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This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/150538> since 2015-12-01T12:21:48Z

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UNIVERSITÀ DEGLI STUDI DI TORINO

This is an author version of the contribution published on:

Questa è la versione dell'autore dell'opera:

[Lancet Oncol. 2013 Oct;14(11):1055-66. doi: 10.1016/S1470-2045(13)70380-2.
Epub 2013 Sep 3]

The definitive version is available at:

La versione definitiva è disponibile alla URL:

[<http://www.sciencedirect.com.offcampus.dam.unito.it/science/article/pii/S1470204513703802#>]

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

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Summary

Background

Few effective treatments exist for patients with refractory or relapsed and refractory multiple myeloma not responding to treatment with bortezomib and lenalidomide. Pomalidomide alone has shown limited efficacy in patients with relapsed multiple myeloma, but synergistic effects have been noted when combined with dexamethasone. We compared the efficacy and safety of pomalidomide plus low-dose dexamethasone with high-dose dexamethasone alone in these patients.

Methods

This multicentre, open-label, randomised phase 3 trial was undertaken in Australia, Canada, Europe, Russia, and the USA. Patients were eligible if they had been diagnosed with refractory or relapsed and refractory multiple myeloma, and had failed at least two previous treatments of bortezomib and lenalidomide. They were assigned in a 2:1 ratio with a validated interactive voice and internet response system to either 28 day cycles of pomalidomide (4 mg/day on days 1–21, orally) plus low-dose dexamethasone (40 mg/day on days 1, 8, 15, and 22, orally) or high-dose dexamethasone (40 mg/day on days 1–4, 9–12, and 17–20, orally) until disease progression or unacceptable toxicity. Stratification factors were age (≤ 75 years vs > 75 years), disease population (refractory vs relapsed and refractory vs bortezomib intolerant), and number of previous treatments (two vs more than two). The primary endpoint was progression-free survival (PFS). Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01311687, and with EudraCT, number 2010-019820-30.

Findings

The accrual for the study has been completed and the analyses are presented. 302 patients were randomly assigned to receive pomalidomide plus low-dose dexamethasone and 153 high-dose dexamethasone. After a median follow-up of 10.0 months (IQR 7.2–13.2), median PFS with pomalidomide plus low-dose dexamethasone was 4.0 months (95% CI 3.6–4.7) versus 1.9 months (1.9–2.2) with high-dose dexamethasone (hazard ratio 0.48 [95% CI 0.39–0.60]; $p < 0.0001$). The most common grade 3–4 haematological adverse events in the pomalidomide plus low-dose dexamethasone and high-dose dexamethasone groups were neutropenia (143 [48%] of 300 vs 24

[16%] of 150, respectively), anaemia (99 [33%] vs 55 [37%], respectively), and thrombocytopenia (67 [22%] vs 39 [26%], respectively). Grade 3–4 non-haematological adverse events in the pomalidomide plus low-dose dexamethasone and high-dose dexamethasone groups included pneumonia (38 [13%] vs 12 [8%], respectively), bone pain (21 [7%] vs seven [5%], respectively), and fatigue (16 [5%] vs nine [6%], respectively). There were 11 (4%) treatment-related adverse events leading to death in the pomalidomide plus low-dose dexamethasone group and seven (5%) in the high-dose dexamethasone group.

Interpretation

Pomalidomide plus low-dose dexamethasone, an oral regimen, could be considered a new treatment option in patients with refractory or relapsed and refractory multiple myeloma.

Funding

Celgene Corporation.

Introduction

The prognosis for patients with multiple myeloma who are refractory to proteasome inhibitors such as bortezomib, and to immunomodulatory drugs such as lenalidomide is poor: with further treatment, median overall survival is 9 months, and 3 months without further treatment.¹ There are few treatment options, with corticosteroids alone or combined with other drugs being the most commonly used.¹

Lenalidomide and pomalidomide have direct antimyeloma, immunomodulatory, and stromal-cell effects.² Unlike lenalidomide, of which about 82% is excreted as the parent drug in the urine, 2% of pomalidomide is excreted unchanged through the kidneys. The results of an ongoing phase 1 study should confirm the dose of pomalidomide to be used in patients with renal impairment.³ Pomalidomide has limited activity as monotherapy in patients with relapsed multiple myeloma,^{4 and 5} but has synergistic effects when used in combination with dexamethasone.^{6, 7 and 8} This combination has shown clinical efficacy in patients with multiple myeloma who had been treated with bortezomib or lenalidomide, or both, with 25–35% of patients in phase 2 studies achieving a partial response or better.^{6, 7 and 9} We undertook a phase 3 study to compare the efficacy and safety of pomalidomide plus low-dose dexamethasone with high-dose dexamethasone in patients with refractory or relapsed and refractory multiple myeloma.

Methods

Study design and participants

MM-003 is an open-label, randomised phase 3 trial undertaken in 93 centres in Europe, Russia, Australia, Canada, and the USA (appendix). For inclusion in the trial, patients had to be refractory to their previous treatment;^{10 and 11} judged to have refractory or relapsed and refractory disease; had to have received at least two previous consecutive cycles of bortezomib and lenalidomide, alone or in combination; had adequate alkylator treatment (at least six cycles of alkylator treatment, or progressive disease after at least two cycles of alkylator treatment, or received alkylator treatment

as part of a stem-cell transplant); and be older than 18 years. Patients must have failed (progressive disease on or before 60 days of treatment, progressive disease ≤ 6 months after achieving partial response, or intolerance to bortezomib) treatment with bortezomib or lenalidomide. Patients were classified on the basis of their disease status. They were thought to be refractory if they had progressed on or within 60 days of treatment with bortezomib and lenalidomide (and had developed progressive disease on or within 60 days after completing their last treatment) or relapsed and refractory if they had achieved at least a partial response to previous treatment with bortezomib or lenalidomide, or both, but progressed within 6 months (and had developed progressive disease on or within 60 days after completing their last treatment). Also included were patients who developed treatment intolerance after a minimum of two cycles of bortezomib and had developed progressive disease on or before 60 days after completing their last treatment.

Patients were ineligible if they had previously received pomalidomide, had hypersensitivity to thalidomide, lenalidomide, or dexamethasone, or had resistance to high-dose dexamethasone (progressive disease on or within 60 days of the last dose used in their previous treatment). Patients were also considered ineligible if they had peripheral neuropathy of grade 2 or more; substantial cardiac disease (New York Heart Association Class III or IV, congestive heart failure, myocardial infarction on or within 12 months or unstable or poorly controlled angina); or showed any of the following laboratory abnormalities: absolute neutrophil count of less than 1×10^9 per L, platelet count of less than 75×10^9 per L ($<30 \times 10^9$ per litre if $\geq 50\%$ of bone marrow nucleated cells were plasma cells); creatinine clearance of less than 45 mL/min according to the Cockcroft-Gault formula or 24 h urine collection; corrected serum calcium greater than 3.5 mmol/L; total bilirubin greater than 34.2 $\mu\text{mol/L}$; haemoglobin less than 80 g/L (4.9 mmol/L); or liver enzyme concentrations greater than three times the upper limit of normal.

All patients provided written informed consent. The study was approved by institutional review boards or independent ethics committees at all participating centres and done in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines on Good Clinical Practice.

