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Authors

Siegel, David S
Schiller, Gary J
Song, Kevin W
et al.

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Pomalidomide plus low-dose dexamethasone in relapsed refractory multiple myeloma after lenalidomide treatment failure

David S. Siegel,[1] Gary J. Schiller,[2] Kevin W. Song,[3] Richy Agajanian,[4] Keith Stockerl-Goldstein,[5] Hakan Kaya,[6] Michael Sebag,[7] Christy Samaras,[8] Ehsan Malek,[9] Giampaolo Talamo,[10] Christopher S. Seet,[2] Jorge Mouro,[11] William E. Pierceall,[11] Faiza Zafar,[11] Weiyuan Chung,[11] Shankar Srinivasan,[11] Amit Agarwal[11] and Nizar J. Bahlis[12]

[1]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, [2]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA, [3]Vancouver General Hospital, Vancouver, BC, Canada, [4]The Oncology Institute of Hope and Innovation, Downey, CA, [5]Washington University School of Medicine, St. Louis, MO, [6]Cancer Care Northwest, Spokane, WA, USA, [7]McGill University Health Centre, Montreal, QC, Canada, [8]Cleveland Clinic, [9]University Hospitals Case Medical Center, Cleveland, OH, [10]Penn State Hershey Cancer Institute, Hershey, PA, [11]Celgene Corporation, Summit, NJ, USA and [12]University of Calgary, Calgary, AB, Canada

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Correspondence: David S. Siegel, John Theurer Cancer Center, Hackensack University Medical Center, 92 2nd St Suite 340, Hackensack, NJ 07601, USA.
E-mail: davids.siegel@hackensackmeridian.org

Summary

Patients with relapsed/refractory multiple myeloma (RRMM) for whom the benefits of lenalidomide have been exhausted in early treatment lines need effective therapies. In cohort A of the phase 2 MM-014 trial, we examined the safety and efficacy of pomalidomide plus low-dose dexamethasone immediately after lenalidomide-based treatment failure in patients with RRMM and two prior lines of therapy. Pomalidomide 4 mg was given on days 1 to 21 of 28-day cycles. Dexamethasone 40 mg (20 mg for patients aged >75 years) was given on days 1, 8, 15 and 22 of 28-day cycles. The primary endpoint was overall response rate (ORR), and secondary endpoints included progression-free survival (PFS), overall survival (OS) and safety. The intention-to-treat population comprised 56 patients; all received prior lenalidomide (87·5% lenalidomide refractory) and 39 (69·6%) received prior bortezomib. ORR was 32·1% (28·2% in the prior-bortezomib subgroup). Median PFS was 12·2 months (7·9 months in the prior-bortezomib subgroup). Median OS was 41·7 months (38·6 months in the prior-bortezomib subgroup). The most common grade 3/4 treatment-emergent adverse events were anaemia (25·0%), pneumonia (14·3%) and fatigue (14·3%). These findings support earlier sequencing of pomalidomide-based therapy in lenalidomide-pretreated patients with RRMM, including those who have become refractory to lenalidomide.

Trial registration: www.ClinicalTrials.gov identifier NCT01946477.

Keywords: pomalidomide, dexamethasone, lenalidomide, multiple myeloma, refractory.

Nearly all patients with multiple myeloma (MM) relapse regardless of the frontline regimen they receive (Kumar *et al*, 2004; Sonneveld & Broijl, 2016; Moreau & de Wit, 2017). Treatment of relapsed/refractory MM (RRMM) is complex, and the selection of a regimen depends on a number of factors, such as patient age, response to previous therapies, cytogenetic status and aggressiveness of the current relapse (Sonneveld & Broijl, 2016; Moreau *et al*, 2019). Moreover, drug resistance and increased genetic heterogeneity develop throughout the disease course (Keats *et al*, 2012; Leich *et al*, 2013; Lohr *et al*, 2014; Binder *et al*, 2016; Kumar *et al*, 2017; Robak *et al*, 2018). With each relapse, patient outcomes worsen and the time between relapses decreases; effective treatment of early relapses is thus critical to delay onset of further relapses (Kumar *et al*, 2004; Magrangeas *et al*, 2013; Sonneveld & Broijl, 2016; Yong *et al*, 2016; Harousseau & Attal, 2017).

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Immune dysfunction is a hallmark of MM, and immunosuppression increases as the disease progresses (Kumar & Anderson, 2016; Rasche *et al*, 2017; Tamura, 2018). Therefore, therapies that stimulate the immune system can benefit patients, both early in their disease course and after relapse (Kumar & Anderson, 2016; Guillerey *et al*, 2016). Pomalidomide is an immunomodulatory agent that exerts potent direct tumoricidal and immune-stimulating effects through binding to its target cereblon, a protein in the E3 ubiquitin ligase complex, and subsequent proteasomal degradation of the transcription factors Ikaros and Aiolos (Lopez-Girona *et al*, 2012; Bjorklund *et al*, 2015). Compared with lenalidomide, pomalidomide has increased potency against cereblon, different substrate degradation kinetics, and a distinct gene activation profile, and thus, pomalidomide has antitumor and immune stimulating properties distinct from those of lenalidomide (Lopez-Girona *et al*, 2012; Bjorklund *et al*, 2015; Ocio *et al*, 2015; Sehgal *et al*, 2015). Pomalidomide also has activity in lenalidomide-resistant cell lines and animal models, and pomalidomide-based therapy has exhibited efficacy in patients refractory to lenalidomide in clinical trials (Lopez-Girona *et al*, 2012; Leleu *et al*, 2013; San Miguel *et al*, 2013; Richardson *et al*, 2014; Ocio *et al*, 2015; Rychak *et al*, 2016; Dimopoulos *et al*, 2016a).

