Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial

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Summary

Background As lenalidomide becomes increasingly established for upfront treatment of multiple myeloma, patients refractory to this drug represent a population with an unmet need. The combination of pomalidomide, bortezomib, and dexamethasone has shown promising results in phase 1/2 trials of patients with relapsed or refractory multiple myeloma. We aimed to assess the efficacy and safety of this triplet regimen in patients with relapsed or refractory multiple myeloma who previously received lenalidomide.

Methods We did a randomised, open-label, phase 3 trial at 133 hospitals and research centres in 21 countries. We enrolled patients (aged ≥18 years) with a diagnosis of multiple myeloma and measurable disease, an Eastern Cooperative Oncology Group performance status of 0–2, who received one to three previous regimens, including a lenalidomide-containing regimen for at least two consecutive cycles. We randomly assigned patients (1:1) to bortezomib and dexamethasone with or without pomalidomide using a permutated blocked design in blocks of four, stratified according to age, number of previous regimens, and concentration of β_2 microglobulin at screening. Bortezomib (1·3 mg/m²) was administered intravenously until protocol amendment 1 then either intravenously or subcutaneously on days 1, 4, 8, and 11 for the first eight cycles and subsequently on days 1 and 8. Dexamethasone (20 mg [10 mg if age >75 years]) was administered orally on the same days as bortezomib and the day after. Patients allocated pomalidomide received 4 mg orally on days 1–14. Treatment cycles were every 21 days. The primary endpoint was progression-free survival in the intention-to-treat population, as assessed by an independent review committee. Safety was assessed in all patients who received at least one dose of study medication. This trial is registered at ClinicalTrials.gov, number NCT01734928; patients are no longer being enrolled.

Findings Between Jan 7, 2013, and May 15, 2017, 559 patients were enrolled. 281 patients were assigned pomalidomide, bortezomib, and dexamethasone and 278 were allocated bortezomib and dexamethasone. Median follow-up was 15·9 months (IQR 9·9–21·7). Pomalidomide, bortezomib, and dexamethasone significantly improved progression-free survival compared with bortezomib and dexamethasone (median 11·20 months [95% CI 9·66–13·73] *vs* 7·10 months [5·88–8·48]; hazard ratio 0·61, 95% CI 0·49–0·77; p<0·0001). 278 patients received at least one dose of pomalidomide, bortezomib, and dexamethasone and 270 patients received at least one dose of bortezomib and dexamethasone, and these patients were included in safety assessments. The most common grade 3 or 4 treatment-emergent adverse events were neutropenia (116 [42%] of 278 patients *vs* 23 [9%] of 270 patients; nine [3%] *vs* no patients had febrile neutropenia), infections (86 [31%] *vs* 48 [18%]), and thrombocytopenia (76 [27%] *vs* 79 [29%]). Serious adverse events were reported in 159 (57%) of 278 patients versus 114 (42%) of 270 patients. Eight deaths were related to treatment; six (2%) were recorded in patients who received pomalidomide, bortezomib, and dexamethasone (pneumonia [n=2], unknown cause [n=2], cardiac arrest [n=1], cardiorespiratory arrest [n=1]) and two (1%) were reported in patients who received bortezomib and dexamethasone (pneumonia [n=1], hepatic encephalopathy [n=1]).

Interpretation Patients with relapsed or refractory multiple myeloma who previously received lenalidomide had significantly improved progression-free survival when treated with pomalidomide, bortezomib, and dexamethasone compared with bortezomib and dexamethasone. Adverse events accorded with the individual profiles of pomalidomide, bortezomib, and dexamethasone. This study supports use of pomalidomide, bortezomib, and dexamethasone as a treatment option in patients with relapsed or refractory multiple myeloma who previously received lenalidomide.

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Research in context

Evidence before this study

We searched PubMed and proceedings from the American Society of Hematology, the American Society of Clinical Oncology, and the European Hematology Association for clinical trial results published between Jan 1, 2012, and June 30, 2018. Search terms included "multiple myeloma", "relapse", "refractory", "phase III", "phase 3", and "dexamethasone". We identified seven randomised phase 3 trials that investigated novel doublet or triplet regimens in patients with relapsed or refractory multiple myeloma who had received a median of one or two previous lines of treatment. However, only three of the seven trials included patients refractory to lenalidomide, who comprised 7–24% of the overall study population. The only randomised phase 3 evidence for effectiveness in the context of lenalidomide resistance was with pomalidomide in later lines of treatment (median five previous lines). No randomised phase 3 trials have been published including lenalidomide-refractory patients in early line of therapy after relapse. Data from two early-phase trials showed promising clinical activity and safety of the pomalidomide, bortezomib, and dexamethasone regimen in patients previously treated with lenalidomide.

Added value of this study

To our knowledge, our phase 3 trial is the first to assess a triplet regimen in patients with multiple myeloma in early lines of treatment for relapsed or refractory disease who received previous lenalidomide, including those who were refractory to lenalidomide. Treatment with pomalidomide, bortezomib, and dexamethasone showed a clinically meaningful improvement in progression-free survival compared with bortezomib and dexamethasone. Grade 3 or 4 neutropenia and infection were reported more frequently in patients treated with pomalidomide, bortezomib, and dexamethasone compared with bortezomib and dexamethasone.

Implications of all the available evidence

A growing population of patients with lenalidomide-pretreated multiple myeloma, including those considered refractory to lenalidomide, need early-line treatment after relapse or refractory disease develops. To date, these patients have been poorly studied. The improvement in progression-free survival seen with pomalidomide, bortezomib, and dexamethasone in this patient population underscores the potential for this combination regimen as a treatment option.

Introduction

Treatment of relapsed or refractory multiple myeloma remains challenging, particularly the management of patients who—regardless of the treatment used—have become refractory to initial treatments. The depth and duration of response decrease with every treatment leading to progressively more aggressive and resistant disease.[1,2] Moreover, the immune systems of patients with myeloma become increasingly dysfunctional with every subsequent line of treatment.[3] By combining compounds with different mechanisms of action, including tumouricidal and immunostimulatory properties, multiagent regimens offer a viable approach for overcoming intratumour heterogeneity and drug resistance and for keeping the immune system engaged. Thus, triplet regimens have emerged as the therapeutic option of choice in relapsed or refractory multiple myeloma, leading to improved outcomes compared with doublet regimens.[4]

Lenalidomide is a preferred drug for newly diagnosed multiple myeloma. Patients who receive lenalidomide early in their treatment—many of whom will become refractory to the drug while on treatment—represent a clinically relevant population for whom proven treatment options are needed.[5–7] Therefore, randomised phase 3 trials specifically designed to address further lines of treatment in this patient population, which until now has largely been excluded from phase 3 studies,[8–11] are necessary.

Pomalidomide (similar to lenalidomide) is an immunomodulatory agent that exerts potent, direct tumouricidal and immune-enhancing effects through binding to cereblon (CRBN)—a protein in the E3 ubiquitin ligase complex—and subsequent proteasomal degradation of the transcription factors ikaros (IKZF1) and aiolos (IKZF3).[12,13] Pomalidomide is pharmacologically distinct from lenalidomide in several ways; it has, for example, a higher potency against cereblon, different substrate degradation kinetics, and a distinct gene-activation profile leading to differentiated antitumour and immunostimulating properties.[12–15] Pomalidomide is also active in the context of lenalidomide-resistant cell lines and animal models.[13,14,16] This activity has been recorded in clinical trials in which patients refractory to lenalidomide achieved clinical benefit with pomalidomide.[17–20]

The combination of pomalidomide, bortezomib, and dexamethasone has shown activity in early-phase clinical trials in patients with relapsed or refractory multiple myeloma.[21,22] A phase 1 dose-escalation study of pomalidomide with twice-weekly bortezomib and dexamethasone showed encouraging clinical activity and safety in heavily pretreated lenalidomide-refractory and proteasome inhibitor-exposed patients (overall response achieved by 65%).[21] In a phase 1/2 trial assessing pomalidomide plus once-weekly bortezomib and dexamethasone in patients with relapsed lenalidomide-refractory multiple myeloma who had received a median of two previous lines of treatment, an overall response was achieved by 86% (95% CI 73–94) of patients and a stringent complete response (defined according to International Myeloma Working Group [IMWG] criteria)[23] was achieved by 12%, with median progression-free survival of 13·7 months (95% CI 9·7–17·7).[22]

Based on these promising clinical results, we did an international phase 3 trial (OPTIMISMM) to compare the efficacy and safety of pomalidomide, bortezomib, and dexamethasone versus bortezomib and dexamethasone in patients with multiple myeloma in early lines of treatment after relapsed or refractory disease and who received previous lenalidomide, including patients considered refractory to lenalidomide.

Methods

Study design and participants

OPTIMISMM is a randomised, open-label, controlled, phase 3 trial done at 133 hospitals and research centres in 21 countries (appendix pp 6–8). Patients were eligible to participate in the study if they were aged 18 years or older and had a diagnosis of multiple myeloma, had measurable disease based on serum (≥0·5 g/dL) or urine (≥200 mg/24 h) protein levels, and had an Eastern Cooperative Oncology Group performance status of 0–2. Further eligibility criteria were that the patient had received one to three previous regimens (including two or more cycles of lenalidomide treatment) and had investigator-determined progressive disease during or after their last antimyeloma regimen.