Randomisation and masking

Patients were randomly assigned in a 2:1 ratio to pomalidomide plus low-dose dexamethasone or high-dose dexamethasone with a validated interactive voice and internet response system using a randomly permuted block within strata. The sponsor reviewed the enrolment and screening. Stratification factors were age (≤ 75 years vs >75 years), disease status (refractory vs relapsed and refractory vs bortezomib intolerant), and number of previous treatments (two vs three or more).

Procedures

Patients assigned to the pomalidomide plus low-dose dexamethasone group were given 28 day cycles of pomalidomide (4 mg/day on days 1–21, orally) plus low-dose dexamethasone (40 mg/day on days 1, 8, 15, and 22, orally). Patients assigned to the high-dose dexamethasone group were given 28 day cycles of high-dose dexamethasone (40 mg/day on days 1–4, 9–12, and 17–20). Dexamethasone dose was reduced to 20 mg/day in all patients older than 75 years. Treatment was continued until progressive disease or unacceptable toxicity occurred. Per protocol, pomalidomide was to be withheld for grade 4 and greater neutropenia, febrile neutropenia, and thrombocytopenia, grade 3 and greater venous thromboembolism, constipation, peripheral neuropathy, rash, and all other grade 3 or greater treatment-related adverse events, and also withheld for grade 2 or greater hypothyroidism or hyperthyroidism. On day 1 of the next treatment cycle, the dose of pomalidomide was to be reduced by 1 mg. Pomalidomide was to be discontinued in the event of

grade 4 rash or rash with blistering, or grade 4 peripheral neuropathy. Dose modifications for dexamethasone were in accordance with the institutional guidelines. Appropriate concomitant treatments for adverse events were permitted.

Follow-up for overall survival and new cancers (second primary malignancy) was planned to occur every 84 days for up to 5 years after randomisation. Patients progressing on high-dose dexamethasone could receive pomalidomide at the same dose, but without dexamethasone in a companion trial (MM-003C). Thromboprophylaxis was required for patients receiving pomalidomide or those at high risk of developing thrombosis. Choice of thromboprophylaxis and use of myeloid and erythroid growth factors was left to the physician's discretion. Severity of adverse events was graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Serious adverse events were defined as fatal, life-threatening, requiring or prolonging hospitalisation, causing persistent or substantial disability or incapacity, involving a congenital anomaly or a birth defect, or constituting any other important medical event.

Statistical analysis

The primary endpoint was progression-free survival (PFS). The key secondary endpoint was overall survival. Other secondary endpoints were the overall response rate (the proportion of patients who achieved at least a partial response according to the International Myeloma Working Group criteria¹² or European Group for Blood and Marrow Transplantation criteria for minor response only),¹³ time to progression, duration of response, safety, and quality of life. PFS and proportion of patients with an overall response presented in this report were based on investigator assessment of response and progressive disease in accordance with the International Myeloma Working Group criteria.¹² Overall survival was to be tested only if the difference in PFS between treatment groups was significant. α was controlled at the 0.05 level with a two-sided test for both PFS and overall survival. Treatment effects were assessed in subgroups by stratification. Stratification per protocol was by age 75 years and younger versus more than 75 years; however, few data are presented because of the small number of patients. The subgroup analysis was by age 65 years and younger versus more than 65 years. Efficacy assessments were done in the intention-to-treat population (all randomly assigned patients) and safety assessment was done in the safety population (all patients who received at least one dose of study treatment). Relative dose intensity was calculated as the ratio of actual dose intensity to planned dose intensity (the ratio of cumulative dose to treatment duration).

Target accrual was 426 patients (284 in the pomalidomide plus low-dose dexamethasone group and 142 in the high-dose dexamethasone group) to have 242 PFS events (disease progression or death) with 85% power to detect a 50% improvement in median PFS (hazard ratio [HR] 1.5 for pomalidomide plus low-dose dexamethasone vs high-dose dexamethasone) at a two-sided significance level of 0.05. An interim analysis was planned for PFS using a group sequential procedure at 121 PFS events (50% information). If the futility boundary was crossed, the independent data monitoring committee could stop the trial. PFS was estimated with the Kaplan-Meier product-limit method and a log-rank test (stratified by the three randomisation stratification variables) was used as the primary analytic method to compare survivorship functions between treatment groups. The final overall survival analysis was to be done after 212 patients from both treatment groups died during the study. An interim survival analysis was also planned at either the same time as the final PFS analysis or when 106 deaths (50% overall survival information) had occurred, whichever happened later. The O'Brien-Fleming boundary for superiority was used for the interim survival analysis and was based on the actual numbers of events (deaths). The α level

for the final survival analysis was to be adjusted accordingly. Statistical analysis was done with the SAS software (version 9.2).

This study is registered with ClinicalTrials.gov, number NCT01311687, and with EudraCT, number 2010-019820-30.

Role of the funding source

The trial was designed by the investigators in collaboration with the manufacturers of pomalidomide (Celgene Corporation, Summit, NJ, USA). The study design was decided by the sponsor in collaboration with the study steering committee. All authors and the sponsor were involved in the data gathering, analysis, review, and interpretation, and writing of the report. The corresponding author had final responsibility for the decision to submit for publication.

Results

455 patients were enrolled in the MM-003 trial between March 18, 2011, and Aug 30, 2012; 302 patients were randomly assigned to receive pomalidomide plus low-dose dexamethasone and 153 to receive high-dose dexamethasone (figure 1). At data cutoff (prespecified final PFS and interim overall survival, Sept 7, 2012), 267 PFS events had occurred (median follow-up 4.2 months [IQR 2.0–7.1]). The interim survival analysis was done at this time, when 134 deaths had occurred. The independent data monitoring committee indicated that the trial met the primary endpoint of PFS and that the upper boundary for superior overall survival had been crossed even though 45 patients in the high-dose dexamethasone group crossed over and received pomalidomide. In accordance with the stopping rules, the committee recommended that patients assigned to high-dose dexamethasone who had not progressed should have access to pomalidomide (with or without dexamethasone). By March 1, 2013 (median follow-up 10.0 months [IQR 7.2–13.2]), the number of events was reached for the final overall survival analysis. Follow-up and analyses for the study are ongoing, but accrual is complete. Key results from Sept 7, 2012, and March 1, 2013 (updated PFS and final overall survival, response, and safety analyses) are presented.

