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original article

Treatment outcomes in patients with relapsed and refractory multiple myeloma and high-risk cytogenetics receiving single-agent carfilzomib in the PX-171-003-A1 study

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Several cytogenetic abnormalities are associated with poor outcomes in multiple myeloma (MM). We prospectively analyzed the impact of cytogenetic abnormalities on outcomes during the phase 2 PX-171-003-A1 study of single-agent carfilzomib for relapsed and refractory MM. In the response-evaluable population (257/266), fluorescence in situ hybridization (FISH)/conventional cytogenetic profiles were available for 229 patients: 62 (27.1%) had high-risk cytogenetics—del 17p13, t(4;14) or t(14;16) by interphase FISH or deletion 13 or hypodiploidy by metaphase cytogenetics—and 167 (72.9%) had standard-risk profiles. Generally, baseline characteristics were similar between the subgroups, but International Staging System stage III disease was more common in higher-risk vs standard-risk patients (41.9% vs 27.5%) as was Eastern Cooperative Oncology Group performance status 1/2 (85.5% vs 68.3%). Overall response was comparable between the subgroups (25.8% vs 24.6%, respectively; P = 0.85), while time-to-event end points showed a trend of shorter duration in high-risk patients, including median duration of response (5.6 months (95% confidence interval (CI) 3.7–7.8) vs 8.3 months (95% CI 5.6–12.3)) and overall survival (9.3 (95% CI 6.5–13.0) vs 19.0 months (95% CI 15.4–NE); P = 0.0003). Taken together, these findings demonstrate that single-agent carfilzomib is efficacious and has the potential to at least partially overcome the impact of high-risk cytogenetics in heavily pre-treated patients with MM.

Keywords: multiple myeloma; cytogenetics; proteasome inhibitor; carfilzomib; relapsed; refractory

INTRODUCTION

Chromosomal abnormalities are a hallmark of multiple myeloma (MM) and are often complex, involving changes in both the number and structure of the chromosomes.1–5 Generally, the primary lesions are reciprocal translocations (t) involving the immunoglobulin heavy chain gene locus on chromosome 14 and various partner loci.6 These include t(11;14), t(4;14), t(14;16) and t(14;20), with the latter three indicative of poorer prognosis.4 As the disease progresses, secondary aberrations are common and are associated with more aggressive disease. These include translocations of the MYC gene, the loss or deletion of chromosome 13, deletion of 17p13 and complex changes involving chromosomes 1, 2, 4, 7, 8. It is not uncommon for patients to acquire multiple karyotypic changes over the course of their disease, resulting in an increasingly complex and aggressive disease that proves difficult to treat.4

Chromosomal abnormalities have a variable impact on therapeutic response and time-to-event end points in patients with MM.5,6,10 Before the introduction of targeted therapy with proteasome inhibitors and immunomodulatory drugs, response rates were lower and duration of response (DOR) and event-free and overall survival (OS) shorter in patients with high-risk cytogenetic abnormalities compared with standard-risk patients.7 The proteasome inhibitor bortezomib and the immunomodulators thalidomide and lenalidomide have demonstrated some benefit in patients with high-risk cytogenetic characteristics, but outcomes can be variable and dependent on the specific marker and treatment regimen (for example, single agent vs multi-agent).11,13–22 In the case of bortezomib, a number of studies provide evidence that it can reduce or eliminate the impact of certain adverse cytogenetic markers.13–18 For immunomodulatory drugs, the evidence is less established but lenalidomide and pomalidomide both appear to provide benefit in certain high-risk cytogenetic subgroups, whereas few studies have demonstrated a favorable outcome with thalidomide.11,19–22 Because of their impact on treatment, cytogenetic risk status has become a standard stratification factor in MM trials evaluating established and novel agents.13,23