Pomalidomide plus low-dose dexamethasone is a standard treatment option for RRMM (Moreau & de Wit, 2017; Moreau *et al*, 2017). The combination is approved in the United States and the European Union for the treatment of patients with RRMM who have received ≥2 prior therapies, including lenalidomide and a proteasome inhibitor (bortezomib in the European Union) (https://media.celgene.com/content/uploads/pomalyst-pi.pdf; https://www.ema.europa.eu/en/documents/product-information/imnovid-epar-product-information_en.pdf). In the United States, the triplet combination of pomalidomide, daratumumab and low-dose dexamethasone is approved for the same indication as the pomalidomide plus low-dose dexamethasone doublet combination (Darzalex, 2018). Lenalidomide-based therapy until progressive disease (PD) is an established front-line treatment modality in MM (Sonneveld & Broijl, 2016; Moreau & de Wit, 2017; Moreau *et al*, 2017; https://media.celgene.com/content/uploads/revlimid-pi.pdf). Therefore, patients for whom the benefits of lenalidomide have been exhausted in early lines of treatment are a clinically relevant population. However, patients who are refractory to lenalidomide have largely been excluded from recent RRMM clinical trials investigating novel regimens in early lines of treatment (Lonial *et al*, 2015; Stewart *et al*, 2015; Moreau *et al*, 2016; Dimopoulos *et al*, 2016b). To address the unmet need for effective treatment options sequenced after patients become refractory to lenalidomide early in their treatment course, the phase 2 MM-014 trial, comprising two cohorts, is investigating the outcomes of sequencing a pomalidomide-based doublet (pomalidomide plus low-dose dexamethasone; cohort A) or triplet (pomalidomide, low-dose dexamethasone, and daratumumab) regimen immediately after lenalidomide-based treatment failure. Here we report results from cohort A.

Patients and methods

Study design and participants

MM-014 is a phase 2, nonrandomized, multicentre, open-label clinical trial conducted at 39 study sites in the United States and Canada. This study is registered with ClinicalTrials.gov as NCT01946477. The primary endpoint was overall response rate (ORR). The secondary endpoints were time to response (TTR), duration of response (DOR), progression-free survival (PFS), time to progression (TTP), overall survival and safety, including adverse events (AEs) and second primary malignancies (SPMs). Exploratory endpoints were potential molecular, immune and cellular markers for response or resistance to pomalidomide plus low-dose dexamethasone.

Eligible patients were ≥18 years of age with documented diagnosis of MM, measurable disease and an Eastern Cooperative Oncology Group performance status ≤2. Patients must have had two prior lines of antimyeloma therapy and documented PD during or after their last antimyeloma therapy. Additionally, patients must have received prior treatment with lenalidomide or a lenalidomide-containing regimen for ≥2 consecutive cycles as their most recent regimen. Patients who were relapsed or refractory to lenalidomide were eligible for inclusion. Refractory disease was defined as disease that was nonresponsive to therapy or the occurrence of PD within 60 days of the last dose, inclusive. Patients defined as lenalidomide refractory were refractory to lenalidomide therapy in the last lenalidomide-containing regimen.

This study was approved by each site's institutional review board or ethics committee. All patients provided written informed consent. The study was executed in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation's Guideline for Good Clinical Practice.

Treatment

Patients received pomalidomide plus low-dose dexamethasone in 28-day cycles until PD or unacceptable toxicity. Pomalidomide at a dose of 4 mg/day was given on days 1 to 21 of each 28-day cycle. Dexamethasone at a dose of 40 mg/day (20 mg/day for patients >75 years of age) was given on days 1, 8, 15 and 22 of each 28-day cycle. Both agents were administered orally. Dose interruptions and reductions were permitted throughout the study.

Toxicity and response assessments

Safety monitoring included pregnancy testing and counselling, physical examination, clinical laboratory evaluations,

venous thromboembolism monitoring and electrocardiograms. AEs were coded according to the Medical Dictionary for Regulatory Activities (version 20.0; https://www.meddra.org/) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). If a patient experienced the same AE multiple times, only the event with the worst severity was counted. SPMs were monitored as events of interest.

Efficacy assessments included bone marrow aspiration and/or biopsy, extramedullary plasmacytoma measurements [assessed clinically or radiographically via x-ray and/or conventional (spiral) computed tomography/magnetic resonance imagery], skeletal survey, measurement of myeloma paraprotein via protein electrophoresis and immunofixation, serum immunoglobulin assessment and serum free light chain assays. Tumour response was assessed according to modified International Myeloma Working Group criteria (Durie *et al*, 2006). TTR, DOR, TTP and PFS were calculated based on investigator's response assessment. Efficacy assessments were performed at the start of each new treatment cycle.

All laboratory assessments for safety and efficacy parameters were performed and reviewed by the central laboratory. Tests for factors that might result in dose modification or interruption were also performed locally to allow for treatment-related decisions during patient visits to the site.

Full details regarding exclusion criteria, additional treatment, biomarkers and immune profile assessments, statistical analysis and the data sharing statement are provided in Appendix S1.

Results

Patients and treatment

Fifty-six patients were enrolled in cohort A (Fig 1). Table I shows patients' demographic and baseline characteristics. Most patients were male (57·1%), and the median age was 68 years. Median time from diagnosis was 4·5 years (range, 1·3–13·3 years). Per protocol, all patients had two prior lines of therapy. Median number of prior antimyeloma regimens was 2 (range, 2–5). All patients had received lenalidomide in the line of therapy immediately prior to study enrolment. Forty-one patients (73·2%) had received prior treatment with a proteasome inhibitor, and 39 (69·6%) had received prior treatment with bortezomib (prior-bortezomib subgroup). Patients in the prior-bortezomib subgroup were either exposed or relapsed and/or refractory to bortezomib. The baseline characteristics of the prior-bortezomib subgroup were similar to those of the intention-to-treat (ITT) population. Previous stem cell transplant had been performed in 64·3% of the ITT population and 61·5% of the prior-bortezomib subgroup. All patients were either relapsed (12·5%) or refractory (87·5%) to their immediately prior lenalidomide-containing treatment. In the prior-bortezomib subgroup, a similarly high proportion of patients was lenalidomide refractory (89·7%). Median duration of the lenalidomide-based treatment received immediately prior to study entry was 23·6 months in the ITT population and 18·2 months in the prior-bortezomib subgroup. The most recent prior lenalidomide dose was 25 mg in 62·5% of the ITT population and 61·5% of the prior-bortezomib subgroup.

As of the data cut-off of 9 April 2018, 53 patients in the ITT population have discontinued treatment. The most frequent reason for treatment discontinuation was PD (56·6%); additional causes of treatment discontinuations were AEs (13·2%), patient withdrawal (13·2%), lack of efficacy (5·7%), death (3·8%) and other reasons (7·5%). Eleven patients (19·6%) had ≥ 1 pomalidomide dose reduction; three patients (5·4%) had ≥2. Median time to the first pomalidomide dose reduction was 57 days. Median duration of treatment was 5·1 months with both pomalidomide and low-dose dexamethasone. Patients received a median of six cycles of pomalidomide treatment. Median relative dose intensity was 0·9 for both pomalidomide and low-dose dexamethasone.