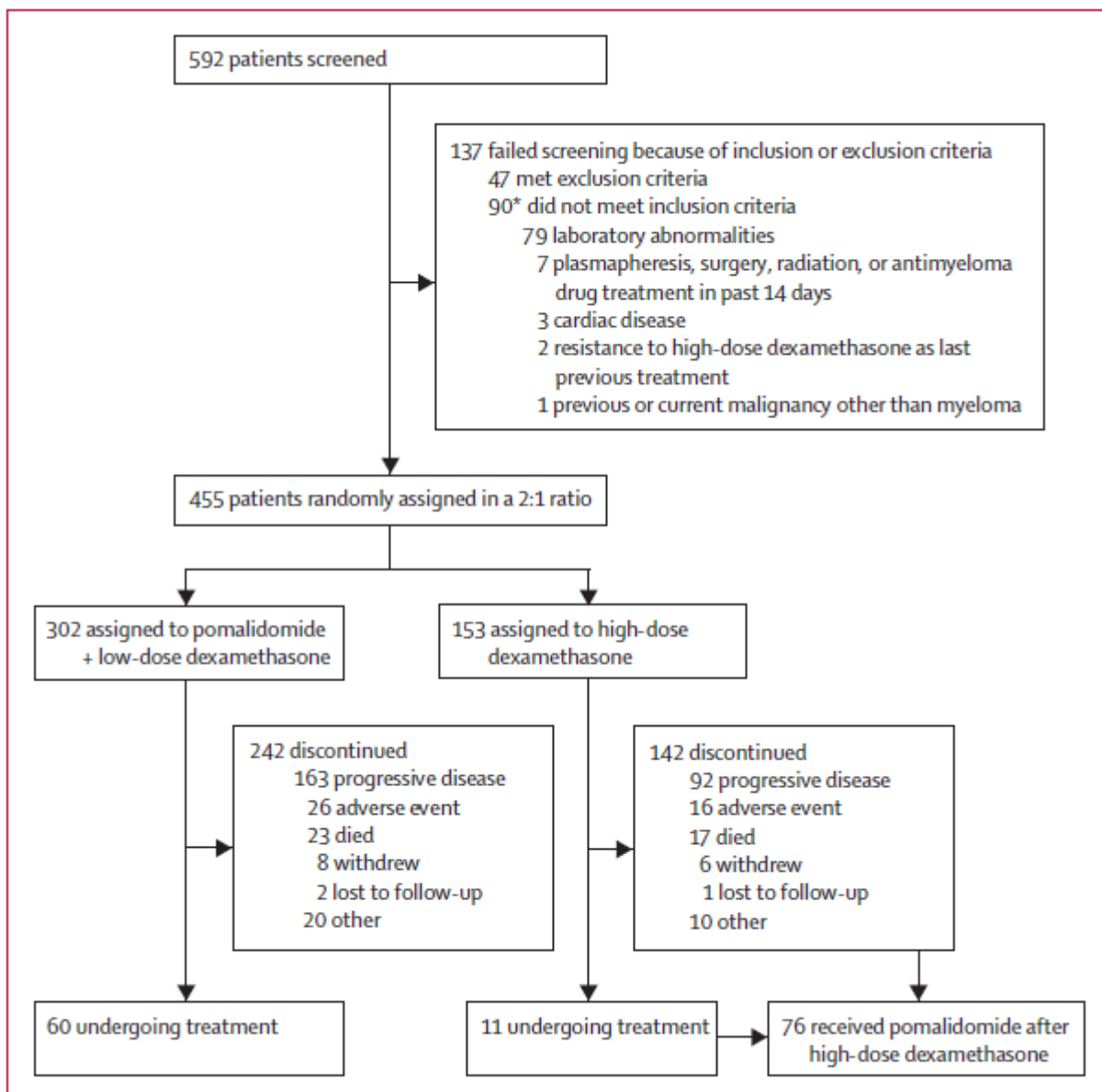


Figure 1. Trial profile

*Two patients excluded for more than one reason.

Treatment groups were balanced for the baseline characteristics, with median time from diagnosis being similar in both treatment groups, and both groups having a median number of five previous treatments (table 1). Most patients were refractory to lenalidomide (95% in the pomalidomide plus low-dose dexamethasone group and 92% in the high-dose dexamethasone group; table 1). In the pomalidomide and low-dose dexamethasone group, 233 (81%) of 286 patients refractory to lenalidomide had progressed on lenalidomide at a dose of at least 25 mg/day. Most patients were also refractory to both lenalidomide and bortezomib (75% in the pomalidomide plus low-dose dexamethasone group and 74% in the high-dose dexamethasone group; table 1). Few patients were classified as having achieved a partial response or better and progressing within 6 months of completing their last previous treatment with lenalidomide or bortezomib-containing regimens (3% in each group; eight patients in the pomalidomide and low-dose dexamethasone group and five in the high-dose dexamethasone group), preventing meaningful subgroup analyses.

Table 1. Baseline characteristics of patients

	Pomalidomide plus low-dose dexamethasone (n=302)	High-dose dexamethasone (n=153)
Age (years)	64 (35–84)	65 (35–87)
>65	135 (45%)	72 (47%)
>75	24 (8%)	12 (8%)
Sex		
Male	181 (60%)	87 (57%)
Female	121 (40%)	66 (43%)
Time from diagnosis (years)	5.3 (0.6–30.0)	6.1 (0.9–21.1)
ECOG performance status score		
0–1	248 (82%)	122 (80%)
2–3	52 (17%)	28 (18%)
Missing	2 (<1%)	3 (2%)
International Staging System		
I–II	197 (65%)	93 (61%)
III	93 (31%)	54 (35%)
Missing	12 (4%)	6 (4%)
Creatinine clearance, <60 mL/min	95 (31%)	59 (39%)
Number of previous treatments	5 (2–14)	5 (2–17)
More than two	285 (94%)	145 (95%)
Previous treatments		
Dexamethasone	295 (98%)	152 (99%)
Thalidomide	173 (57%)	93 (61%)
Autologous stem-cell transplantation	214 (71%)	105 (69%)
Lenalidomide	302 (100%)	153 (100%)
Bortezomib	302 (100%)	153 (100%)
Refractory multiple myeloma	249 (82%)	125 (82%)
Intolerant to bortezomib	45 (15%)	23 (15%)
Refractory to lenalidomide	286 (95%)	141 (92%)
Refractory to bortezomib	238 (79%)	121 (79%)
Refractory to both bortezomib and lenalidomide	225 (75%)	113 (74%)

Data are median (range) or number (%). ECOG=Eastern Cooperative Oncology Group.

At the time of the updated PFS analysis, 242 (80%) of 302 patients in the pomalidomide plus low-dose dexamethasone group and 142 (93%) of 153 in the high-dose dexamethasone group had discontinued study treatment (figure 1). Progressive disease was the most common reason for discontinuation: 163 patients (54%) in the pomalidomide plus low-dose dexamethasone group and 92 patients (60%) in the high-dose dexamethasone group (figure 1).

At the time of the final PFS and interim overall survival analyses (median follow-up 4.2 months [IQR 2.0–7.1]), both median PFS (3.8 months [95% CI 3.4–4.6] vs 1.9 months [1.9–2.1]; $p < 0.0001$; HR 0.41 [0.32–0.53]; $p < 0.001$) and overall survival (11.9 months [10.4–15.5] vs 7.8 months [6.4–9.2]; 0.53 [0.37–0.74]; $p = 0.0002$) were significantly longer in the pomalidomide plus low-dose dexamethasone group than in the high-dose dexamethasone group.

At the time of the updated PFS and final overall survival analyses (median follow-up 10.0 months), the PFS data continued to show an advantage for pomalidomide plus low-dose dexamethasone compared with the high-dose dexamethasone group (4.0 months [95% CI 3.6–4.7] vs 1.9 months [1.9–2.2]; HR 0.48 [0.39–0.60]; $p < 0.0001$; figure 2A). Median PFS was significantly longer with pomalidomide plus low-dose dexamethasone irrespective of previous treatment in the subgroup analyses (figure 2B), including in patients refractory to lenalidomide (3.9 months [3.5–4.6] vs 1.9 months [1.9–2.2]; $p < 0.0001$), refractory to both bortezomib and lenalidomide (3.7 months [3.0–4.6] vs 2.0 months [1.9–2.2]; $p < 0.0001$), intolerant to bortezomib (4.0 months [2.8–6.7] vs 2.0 months [1.9–3.7]; $p = 0.0073$), with lenalidomide as their last treatment (4.6 months [3.5–6.0] vs 1.9 months [1.1–2.5]; $p < 0.0001$), and with bortezomib as their last treatment (3.8 months [2.8–4.9] vs 1.9 months [1.8–2.6]; $p < 0.0001$; figure 2B).