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Keywords: multiple myeloma; cytogenetics; proteasome inhibitor; carfilzomib; relapsed; refractory
Carfilzomib, a selective proteasome inhibitor, has demonstrated durable single-agent activity in patients with advanced MM.\textsuperscript{24–27} Carfilzomib was recently approved in the United States for the treatment of relapsed and refractory MM (RRMM)\textsuperscript{28} based on efficacy and safety results from the pivotal phase 2 study PX-171-003-A1.\textsuperscript{29,30} In this trial, 266 patients with RRMM were enrolled with a median age of 63 years, a median of 5.4 years since diagnosis and a median of five previous treatment regimens for MM. Nearly all patients (99.6%) had received bortezomib before and 73% were refractory to bortezomib. The overall response rate (ORR) was 23.7% in the response-evaluable population (n = 257) with a median DOR of 7.8 months, a median progression-free survival (PFS) of 3.7 months and a median OS of 15.6 months. Adverse events were manageable without cumulative toxicities. The most common events included fatigue (49%), anemia (46%), nausea (45%) and thrombocytopenia (39%); 12.4% of patients experienced Grade 1 or 2 peripheral neuropathy.

The primary objective of the present analysis was to prospectively evaluate the effect of cytogenetic abnormalities on the response rate from the PX-171-003-A1 study and secondarily to evaluate their impact on time-to-event end points, including DOR, time to progression (TTP), PFS and OS.

**PATIENTS AND METHODS**

The methodology for PX-171-003-A1 has been described previously.\textsuperscript{24} Briefly, this was a multicenter, open-label, single-arm, phase 2 study (Clinicaltrials.gov NCT00511238) involving 31 centers in the United States and Canada. Patients ≥ 18 years of age with measurable progressive MM were eligible for this trial if they had received ≥ 2 previous regimens, including bortezomib, thalidomide or lenalidomide, an alkylating agent, or an anthracycline, unless contraindicated, and had achieved a response to ≥ 1 previous regimen. Patients had to be refractory to their most recent therapy (that is, < 25% response or progression during treatment or within 60 days of last dose), have an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2 and adequate bone marrow (platelet count ≥ 50 000/mm\textsuperscript{3}, hepatic (for example, serum aspartate aminotransferase concentrations < 3 times the upper limit of normal) and renal function (creatinine clearance ≥ 30 ml/min).

Single-agent carfilzomib was administered intravenously over 2–10 min on Days 1, 2, 8, 9 and 15 of each 28-day cycle. The dose for Cycle 1 was 20 mg/m\textsuperscript{2}, which was then escalated to 27 mg/m\textsuperscript{2} for all cycles thereafter up to a maximum of 12 cycles.\textsuperscript{29}

The primary end point was ORR,\textsuperscript{29} and secondary efficacy end points included the clinical benefit rate (CBB = ORR + minimal response), DOR, TTP, PFS and OS. Responses were assessed on Day 15 of Cycle 1, Day 1 of subsequent cycles and at the end of the study according to the International Myeloma Working Group (IMWG) criteria modified to include minimal response as defined by the European Group for Blood and Marrow Transplantation.\textsuperscript{9,30} Response and disease progression (when clinically possible) were confirmed by two consecutive assessments. Thus, the earliest confirmation could occur within Cycle 2. Of note, response by the cytogenetic risk subgroup (high-risk vs standard-risk) was a prospectively planned analysis.

Conventional metaphase cytogenetic and/or interphase fluorescence in situ hybridization (FISH) were conducted at a local laboratory of the participating center per standard of practice at the time of the trial and included the use of unpurified bone marrow samples for most patients. Patients were classified as having standard-risk or high-risk cytogenetic abnormalities per the criteria of the IMWG.\textsuperscript{1–3} High-risk cytogenetic markers included del 13 or hypodiploidy by metaphase cytogenetic analysis and/or del 17p13, t(4;14), t(14;16) by interphase FISH. For this analysis, patients without these abnormal markers were considered standard risk. Of note, del 13q14 by FISH alone was not considered a high-risk marker.\textsuperscript{3,11,12}

Statistical analysis

Analyses were conducted with the response-evaluable population, which was defined as patients who received at least one dose of carfilzomib and underwent baseline disease response assessments and at least one post-baseline disease assessment or patients who discontinued protocol treatment before the first day of Cycle 2 due to an adverse event that was considered to be possibly or probably related to carfilzomib. ORR, CBR, disease control rate (DCR = CBR + stable disease) and time-to-event end points (that is, DOR, TTP, PFS and OS) were determined by the status of cytogenetic abnormalities (high risk vs standard risk). In addition, response was assessed by the number of cytogenetic abnormalities (1 vs ≥ 2) and for specific abnormalities—del 13, hypodiploidy, del 17p13, t(14;16) and t(14;16).