Efficacy

Median study follow-up was 24·1 months as of the data cut-off; three patients remain on treatment. The ORR was 32·1% in the ITT population and 28·2% in the prior-bortezomib subgroup (Table II). ORR was mostly similar regardless of the analysed subgroup (Fig 2); the lowest ORR (25·0%) was reported in the subgroup of patients without prior stem cell transplant ($n = 20$). The ORR was 42·9% and 25·7% in patients whose most recent prior lenalidomide dose was ≤15 mg ($n = 21$) and >15 mg ($n = 35$), respectively. Clinical benefit rate [≥minimal response (MR)] was 46·4% in the ITT population and 38·5% in the prior-bortezomib subgroup. Among patients in the ITT population, median TTR was 1·9 months and median DOR was 16·6 months. Median duration of pomalidomide treatment was 5·1 months. Figure 3 shows median duration of pomalidomide treatment by best response. Median duration of pomalidomide treatment was 12·7 months in patients who achieved ≥partial response (PR; $n = 18$) and 10·8 months in those who achieved MR ($n = 8$).

Median PFS was 12·2 months in the ITT population (Fig 4). The 1- and 2-year PFS rates were 50·2% and 29·8%, respectively. Median PFS in the efficacy-evaluable (EE) population was also 12·2 months, and 1- and 2-year PFS rates for the EE population were similar to those in the ITT population (52·1% and 30·9%, respectively). Median PFS in patients who achieved MR and ≥PR was 13·9 and 28·5 months, respectively. In the prior-bortezomib subgroup, median PFS was 7·9 months. In both the ITT and EE populations, median TTP was 13·8 months. Median TTP was 8·7 months in the prior-bortezomib subgroup. Follow-up for OS is ongoing. At the time of data cut-off, median OS was 41·7 months

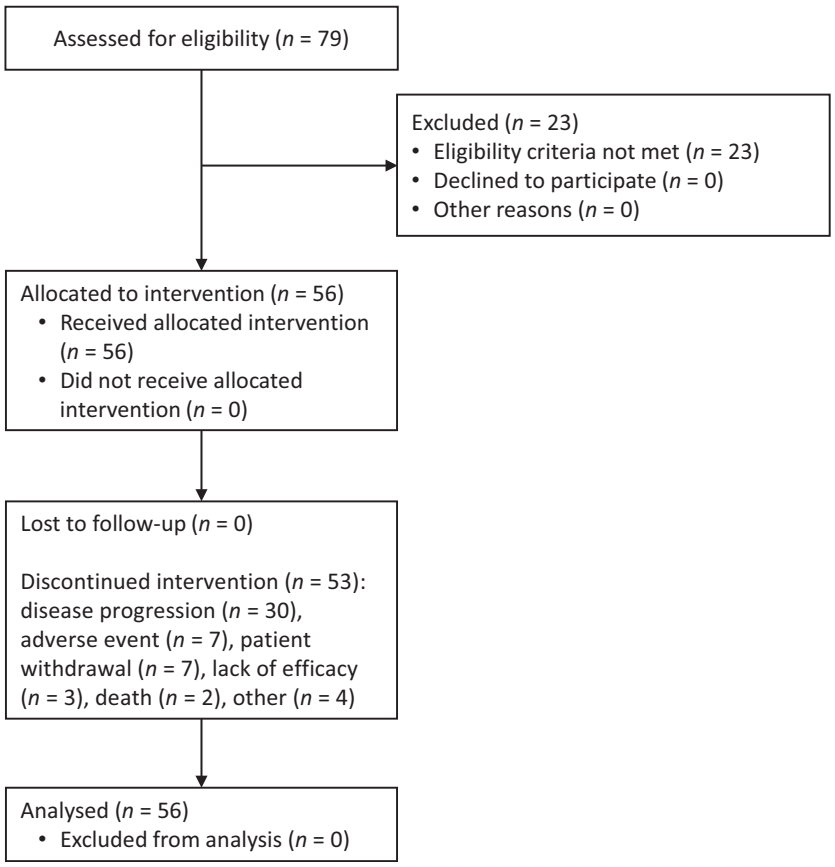

Fig 1. CONSORT flow diagram of cohort A of MM-014. Cohort A enrolled 56 patients.

in both the ITT and EE populations. The 1- and 2-year OS rates were 89·3% and 76·6%, respectively, in the ITT population, and 92·5% and 79·1%, respectively, in the EE population. In the prior-bortezomib subgroup, median OS was 38·6 months.

An immune profile analysis was conducted to observe the effect of pomalidomide-based therapy on T-cell populations in lenalidomide pre-treated patients. Flow cytometry assessment of peripheral blood cells from consenting patients ($n = 36$) showed significant increases in both $CD3^+$ and $CD8^+$ T-cell populations on day 1 of treatment cycle 3 ($P = 0{\cdot}014$ and $P = 0{\cdot}034$, respectively; Figure S1) and day 1 of treatment cycle 5 ($P = 0{\cdot}039$ and $P = 0{\cdot}020$, respectively). Conversely, $CD4^+$ T cells were stable following treatment.

Safety

Treatment-emergent AEs (TEAEs) are shown in Table III. The most common grade 3/4 haematological TEAEs were anaemia (25·0%) and neutropenia (10·7%). The most common grade 3/4 non-haematological TEAEs were pneumonia and fatigue, each reported in 14·3% of patients. Grade 3/4 TEAE frequencies were similar between the overall safety population and the prior-bortezomib subgroup. Peripheral sensory neuropathy was reported in four patients (7·1%); all events were grade 1/2. There were two reported SPMs: one case of anaplastic astrocytoma and one case of basal cell carcinoma.

Pomalidomide treatment discontinuations due to ≥1 TEAE were reported in seven patients (12·5%); low-dose dexamethasone treatment discontinuations due to ≥1 TEAE were reported in eight patients (14·3%). Dose reductions due to ≥1 TEAE were reported in 12 patients (21·4%) taking pomalidomide and nine patients (16·1%) taking low-dose dexamethasone. Similar proportions of patients had dose interruptions due to ≥1 TEAE with pomalidomide [31 (55·4%)] and low-dose dexamethasone [30 (53·6%)].

Discussion

The findings from cohort A of this phase 2 trial show that pomalidomide plus low-dose dexamethasone was effective and well-tolerated when sequenced immediately after treatment failure of a lenalidomide-based regimen. Patients had a median of two prior lines of therapy, all had been treated previously with lenalidomide in the line of therapy immediately prior to enrolling in the study and the majority (87·5%) were refractory to their most recent lenalidomide-containing regimen. These characteristics are reflective of a patient population in which the benefits of lenalidomide have largely been exhausted in early lines of treatment. The primary endpoint of ORR was achieved by 32·1% of patients, with a majority of patients having disease

Table I. Demographic and baseline characteristics.