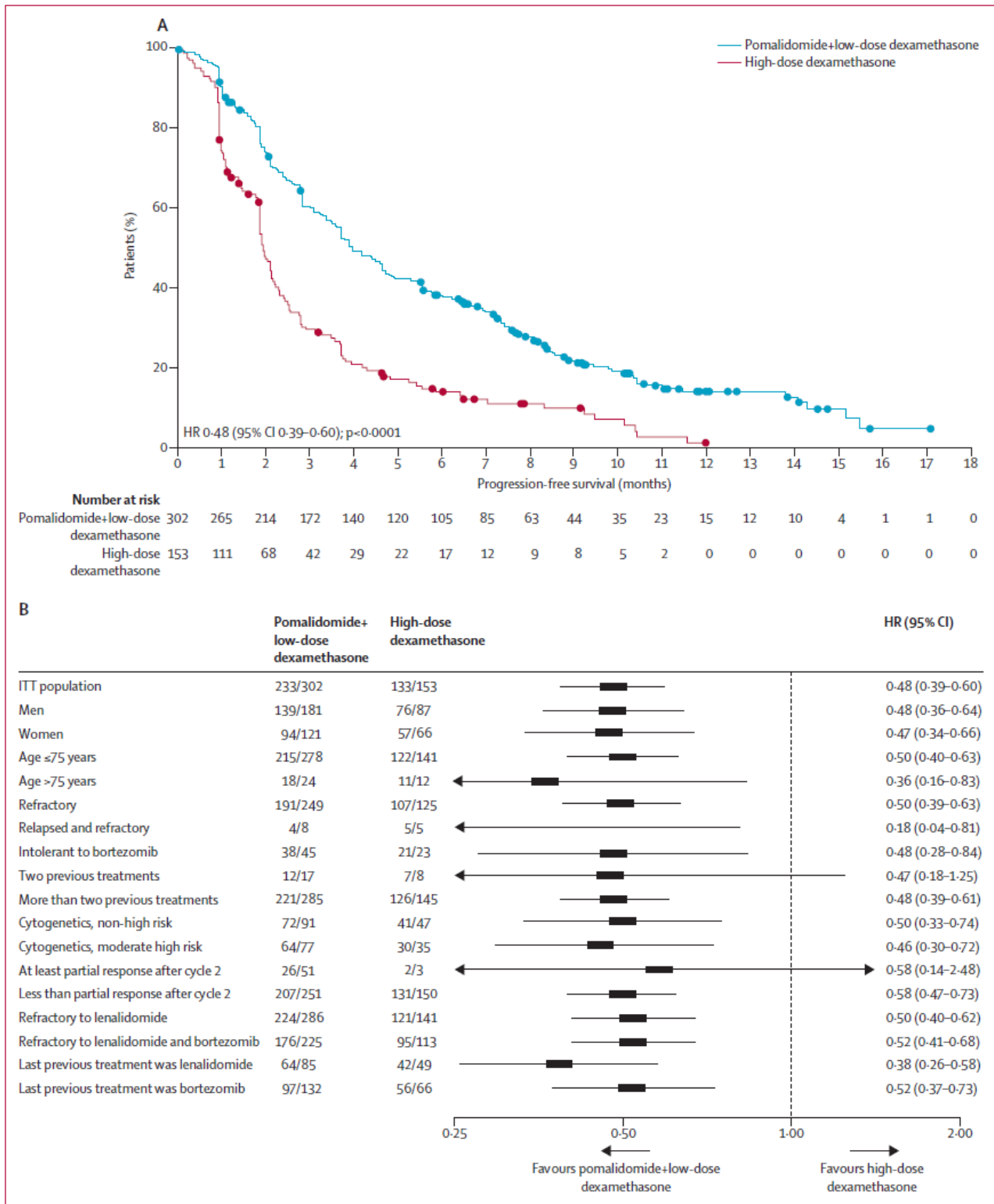


Figure 2. Progression-free survival

(A)Kaplan-Meier progression-free survival curves by treatment group in the ITT population. (B) Forest plot for progression-free survival for subgroup analysis by age, sex, and nature of previous treatments. Data are presented until the cutoff date (March 1, 2013). For (B) patients could be included in more than one subgroup. ITT=intention to treat. HR=hazard ratio.

(B) In the final overall survival analysis, median overall survival was significantly longer in the pomalidomide plus low-dose dexamethasone group than in the high-dose dexamethasone group (12.7 months [95% CI 10.4–15.5] vs 8.1 months [6.9–10.8]; HR 0.74 [0.56–0.97]; $p=0.0285$; figure 3A and 3B). Longer overall survival was also noted with pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in patients refractory to lenalidomide (12.7 months [10.4–15.5] vs 8.0 months [6.4–10.1]; $p=0.0234$; figure 3B) and in patients with lenalidomide as their last therapy (12.3 months [9.8–16.4] vs 7.3 months [4.5–10.1] respectively; $p=0.0097$; figure 3B). No significant differences were noted between treatment groups for patients who were refractory to both lenalidomide and bortezomib (11.1 months [9.2–15.5] vs 7.7 months [5.4–10.1], $p=0.0957$), were intolerant to bortezomib (15.5 months [11.1–19.2] vs 8.6 months [5.4–not reached], $p=0.1405$), or had last received bortezomib (13.1 months [10.4–16.4] vs 12.3 months [6.2–not reached], $p=0.5457$; figure 3B). Statistical analysis showed there was no significant difference in PFS or overall survival between the sexes. 76 (50%) of 153 patients in the high-dose dexamethasone group had received pomalidomide at a median follow-up of 10.0 months compared with 45 (29%) at a median follow-up of 4.2 months (IQR 2.0–7.1). Based on our data, we estimate that all patients in the high-dose dexamethasone group would have received pomalidomide after 16 months of follow-up (figure 4).