Categorical end points and continuous variables were summarized with descriptive statistics. For time-to-event end points, medians and 95% confidence intervals (CIs) were estimated by the Kaplan–Meier method. Comparisons between the high- and standard-risk subgroups were made using the Chi-square test for categorical end points and the Log-rank test for time-to-event end points. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

**RESULTS**

A total of 266 patients were enrolled in the PX-171-003-A1 study. Of the response-evaluable population (257 patients), metaphase cytogenetic and/or FISH data were available for 229 patients. These patients were the focus of this analysis, with 167 (72.9%) identified as standard risk and 62 (27.1%) identified as high risk. The incidence of a single high-risk abnormality was 18.8%, and 8.3% of patients had multiple (≥ 2) high-risk abnormalities (Table 1). The most common cytogenetic abnormality was del 17p13 (13.1%), while t(14;16) was the least frequent (1.3%). Cytogenetic deletion 13 was observed in 14 patients (6.1%). In the standard-risk subgroup, del 13q14 by FISH was reported as a single abnormality in 9 patients (3.9%). Baseline characteristics were generally comparable between the high- and standard-risk subgroups with some exceptions, most notably International Staging System (ISS) stage and ECOG performance status (Table 2). ISS stage III disease was more common in the high-risk than in the standard-risk subgroup (41.9% vs 27.5%), as was ECOG performance status of 1 or 2 (85.5% vs 68.3%).

The ORR was similar between the high-risk and standard-risk subgroups (25.8% vs 24.6%, respectively), while the CBR was lower for the high-risk subgroup (30.7% vs 40.7%) (Table 3). The rate of greater than or equal to very good partial response was 0% and 8.4%, respectively. The incidence of progressive disease was comparable between the two subgroups (22.6% vs 27.5%, respectively), but the rate of treatment discontinuation due to progressive disease within the first two cycles was 29.0% (18/62) in the high-risk subgroup vs 20.4% (34/167) in the standard-risk subgroup.

With respect to time-to-event end points, there was a general trend of shorter duration in the high-risk subgroup compared with the standard-risk subgroup, including median DOR (5.6 vs 8.3 months). For survival outcomes, median PFS was 3.5 vs 4.6 months (P = 0.06), respectively, and median OS was 9.3 vs 19.0 months, respectively (P = 0.0003) (Figure 1).

Analysis of outcomes by specific abnormalities (see Supplementary Table) showed that patients with t(4;14) had the highest ORR (38.9%), whereas patients with del 17p13 had the lowest (16.7%). Furthermore, patients with t(4;14) had the longest median OS at 11.8 months (95% CI 3.1–NE), whereas those with del 17p13 had the shortest at 7.0 months (95% CI 4.0–20.7). It is important to note that these subgroups are not independent of each other because patients with ≥ 2 abnormalities were counted in multiple subgroups. An analysis of the high-risk subgroup suggested differences in outcomes based on the number of abnormalities present (1 vs ≥ 2). The ORR in patients with one abnormality was 30.2% compared with 15.8% for those having ≥ 2 abnormalities, the median PFS was 3.6 months (95% CI 2.8–4.6) vs 2.1 months (95% CI 0.8–4.6) and the median OS was 10.6 months (95% CI 4.9–20.7) vs 8.4 months (95% CI 3.1–14.7). In patients isolated with t(4;14) as a single abnormality, the ORR was 63.6% with a median PFS of 4.5 months (95% CI 2.8–11.5) and a median OS of 15.8 months (95% CI 4.2–NE).
DISCUSSION

This report represents the first prospective analysis to evaluate the impact of cytogenetics on treatment outcomes with single-agent carfilzomib. In multiple studies, high-risk cytogenetic abnormalities, including del 13, hypodiploidy, del 17p13, t(4;14) and t(14;16), have been associated with poor response and shorter DOR, PFS and/or OS. Del 17p13 assessed by FISH is usually a late event in the evolution of MM. It is indicative of more aggressive disease and has consistently been shown to be one of the more significant prognostic factors among high-risk cytogenetic abnormalities regardless of the treatment strategy, including conventional chemotherapy or targeted therapies. Although t(4;14) is also associated with poor prognosis, its impact appears to be less pronounced than del 17p13, and Del 13 by cytogenetics can be a primary or secondary aberration and is indicative of a highly proliferative disease state.