Characteristic	ITT population	
	Overall (N = 56)*	Prior-bortezomib subgroup (n = 39)*
Age, median (range), years	68 (44–85)	68 (45–85)
> 65 years, *n* (%)	35 (62·5)	25 (64·1)
Male, *n* (%)	32 (57·1)	22 (56·4)
Time from diagnosis, median (range), years	4·5 (1·3–13·3)	3·8 (1·3–9·2)
ECOG PS, *n* (%)		
0	21 (37·5)	15 (38·5)
1	31 (55·4)	22 (56·4)
2	4 (7·1)	2 (5·1)
Calculated R-ISS stage, *n* (%)		
I	23 (41·1)	17 (43·6)
II	24 (42·9)	18 (46·2)
III	3 (5·4)	2 (5·1)
NE	6 (10·7)	2 (5·1)
Number of prior antimyeloma regimens, median (range)	2 (2–5)	2 (2–5)
Prior therapies, *n* (%)		
LEN	56 (100)	39 (100)
Proteasome inhibitor†	41 (73·2)	39 (100)
BORT	39 (69·6)	39 (100)
CFZ	4 (7·1)	2 (5·1)
IXA	1 (1·8)	1 (2·6)
SCT	36 (64·3)	24 (61·5)
Refractory to most recent prior LEN-containing regimen, *n* (%)	49 (87·5)	35 (89·7)
Duration of most recent prior LEN-containing regimen, median (range), months	23·6 (3·5–107·0)	18·2 (3·5–60·3)
Most recent prior LEN dose, *n* (%)		
25 mg	35 (62·5)	24 (61·5)
15 mg	11 (19·6)	7 (17·9)
≤ 10 mg	10 (17·9)	8 (20·5)

BORT, bortezomib; CFZ, carfilzomib; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; IXA, ixazomib; LEN, lenalidomide; NE, not evaluable; R-ISS, revised International Staging System; SCT, stem cell transplantation.
*All patients received prior treatment with lenalidomide.
†Patients may have received more than one proteasome inhibitor.

Table II. Response by mIMWG criteria.

Response, *n* (%)	ITT population	
	Overall (N = 56)	Prior-bortezomib subgroup (n = 39)
CBR (≥MR)	26 (46·4)	15 (38·5)
ORR (≥PR)	18 (32·1)	11 (28·2)
CR	2 (3·6)	0
VGPR	6 (10·7)	3 (7·7)
PR	10 (17·9)	8 (20·5)
MR	8 (14·3)	4 (10·3)
SD	24 (42·9)	18 (46·2)
PD	3 (5·4)	3 (7·7)
Missing	3 (5·4)	3 (7·7)

CBR, clinical benefit response; CR, complete response; ITT, intention-to-treat; mIMWG, modified International Myeloma Working Group; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

control and no patients experiencing clinical relapse. Half of the patients were alive and had remained progression free for >1 year. Median OS was 41·7 months.

The median pomalidomide treatment duration was 5·1 months in the ITT population. Notably, pomalidomide treatment duration was more than doubled in patients who achieved MR (median, 10·8 months) and ≥PR (median, 12·7 months). The median PFS in patients who achieved MR (13·9 months) and those with ≥ PR (28·5 months) was higher than that in the ITT population (12·2 months). The benefit of achieving MR is underscored by the longer treatment duration observed in patients who achieved MR *versus* the ITT population. These findings indicate that sustained treatment with pomalidomide may improve long-term patient outcomes in this setting.

The safety findings were consistent with pomalidomide's known safety profile (https://media.celgene.com/content/uploads/pomalyst-pi.pdf; https://www.ema.europa.eu/en/documents/product-information/imnovid-eparproduct- information_en.pdf). Anaemia was the most frequently reported grade 3/4 haematological TEAE, and pneumonia and fatigue were the most common grade 3/4 non-haematological TEAEs. No patient developed grade 3/4 peripheral sensory neuropathy. There were only two incidences of SPM; notably, both patients had received melphalan prior to stem cell transplant. In the patient with basal cell carcinoma, the SPM resolved, and the patient continued treatment on-study. The patient who developed anaplastic astrocytoma had a previous history of the disease. Although this was probably a recurrence and therefore unrelated to pomalidomide treatment, the event was classified as an SPM due to the length of time since its last occurrence.

These results from cohort A of MM-014 compare favourably with those from the registrational MM-002 and NIMBUS (MM-003) trials, as well as the STRATUS (MM-010) trial, all of which investigated pomalidomide plus low-dose dexamethasone in later lines of therapy (median of five prior lines of therapy *versus* two in this study) (San Miguel *et al*, 2013; Richardson *et al*, 2014; Dimopoulos *et al*, 2016a). While the ORR in the present study (32·1%) was similar to that reported in the pomalidomide plus low-dose dexamethasone arms of MM-002 (33%), NIMBUS (31%) and STRATUS (32·6%), the median PFS observed in this analysis

