasma cells.

*Defined as del17p13 and/or t(4p16/14q32).

*Defined as high risk on gene expression (GEP70 or GEP80 signatures), elevated LDH, or having abnormal metaphase cytogenetics.

CI, confidence interval; D, dexamethasone; DOR, duration of response; EFS, event-free survival; FISH, fluorescence in situ hybridization; GEP, gene expression profile; HR, hazard ratio; KrD, carfilzomib–lenalidomide–dexamethasone; LDH, lactate dehydrogenase; ORR, overall response rate; OS, overall survival; P, pomalidomide; PFS, progression-free survival; Rd, lenalidomide–dexamethasone; TTP, time to progression.
cytogenetic risk at study entry. Among patients with high-risk cytogenetics, the PFS hazard ratio was 0.70 (95% CI 0.43–1.16) for KRd versus Rd.

Overall, the results suggest that carfilzomib can at least partially overcome the adverse impact of certain cytogenetic aberrations, particularly t(4;14), such that these unfavorable cytogenetic/FISH markers do not adversely affect response rates in patients treated with single-agent carfilzomib or the PFS benefit observed for KRd versus Rd [64].

pomalidomide

In the MM-002 study, pomalidomide plus low-dose dexamethasone showed encouraging activity in patients with del17p and/or t(4;14) (n = 30), where the median PFS was 3 months, ORR was 23%, and median DOR was 5 months [10, 59]. In comparison, the median PFS was 4 months, ORR was 33%, and median DOR was 8 months overall in patients treated with pomalidomide plus low-dose dexamethasone (n = 113) [10]. Similar results were reported in a phase II trial (NCT01177735) that examined the use of single-agent pomalidomide in patients with relapsed and refractory MM with high-risk disease, which was defined by gene expression profiling, elevated lactate dehydrogenase, or the presence of abnormal metaphase cytogenetics [60]. Pomalidomide was found to be active in these heavily pretreated patients, with an ORR of 28%.

In the MM-003 study, 25% of patients who received pomalidomide plus low-dose dexamethasone treatment had high-risk cytogenetics (based on the presence of del17p or t(4;14)) [11, 61]. Treatment with pomalidomide plus low-dose dexamethasone led to significantly better ORR and PFS compared with treatment with high-dose dexamethasone, regardless of patients’ cytogenetic risk, although the median OS was lower in patients with high-risk cytogenetics who were treated with pomalidomide (10 months) relative to patients with standard-risk cytogenetics (14 months).

While these results demonstrate that pomalidomide is active in patients with high-risk cytogenetics, additional research suggests that patients with high-risk cytogenetics still have poorer outcomes relative to the intent-to-treat population when treated with pomalidomide plus low-dose dexamethasone. In the IFM 2009-02 study, 21 (38%) of the bortezomib- and lenalidomide-refractory patients who were treated with pomalidomide plus dexamethasone had high-risk cytogenetics, defined as the presence of del17p and/or t(4;14) [62]. Of the 15 patients with del17p, five achieved a partial response or better, while only one of six patients with t(4;14) achieved a partial response or better. PFS and OS rates at 1 year were significantly poorer in patients with high-risk cytogenetics compared with the intent-to-treat population [PFS 44% versus 95%, respectively (P = 0.005); OS 27% versus 67%, respectively (P = 0.0002)].

In the follow-up study IFM 2010-02 (NCT01745640), the efficacy of pomalidomide plus low-dose dexamethasone was specifically investigated in patients with relapsed and refractory MM who had either del17p (46% of patients) or t(4;14) chromosomal abnormalities (64%) [63]. Preliminary results suggest that patients with del17p derive greater benefit from treatment with pomalidomide plus low-dose dexamethasone than do patients with t(4;14), where the median time to progression was 8 versus 3 months, respectively, and the median OS was not reached versus 9 months, respectively. Similar findings were reported in the MM-003 study: patients with del17p had increased median OS compared with patients with t(4;14) (13 versus 8 months, respectively) [61]. However, further follow-up is needed to confirm these results.

scenario-based treatment recommendation

Based on the available data, treatment with pomalidomide and low-dose dexamethasone may be preferred in patients with del17p, since these patients seem to derive greater benefit compared with patients with t(4;14). Carfilzomib may be preferred in patients with t(4;14), especially if this is the single cytogenetic abnormality identified in the patient and del17p is not present. However, the cross-trial comparisons of efficacy and safety upon which this recommendation is based should be interpreted with caution.

conclusion

Patients with relapsed and/or refractory MM are a heterogeneous population that may have a number of pre-existing comorbidities or treatment-emergent toxicities that may impact the efficacy and safety of carfilzomib or pomalidomide treatment. Furthermore, such patients may have acquired additional high-risk features, such as dominant clones bearing del17p or other cytogenetic abnormalities, which may decisively impact disease outcomes. An understanding of patient- and disease-specific factors is important when attempting to balance treatment efficacy and toxicity in these patients. Within this context, we have provided scenario-specific recommendations based on available clinical data to aid the clinician in selecting between carfilzomib and pomalidomide treatment. These common scenarios are based on the impact of both patient-related factors (such as comorbidities, prior toxicities) and also disease-specific scenarios (renal dysfunction, high-risk cytogenetics). However, additional prospective studies are needed to define the optimal strategy for the implementation of these drugs in the everyday clinical practice in patients with relapsed/refractory MM and to better understand the efficacy and safety of these agents in patients with baseline risk factors and comorbidities.

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and Onyx. JS has served as an advisor for Millennium, Celgene, Novartis, Onyx, Janssen, Bristol-Myers Squibb, and MSD.

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