### Table 1. Cytogenetic status in the response-evaluable population (n = 229)

| Cytogenetics | FISH |
|--------------|------|
| Del 13       | Del 17p13 | t(4;14) | t(14;16) |
| Standard risk| —      | —       | —       | —        |
| —            | —      | —       | —       | 167 (72.9) |
| High risk    | 14 (6.1) | 23 (10.0) | 30 (13.1) | 18 (7.9) | 3 (1.3) | 62 (27.1) |
| Single abnormality | * | — | — | — | 2 (0.9) |
| —            | —      | —       | —       | —       | 11 (4.8) | 17 (7.4) |
| —            | —      | —       | —       | —       | 2 (0.9) |
| —            | —      | —       | —       | —       | 19 (8.3) |
| Multiple abnormalities | * | * | — | — | 5 (2.2) |
| —            | —      | —       | —       | —       | 1 (0.4) |
| —            | —      | —       | —       | —       | 4 (1.7) |
| —            | —      | —       | —       | —       | 1 (0.4) |
| —            | —      | —       | —       | —       | 1 (0.4) |
| —            | —      | —       | —       | —       | 6 (2.6) |
| Abbreviations: Del, deletion; FISH, fluorescence in situ hybridization; t, translocation. *Indicates abnormality present.

### Table 2. Baseline characteristics for response-evaluable patients by cytogenetic status (N = 229)

| Characteristic | Standard risk (n = 167) | High risk (n = 62) |
|---------------|-------------------------|-------------------|
| Age, years, median (range) | 65 (37–87) | 63 (39–84) |
| Male, n (%) | 91 (54.5) | 41 (66.1) |
| Time from diagnosis, years, median (range) | 5.6 (0.5–21.2) | 5.3 (1.3–22.3) |
| Plasma cells on bone marrow biopsy, median, n (%) | 65 (38.9) | 29 (46.8) |
| Unknown/not specified | 6 (3.6) | 3 (4.8) |
| International Staging System stage, n (%) | | |
| I | 56 (33.5) | 10 (16.1) |
| II | 63 (37.7) | 24 (38.7) |
| III | 46 (27.5) | 26 (41.9) |
| Unknown/not specified | 2 (1.2) | 2 (3.2) |
| ECOG performance status, n (%) | | |
| 0 | 53 (31.7) | 9 (14.5) |
| 1 | 94 (56.3) | 45 (72.6) |
| 2 | 20 (12.0) | 8 (12.9) |
| Previous regimens, median (range) | 5 (1–20) | 5 (2–12) |
| ≥ 4, n (%) | 133 (79.6) | 51 (82.3) |
| Refractory to last regimen, n (%) | | |
| Progressive disease on therapy | 118 (70.7) | 53 (85.5) |
| Progressive disease within 60 days ≤ 25% response | 23 (13.8) | 6 (9.7) |
| Previous agents, n (%) | | |
| Bortezomib | 166 (99.4) | 62 (100) |
| Lenalidomide or thalidomide | 167 (100) | 62 (100) |
| Corticosteroid | 163 (97.6) | 62 (100) |
| Alkylating agent | 153 (91.6) | 57 (91.9) |
| Stem cell transplant | 119 (71.3) | 45 (72.6) |
| Anthracycline | 107 (64.1) | 39 (62.9) |