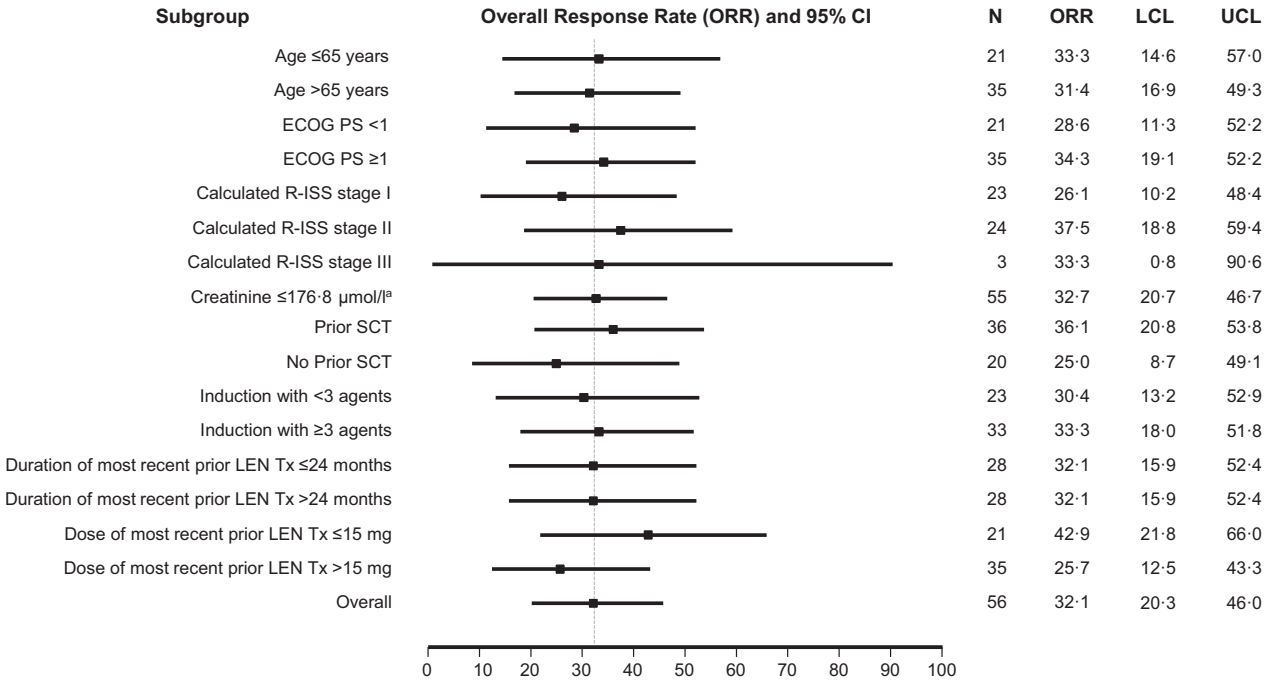

Fig 2. ORR subgroup analysis. The dashed vertical line indicates 32·1%, which was the ORR (primary study endpoint) in the ITT population. ORR was mostly similar regardless of subgroup. [a]One patient had creatinine >176·8 µmol/l. ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; LCL, lower control limit; LEN Tx, lenalidomide treatment; ORR, overall response rate; R-ISS, revised International Staging System; SCT, stem cell transplantation; UCL, upper control limit.

(12·2 months) is longer than that reported in each of the previous studies (4·0–4·6 months). The longer PFS observed in cohort A of MM-014 may be attributable to a variety of factors, including the previously noted difference in median prior lines of therapy. Additionally, patients in the present study generally had deeper responses than patients in the previous trials: 14·3% of patients in cohort A of MM-014 achieved ≥very good partial response *versus* 5·6% in NIMBUS and 8·2% in STRATUS. Median DOR in the present study (16·6 months) was at least double that reported in the previous trials (7·0–8·3 months; San Miguel *et al*, 2013; Richardson *et al*, 2014; Dimopoulos *et al*, 2016a). There are also notable differences in safety; the rates of grade 3/4 neutropaenia and thrombocytopenia reported in this analysis (10·7% and 8·9%, respectively) were markedly lower than those reported with pomalidomide plus low-dose dexamethasone treatment in each of the previous studies (neutropaenia, 41–50%; thrombocytopenia, 19–24%). Although cross-trial comparisons should be interpreted cautiously, the results reported here support earlier sequencing of pomalidomide-containing regimens in RRMM, including immediately after the failure of lenalidomide-based treatment.

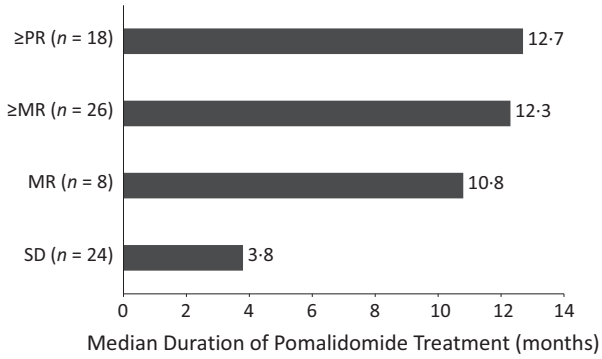

Fig 3. Pomalidomide treatment duration by best response. Median duration of pomalidomide treatment was 12·7 months in patients who achieved ≥PR, 12·3 months in patients who achieved ≥MR, 10·8 months in patients who achieved MR and 3·8 months in patients with SD. MR, minimal response; PR, partial response; SD, stable disease.

These findings, together with previous reports, continue to demonstrate that pomalidomide is effective following progression on lenalidomide and that there is no evidence-based rationale for abandoning IMiD agent-based therapy. Pomalidomide has important pharmacological differences from lenalidomide, including higher affinity to cereblon, different Aiolos and Ikaros degradation kinetics and a different gene expression profile; furthermore, pomalidomide has demonstrated activity in lenalidomide-resistant cells and is effective in patients who are relapsed or refractory to lenalidomide (Lopez-Girona *et al*, 2012; Leleu *et al*, 2013; San Miguel *et al*, 2013; Richardson *et al*, 2014; Bjorklund *et al*, 2015; Ocio *et al*, 2015; Sehgal *et al*, 2015; Dimopoulos *et al*, 2016a; Rychak *et al*, 2016). One potential mechanism by which pomalidomide overcomes lenalidomide resistance may be continued immune stimulation. In exploratory immune

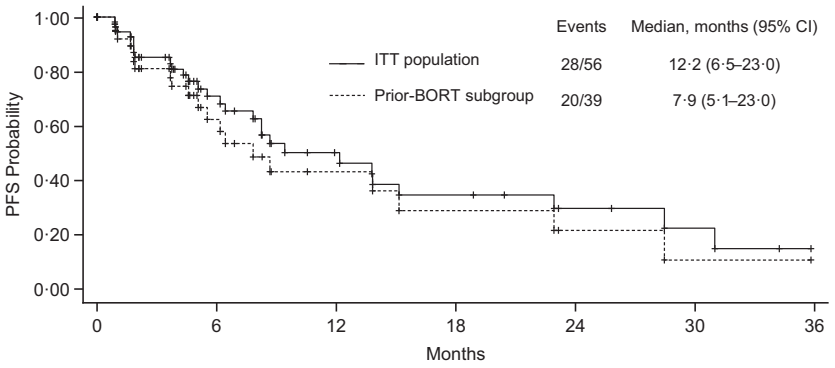

Fig 4. Progression-free survival in the ITT population and prior-bortezomib subgroup. Median PFS was 12.2 months in the ITT population and 7.9 months in the prior-bortezomib subgroup. BORT, bortezomib; ITT, intention-to-treat; PFS, progression-free survival.

analyses, sequencing pomalidomide immediately following lenalidomide-based treatment resulted in persistent T cell stimulatory activity, including enhanced immune pharmacodynamic content for $CD8^+$ T cells without a decrease in $CD4^+$ subsets. Within the $CD3^+$ subset, the *P* value at day 1 of treatment cycle 5 ($P = 0{\cdot}039$) was closer to the threshold for significance than the *P* value at day 1 of treatment cycle 3 ($P = 0{\cdot}014$), but this is probably less a function of the diminution of immune pharmacodynamics than of the fewer patients available for analysis at the later timepoint; importantly, statistical significance was maintained at both timepoints. Moreover, within the $CD8^+$ subset, the *P* value at day 1 of treatment cycle 5 ($P = 0{\cdot}020$) was farther from the significance threshold than the *P* value at day 1 of treatment cycle 3 ($P = 0{\cdot}034$), despite the decreased power at the later timepoint.