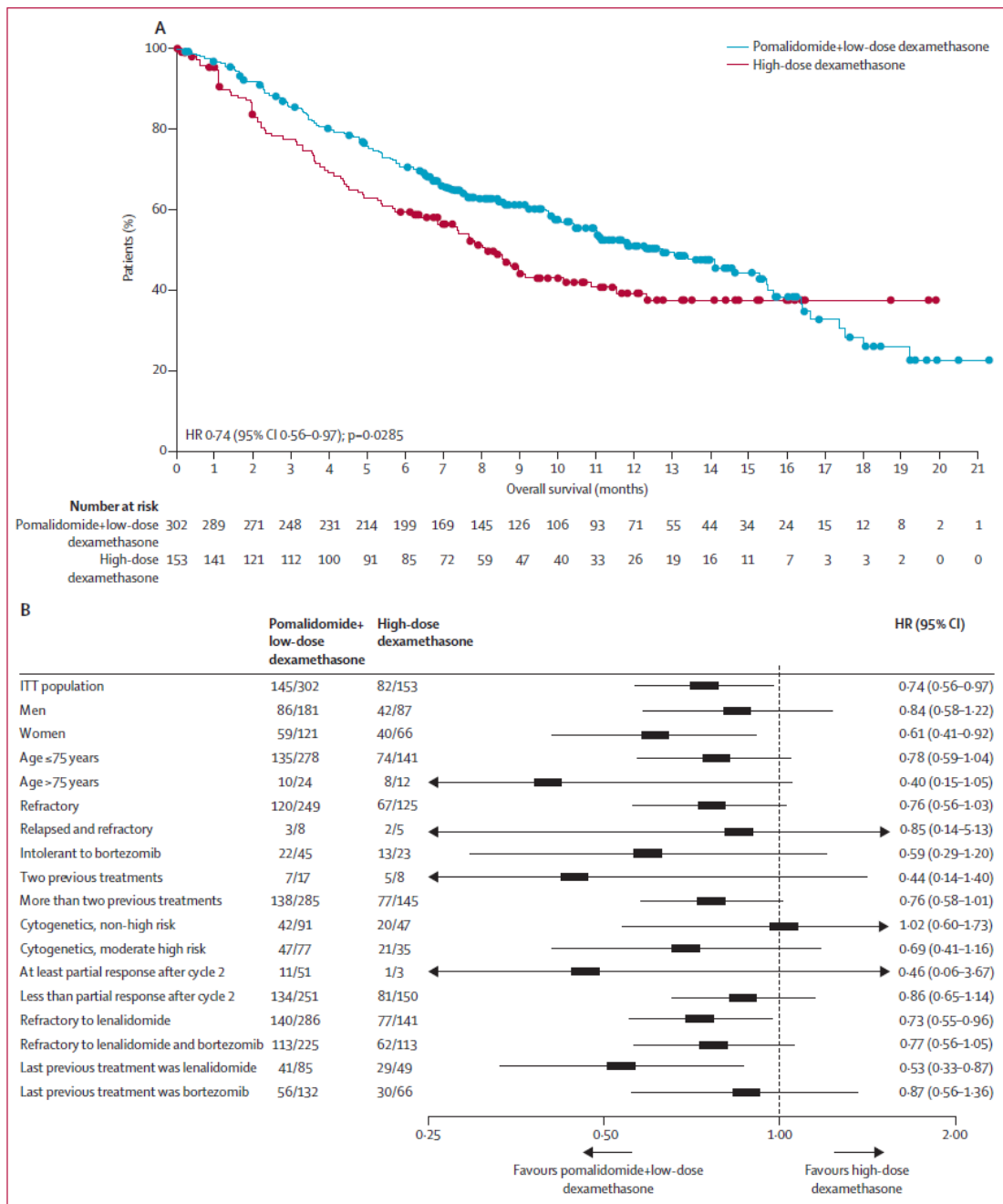


Figure 3. Overall survival

(A)Kaplan-Meier overall survival curves by treatment group in the ITT population. (B) Forest plot for overall survival for subgroup analysis by age, sex, and nature of previous treatments. Data are presented until the cutoff date (March 1, 2013). For (B) patients could be included in more than one subgroup. ITT=intention to treat. HR=hazard ratio.

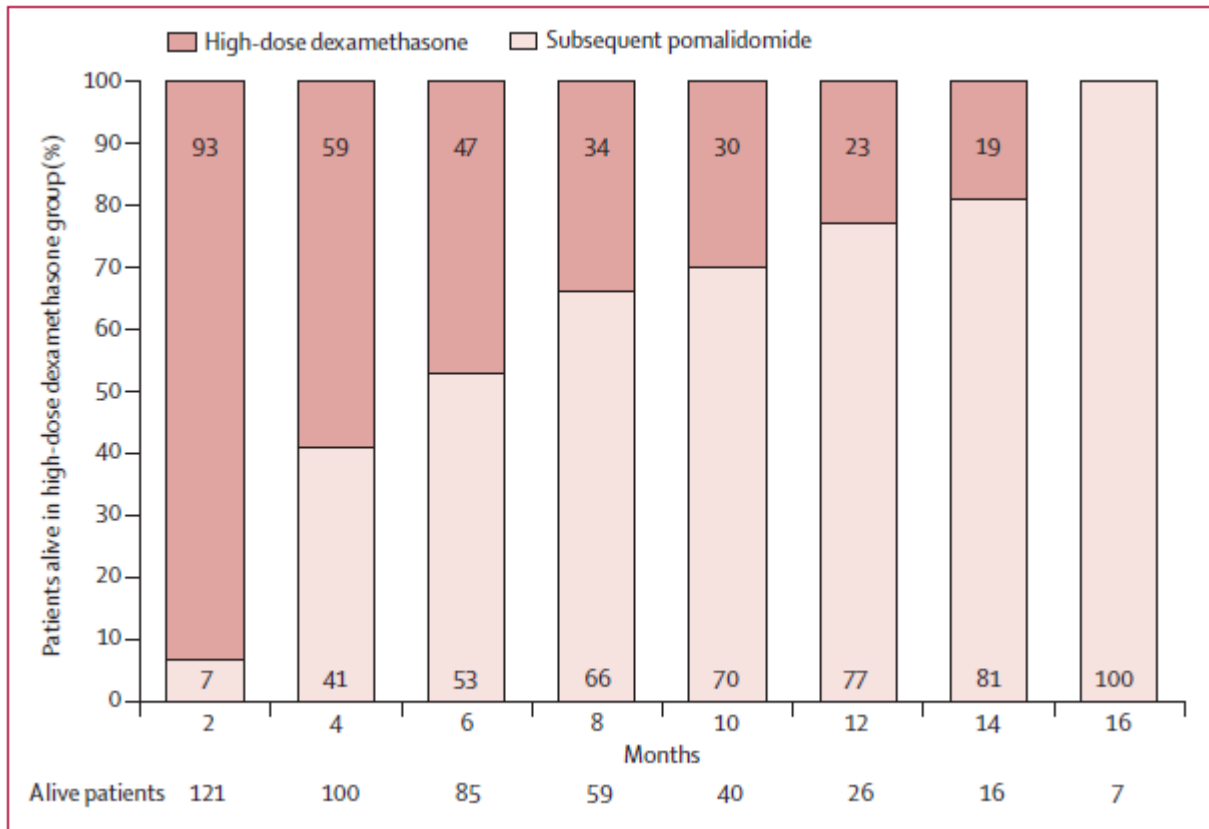


Figure 4. Patients on high-dose dexamethasone receiving pomalidomide as salvage treatment