Patients refractory to lenalidomide, including those who received lenalidomide in their last previous regimen, were eligible. We defined refractory patients as those with disease that was non-responsive to treatment (failure to achieve minimum response or development of progressive disease) or progression within 60 days of the last dose, inclusive. Patients exposed to bortezomib were eligible for the study as long as they did not have progressive disease during treatment or within 60 days of the last dose of a bortezomib-containing regimen (dosing schedule 1·3 mg/m² of body surface area twice weekly). Patients who progressed on or within 60 days of a once-weekly bortezomib schedule or on a lower dose of bortezomib were eligible to participate and were regarded as the bortezomib-refractory patient population in this trial.

We excluded patients with creatinine clearance lower than 30 mL/min requiring dialysis, grade 3 or worse peripheral neuropathy, or grade 2 peripheral neuropathy with pain. Additional details about eligibility criteria and the full study protocol are provided in the appendix (pp 1, 23–131).

All patients provided written informed consent. The protocol was approved by the institutional review board or central or local ethics committee at every participating site. The study was designed and done in accordance with the principles of Good Clinical Practice according to the International Conference on Harmonisation requirements and the Declaration of Helsinki.

Randomisation and masking

Eligible patients were randomly assigned 1:1 to bortezomib and dexamethasone with or without pomalidomide (appendix p 2), using a validated interactive response technology system. Randomisation was done using a permutated blocked design with a block size of four, stratified according to age (≤75 years *vs* >75 years), number of previous regimens (1 *vs* >1), and the concentration of β_2 microglobulin at screening (<3·5 mg/L *vs* 3·5–5·5 mg/L *vs* >5·5 mg/L). Because the trial was open label, study centre personnel and enrolled patients were not masked to treatment assignment. The funder of the study was unaware of aggregate treatment assignments in the statistical analyses and treatment-level analysis results.

Procedures

All patients received treatment in cycles of 21 days until progressive disease or unacceptable toxicity. Bortezomib (1·3 mg/m² of body surface area) was administered intravenously until protocol amendment 1 (on March 27, 2014) then either intravenously or subcutaneously on days 1, 4, 8, and 11 of cycles one to eight and on days 1 and 8 of cycle nine and beyond. Dexamethasone (20 mg if aged ≤75 years, otherwise 10 mg) was administered orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of cycles one to eight and on days 1, 2, 8, and 9 of cycle nine and beyond. Patients allocated pomalidomide received the drug at a dose of 4 mg orally on days 1–14 of each cycle. The dosing schedule for pomalidomide, bortezomib, and dexamethasone was based on the results of the preceding phase 1 dose-escalation study.[21]

See Online for appendix

Per protocol, patients could discontinue from the study treatment phase because of adverse events, pregnancy, progressive disease, protocol violation, withdrawal of consent, death, loss to follow-up, or study termination by the funder. Dose interruptions and reductions were permitted for any study drug throughout the study. All patients who received pomalidomide, bortezomib, and dexamethasone, and those with a history of deep vein thrombosis or pulmonary embolism (regardless of treatment group assignment), were given low-dose aspirin, low-molecular-weight heparin, or other equivalent antithrombotic or anticoagulant treatment. Antiviral prophylactic treatment could be administered to all patients at the discretion of the investigator. Antibiotics and antifungals were used as per site standard and were permitted by protocol. Additional permitted concomitant treatments are listed in the appendix (p 1).

Laboaratory assessments for efficacy included electrophoresis and immunofixation of serum and urine monoclonal proteins, quantitative measurement of serum immunoglobulins and corrected serum calcium, and serum free light chain assays. Baseline measurements were made on day 1 of cycle one. Samples were obtained at screening, on day 1 of each cycle, at treatment discontinuation, and every 3 weeks during and at the end of the progression-free survival follow-up phase. Bone marrow samples were obtained from patients at screening—including for qualitative cytogenetic assessment by fluorescence in situ hybridisation—and at time of

complete response. High-risk cytogenetics were defined as detection of at least one high-risk abnormality—del(17p), t(4;14), or t(14;16). Radiographic assessment of lytic bone lesions (skeletal survey) was done at screening and when clinically indicated thereafter. For extramedullary plasmacytomas that could only be assessed radiographically, we did assessments at screening, on day 1 of cycle three and every three cycles thereafter, at treatment discontinuation, every 3 weeks during and at the end of the progression-free survival follow-up phase, and when clinically indicated to confirm a response. Laboratory assessments were done centrally (ICON Laboratory Services; Dublin Ireland; Farmingdale, NY, USA; and Singapore) except for analyses of percentages of plasma cells in bone marrow and plasmacytomas, which were done locally.

Safety assessments comprised assessment of adverse events, clinical laboratory tests, electrocardiograms, measurement of vital signs, and physical examinations. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0 or higher) and were summarised by system organ class and preferred term. Second primary malignancies were monitored and reported as serious adverse events.

Myeloma response and progression were assessed by an independent review adjudication committee (IRAC) according to IMWG criteria.[23] IRAC reviewers were masked to treatment assignment, demographic information, study site, and investigator assessment. Safety and efficacy data were monitored by an independent data monitoring committee (IDMC), who reviewed unmasked data at predetermined times throughout the trial.

Health-related quality of life (HRQOL) was assessed using the global health status/QoL domain of the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire on day 1 of every 21-day cycle before treatment administration and at the end of treatment. We assessed HRQOL in all patients who were randomly assigned who completed the EORTC QLQ-C30 assessment at baseline and had one or more post-baseline visits.

Outcomes

The primary endpoint was progression-free survival, defined as time from randomisation to disease progression or death. Prespecified secondary endpoints were overall survival (time from randomisation to death due to any cause), overall response (partial response or better) according to IMWG criteria, duration of response (time of first documented response to confirmed progressive disease or death due to any cause for all responders), and safety.

Prespecified exploratory endpoints presented here were time to response (time from randomisation to the first documented response), progression-free survival after next-line treatment (time from randomisation to second objective disease progression, or death from any cause, whichever occurred first), HRQOL, and subgroup efficacy analyses. Additional exploratory endpoints not reported here are listed in the appendix (p 1).

Statistical analysis

We estimated the analysis of progression-free survival would provide 80% power to detect a hazard ratio (HR) of 0·73 for disease progression or death with pomalidomide, bortezomib, and dexamethasone. Efficacy analyses included one interim analysis for futility (at approximately 50% of progression-free survival events) and one final analysis for progression-free survival. Using a two-sided significance level of 5%, with one interim analysis for futility only at 50% of events, we initially estimated that 381 events would be needed to detect a 33% increase in median progression-free survival in patients assigned pomalidomide, bortezomib, and dexamethasone (12 months) versus bortezomib and dexamethasone (9 months), with 80% power. The protocol was amended (amendment 5) on June 14, 2017, to do the final progression-free survival analysis earlier than originally planned because published data from several phase 3 studies showed that progression-free survival with bortezomib and dexamethasone was expected to be shorter in patients previously exposed to lenalidomide (an inclusion criterion of OPTIMISMM).[24–26] Therefore, the final analysis of progression-free survival was done when approximately 320 events had occurred, representing an approximate 57% of events in 559 patients who were randomly assigned.

Both the interim and final analysis results were based on data reviewed by the IRAC. The interim analysis for futility had a non-binding stopping boundary based on gamma function ($\gamma=-6$). At the interim analysis of progression-free survival (data cutoff Jan 20, 2017), the futility boundary was not crossed; therefore, the recommendation of the IDMC was to allow the study to continue. At data cutoff (Oct 26, 2017) the study was still ongoing for collection of additional time-to-event data, including overall survival. An interim analysis of overall survival was planned at the final progression-free survival analysis; however, with less than a third of accumulated events, data were not mature. According to the next prespecified (final) overall survival analysis, a total of 379 deaths would be needed to detect a 33% increase in median overall survival in the pomalidomide, bortezomib, and dexamethasone group (median 40 months) compared with the bortezomib and dexamethasone group (median 30 months) with 75% power.

Primary, secondary, and prespecified exploratory analyses were done in the intention-to-treat population, which included all patients who were randomly assigned. Safety assessments were done in the safety population, which included all patients who received at least one dose of study medication. The intention-to-treat population, efficacy-assessable population (which

included all patients who received at least one dose of study medication and had a baseline and at least one post-baseline efficacy assessment), and all efficacy analyses except for duration of response were adjusted by stratification factors (age, number of previous regimens, and concentration of β_2 microglobulin at screening). However, subgroup analyses for efficacy endpoints were not adjusted by stratification factors. A sensitivity analysis for progression-free survival was done based on the investigator's assessment to support the robustness of the primary data. An unmasked, independent external statistician generated analysis reports for external IDMC review and interim analysis. Treatment groups were unmasked on data lock for the primary analysis.