Table III. Grade 3/4 TEAEs reported in ≥5% of the safety population and any grade TEAEs of special interest.

	Safety population	
TEAEs, *n* (%)*	Overall ($N = 56$)	Prior-bortezomib subgroup ($n = 39$)
≥1 grade 3/4 TEAE	41 (73·2)	27 (69·2)
Grade 3/4 haematological TEAEs		
Anaemia	14 (25·0)	11 (28·2)
Neutropenia	6 (10·7)	3 (7·7)
Thrombocytopenia	5 (8·9)	4 (10·3)
Grade 3/4 non-haematological TEAEs		
Pneumonia	8 (14·3)	3 (7·7)
Fatigue	8 (14·3)	5 (12·8)
Dyspnoea	5 (8·9)	3 (7·7)
Influenza	4 (7·1)	1 (2·6)
Hypertension	3 (5·4)	2 (5·1)
Any grade TEAE of special interest		
Peripheral sensory neuropathy	4 (7·1)	3 (7·7)
DVT/PE	3 (5·4)	3 (7·7)
PE	2 (3·6)	2 (5·1)
DVT	1 (1·8)	1 (2·6)

DVT, deep vein thrombosis; PE, pulmonary embolism; TEAE, treatment-emergent adverse event.

*TEAE severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.

Doublet regimens, such as pomalidomide plus low-dose dexamethasone, are appropriate choices for patients who cannot tolerate triplets (such as frail patients) or those who may not have access to the newer agents included in triplet regimens (Offidani *et al*, 2018). Nevertheless, it is important to acknowledge that triplet regimens are now standard in the treatment of MM (Sonneveld & Broijl, 2016; Moreau *et al*, 2017). In the context of the triplet regimen-focused treatment landscape of MM, these results demonstrate the safety and efficacy of pomalidomide plus low-dose dexamethasone in a patient population in need of effective treatment options and contribute to the growing body of data supporting the addition of novel agents to this doublet regimen. Interim results of cohort B of this study indicate that the triplet regimen of pomalidomide, low-dose dexamethasone and daratumumab in patients with RRMM after one or two prior lines of treatment is active and safe (Siegel *et al*, 2018). Results from the phase 3 OPTIMISMM study, which evaluated pomalidomide, bortezomib and low-dose dexamethasone in a 100% lenalidomide-exposed (and predominately lenalidomide-refractory) patient population, have demonstrated that this regimen significantly improved PFS *versus* bortezomib plus dexamethasone {median, 11·20 months vs. 7·10 months; hazard ratio [HR], 0·61 [95% confidence interval (CI), 0·49–0·77]; $P < 0{\cdot}0001$} (Richardson *et al*, 2019). The PFS advantage was generally consistent across the evaluated subgroups, including patients who were refractory to lenalidomide. Notably, in patients who had received only one line of treatment, pomalidomide, bortezomib and low-dose dexamethasone demonstrated a marked improvement in PFS *versus* bortezomib and low-dose dexamethasone (median, 20·73 months vs. 11·63 months; HR, 0·54 [95% CI, 0·36–0·82]; $P < 0{\cdot}01$). Toxicity was as expected. In the randomized phase 2 ELOQUENT-3 trial, the addition of elotuzumab to pomalidomide plus low-dose dexamethasone resulted in a 46% reduction in the risk of death or progression *versus* pomalidomide plus low-dose dexamethasone alone ($P = 0{\cdot}008$) (Dimopoulos *et al*, 2018). Other phase 2 and phase 3 RRMM trials are currently evaluating pomalidomide plus low-dose dexamethasone with agents such as carfilzomib (NCT01464034) (Shah *et al*, 2015), daratumumab (NCT03180736) and isatuximab (NCT02990338) (Richardson

et al, 2018). Further, the combination of pomalidomide, daratumumab and low-dose dexamethasone is already approved in the United States, with the same indication as pomalidomide plus low-dose dexamethasone (http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX-pi.pdf).

In conclusion, pomalidomide plus low-dose dexamethasone is safe and effective as third-line therapy in patients with RRMM in whom lenalidomide-based treatment failed, a clinically relevant patient population with poor representation in clinical trials. Immune profile analyses suggest that this regimen has persistent T cell stimulatory activity directly following lenalidomide-based treatment. These results support not only earlier sequencing of pomalidomide-based therapy after patients become refractory to lenalidomide, but also the continued use and investigation of pomalidomide-based regimens that incorporate agents with complementary mechanisms of action in this patient population.

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Author contributions

All authors have contributed to the acquisition, analysis or interpretation of data for this article, contributed to drafts of the article, revised the manuscript critically for important intellectual content, approved the final version to be published and agreed to be accountable for all aspects of the article. The investigators designed the study in conjunction with the sponsor, Celgene Corporation. The sponsor compiled and maintained the data.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Supplementary methods.

References

Binder, M., Rajkumar, S., Ketterling, R., Dispenzieri, A., Lacy, M., Gertz, M., Buadi, F., Hayman, S., Hwa, Y. & Zeldenrust, S. (2016) Occurrence and prognostic significance of cytogenetic evolution in patients with multiple myeloma. *Blood Cancer Journal*, **6**, e401.

Bjorklund, C.C., Lu, L., Kang, J., Hagner, P.R., Havens, C.G., Amatangelo, M., Wang, M., Ren, Y., Couto, S., Breider, M., Ning, Y., Gandhi, A.K., Daniel, T.O., Chopra, R., Klippel, A. & Thakurta, A.G. (2015) 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 Journal*, **5**, e354.

Dimopoulos, M.A., Palumbo, A., Corradini, P., Cavo, M., Delforge, M., Di Raimondo, F., Weisel, K.C., Oriol, A., Hansson, M., Vacca, A., Blanchard, M.J., Goldschmidt, H., Doyen, C., Kaiser, M., Petrini, M., Anttila, P., Cafro, A.M., Raymakers, R., San Miguel, J., de Arriba, F., Knop, S., Röllig, C., Ocio, E.M., Morgan, G., Miller, N., Simcock, M., Peluso, T., Herring, J., Sternas, L., Zaki, M.H. & Moreau, P. (2016a) Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS (MM-010): a phase 3b study in refractory multiple myeloma. *Blood*, **128**, 497–503.