Time to progression was longer in the pomalidomide plus low-dose dexamethasone group (median 4.7 months [95% CI 4.0–6.0] vs 2.1 months [1.9–2.5], respectively; HR 0.46 [0.36–0.59]; $p < 0.0001$). Overall response rate after a median follow-up of 10.0 months was documented in 31% of 302 patients in the pomalidomide plus low-dose dexamethasone group versus 10% of 153 in the high-dose dexamethasone group (odds ratio [OR] 4.22 [2.35–7.58]; $p < 0.0001$; table 2). In patients with at least partial response, median response duration was 7.0 months (5.8–9.0) and 6.1 months (1.4–8.5), respectively (HR 0.52 [0.25–1.05]; $p = 0.0631$; table 2). In patients who were refractory to lenalidomide, overall responses were noted in 30% of those in the pomalidomide plus low-dose dexamethasone group and 9% in the high-dose dexamethasone group (OR 4.16 [2.23–7.77]; $p < 0.0001$; table 3), 31% and 13%, respectively, in patients who were intolerant to bortezomib (3.01 [0.77–11.82]; $p = 0.1423$; table 3); 28% and 12%, respectively, in patients who were refractory to both bortezomib and lenalidomide (3.06 [1.60–5.84]; $p = 0.0003$; table 3); 33% and 6%, respectively, in patients with lenalidomide as their last treatment (7.53 [2.15–26.35]; $p = 0.0003$; table 3), and 34% and 12%, respectively, in patients with bortezomib as their last treatment (3.75 [1.65–8.53]; $p = 0.0011$; table 3). Median duration of response in patients who were refractory to lenalidomide was 7.0 months (5.8–8.8) in the pomalidomide plus low-dose dexamethasone group and 7.4 months (1.4–9.4) in the high-dose dexamethasone group ($p = 0.3322$). In patients who were refractory to both bortezomib and lenalidomide, duration of response was 7.0 months (5.8–9.0) in the pomalidomide plus low-dose dexamethasone group and 7.4 months (1.4–9.4) in the high-dose dexamethasone group ($p = 0.3149$). PFS was 8.0 months (7.4–9.4) in patients achieving a minor response or better with pomalidomide plus low-dose dexamethasone and 9.5 months (5.3–33.4) in patients receiving high-dose dexamethasone ($p = 0.251$).

Table 2. Best response based on investigator's assessment* as of data cutoff (March 1, 2013)

	Pomalidomide plus low-dose dexamethasone (n=302)	High-dose dexamethasone (n=153)
Overall response	95 (31%)	15 (10%)†
Complete or stringent complete response	3 (1%)	0
Very good partial response	14 (5%)	1 (<1%)
Partial response	78 (26%)	14 (9%)
Minor response	23 (8%)	9 (6%)
Stable disease	129 (43%)	70 (46%)
Progressive disease	29 (10%)	41 (27%)
Not estimable	26 (9%)	18 (12%)
Duration of response in patients with at least a partial response (months)	7.0 (6.0–9.0)	6.1 (1.4–8.5)

Data are median (range) or number (%). *In accordance with the International Myeloma Working Group criteria²¹ (except for minor response, which was in accordance with the European Group for Blood and Marrow Transplantation criteria²²). †p<0.0001 versus pomalidomide plus low-dose dexamethasone.

Table 3. Patients with an overall response based on investigator's assessment by subgroup analyses, as of data cutoff (March 1, 2013)

	Pomalidomide plus low-dose dexamethasone	High-dose dexamethasone
Refractory to lenalidomide	85/286 (30%)	13/141 (9%)
Intolerant to bortezomib	14/45 (31%)	3/23 (13%)
Refractory to both bortezomib and lenalidomide	64/225 (28%)	13/113 (12%)
Lenalidomide as last previous treatment	28/85 (33%)	3/49 (6%)
Bortezomib as last previous treatment	45/132 (34%)	8/66 (12%)

Data are n/N (%).

Median PFS was similar in patients 65 years and younger and those older than 65 years receiving pomalidomide plus low-dose dexamethasone (3.9 months [95% CI 3.48–5.61] and 4.0 months [3.09–4.87], respectively), as were median overall survival (12.7 months [10.08–16.41] and 13.1 months [9.78–15.53], respectively), overall response rate (52 [31%] of 167 and 43 [32%] of 135, respectively), and median duration of response (7.1 months [5.61–13.08] and 6.6 months [5.63–9.00], respectively). Results in the 24 patients older than 75 years were also similar, but statistical analyses were limited by the small number of patients (data not shown).

The safety population (all patients receiving at least one dose of pomalidomide) consisted of 300 patients in the pomalidomide plus low-dose dexamethasone group and 150 in the high-dose dexamethasone group. In the pomalidomide plus low-dose dexamethasone group, 201 (67%) of 300 patients required pomalidomide dose interruptions and 82 (27%) required pomalidomide dose reductions; the median relative dose intensity was 0.9 (range 0.3–1.3). In the high-dose

dexamethasone group, 42 (28%) of 150 patients had dose interruptions and 48 (32%) had dose reductions; median relative dose intensity was 1.0 (0.3–2.0). Few patients discontinued treatment because of treatment-related adverse events (11 [4%] of 300 patients in the pomalidomide plus low-dose dexamethasone group and nine [6%] of 150 patients in the high-dose dexamethasone group).

Treatment-related adverse events are shown in table 4. The pattern of adverse events was generally similar across subgroups based on risk stratification factors (data not shown). The most common grade 3–4 haematological adverse events in the pomalidomide plus low-dose dexamethasone and high-dose dexamethasone groups were neutropenia (143 [48%] of 300 vs 24 [16%] of 150, respectively), anaemia (99 [33%] vs 55 [37%], respectively), and thrombocytopenia (67 [22%] vs 39 [26%], respectively). Baseline characteristics of patients with and without treatment-emergent grade 3–4 neutropenia were similar (data not shown). Grade 3–4 non-haematological adverse events in the pomalidomide plus low-dose dexamethasone and high-dose dexamethasone groups included pneumonia (38 [13%] vs 12 [8%], respectively), bone pain (21 [7%] vs seven [5%], respectively), and fatigue (16 [5%] vs nine [6%], respectively). Incidence of pneumonia (any grade) was similar in the two groups (46 [15%] vs 16 [11%]; table 4). Occurrence of neutropenia did not seem to affect the incidence of infections, and grade 3–4 infections occurred in 91 (30%) patients in the pomalidomide plus low-dose dexamethasone group and 36 (24%) in the high-dose dexamethasone group. Most infections (any grade) occurred in the absence of neutropenia (133 [66%] of 203 vs 68 [86%] of 79, respectively). In the pomalidomide plus low-dose dexamethasone group the incidence of grade 3 or worse febrile neutropenia (29 [10%]) was fairly low; however, the rate was lower in the high-dose dexamethasone group (one [$<1\%$] grade <3). The rate of pomalidomide discontinuation due to infection (seven [2%]) was low (data not shown). Granulocyte colony-stimulating factor was used in 130 (43%) patients in the pomalidomide plus low-dose dexamethasone group and 19 (13%) in the high-dose dexamethasone group. 268 (89%) and 127 (85%) patients, respectively, used anti-infective agents (antibiotics, antifungal drugs, and antiviral drugs). 148 (49%) patients in the pomalidomide plus low-dose dexamethasone group and 79 (53%) in the high-dose dexamethasone group required red blood-cell transfusions, and 61 (20%) and 32 (21%) patients, respectively, required platelet transfusions.