We used the Kaplan-Meier method to estimate progression-free survival. The treatment effect (measured by HR and 95% CI) was estimated using a stratified Cox proportional hazards model. A stratified Cochran-Mantel-Haenszel test was used to compare responses. If the study primary endpoint was significant at the final analysis, overall responses and overall survival were to be sequentially tested using a step-down approach. Specifically, if the value of the log-rank statistic for progression-free survival was significant, then the overall response would be tested next, at the same significance level of 0·05 (two-sided). If the overall response was significant, then the interim overall survival analysis would be done, with Lan-DeMets implementation of the Pocock boundaries. Type I error was controlled for these endpoints and analyses.

The observed change in HRQOL score from baseline was calculated using a mixed-model repeated measure approach, using baseline covariates where appropriate to estimate the least square means (95% CI and p value) for changes from baseline across all scheduled visits (excluding the visit at the end of treatment) and on day 1 of cycles five, nine, 19, and 25 within each treatment group, as well as the difference in the least square means between treatment groups.

We used SAS software (version 9.2) for the statistical analysis. This study is registered with ClinicalTrials.gov, number NCT01734928.

Role of the funding source

The funder contributed to study design, data collection, data analysis, and data interpretation, and funded a professional medical writer to assist with preparation of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 7, 2013, and May 15, 2017, 712 patients were screened for eligibility and 559 patients were enrolled into the OPTIMISMM trial (appendix p 6). The intention-to-treat population included 281 patients assigned pomalidomide, bortezomib, and dexamethasone and 278 patients allocated bortezomib and dexamethasone (figure 1). The safety population comprised 278 patients who received at least one dose of pomalidomide, bortezomib, and dexamethasone and 270 patients who received at least one dose of bortezomib and dexamethasone. Bortezomib was administered intravenously in 15 patients assigned pomalidomide, bortezomib, and dexamethasone and in 19 patients allocated bortezomib and dexamethasone. After protocol amendment 1, four patients and five patients, respectively, changed to subcutaneous bortezomib injections. Baseline characteristics were generally well balanced between treatment groups (table 1; appendix pp 9, 10) and were representative of patients with early-line relapsed multiple myeloma.

All 559 enrolled patients had received previous treatment with lenalidomide and 391 (70%) patients were lenalidomide-refractory. Of the patients who received one previous line of treatment, 64 (58%) of 111 patients assigned pomalidomide, bortezomib, and dexamethasone and 65 (57%) of 115 patients allocated bortezomib and dexamethasone were refractory to lenalidomide.

At data cutoff (Oct 26, 2017), 185 (67%) of 278 patients in the pomalidomide, bortezomib, and dexamethasone

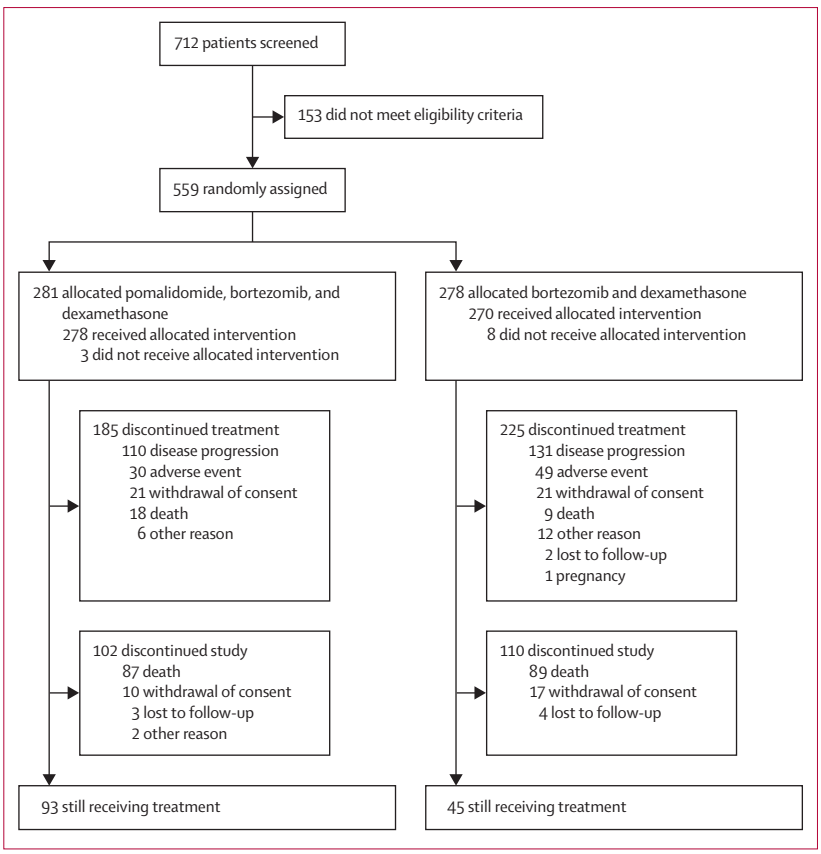

Figure 1: **Trial profile**

	Pomalidomide, bortezomib, and dexamethasone group (n=281)	Bortezomib and dexamethasone group (n=278)
Age (years)	67 (60–73)	68 (59–73)
≤65	123 (44%)	120 (43%)
>65	158 (56%)	158 (57%)
≤75	235 (84%)	231 (83%)
>75	46 (16%)	47 (17%)
Sex		
Male	155 (55%)	147 (53%)
Female	126 (45%)	131 (47%)
ECOG performance status		
0	149 (53%)	137 (49%)
1	121 (43%)	119 (43%)
2	11 (4%)	22 (8%)
ISS disease stage		
I	149 (53%)	138 (50%)
II	85 (30%)	90 (32%)
III	47 (17%)	50 (18%)
Cytogenetic profile by FISH		
Standard risk	137 (49%)	132 (47%)
High risk	61 (22%)	49 (18%)
Time since diagnosis (years)	4·0 (2·6–6·5)	4·3 (2·5–6·4)
Previous lines of treatment	2 (1–2)	2 (1–2)
Lines of treatment		
1	111 (40%)	115 (41%)
2	117 (42%)	104 (37%)
≥3*	53 (19%)	59 (21%)
Previous stem-cell transplant	161 (57%)	163 (59%)
Creatinine clearance (mL/min)		
<60	91 (32%)	76 (27%)
≥60	190 (68%)	202 (73%)
Previous immunomodulatory treatment	281 (100%)	278 (100%)
Lenalidomide	281 (100%)	278 (100%)
Previous alkylating agent	237 (84%)	232 (83%)
Previous proteasome inhibitor	212 (75%)	213 (77%)
Bortezomib	201 (72%)	203 (73%)
Carfilzomib	8 (3%)	11 (4%)
Ixazomib	9 (3%)	5 (2%)
Refractory disease to immunomodulatory drug	202 (72%)	193 (69%)
Lenalidomide	200 (71%)	191 (69%)
Lenalidomide in the last previous antimyeloma regimen before study entry	178 (63%)	167 (60%)
Refractory disease to proteasome inhibitor	37 (13%)	37 (13%)
Bortezomib	24 (9%)	32 (12%)
Refractory disease to last previous regimen	196 (70%)	184 (66%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. ISS=International Staging System. FISH=fluorescence in-situ hybridisation. *One patient assigned bortezomib and dexamethasone received more than three previous lines of treatment.

Table 1: **Baseline characteristics**

group and 225 (83%) of 270 patients in the bortezomib and dexamethasone group had discontinued treatment (figure 1). Of 93 patients who remained on treatment with pomalidomide, bortezomib, and dexamethasone, 71 (76%) were receiving all three drugs. All 45 patients who remained on treatment with bortezomib and dexamethasone were receiving both drugs. The most common reasons for treatment discontinuation were progressive disease (110 [40%] of 278 patients *vs* 131 [49%] of 270 patients) and adverse events (30 [11%] *vs* 49 [18%]), respectively.

Median treatment duration was 8·8 months (IQR 4·4–15·4) with pomalidomide, bortezomib, and dexamethasone versus 4·9 months (2·1–9·0) with bortezomib and dexamethasone. The median number of treatment cycles was 12 (IQR 6–21) of pomalidomide, bortezomib, and dexamethasone versus seven (3–12) of bortezomib and dexamethasone. The median relative dose intensity was 0·85 (IQR 0·70–0·90) for pomalidomide, 0·80 (0·70–0·90) for bortezomib, and 0·80 (0·60–1·00) for dexamethasone in patients assigned pomalidomide, bortezomib, and dexamethasone versus 0·90 (0·80–1·00) for bortezomib and 0·90 (0·70–1·00) for dexamethasone in patients allocated bortezomib and dexamethasone. Treatment exposure data and dosing information for individual drugs in each treatment regimen are provided in the appendix (pp 10, 11).