Dimopoulos, M.A., Oriol, A., Nahi, H., San-Miguel, J., Bahlis, N.J., Usmani, S.Z., Rabin, N., Orlowski, R.Z., Komarnicki, M., Suzuki, K., Plesner, T., Yoon, S.S., Ben Yehuda, D., Richardson, P.G., Goldschmidt, H., Reece, D., Lisby, S., Khokhar, N.Z., O'Rourke, L., Chiu, C., Qin, X., Guckert, M., Ahmadi, T., Moreau, P. & for the POLLUX Investigators (2016b) Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *New England Journal of Medicine*, **375**, 1319–1331.

Dimopoulos, M.A., Dytfeld, D., Grosicki, S., Moreau, P., Takezako, N., Hori, M., Leleu, X., LeBlanc, R., Suzuki, K., Raab, M.S., Richardson, P.G., McKiver, M.P., Jou, Y.M., Shelat, S.G., Robbins, M., Rafferty, B. & San Miguel, J. (2018) Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. *New England Journal of Medicine*, **379**, 1811–1822.

Durie, B.G., Harousseau, J.L., Miguel, J.S., Bladé, J., Barlogie, B., Anderson, K., Gertz, M., Dimopoulos, M., Westin, J., Sonneveld, P., Ludwig, H., Gahrton, G., Beksac, M., Crowley, J., Belch, A., Boccadaro, M., Cavo, M., Turesson, I., Joshua, D., Vesole, D., Kyle, R., Alexanian, R., Tricot, G., Attal, M., Merlini, G., Powles, R., Richardson, P., Shimizu, K., Tosi, P., Morgan, G., Rajkumar, S.V. & on behalf of the International Myeloma Working Group (2006) International uniform response criteria for multiple myeloma. *Leukemia*, **20**, 1467–1473.

Guillerey, C., Nakamura, K., Vuckovic, S., Hill, G.R. & Smyth, M.J. (2016) Immune responses in multiple myeloma: role of the natural immune surveillance and potential of immunotherapies. *Cellular and Molecular Life Sciences*, **73**, 1569–1589.

Harousseau, J.L. & Attal, M. (2017) How I treat first relapse of myeloma. *Blood*, **130**, 963–973.

Keats, J.J., Chesi, M., Egan, J.B., Garbitt, V.M., Palmer, S.E., Braggio, E., Van Wier, S.,

Blackburn, P.R., Baker, A.S., Dispenzieri, A., Kumar, S., Rajkumar, S.V., Carpten, J.D., Barrett, M., Fonseca, R., Stewart, A.K. & Bergsagel, P.L. (2012) Clonal competition with alternating dominance in multiple myeloma. *Blood*, **120**, 1067–1076.

Kumar, S.K. & Anderson, K.C. (2016) Immune therapies in multiple myeloma. *Clinical Cancer Research*, **22**, 5453–5460.

Kumar, S.K., Therneau, T.M., Gertz, M.A., Lacy, M.Q., Dispenzieri, A., Rajkumar, S.V., Fonseca, R., Witzig, T.E., Lust, J.A., Larson, D.R., Kyle, R.A. & Greipp, P.R. (2004) Clinical course of patients with relapsed multiple myeloma. *Mayo Clinic Proceedings*, **79**, 867–874.

Kumar, S., Dimopoulos, M., Kastritis, E., Terpos, E., Nahi, H., Goldschmidt, H., Hillengass, J., Leleu, X., Beksac, M. & Alsina, M. (2017) Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. *Leukemia*, **31**, 2443–2448.

Leich, E., Weissbach, S., Klein, H., Grieb, T., Pischimarov, J., Stühmer, T., Chatterjee, M., Steinbrunn, T., Langer, C. & Eilers, M. (2013) Multiple myeloma is affected by multiple and heterogeneous somatic mutations in adhesion- and receptor tyrosine kinase signaling molecules. *Blood Cancer Journal*, **3**, e102.

Leleu, X., Attal, M., Arnulf, B., Moreau, P., Traulle, C., Marit, G., Mathiot, C., Petillon, M.O., Macro, M., Roussel, M., Pegourie, B., Kolb, B., Stoppa, A.M., Hennache, B., Brechignac, S., Meuleman, N., Thielemans, B., Garderet, L., Royer, B., Hulin, C., Benboubker, L., Decaux, O., Escoffre-Barbe, M., Michallet, M., Caillot, D., Fermand, J.P., Avet-Loiseau, H., Facon, T. & on behalf of Intergroupe Francophone du Myelome (2013) Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: Intergroupe Francophone du Myelome 2009–02. *Blood*, **121**, 1968–1975.

Lohr, J.G., Stojanov, P., Carter, S.L., Cruz-Gordillo, P., Lawrence, M.S., Auclair, D., Sougnez, C., Knoechel, B., Gould, J. & Saksena, G. (2014) Widespread genetic heterogeneity in multiple myeloma: implications for targeted therapy. *Cancer Cell*, **25**, 91–101.

Lonial, S., Dimopoulos, M., Palumbo, A., White, D., Grosicki, S., Spicka, I., Walter-Croneck, A., Moreau, P., Mateos, M. & Magen, H. (2015) Elotuzumab therapy for relapsed or refractory multiple myeloma. *New England Journal of Medicine*, **373**, 621–631.

Lopez-Girona, A., Mendy, D., Ito, T., Miller, K., Gandhi, A., Kang, J., Karasawa, S., Carmel, G., Jackson, P. & Abbasian, M. (2012) Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. *Leukemia*, **26**, 2326–2335.

Magrangeas, F., Avet-Loiseau, H., Gouraud, W., Lodé, L., Decaux, O., Godmer, P., Garderet, L., Voillat, L., Facon, T. & Stoppa, A.M. (2013) Minor clone provides a reservoir for relapse in multiple myeloma. *Leukemia*, **27**, 473–481.

Moreau, P. & de Wit, E. (2017) Recent progress in relapsed multiple myeloma therapy: implications for treatment decisions. *British Journal of Haematology*, **179**, 198–218.

Moreau, P., Masszi, T., Grzasko, N., Bahlis, N.J., Hansson, M., Pour, L., Sandhu, I., Ganly, P., Baker, B.W., Jackson, S.R., Stoppa, A.M., Simpson, D.R., Gimsing, P., Palumbo, A., Garderet, L., Cavo, M., Kumar, S., Touzeau, C., Buadi, F.K., Laubach, J.P., Berg, D.T., Lin, J., Di Bacco, A., Hui, A.M., van de Velde, H. & Richardson, P.G. & for the TOURMALINE-MM1 Study Group (2016) Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *New England Journal of Medicine*, **374**, 1621–1634.