### Table 3. Response rates and time-to-event data by cytogenetic status in response-evaluable patients

| Characteristic | Standard risk (n = 167) | High risk (n = 62) | P-value |
|---------------|-------------------------|-------------------|--------|
| Best response | | |
| CR | 1 (0.6) | 0 (0) |
| VGPR | 13 (7.8) | 0 (0) |
| PR | 27 (16.2) | 16 (25.8) |
| MR | 27 (16.2) | 3 (4.8) |
| SD | 46 (27.5) | 25 (40.3) |
| PD | 46 (27.5) | 14 (22.6) |
| NE | 7 (4.2) | 4 (6.5) |
| ORR (CR + VGPR + PR) | 41 (24.6) | 16 (25.8) | 0.85 |
| CBR (ORR + MR) | 68 (40.7) | 19 (30.7) | 0.16 |
| DCR (CBR + SD) | 114 (68.3) | 44 (71.0) | 0.69 |
| Time-to-event variable, median (95% CI), months | | |
| DORb | 8.3 (5.6–12.3) | 5.6 (3.7–7.8) | — |
| TTP | 4.6 (2.8–6.5) | 3.6 (2.3–4.6) | 0.10 |
| PFS | 4.6 (2.8–5.8) | 3.5 (2.1–4.5) | 0.06 |
| OS | 19.0 (15.4–NE) | 9.3 (6.5–13.0) | 0.0003 |

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; MR, minimal response; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time to progression; VGPR, very good partial response. *Based on enrolled population.

bIncludes only patients who achieved PR or better; presented descriptively because of the limited number of responders for statistical comparison.
The prognostic impact of del 13 may be related to its association with del 17p13 and t(4;14).12 The primary analysis of PX-171-003-A1 demonstrated that single-agent carfilzomib was clinically efficacious with a favorable safety profile in patients with RRMM who were heavily pretreated and had limited treatment options.24 Overall, patients were able to achieve clinically meaningful and durable responses. In this prospectively planned subgroup analysis, single-agent carfilzomib was efficacious in patients with high-risk and standard-risk cytogenetics. Response rates were comparable between these subgroups and consistent with the overall study results.24 There was, however, a general trend in the time-to-event end points that suggested a shorter duration in the high-risk subgroup for DOR, PFS and OS. The presence of del 17p13 appeared to have the greatest impact on response and OS, whereas t(4;14) did not. Taken together, our findings suggest that carfilzomib as a single agent has the potential to, at least partially, overcome the adverse impact of certain cytogenetic abnormalities. In terms of putting these findings into context with historical data, as noted earlier, studies have shown variable activity for bortezomib15–17 and lenalidomide in patients with high-risk cytogenetics.11,21,22 either alone or in combination with dexamethasone. In the SUMMIT study, a single-arm, phase 2 trial of bortezomib ± dexamethasone for RRMM,16 there was a trend of lower ORR (24% vs 33%; P = NS (not significant)) and shorter OS (median, 10 vs 15 months; P = 0.14) in patients with del 13 by metaphase cytogenetics compared with those without del 13, with matched-pairs analysis showing a similar trend. In a matched-pairs analysis of patients enrolled in the APEX study, a phase 3 trial in relapsed MM that compared bortezomib with high-dose dexamethasone, there was a similar trend in patients with and without del 13 by metaphase cytogenetics with respect to ORR (25% vs 35%; P = NS) and OS (median 12.5 months vs NR (not reported); P = 0.79).16 In the high-dose dexamethasone arm, there was no statistical difference for ORR (9% vs 26%, respectively), but OS was significantly shorter for patients with del 13 (median 3.3 months vs NR; P < 0.002). Additionally, a retrospective study in 65 patients with relapsed or refractory MM treated with bortezomib showed no statistical difference in outcomes between patients with and without t(4;14) by FISH for ORR (67% vs 56%), PFS (median 10.5 vs 6.8 months) and OS (median 15.1 vs 12.3 months).17 In a separate prospective study, Dimopoulos et al.10 examined the impact of high-risk cytogenetics (defined similarly as in our study) in 99 patients with relapsed/refractory MM treated with lenalidomide and dexamethasone (RD, n = 50) or bortezomib with RD (VRD, n = 49). High-risk cytogenetics was associated with a lower response rate compared with standard-risk cytogenetics (44% vs 74%; P = 0.007) and shorter PFS (10.1 vs 5.6 months; P = 0.003) in the overall population. In the subgroup receiving RD, the ORR was also lower in patients with high-risk cytogenetics (31% vs 74%; P = 0.01), with a similar trend in the subgroup receiving VRD (55% vs 74%; P = 0.22). With respect to individual abnormalities, only del 17p was retained as a significant predictor of response in multivariate analysis (odds ratio 43.91; 95% CI 3.92–490.96; P = 0.002), which has also been observed in other studies with bortezomib and lenalidomide.15,21,22