At median follow-up of 15·9 months (IQR 9·9–21·7), 154 (55%) of 281 patients assigned pomalidomide, bortezomib, and dexamethasone and 162 (58%) of 278 patients allocated bortezomib and dexamethasone had disease progression or death. Progression-free survival was significantly improved with pomalidomide, bortezomib, and dexamethasone (median 11·20 months [95% CI 9·66–13·73]) versus bortezomib and dexamethasone (7·10 months [5·88–8·48]; HR 0·61, 95% CI 0·49–0·77; p<0·0001; figure 2A). Pomalidomide, bortezomib, and dexamethasone also significantly improved median progression-free survival in patients who were considered refractory to lenalidomide (median 9·53 months [95% CI 8·05–11·30]) versus bortezomib and dexamethasone (5·59 months [4·44–7·00]; HR 0·65, 95% CI 0·50–0·84; p=0·0008; figure 2B) and in patients with one previous line of treatment (median 20·73 months [95% CI 15·11–27·99] *vs* 11·63 months [7·52–15·74]; HR 0·54, 95% CI 0·36–0·82; p=0·0027; figure 2C). 120 (60%) of 200 patients in the pomalidomide, bortezomib, and dexamethasone group who were refractory to lenalidomide and 118 (62%) of 191 patients in the bortezomib and dexamethasone group had a progression event or died. 45 (41%) of 111 patients in the pomalidomide, bortezomib, and dexamethasone group who had one previous line of treatment and 52 (45%) of 115 patients in the bortezomib and dexamethasone group had a progression event or died. Patients who had received one previous line of treatment and were refractory to lenalidomide had a median progression-free survival of

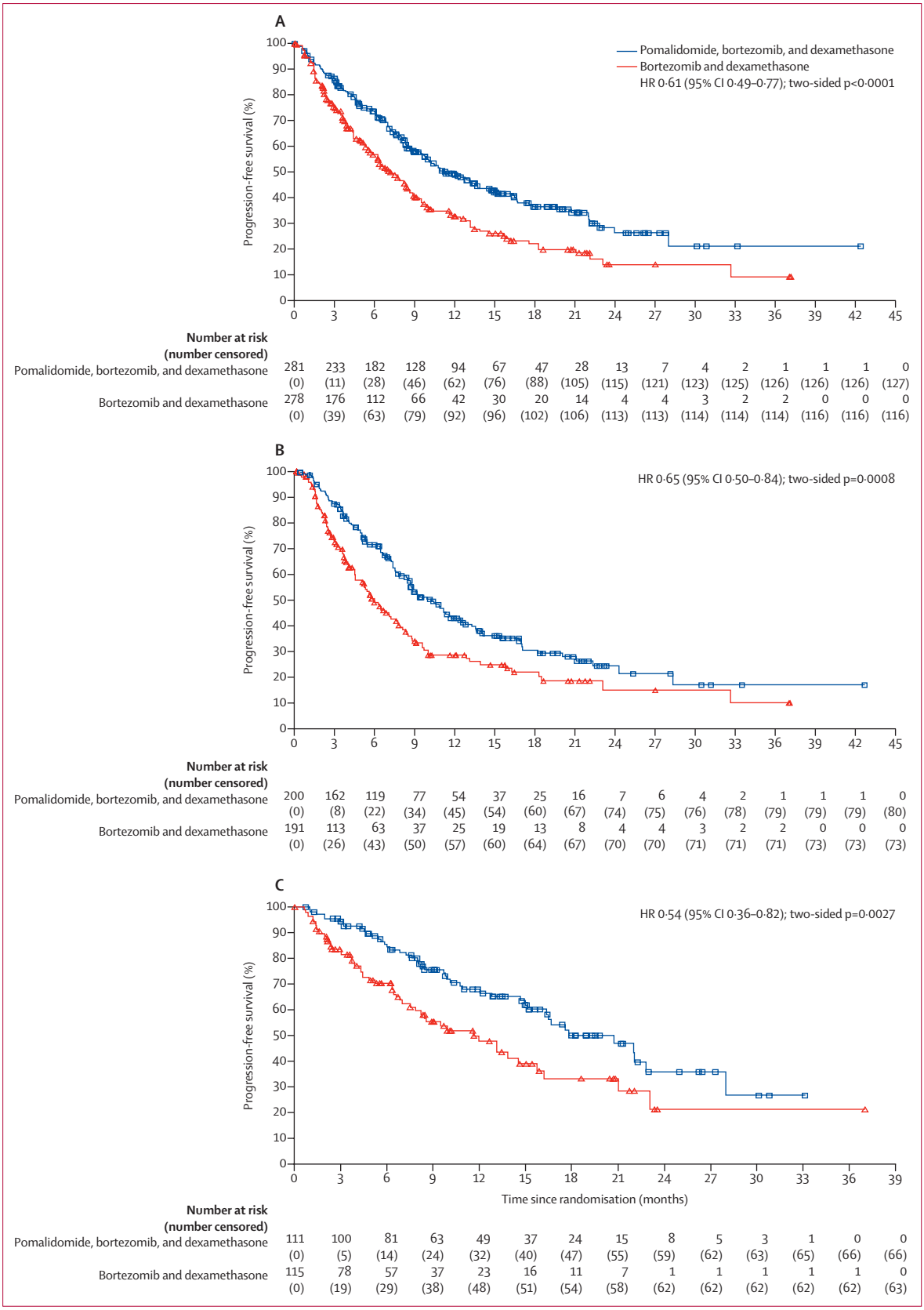

Figure 2: **Kaplan-Meier estimates of progression-free survival**
Survival curves are for patients in the intention-to-treat population (A), lenalidomide-refractory patients (B), and patients with only one previous line of treatment (C).

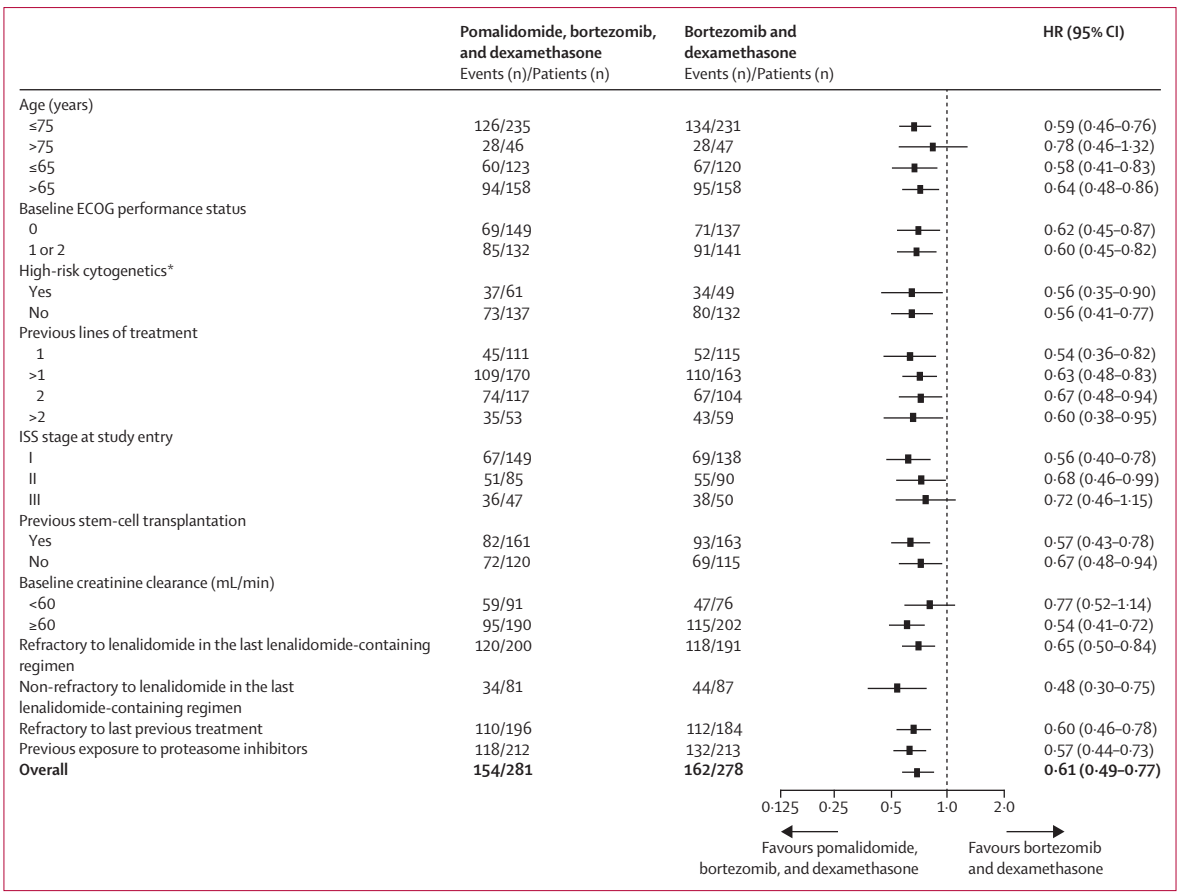

Figure 3: **Prespecified subgroup analyses for progression-free survival**
HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group. ISS=International Staging System. *Defined as at least one high-risk abnormality—del(17p), t(4;14), or t(14;16).