Table 4. Summary of the most commonly reported adverse events occurring in more than 10% of the safety population

	Pomalidomide plus low-dose dexamethasone (n=300)				High-dose dexamethasone (n=150)			
	Total	Grade 3	Grade 4	Grade 5	Total	Grade 3	Grade 4	Grade 5
Infections and infestations	203 (68%)	72 (24%)	19 (6%)	11 (4%)	79 (53%)	28 (19%)	8 (5%)	13 (9%)
Anaemia	157 (52%)	93 (31%)	6 (2%)	..	76 (51%)	48 (32%)	7 (5%)	..
Neutropenia	152 (51%)	77 (26%)	66 (22%)	..	31 (21%)	13 (9%)	11 (7%)	..
Fatigue	103 (34%)	16 (5%)	41 (27%)	9 (6%)
Thrombocytopenia	90 (30%)	27 (9%)	40 (13%)	..	44 (29%)	13 (9%)	26 (17%)	..
Pyrexia	80 (27%)	8 (3%)	1 (<1%)	..	34 (23%)	5 (3%)	2 (1%)	..
Diarrhoea	66 (22%)	3 (1%)	28 (19%)	2 (1%)
Constipation	65 (22%)	7 (2%)	22 (15%)
Cough	61 (20%)	1 (<1%)	1 (<1%)	..	15 (10%)	1 (<1%)
Back pain	59 (20%)	13 (4%)	2 (1%)	..	24 (16%)	5 (3%)	1 (<1%)	..
Dyspnoea	59 (20%)	13 (4%)	2 (1%)	..	21 (14%)	7 (5%)
Bone pain	52 (17%)	20 (7%)	1 (<1%)	..	19 (13%)	7 (5%)
Peripheral oedema	52 (17%)	4 (1%)	17 (11%)	3 (2%)
Upper respiratory tract infection	48 (16%)	5 (2%)	12 (8%)	2 (1%)
Asthenia	48 (16%)	10 (3%)	1 (<1%)	..	26 (17%)	9 (6%)
Muscle spasms	47 (16%)	1 (<1%)	11 (7%)	1 (<1%)
Pneumonia	46 (15%)	30 (10%)	8 (3%)	4 (1%)	16 (11%)	10 (7%)	2 (1%)	3 (2%)
Nausea	45 (15%)	2 (1%)	16 (11%)	2 (1%)
Leukopenia	38 (13%)	20 (7%)	6 (2%)	..	8 (5%)	2 (1%)	3 (2%)	..
Dizziness	37 (12%)	4 (1%)	12 (8%)	2 (1%)
Decreased appetite	36 (12%)	2 (1%)	12 (8%)	2 (1%)
Insomnia	31 (10%)	3 (1%)	30 (20%)	5 (3%)
Bronchitis	30 (10%)	3 (1%)	8 (5%)
Febrile neutropenia	29 (10%)	23 (8%)	5 (2%)	..	1 (<1%)
Epistaxis	28 (9%)	2 (<1%)	1 (<1%)	..	15 (10%)	2 (1%)	1 (<1%)	..
Hypercalcaemia	21 (7%)	6 (2%)	7 (2%)	..	16 (11%)	6 (4%)	2 (1%)	..
Muscle weakness	11 (4%)	3 (1%)	19 (13%)	5 (3%)

Data are number (%).

46 (15%) of 300 patients in the pomalidomide plus low-dose dexamethasone group and 16 (11%) of 150 in the high-dose dexamethasone group had peripheral neuropathy of any grade; four (1%) patients in the pomalidomide plus low-dose dexamethasone group and two (1%) in the high-dose dexamethasone group developed grade 3 or greater neuropathy. With thromboprophylaxis, deep-vein thrombosis and pulmonary embolism were infrequent in the pomalidomide plus low-dose dexamethasone and high-dose dexamethasone groups (any grade, six [2%] of 300 vs two [1%] of 150 patients, respectively; grade 3–4, three [1%] vs zero, respectively). The median time to onset of deep-vein thrombosis or pulmonary embolism was 4.0 months (range 1.0–6.2) in the pomalidomide plus low-dose dexamethasone group and 2.3 months (1.1–3.5) in the high-dose dexamethasone group. So far, one patient in each group has died of deep-vein thrombosis or pulmonary embolism as a consequence of disease progression. Four patients in the pomalidomide plus low-dose dexamethasone group and one in the high-dose dexamethasone group developed a second primary malignancy. Two patients in the pomalidomide plus low-dose dexamethasone group had invasive solid cancers, and two patients in this group and one in the high-dose dexamethasone group had non-invasive (basal-cell) skin cancers.

Serious adverse events (defined as grade 5, requiring hospitalisation, or resulting in disability or incapacity) were reported in 183 (61%) of 300 patients in the pomalidomide plus low-dose dexamethasone group and 80 (53%) of 150 patients in high-dose dexamethasone group; 144 (48%) and 80 (53%) patients died, respectively. The most common cause of death was progression of

multiple myeloma, which accounted for 98 (68%) deaths in the pomalidomide plus low-dose dexamethasone and 51 (64%) in the high-dose dexamethasone groups. Overall, infection was the second most common cause of death, but accounted for more deaths in the high-dose dexamethasone group than in the pomalidomide plus low-dose dexamethasone group (14 [10%] of 144 deaths vs 15 [19%] of 80). There were 11 (4%) treatment-related deaths in the pomalidomide plus low-dose dexamethasone group (eight cases of infections and infestations, two cases of multiorgan failure or sudden death, and one nervous system disorder) and seven (5%) in the high-dose dexamethasone group (all infections and infestations).

Discussion

Pomalidomide plus low-dose dexamethasone resulted in significantly longer PFS and overall survival, and a greater number of responses compared with high-dose dexamethasone in patients with advanced refractory or relapsed and refractory multiple myeloma (panel).

Panel.

Research in context

Systematic review

We undertook a systematic search of PubMed, ClinicalTrials.gov, and recent (2010–11) international congresses (American Society of Hematology, American Society of Clinical Oncology, and European Hematology Association) using the search terms “multiple myeloma”, “relapsed and/or refractory”, “refractory myeloma”, and “salvage therapy”. From the search, we noted that patients with relapsed or refractory multiple myeloma in whom treatment with bortezomib and lenalidomide had been exhausted had few treatment options and poor outcomes.¹ The safety and efficacy of pomalidomide 4 mg/day on days 1–21 of each 28 day cycle in combination with low-dose dexamethasone in heavily pretreated patients had been shown in two phase 2 trials.^{5 and 6} To our knowledge, this study is the first phase 3 trial designed to compare the efficacy and safety of pomalidomide plus low-dose dexamethasone with high-dose dexamethasone, which was chosen as the comparator for registration trials of bortezomib and lenalidomide.^{14, 15 and 16}

Interpretation

Pomalidomide plus low-dose dexamethasone significantly prolonged median progression-free survival and overall survival compared with high-dose dexamethasone, even though 50% of patients assigned to high-dose dexamethasone had received pomalidomide at the time of the final analysis. With appropriate dose modifications, the safety profile of the combination was predictable, manageable, and generally well-tolerated in this heavily pretreated population. Few patients discontinued treatment because of treatment-related adverse events. Based on our results, pomalidomide plus low-dose dexamethasone could be a treatment option for patients with advanced refractory or relapsed and refractory multiple myeloma in whom treatment with bortezomib and lenalidomide has been unsuccessful.