Moreau, P., San Miguel, J., Sonneveld, P., Mateos, M.V., Zamagni, E., Avet-Loiseau, H., Hajek, R., Dimopoulos, M.A., Ludwig, H., Einsele, H., Zweegman, S., Facon, T., Cavo, M., Terpos, E., Goldschmidt, H., Attal, M., Buske, C.on behalf of the ESMO Guidelines Committee (2017) Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, **28**, iv52–iv61.

Moreau, P., Zamagni, E. & Mateos, M.V. (2019) Treatment of patients with multiple myeloma progressing on frontline-therapy with lenalidomide. *Blood Cancer Journal*, **9**, 38.

Ocio, E.M., Fernández-Lázaro, D., San-Segundo, L., Lopez-Corral, L., Corchete, L.A., Gutiérrez, N.C., Garayoa, M., Paíno, T., García-Gómez, A. & Delgado, M. (2015) In vivo murine model of acquired resistance in myeloma reveals differential mechanisms for lenalidomide and pomalidomide in combination with dexamethasone. *Leukemia*, **29**, 705–714.

Offidani, M., Corvatta, L. & Gentili, S. (2018) Triplet vs. doublet drug regimens for managing multiple myeloma. *Expert Opinion on Pharmacotherapy*, **19**, 137–149.

Rasche, L., Weinhold, N., Morgan, G.J., van Rhee, F. & Davies, F.E. (2017) Immunologic approaches for the treatment of multiple myeloma. *Cancer Treatment Reviews*, **55**, 190–199.

Richardson, P.G., Siegel, D.S., Vij, R., Hofmeister, C.C., Baz, R., Jagannath, S., Chen, C., Lonial, S., Jakubowiak, A., Bahlis, N., Song, K., Belch, A., Raje, N., Shustik, C., Lentzsch, S., Lacy, M., Mikhael, J., Matous, J., Vesole, D., Chen, M., Zaki, M.H., Jacques, C., Yu, Z. & Anderson, K. (2014) Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. *Blood*, **123**, 1826–1832.

Richardson, P.G., Attal, M., Campana, F., Le-Guennec, S., Hui, A., Risse, M., Corzo, K. & Anderson, K.C. (2018) Isatuximab plus pomalidomide/dexamethasone versus pomalidomide/dexamethasone in relapsed/refractory multiple myeloma: ICARIA phase III study design. *Future Oncology*, **14**, 1035–1047.

Richardson, P.G., Oriol, A., Beksac, M., Liberati, A.M., Galli, M., Schjesvold, F., Lindsay, J., Weisel, J., White, D., Facon, T., San Miguel, J., Sunami, K., O'Gorman, P., Sonneveld, P., Robak, P., Semochkin, S., Schey, S., Yu, X., Doerr, T., Bensmaine, A., Biyukov, T., Peluso, T., Zaki, M., Anderson, K., Dimopoulos, M. & on behalf of the OPTIMISMM Trial Investigators (2019) Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. *Lancet Oncology*, **20**, 781–794.

Robak, P., Drozdz, I., Szemraj, J. & Robak, T. (2018) Drug resistance in multiple myeloma. *Cancer Treatment Reviews*, **70**, 199–208.

Rychak, E., Mendy, D., Shi, T., Ning, Y., Leisten, J., Lu, L., Miller, K., Narla, R.K., Orlowski, R.Z., Raymon, H.K., Bjorklund, C.C., Thakurta, A., Gandhi, A.K., Cathers, B.E., Chopra, R., Daniel, T.O. & Lopez-Girona, A. (2016) Pomalidomide in combination with dexamethasone results in synergistic anti-tumour responses in pre-clinical models of lenalidomide-resistant multiple myeloma. *British Journal of Haematology*, **172**, 889–901.

San Miguel, J., Weisel, K., Moreau, P., Lacy, M., Song, K., Delforge, M., Karlin, L., Goldschmidt, H., Banos, A., Oriol, A., Alegre, A., Chen, C., Cavo, M., Garderet, L., Ivanova, V., Martinez-Lopez, J., Belch, A., Palumbo, A., Schey, S., Sonneveld, P., Yu, X., Sternas, L., Jacques, C., Zaki, M. & Dimopoulos, M. (2013) 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 Oncology*, **14**, 1055–1066.

Sehgal, K., Das, R., Zhang, L., Verma, R., Deng, Y., Kocoglu, M., Vasquez, J., Koduru, S., Ren, Y. & Wang, M. (2015) Clinical and pharmacodynamic analysis of pomalidomide dosing strategies in myeloma: impact of immune activation and cereblon targets. *Blood*, **125**, 4042–4051.

Shah, J.J., Stadtmauer, E.A., Abonour, R., Cohen, A.D., Bensinger, W.I., Gasparetto, C., Kaufman, J.L., Lentzsch, S., Vogl, D.T., Gomes, C.L., Pascucci, N., Smith, D.D., Orlowski, R.Z. & Durie, B.G. (2015) Carfilzomib, pomalidomide, and dexamethasone for relapsed or refractory myeloma. *Blood*, **126**, 2284–2290.

Siegel, D.S., Schiller, G.J., Samaras, C.J., Sebag, M., Berdeja, J.G., Ganguly, S., Matous, J.V., Song, K., Seet, C.S., Talamo, G., Acosta-Rivera, M., Bar, M., Quick, D.P., Anz, B., Fonseca, G., Reece, D., Agarwal, A., Chung, W., Zafar, F. & Bahlis, N. (2018) Pomalidomide + low-dose dexamethasone + daratumumab in relapsed and/or refractory multiple myeloma after lenalidomide-based treatment failure. *Blood*, **132**, 3271.

Sonneveld, P. & Broijl, A. (2016) Treatment of relapsed and refractory multiple myeloma. *Haematologica*, **101**, 396–406.

Stewart, A.K., Rajkumar, S.V., Dimopoulos, M.A., Masszi, T., Špička, I., Oriol, A., Hajek, R., Rosinol, L., Siegel, D.S. & Mihaylov, G.G. (2015) Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *New England Journal of Medicine*, **372**, 142–152.

Tamura, H. (2018) Immunopathogenesis and immunotherapy of multiple myeloma. *International Journal of Hematology*, **107**, 278–285.

Yong, K., Delforge, M., Driessen, C., Fink, L., Flinois, A., Gonzalez-McQuire, S., Safaei, R., Karlin, L., Mateos, M.V., Raab, M.S., Schoen, P. & Cavo, M. (2016) Multiple myeloma: patient outcomes in real-world practice. *British Journal of Haematology*, **175**, 252–264.