	Pomalidomide, bortezomib, and dexamethasone group (n=281)	Bortezomib and dexamethasone group (n=278)
Overall response*	231 (82·2% [77·2–86·5])	139 (50·0% [44·0–56·0])
Stringent complete response	9 (3·2% [1·5–6·0])	2 (0·7% [0·1–2·6])
Complete response	35 (12·5% [8·8–16·9])	9 (3·2% [1·5–6·1])
Very good partial response	104 (37·0% [31·4–42·9])	40 (14·4% [10·5–19·1])
Partial response	83 (29·5% [24·3–35·2])	88 (31·7% [26·2–37·5])
Stable disease	32 (11·4% [7·9–15·7])	106 (38·1% [32·4–44·1])
Progressive disease	11 (3·9% [2·0–6·9])	16 (5·8% [3·3–9·2])
Not assessable	7 (2·5% [1·0–5·1])	17 (6·1% [3·6–9·6])

Data are n (% [95% CI]). *Defined as patients who achieved either a partial response or a complete response.

Table 2: **Responses in the intention-to-treat population**

17·84 months (95% CI 12·02–not estimable [NE]) with pomalidomide, bortezomib, and dexamethasone versus 9·49 months (6·34–16·20) with bortezomib and dexamethasone (HR 0·55, 95% CI 0·33–0·94; p=0·03; appendix p 3). Improved progression-free survival with pomalidomide, bortezomib, and dexamethasone versus bortezomib and dexamethasone was also seen in several clinically relevant prespecified subgroups (figure 3), including patients with high-risk cytogenetics (median 8·44 months [95% CI 4·86–13·73] *vs* 5·32 months [2·27–8·31]; HR 0·56, 95% CI 0·35–0·90; p=0·021) and those with previous exposure to proteasome inhibitors (median 10·91 months [95% CI 8·41–13·73] *vs* 6·31 months [5·19–8·31]; HR 0·57, 95% CI 0·44–0·73; p<0·0001).

The proportion of patients who achieved an overall response (partial response or better according to IMWG criteria) was significantly higher with pomalidomide, bortezomib, and dexamethasone (231 [82·2%; 95% CI 77·2–86·5] of 281) versus bortezomib and dexamethasone (139 [50·0%; 95% CI 44·0–56·0] of 278; odds ratio [OR] 5·02, 95% CI 3·35–7·52; p<0·0001; table 2). A very good partial response or better was achieved by 148 patients (52·7%; 95% CI 46·7–58·6) assigned pomalidomide, bortezomib, and dexamethasone versus 51 patients (18·3%; 95% CI 14·0–23·4) allocated bortezomib and dexamethasone (OR 5·0, 95% CI 3·4–7·4; p<0·0001). Median time to response among those achieving an overall response was 0·9 months (IQR 0·8–1·4) with

	Pomalidomide, bortezomib, and dexamethasone group (n=278)			Bortezomib and dexamethasone group (n=270)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Common haematological adverse events						
Anaemia	40 (14%)	37 (13%)	1 (<1%)	35 (13%)	34 (13%)	4 (1%)
Thrombocytopenia	26 (9%)	27 (10%)	49 (18%)	24 (9%)	49 (18%)	30 (11%)
Neutropenia	14 (5%)	82 (29%)	34 (12%)	6 (2%)	21 (8%)	2 (<1%)
Common non-haematological adverse events						
Peripheral sensory neuropathy	110 (40%)	22 (8%)	1 (<1%)	88 (33%)	12 (4%)	0
Constipation	95 (34%)	7 (3%)	0	64 (24%)	1 (<1%)	0
Peripheral oedema	89 (32%)	5 (2%)	0	52 (19%)	2 (<1%)	0
Fatigue	80 (29%)	23 (8%)	0	61 (23%)	10 (4%)	0
Diarrhoea	74 (27%)	20 (7%)	0	72 (27%)	8 (3%)	1 (<1%)
Pyrexia	58 (21%)	5 (2%)	1 (<1%)	30 (11%)	2 (<1%)	0
Cough	57 (21%)	0	0	40 (15%)	0	0
Upper respiratory tract infection	55 (20%)	3 (1%)	0	45 (17%)	3 (1%)	0
Back pain	49 (18%)	3 (1%)	0	32 (12%)	4 (1%)	0
Nausea	48 (17%)	1 (<1%)	0	53 (20%)	1 (<1%)	0
Dyspnoea	48 (17%)	8 (3%)	0	30 (11%)	3 (1%)	0
Dizziness	47 (17%)	1 (<1%)	0	27 (10%)	1 (<1%)	0
Asthenia	40 (14%)	8 (3%)	0	40 (15%)	7 (3%)	1 (<1%)
Insomnia	40 (14%)	5 (2%)	0	51 (19%)	2 (<1%)	0
Bronchitis	35 (13%)	4 (1%)	0	16 (6%)	3 (1%)	0
Muscular weakness	35 (13%)	3 (1%)	0	12 (4%)	1 (<1%)	0
Viral upper respiratory tract infection	31 (11%)	0	0	14 (5%)	0	0
Pain in extremity	31 (11%)	2 (<1%)	0	34 (13%)	2 (<1%)	0
Headache	30 (11%)	1 (<1%)	0	25 (9%)	0	0
Arthralgia	30 (11%)	2 (<1%)	0	29 (11%)	2 (<1%)	0
Tremor	29 (10%)	1 (<1%)	0	8 (3%)	0	0
Vomiting	29 (10%)	3 (1%)	0	26 (10%)	1 (<1%)	0
Hypokalaemia	26 (9%)	16 (6%)	1 (<1%)	19 (7%)	10 (4%)	1 (<1%)
Pneumonia	21 (8%)	23 (8%)	8 (3%)	20 (7%)	15 (6%)	1 (<1%)
Hyperglycaemia	15 (5%)	24 (9%)	1 (<1%)	16 (6%)	14 (5%)	0
Syncope	3 (1%)	14 (5%)	0	5 (2%)	6 (2%)	0

Data are n (%). Adverse events of grade 1–2 occurring in at least 10% of patients and adverse events of grade 3 or worse occurring in 5% of patients in either group are shown. All grade 3 or higher adverse events not shown here are listed in the appendix (pp 12–19). Eight deaths were reported as related to treatment: six (2%) in the pomalidomide, bortezomib, and dexamethasone group (causes of death were pneumonia [n=2], unknown cause [n=2], cardiac arrest [n=1], and cardiorespiratory arrest [n=1]) and two (1%) in the bortezomib and dexamethasone group (causes of death were pneumonia [n=1] and hepatic encephalopathy [n=1]).

Table 3: **Adverse events in the safety population**

pomalidomide, bortezomib, and dexamethasone versus 1·4 months (0·8–1·9) with bortezomib and dexamethasone (p=0·0002); the median duration of response was 13·7 months (95% CI 10·9–18·1) and 10·9 months (8·1–14·8), respectively (p=0·06).

At data cutoff (Oct 26, 2017), data were not mature for the planned interim analysis of overall survival. The difference in overall survival between treatment groups (HR 0·98, 95% CI 0·73–1·32; p=0·89) did not cross the prespecified superiority boundary. 176 (31%) overall survival events were reported in 559 patients. The collection of overall survival data is continuing and the final overall survival analysis will take place once 379 (68%) events in 559 patients occur.

Median progression-free survival after next-line treatment was 22·44 months (95% CI 18·96–NE) with pomalidomide, bortezomib, and dexamethasone versus 16·95 months (14·69–21·09) with bortezomib and dexamethasone (HR 0·76, 95% CI 0·59–0·99; p=0·04; appendix p 4). Time to next line of treatment (ie, time

from randomisation to start of subsequent antimyeloma treatment) was longer with pomalidomide, bortezomib, and dexamethasone (median 22·24 months [95% CI 17·18–29·50]) versus bortezomib and dexamethasone (8·51 months [7·26–10·02]; HR 0·42, 95% CI 0·33–0·54; p<0·0001; appendix p 5). 163 (59%) of 278 patients allocated bortezomib and dexamethasone received subsequent treatments and 109 (39%) received pomalidomide. Thus, of 163 patients allocated bortezomib and dexamethasone who received subsequent treatment, two-thirds (109 [67%] of 163) received pomalidomide. Of note, 21 (7%) of 281 patients assigned pomalidomide, bortezomib, and dexamethasone received pomalidomide as subsequent treatment.