To our knowledge, MM-003 is the first phase 3 study of pomalidomide in patients with advanced refractory or relapsed and refractory multiple myeloma in whom treatment with bortezomib and lenalidomide has been exhausted. At the time this study was initiated, there was no standard of care

for these patients, and high-dose dexamethasone was a commonly used rescue treatment for heavily pretreated patients. Therefore, the study steering committee chose high-dose dexamethasone as the comparator to isolate the effects of pomalidomide. In previous registration studies of lenalidomide^{15 and 16} and bortezomib¹⁷ in patients with relapsed or refractory multiple myeloma, high-dose dexamethasone was also used as a comparator. In these studies, overall response rates to high-dose dexamethasone ranged from 18% to 24%, and median time to progression was 3.5–4.7 months in patients who had received at least one previous treatment. Patients in our study had received many more previous treatments than did those in the lenalidomide and bortezomib registration studies. The median overall survival of 8.1 months in the control group is consistent with the expected median 9 months in historical controls.¹ Moreover, our findings confirm those of previous phase 2 studies of pomalidomide for advanced myeloma.^{6, 7 and 18} Altogether, these findings suggest that pomalidomide plus low-dose dexamethasone could be a beneficial treatment option for this patient population. Other pomalidomide-based combination treatments show encouraging efficacy, with 30–54% of patients achieving an overall response, and are being assessed in clinical trials.^{19, 20, 21, 22, 23 and 24}

Only two drugs (pomalidomide and carfilzomib) have been approved for the treatment of patients in whom use of bortezomib and lenalidomide has been exhausted. There are few options for salvage treatment, which are limited to rechallenge with a previously used treatment (alone, or in combination with corticosteroids or other novel agents), use of older drugs (eg, thalidomide, melphalan, vincristine, doxorubicin, and carmustine), or enrolment in a clinical trial.¹ Outcomes with subsequent treatment using standard therapies are characterised by short durations of response and increasing drug resistance.²⁵ Therefore, there is a need for effective antimyeloma treatments for patients with advanced multiple myeloma.

Carfilzomib has been approved by the US Food and Drug Administration for patients with relapsed or refractory multiple myeloma who have received at least two previous treatments, including bortezomib and an immunomodulatory agent.²⁶ In a subpopulation of 169 patients refractory to both bortezomib and lenalidomide, carfilzomib monotherapy resulted in a response rate of 15% with a median overall survival of 11.9 months.²⁷ Studies to assess the efficacy of carfilzomib in combination with lenalidomide and low-dose dexamethasone for refractory or relapsed and refractory multiple myeloma (NCT01080391)²⁸ and higher doses of carfilzomib in combination with dexamethasone are underway.²⁹ However, unlike pomalidomide, carfilzomib is not an oral drug.

Our results showed longer overall survival than PFS in patients receiving pomalidomide plus low-dose dexamethasone. This finding is similar to the results of other studies of patients with refractory or relapsed and refractory multiple myeloma,^{15, 16, 17, 30 and 31} and might be explained by progression in advanced disease being biochemical, with clinical manifestation of relapse not occurring until months later. The prolonged overall survival might also indicate the availability of other effective salvage treatments; patients progressing after treatment with pomalidomide plus low-dose dexamethasone might be in better overall health than those who did not receive this treatment³² and, therefore, able to tolerate or benefit from regimens that would otherwise not have been an option.

Adverse events in this trial were consistent with the safety profile of pomalidomide plus low-dose dexamethasone,^{6 and 7} and other immunomodulatory agents for patients with refractory or relapsed and refractory multiple myeloma.^{15 and 16} The main grade 3–4 adverse event was neutropenia, and the incidence of febrile neutropenia was low. In this study, most grade 3–4 infections were unrelated to neutropenia. The incidence of grade 3–4 peripheral neuropathy and deep-vein thrombosis and pulmonary embolism (with thromboprophylaxis) was low ($\leq 1\%$ in each of the treatment groups). Discontinuation of pomalidomide plus low-dose dexamethasone because of

adverse events was uncommon (9%), suggesting that the combination was generally well-tolerated. Cross-sectional, longitudinal, and time-to-worsening analyses for clinically relevant European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 domains (global health status, physical functioning, emotional functioning, fatigue, and pain) are planned and will be published in the future.

A limitation of this study is its open-label design. Additionally, the unmasked nature of the study may have affected the updated PFS analysis in favour of the high-dose dexamethasone group because nine patients crossed over before progressive disease. Furthermore, the crossover of patients receiving high-dose dexamethasone without progressive disease to receive pomalidomide unblinded is expected to have reduced the magnitude of the difference in overall survival between the treatment groups from the interim to the final overall survival analysis.

In conclusion, pomalidomide plus low-dose dexamethasone significantly improved PFS, overall survival, and proportion of patients showing overall response compared with high-dose dexamethasone in patients with refractory or relapsed and refractory multiple myeloma, including patients with disease refractory to both bortezomib and lenalidomide. Studies of different combinations including pomalidomide in patients with refractory or relapsed and refractory multiple myeloma have shown promising results, and the enhanced effects with pomalidomide combinations should be further investigated. Based on these findings and the results of previous trials, pomalidomide plus low-dose dexamethasone could be a new treatment option for patients with advanced refractory or relapsed and refractory multiple myeloma.

Contributors

JSM, KW, PM, ML, KS, MD, LK, HG, AB, AO, AA, CC, MC, LG, VI, JM-L, AB, AP, SS, PS, and MD (senior author) were principal investigators and involved in the data gathering and interpretation. JSM, XY, LS, CJ, and MZ contributed to the statistical analyses and generation of tables and figures. JSM, XY, LS, CJ, MZ, and MD were involved in the development and writing of the report. All authors reviewed and approved the submitted report.

Conflicts of interest

JSM has had a consultancy or advisory role, and has received honoraria from Celgene Corporation, Jansen, Millennium, Novartis, and Onyx. KW has had a consultancy or advisory role and has received honoraria from Celgene Corporation. PM has had a consultancy or advisory role and has received honoraria from Celgene Corporation, Millennium, and Janssen. ML has received research funding from Celgene Corporation. KS has had a consultancy or advisory role, received honoraria, and has received research funding from Celgene Corporation and Janssen. MD and AA have had a consultancy or advisory role and received research funding from Celgene Corporation and Janssen. LK has had a consultancy or advisory role and provided expert testimony for Celgene Corporation, and received honoraria and other remuneration from Celgene Corporation and Janssen. HG has had a consultancy or advisory role, received honoraria and received research funding from Celgene Corporation and Janssen. AO has had a consultancy and advisory role for Celgene Corporation and Janssen. CC has had a consultancy or advisory role, received honoraria, and received research funding from Celgene Corporation. MC has had a consultancy or advisory role and has received honoraria from Celgene Corporation, Janssen, and Millennium. JM-L has received honoraria and research funding from Celgene Corporation. AB has received research funding from Celgene Corporation. AP has received honoraria and was a member of the board of an advisory committee for Celgene Corporation and Janssen-Cilag, and received honoraria from OrthoBiotech. SS has had a consultancy role and received honoraria from Celgene Corporation. PS has received honoraria and

funding from Celgene Corporation, Janssen, and Onyx. XY, LS, CJ, and MZ are employed and have equity ownership with Celgene Corporation. MD has had a consultancy or advisory role for Celgene Corporation and Ortho Biotech, and has received research funding from Genesis Pharma. The other authors declare that they have no conflicts of interest.

Acknowledgements

Acknowledgments

This research was funded by Celgene Corporation. We thank the patients who volunteered to participate in this study and staff members at the study sites who cared for them, and the representatives of the sponsors who were involved in data gathering and analyses. We thank Eva Polk and Anna Georgieva from Excerpta Medica, for their writing assistance, which was funded by Celgene Corporation.

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