The trends in the results reported herein are generally consistent with these historical studies, particularly for t(4;14), and del 17p appeared to be associated with greater risk than others markers. For del 17p, outcomes may be improved with complex multidrug treatments,10,13,14,18,35 but fully overcoming its negative impact will likely require novel approaches or combinations that do not act via apoptosis induction.36 It should be noted that there are a number of important differences between PX-171-003-A1 and these historical studies, making comparisons to historical data difficult. In particular, the PX-171-003-A1 study population differs from that of many earlier studies in which previous exposure to bortezomib was less common and patients were less likely to be refractory to novel agents and had fewer lines and types of previous therapy.24 Furthermore, cytogenetic stratification criteria have evolved over time and therefore are not consistent across studies. For instance, many historical studies considered del 13q by FISH is not prognostically important unless accompanied by del 13 by metaphase cytogenetics or another high-risk marker.3 Despite their inclusion in the most recent IMWG criteria, del 13 and hypodiploidy by metaphase cytogenetics and t(4;14) as markers of risk is also evolving. These abnormalities are currently considered intermediate markers of risk in Mayo Clinic Guidelines.23

Potential limitations specific to the data reported here should be acknowledged, including the single-arm phase 2 study design, imbalances between the high- and standard-risk subgroups in other baseline prognostic factors (for example, ISS stage III disease and ECOG performance status)37 and the small patient numbers, which preclude the use of robust multivariate analyses. In addition, patients’ high-risk cytogenetics without documented treatment for progressive disease within the first two cycles based on a protocol-defined early response assessment on Day 15 before full doses were administered, which may have impacted outcomes. Given these considerations, the response rates in this high-risk patient population are particularly encouraging and warrant additional exploration of carfilzomib and cytogenetic characteristics in various treatment settings and, importantly, in the randomized setting. Preliminary results of a phase 2 study assessing carfilzomib in combination with lenalidomide and low-dose dexamethasone (CRD) in patients with newly diagnosed MM (N = 53) suggest that outcomes are comparable between high-risk and standard-risk patients regardless of age.25,39 It is also of
clinical interest to differentiate carfilzomib activity in specific abnormalities, particularly in view of the potential for improved outcomes in patients with t(4;14) suggested by the data reported here. To this, a number of single-arm as well as phase 3 studies with carfilzomib, as a single agent or as part of multiday drug combinations, have been initiated and should provide more robust data on the impact of high-risk abnormalities on carfilzomib activity and outcomes. These include the FOCUS study (carfilzomib vs corticosteroid ± cyclophosphamide in RRM, NCT01302392), the ASPIRE study (C Ridley vs Rd in relapsed MM, NCT01080391), the ENDEAVOR study (carfilzomib plus dexamethasone vs bortezomib plus dexamethasone in relapsed MM, NCT01568866) and CLARION (carfilzomib, melphalan, prednisone vs bortezomib, melphalan, prednisone in newly diagnosed MM, NCT01818752).

In conclusion, single-agent carfilzomib showed encouraging activity in heavily pretreated patients with high-risk cytogenetic abnormalities who were enrolled in this prospective analysis from the PX-171-003-A1 study. The observation that response rates were similar for high-risk and standard-risk patients and durable across a range of cytogenetic profiles suggests that carfilzomib may be beneficial in patients with high-risk disease. The achievement of a more definitive benefit with regard to time-to-event end points may require combining carfilzomib with other agents. The findings from this study serve as the basis for further evaluation in ongoing and future clinical studies as to the role of high-risk cytogenetic characteristics in the broader context of the clinical development program for carfilzomib.
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