Adverse events in the safety population are presented in table 3 and the appendix (pp 12–19). The most common grade 3 or 4 haematological adverse events were neutropenia (116 [42%] cases among 278 patients in the pomalidomide, bortezomib, and dexamethasone group *vs* 23 [9%] cases among 270 patients in the bortezomib and dexamethasone group) and thrombocytopenia (76 [27%] *vs* 79 [29%]); these events occurred most frequently during the first two treatment cycles. Nine (3%) patients receiving pomalidomide, bortezomib, and dexamethasone reported grade 3 or 4 febrile neutropenia versus no patients who received bortezomib and dexamethasone. The most common grade 3 or 4 non-haematological toxic effect was infection (86 [31%] cases among 278 patients in the pomalidomide, bortezomib, and dexamethasone group *vs* 48 [18%] cases among 270 patients in the bortezomib and dexamethasone group). Most patients in both treatment groups who developed infections did not have concurrent grade 3 or 4 neutropenia, and vice versa. Grade 3 or 4 peripheral sensory neuropathy was reported in 23 (8%) of 278 patients in the pomalidomide, bortezomib, and dexamethasone group versus 12 (4%) of 270 patients in the bortezomib and dexamethasone group. Grade 3 or 4 vascular disorders, including deep vein thrombosis (two [1%] cases *vs* one [<1%] case) and pulmonary embolism (11 [4%] cases *vs* one [<1%] case), were higher with pomalidomide, bortezomib, and dexamethasone compared with bortezomib and dexamethasone, but no events were fatal.

In the safety population, 86 deaths in total were recorded in each treatment group during the treatment and follow-up periods, with no clinically significant difference in the causes of death noted between treatments (appendix p 20). Myeloma progression and infections were the most common causes of death. During the treatment period, 27 (10%) deaths were reported among 278 patients in the pomalidomide, bortezomib, and dexamethasone group (five patients with sepsis or septic shock, four patients with general physical health deterioration, three deaths, two patients each with cardiac arrest, pneumonia, and influenza, and one patient each with anaemia, acute kidney injury, infections, *Clostridioides difficile* colitis, multiple organ dysfunction syndrome, cerebral haemorrhage, acute pulmonary oedema, cardiorespiratory arrest, and plasma cell leukaemia), and 12 (4%) deaths were recorded among 270 patients in the bortezomib and dexamethasone group (four patients with general physical health deterioration and one patient each with pneumonia, lower respiratory tract infection, sepsis, depressed level of consciousness, hepatic encephalopathy, hyperviscosity syndrome, osteorrhagia, and plasmacytoma; appendix pp 12–19). The difference between treatment groups probably reflects the longer treatment duration with pomalidomide, bortezomib, and dexamethasone compared with bortezomib and dexamethasone. During the first 60 days of treatment, eight (3%) deaths were reported among 278 patients who received pomalidomide, bortezomib, and dexamethasone versus ten (4%) deaths among 270 patients treated with bortezomib and dexamethasone. During the first 100 days of treatment, 15 (5%) deaths and 12 (4%) deaths, respectively, were recorded. Eight deaths were reported as related to treatment: six (2%) in the pomalidomide, bortezomib, and dexamethasone group (causes of death were pneumonia [n=2], unknown cause [n=2], cardiac arrest [n=1], and cardiorespiratory arrest [n=1]) and two (1%) in the bortezomib and dexamethasone group (causes of death were pneumonia [n=1] and hepatic encephalopathy [n=1]). During the follow-up period, 59 (21%) deaths were reported among 278 patients who received pomalidomide, bortezomib, and dexamethasone compared with 74 (27%) deaths among 270 patients treated with bortezomib and dexamethasone.

Serious adverse events were reported in 159 (57%) of 278 patients in the pomalidomide, bortezomib, and dexamethasone group versus 114 (42%) of 270 patients in the bortezomib and dexamethasone group. Pneumonia was the most common serious adverse event (32 [12%] *vs* 17 [6%]). 83 (30%) of 278 patients who received pomalidomide, bortezomib, and dexamethasone and 41 (15%) of 270 patients treated with bortezomib and dexamethasone had at least one drug-related serious adverse event, primarily infections (40 [14%] *vs* 22 [8%]) including pneumonia (16 [6%] *vs* 12 [4%]), venous thromboembolic events (12 [4%] *vs* one [<1%]), cardiac arrhythmia (seven [3%] *vs* none), and neutropenia (six [2%] *vs* none). Second primary malignancies—most of which were non-melanoma skin cancers—occurred in nine (3%) of 278 patients who received pomalidomide, bortezomib, and dexamethasone (2·7 cases per 100 person-years) versus four (1%) of 270 patients treated with bortezomib and dexamethasone (1·2 cases per 100 person-years; appendix p 21). The frequencies of invasive second primary malignancies were similar for the pomalidomide, bortezomib, and dexamethasone group and the bortezomib and dexamethasone group (two [1%] cases [one haematological and one solid tumour] *vs* one [<1%] case [solid tumour]; incidence 0·58 cases per 100 person-years *vs* 0·30 per 100 person-years). Time to

onset of the haematological malignancy (myelodysplastic syndrome) in the pomalidomide, bortezomib, and dexamethasone group was 16·8 months, whereas the two solid tumours were diagnosed at 1·3 months (pomalidomide, bortezomib, and dexamethasone group) and 1·0 months (bortezomib and dexamethasone group) after the start of study treatment. The short times to onset suggest that these solid tumour second primary malignancies might have been present at baseline but not detected clinically.

Fewer patients discontinued the lead drug in the pomalidomide, bortezomib, and dexamethasone group (pomalidomide) versus the bortezomib and dexamethasone group (bortezomib) because of at least one adverse event (31 [11%] of 278 patients *vs* 50 [19%] of 270 patients). In the pomalidomide, bortezomib, and dexamethasone group, 67 (24%) of 278 patients discontinued bortezomib. The most common adverse events (reported in at least 1% of patients) that led to treatment discontinuation of the lead drug in each treatment group were peripheral sensory neuropathy (three [1%] of 278 *vs* 21 [8%] of 270), peripheral sensorimotor neuropathy (one [<1%] *vs* three [1%]), fatigue (four [1%] *vs* one [<1%]), and pulmonary embolism (three [1%] *vs* none). Drug-related discontinuations of any study drug because of at least one adverse event occurred in 66 (24%) of 278 patients who received pomalidomide, bortezomib, and dexamethasone *vs* 46 (17%) of 270 patients treated with bortezomib and dexamethasone. Dose reductions of any study drug because of at least one adverse event were reported in 200 (72%) of 278 patients in the pomalidomide, bortezomib, and dexamethasone group versus 139 (51%) of 270 patients in the bortezomib and dexamethasone group. Pomalidomide dose reductions and dose interruptions due to adverse events occurred in 113 (41%) and 223 (80%) of 278 patients in the pomalidomide, bortezomib, and dexamethasone group, respectively. In addition to dose modifications, adverse events were managed using supportive care (appendix p 1).

The HRQOL-assessable population included 240 (85%) of 281 patients assigned pomalidomide, bortezomib, and dexamethasone and 209 (75%) of 278 patients allocated bortezomib and dexamethasone. Based on the number of patients expected to complete the EORTC QLQ-C30 at each visit, HRQOL compliance exceeded 80% up to cycle 20 among both treatment groups.[27] Baseline scores for the global health status/QoL domain of the EORTC QLQ-C30 were similar between groups (mean 61·0 [SD 23·2] for pomalidomide, bortezomib, and dexamethasone and 63·5 [21·3] for bortezomib and dexamethasone). Scores were maintained over time for both treatment groups, with no statistically significant or clinically meaningful differences recorded between treatments at any cycle.

Discussion

The findings of our trial in patients previously treated with lenalidomide-based treatment (of whom 70% were refractory to lenalidomide) showed that pomalidomide, bortezomib, and dexamethasone significantly improved progression-free survival compared with bortezomib and dexamethasone. The risk of disease progression or death was also significantly reduced. Subgroup analyses suggested that the risk of progression or death in patients with one previous line of treatment, including those refractory to lenalidomide after one previous line of treatment, was also decreased significantly with pomalidomide, bortezomib, and dexamethasone. Improvements in progression-free survival were recorded in most prespecified subgroups, including patients with high-risk cytogenetics. Although median progression-free survival in patients with high-risk cytogenetics was lower than that reported in the intention-to-treat population, treatment with pomalidomide, bortezomib, and dexamethasone nonetheless reduced the risk of progression or death, suggesting that this triplet regimen might partly overcome the adverse prognosis of high-risk cytogenetic abnormalities. Further, pomalidomide, bortezomib, and dexamethasone led to durable and deeper responses, with about three times as many patients assigned pomalidomide, bortezomib, and dexamethasone achieving a very good partial response or better, compared with patients allocated bortezomib and dexamethasone. Among patients achieving an overall response (partial response or better), median time to response was more rapid with pomalidomide, bortezomib, and dexamethasone than with bortezomib and dexamethasone, and the median duration of response was numerically longer.

Previous studies have shown that pomalidomide has a positive effect on the immune systems of patients refractory to lenalidomide by enhancing the activity and number of T cells.[15,28] Further, preliminary results of a phase 2 study showed a greater increase in the number of T cells from baseline in patients who responded to pomalidomide compared with patients who had no response.[28] In an exploratory analysis of OPTIMISMM, pomalidomide, bortezomib, and dexamethasone prolonged median time to next line of treatment by approximately 14 months compared with bortezomib and dexamethasone. This indicator of disease control might be attributed to the immune-enhancing effects associated with pomalidomide, and further exploratory assessments of immune biomarkers will address this hypothesis.

At first relapse, many patients with multiple myeloma will have been pretreated with lenalidomide in the USA and other parts of the world.[5,29,30] The OPTIMISMM trial was specifically designed to include a growing and clinically relevant population of patients with early-line, lenalidomide-pretreated, relapsed or refractory multiple myeloma. This patient population has been largely excluded from randomised phase 3 trials that led to the approval of novel combinations in relapsed or refractory multiple myeloma.[8–11,29] Phase 3 trials in early relapsed or refractory multiple myeloma (patients with one or two previous lines of treatment) that assessed triplet

regimens based on lenalidomide and dexamethasone—eg, POLLUX (daratumumab),[11] ASPIRE (carfilzomib),[8] ELOQUENT-2 (elotuzumab),[9] and TOURMALINE-MM1 (ixazomib)[10]—included a small percentage of lenalidomide-exposed patients (5–20%) and excluded lenalidomide-refractory patients, with the exception of a few patients in the ASPIRE study (7% lenalidomide-refractory, but not in their most recent line of treatment).[31] Other phase 3 trials that used bortezomib and dexamethasone as the comparator—eg, daratumumab in CASTOR,[25,32] carfilzomib in ENDEAVOR,[24,33] and panobinostat in PANORAMA-1[26]—included smaller percentages of lenalidomide-pretreated patients (19–38%) or lenalidomide-refractory patients (24%) compared with the OPTIMISMM trial. Because of differences in trial design and patients' characteristics, including, but not restricted to, lines of previous treatment and previous treatment exposure, cross-trial comparisons should be made with caution. Nonetheless, the median progression-free survival for the small subset of lenalidomide-refractory patients in CASTOR (n=60)[32] and ENDEAVOR (n=113)[24] was 7·8 months (95% CI 0·28–0·68) and 8·6 months, respectively. Although no phase 3 studies have been done (other than OPTIMISMM) with a large percentage of lenalidomide-refractory patients, this patient population has been prospectively studied in small early-phase trials that included 91–100% lenalidomide-refractory patients with a median of two previous lines of treatment.[22,34,35] A non-randomised, phase 1b safety study of daratumumab, carfilzomib, and dexamethasone reported median progression-free survival of 14·1 months.[34] Similarly, two single-arm phase 1/2 trials of pomalidomide-based triplet regimens reported median progression-free survival of 13·7 months (95% CI 9·7–17·7) with pomalidomide, bortezomib, and dexamethasone (n=50) and 16·8 months with pomalidomide, carfilzomib, and dexamethasone (n=64).[22,34] Taken together, the results from these studies and OPTIMISMM provide evidence that suggests efficacy of pomalidomide-based treatment immediately after lenalidomide, underscoring the importance of continuous immunomodulation and showing that there is no need for a class switch.

Although previously reported phase 3 trials of triplet regimens have shown an additive effect of combining novel agents with lenalidomide or bortezomib and dexamethasone, the outcomes cannot be generalised to patients who received lenalidomide as early-line treatment.[29] The noted increase in use of lenalidomide at diagnosis and at first relapse is giving rise to more lenalidomide-refractory patients earlier in their disease course and, thus, the population included in the OPTIMISMM trial better reflects the patient population treated in clinical practice today. Moreover, this study presents progression-free survival results in patients who had become refractory to lenalidomide immediately after first-line treatment. Of note, the dose of lenalidomide at the time of disease progression was not obtained prospectively and, therefore, patients refractory to lenalidomide could have been on a maintenance dose or full-dose lenalidomide. The US Food and Drug Administration approved a triplet regimen of pomalidomide, elotuzumab, and dexamethasone based on findings of the phase 2 ELOQUENT-3 trial (n=117),[36] which included a large proportion of patients refractory to lenalidomide (87%). However, this study was much smaller than OPTIMISMM and these patients were not treated in early-line relapsed or refractory multiple myeloma (median three [range two to eight] previous lines of treatment). In a phase 2 study,[37] the combination of pomalidomide, cyclophosphamide, and dexamethasone rescued patients after relapse on upfront lenalidomide treatment (no patients were refractory to lenalidomide), with 85% achieving a partial response or better and 94% of eligible patients proceeding to stem-cell transplantation. 3-year progression-free survival was 54·5% and overall survival was 84·2%.[37] The ongoing phase 3 APOLLO trial (NCT03180736),[38] which is investigating pomalidomide, daratumumab, and dexamethasone in patients who have received one or more previous lines of treatment, and the phase 3 ICARIA trial (NCT02990338),[39] which is investigating pomalidomide, isatuximab, and dexamethasone in patients with two or more previous lines of treatment, are both enrolling patients previously treated with lenalidomide, including patients refractory to lenalidomide in early-line relapse, and although these trials might offer promising new treatment options for patients exposed to lenalidomide, the results are not yet available.

Pomalidomide is approved globally for administration in 28-day cycles at 4 mg per day on days 1–21;[40,41] in our study, pomalidomide was administered at 4 mg per day on days 1–14 of 21-day cycles, in line with the approved schedule of bortezomib.[42] Furthermore, to ensure that the experimental arm (pomalidomide, bortezomib, and dexamethasone) did not have an inherent advantage over the control arm (bortezomib and dexamethasone) by virtue of the effects of continuous treatment, both treatments were given until disease progression or unacceptable toxicity, thus reducing the potential for bias. The safety profile remained consistent with known adverse events of pomalidomide, dexamethasone,[18,19] and bortezomib.[25,26] Neutropenia is frequently associated with immunomodulatory agents, and the incidence of grade 3 or 4 neutropenia noted in the OPTIMISMM trial was similar to that reported for pomalidomide.[18,19] The longer treatment duration with pomalidomide, bortezomib, and dexamethasone compared with bortezomib and dexamethasone might have contributed to the higher frequency of recurring adverse events (eg, infection) and deaths during the treatment period in this group. The occurrence and incidence of haematological and solid tumour second primary malignancies were similar between treatment groups, and were rare. Results from the HRQOL analysis showed that the triplet regimen of pomalidomide, bortezomib, and dexamethasone did not compromise HRQOL in patients pretreated with lenalidomide with relapsed or

refractory multiple myeloma compared with the doublet regimen of bortezomib and dexamethasone.[27]

In summary, data from OPTIMISMM support sequencing of a pomalidomide-based regimen immediately after lenalidomide treatment failure for management of relapsed or refractory multiple myeloma and suggest that a switch in class of agent is not warranted for patients with previous lenalidomide exposure or who have become refractory to lenalidomide. Pomalidomide, bortezomib, and dexamethasone could, therefore, be considered an effective treatment option in this setting.

Contributors

PGR, AO, JSM, PO'G, TD, AB, TB, TP, MZ, KA, and MD contributed to the idea for the study. PGR, AO, TF, JSM, PO'G, TD, AB, TB, TP, MZ, KA, and MD contributed to study design. PGR, AO, MB, AML, MG, FS, JL, KW, DW, TF, JSM, KS, PO'G, PS, PR, SSc, XY, TD, AB, TB, TP, MZ, KA, and MD contributed to data acquisition, data analysis, or data interpretation. PGR, AO, MB, KW, PO'G, PS, PR, SSc, TD, AB, TB, TP, and MD wrote the draft report. PGR, AO, MB, AML, MG, FS, JL, KW, DW, JSM, PO'G, PS, PR, SSe, SSc, TD, AB, TB, TP, KA, and MD revised the report. All authors approved the final version to be published.

Declaration of interests

PGR reports research funding from Celgene, Takeda, Bristol-Myers Squibb, and Oncopeptides; and advisory board fees from Celgene, Takeda, Janssen, and Oncopeptide. AO reports advisory board fees from Celgene, Janssen, and Amgen. MB reports advisory board fees from Janssen Cilag, Amgen, Takeda, and Sanofi; and speakers bureau fees from Janssen Cilag, Celgene, Takeda, and Amgen. MG reports honoraria from Bristol-Myers Squibb, Celgene, Janssen, and Leadiant (formerly Sigma-Tau). FS reports paid lecturer or advisory board fees from Amgen, Celgene, Takeda, AbbVie, Janssen, Bristol-Myers Squibb, Bayer, and Adaptive. JL reports commercial sponsorship and personal fees from Celgene; and non-financial support from Celgene, Takeda, and Amgen. KW reports grants, personal fees, and non-financial support from Celgene, Amgen, and Janssen; personal fees and non-financial support from Bristol-Myers Squibb and Takeda; and grants and personal fees from Sanofi. DW reports grants and personal fees from Amgen, Celgene, Janssen, and Takeda. TF reports speakers bureau and advisory board fees from Celgene, Janssen, and Takeda; and advisory board fees from Karyopharm, Sanofi, and Oncopeptides. JSM reports advisory board fees from Amgen, Bristol-Myers Squibb, Celgene, Janssen, MSD, Novartis, Takeda, Sanofi, and Roche. KS reports research funding and honoraria from Celgene, Takeda, Bristol-Myers Squibb, and Ono; and research funding from Novartis, GlaxoSmithKline, Janssen, AbbVie, Sanofi, MSD, Alexion, and Daiichi Sankyo. PO'G reports research funding from Celgene. PS reports grants and personal fees from Celgene and Janssen; and grants from Amgen, Takeda, and Karyopharm. PR reports research funding from Celgene. SSe reports research funding from Celgene; and fees from lectures and speakers bureau fees from Celgene, Takeda, Janssen, Amgen, and Novartis. XY, TD, AB, TB and TP report employment with and stock ownership in Celgene. MZ reports employment with Celgene. KA reports advisory board fees from Celgene, Millennium, and Bristol-Myers Squibb; board membership with Gilead; and is the scientific founder of Oncopeptides and C4 Therapeutics. MD reports honoraria, consulting fees, and lecture fees from Amgen, Celgene, Takeda, Janssen, and Bristol-Myers Squibb. AML and SSc declare no competing interests.

Data sharing statement

Data requests may be submitted to Celgene and must include a description of the research proposal.

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References

1 Kumar SK, Therneau TM, Gertz MA, et al. Clinical course of patients with relapsed multiple myeloma. *Mayo Clin Proc* 2004; **79:** 867–74.
2 Rajkumar SV, Kumar S. Multiple myeloma: diagnosis and treatment. *Mayo Clin Proc* 2016; **91:** 101–19.
3 Nucci M, Anaissie E. Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. *Clin Infect Dis* 2009; **49:** 1211–25.
4 Landgren O, Iskander K. Modern multiple myeloma therapy: deep, sustained treatment response and good clinical outcomes. *J Intern Med* 2017; **281:** 365–82.
5 Raab MS, Cavo M, Delforge M, et al. Multiple myeloma: practice patterns across Europe. *Br J Haematol* 2016; **175:** 66–76.
6 Kumar SK, Callander NS, Alsina M, et al. NCCN guidelines insights: multiple myeloma, version 3.2018. *J Natl Compr Canc Netw* 2018; **16:** 11–20.
7 Moreau P, de Wit E. Recent progress in relapsed multiple myeloma therapy: implications for treatment decisions. *Br J Haematol* 2017; **179:** 198–218.
8 Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2015; **372:** 142–52.
9 Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med* 2015; **373:** 621–31.
10 Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; **374:** 1621–34.
11 Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; **375:** 1319–31.
12 Bjorklund CC, Lu L, Kang J, et al. Rate of CRL4(CRBN) substrate Ikaros and Aiolos degradation underlies differential activity of lenalidomide and pomalidomide in multiple myeloma cells by regulation of c-Myc and IRF4. *Blood Cancer J* 2015; **5:** e354.
13 Lopez-Girona A, Mendy D, Ito T, et al. Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. *Leukemia* 2012; **26:** 2326–35.
14 Ocio EM, Fernández-Lázaro D, San-Segundo L, et al. In vivo murine model of acquired resistance in myeloma reveals differential mechanisms for lenalidomide and pomalidomide in combination with dexamethasone. *Leukemia* 2015; **29:** 705.
15 Sehgal K, Das R, Zhang L, et al. Clinical and pharmacodynamic analysis of pomalidomide dosing strategies in myeloma: impact of immune activation and cereblon targets. *Blood* 2015; **125:** 4042–51.
16 Rychak E, Mendy D, Shi T, et al. Pomalidomide in combination with dexamethasone results in synergistic anti-tumour responses in pre-clinical models of lenalidomide-resistant multiple myeloma. *Br J Haematol* 2016; **172:** 889–901.
17 Leleu X, Attal M, Arnulf B, et al. Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: Intergroupe Francophone du Myelome 2009–02. *Blood* 2013; **121:** 1968–75.
18 San Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2013; **14:** 1055–66.
19 Dimopoulos MA, Palumbo A, Corradini P, et al. Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS (MM-010): a phase 3b study in refractory multiple myeloma. *Blood* 2016; **128:** 497–503.
20 Richardson PG, Siegel DS, Vij R, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. *Blood* 2014; **123:** 1826–32.
21 Richardson P, Hofmeister C, Raje N, et al. Pomalidomide, bortezomib and low-dose dexamethasone in lenalidomide-refractory and proteasome inhibitor-exposed myeloma. *Leukemia* 2017; **31:** 2695–701.
22 Paludo J, Mikhael JR, LaPlant BR, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed lenalidomide-refractory multiple myeloma. *Blood* 2017; **130:** 1198–204.

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23 Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia* 2006; **20:** 1467–73.

24 Moreau P, Joshua D, Chng WJ, et al. Impact of prior treatment on patients with relapsed multiple myeloma treated with carfilzomib and dexamethasone vs bortezomib and dexamethasone in the phase 3 ENDEAVOR study. *Leukemia* 2017; **31:** 115–22.

25 Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; **375:** 754–66.

26 San-Miguel JF, Hungria VTM, Yoon S-S, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. *Lancet Oncol* 2014; **15:** 1195–206.

27 Weisel K, Dimopoulos M, Moreau P, et al. Health-related quality of life among patients with relapsed or refractory multiple myeloma who received pomalidomide, bortezomib, and low-dose dexamethasone *vs* bortezomib and low-dose dexamethasone: results from the phase 3 OPTIMISMM study. *Blood* 2018; **132** (suppl 1)**:** 1960.

28 Siegel D, Schiller GJ, Song KW, et al. Pomalidomide (POM) + low-dose dexamethasone (LoDEX) after lenalidomide (LEN)-based second-line (2L) treatment (Tx) in patients (Pts) with relapsed/refractory multiple myeloma (RRMM): analysis of progression-free survival (PFS) by level of disease control. *Proc Am Soc Clin Oncol* 2017; **35** (15 suppl)**:** 8027.

29 Rajkumar SV, Kyle RA. Progress in myeloma: a monoclonal breakthrough. *N Engl J Med* 2016; **375:** 1390–92.

30 Cook G, Zweegman S, Mateos MV, Suzan F, Moreau P. A question of class: treatment options for patients with relapsed and/or refractory multiple myeloma. *Crit Rev Oncol Hematol* 2018; **121:** 74–89.

31 Dimopoulos MA, Stewart AK, Masszi T, et al. Carfilzomib-lenalidomide-dexamethasone *vs* lenalidomide-dexamethasone in relapsed multiple myeloma by previous treatment. *Blood Cancer J* 2017; **7:** e554.

32 Usmani SZ, Mateos M-V, Lentzsch S, et al. Efficacy of daratumumab in combination with standard of care regimens in lenalidomide-exposed or -refractory patients with relapsed/refractory multiple myeloma (RRMM): analysis of the CASTOR, POLLUX, and MMY1001 studies. *Blood* 2018; **132** (suppl 1)**:** 3288.

33 Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol* 2016; **17:** 27–38.

34 Chari A, Martinez-Lopez J, Mateos M, et al. Daratumumab (DARA) in combination with carfilzomib and dexamethasone (D-Kd) in lenalidomide (Len)-refractory patients (Pts) with relapsed multiple myeloma (MM): subgroup analysis of MMY1001. *Proc Am Soc Clin Oncol* 2018: **36** (15 suppl)**:** 8002.

35 Jakubowiak AJ, Rosenbaum CA, Stephens L, et al. Final results of phase (ph) 1/2 study of carfilzomib, pomalidomide, and dexamethasone (KPd) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): a multi-center MMRC study. European Society of Hematology Annual Meeting; June 22–25, 2017; Madrid, Spain: P680 (abstract).

36 Dimopoulos MA, Dytfeld D, Grosicki S, et al. Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. *N Engl J Med* 2018; **379:** 1811–22.

37 Garderet L, Kuhnowski F, Berge B, et al. Pomalidomide, cyclophosphamide, and dexamethasone for relapsed multiple myeloma. *Blood* 2018; **132:** 2555–63.

38 Sonneveld P, Terpos E, Dimopoulos MA, et al. Pomalidomide and dexamethasone (pom-dex) with or without daratumumab (DARA) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): a multicenter, randomized, phase 3 study (APOLLO). *Proc Am Soc Clin Oncol* 2018; **36** (15 suppl)**:** TPS8059.

39 Richardson PG, Attal M, Campana F, et al. Isatuximab plus pomalidomide/dexamethasone versus pomalidomide/dexamethasone in relapsed/refractory multiple myeloma: ICARIA phase III study design. *Future Oncol* 2018; **14:** 1035–47.

40 Electronic medicines compendium (eMC). Imnovid 4 mg: summary of product characteristics. Oct 16, 2018. https://www.medicines.org.uk/emc/product/3464/smpc (accessed April 11, 2019).

41 Celegene. Pomalyst (pomalidomide) capsules for oral use: package insert. May, 2018. https://media.celgene.com/content/uploads/pomalyst-pi.pdf (accessed April 11, 2019).

42 Millennium Pharmaceuticals. Velcade (bortezomib) for injection, for subcutaneous or intravenous use: package insert. June, 2017. https://www.velcade.com/files/PDFs/VELCADE_PRESCRIBING_INFORMATION.pdf (accessed April 11, 2019).