Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial

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Summary

Background New treatment options are needed for patients with multiple myeloma that is refractory to proteasome inhibitors and immunomodulatory drugs. We assessed daratumumab, a novel CD38-targeted monoclonal antibody, in patients with refractory multiple myeloma.

Methods In this open-label, multicentre, phase 2 trial done in Canada, Spain, and the USA, patients (age ≥18 years) with multiple myeloma who were previously treated with at least three lines of therapy (including proteasome inhibitors and immunomodulatory drugs), or were refractory to both proteasome inhibitors and immunomodulatory drugs, were randomly allocated in a 1:1 ratio to receive intravenous daratumumab 8 mg/kg or 16 mg/kg in part 1 stage 1 of the study, to decide the dose for further assessment in part 2. Patients received 8 mg/kg every 4 weeks, or 16 mg/kg per week for 8 weeks (cycles 1 and 2), then every 2 weeks for 16 weeks (cycles 3–6), and then every 4 weeks thereafter (cycle 7 and higher). The allocation schedule was computer-generated and randomisation, with permuted blocks, was done centrally with an interactive web response system. In part 1 stage 2 and part 2, patients received 16 mg/kg dosed as in part 1 stage 1. The primary endpoint was overall response rate (partial response [PR] + very good PR + complete response [CR] + stringent CR). All patients who received at least one dose of daratumumab were included in the analysis. The trial is registered with ClinicalTrials.gov, number NCT01985126.

Findings The study is ongoing. In part 1 stage 1 of the study, 18 patients were randomly allocated to the 8 mg/kg group and 16 to the 16 mg/kg group. Findings are reported for the 106 patients who received daratumumab 16 mg/kg in parts 1 and 2. Patients received a median of five previous lines of therapy (range 2–14). 85 (80%) patients had previously received autologous stem cell transplantation, 101 (95%) were refractory to the most recent proteasome inhibitors and immunomodulatory drugs used, and 103 (97%) were refractory to the last line of therapy. Overall responses were noted in 31 patients (29·2%, 95% CI 20·8–38·9)—three (2·8%, 0·6–8·0) had a stringent CR, ten (9·4%, 4·6–16·7) had a very good PR, and 18 (17·0%, 10·4–25·5) had a PR. The median time to first response was 1·0 month (range 0·9–5·6). Median duration of response was 7·4 months (95% CI 5·5–not estimable) and progression-free survival was 3·7 months (95% CI 2·8–4·6). The 12-month overall survival was 64·8% (95% CI 51·2–75·5) and, at a subsequent cutoff, median overall survival was 17·5 months (95% CI 13·7–not estimable). Daratumumab was well tolerated; fatigue (42 [40%] patients) and anaemia (35 [33%]) of any grade were the most common adverse events. No drug-related adverse events led to treatment discontinuation.

Interpretation Daratumumab monotherapy showed encouraging efficacy in heavily pretreated and refractory patients with multiple myeloma, with a favourable safety profile in this population of patients.

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Introduction

Multiple myeloma is a malignant plasma cell disorder that is characterised by bone, renal, haematological, and infectious complications due to accumulation of clonal plasma cells in the bone marrow and pathogenic antibody production.[1] Although survival has improved substantially with new drug classes (eg, proteasome inhibitors and immunomodulatory drugs), along with autologous stem cell transplantation, most patients will die from refractory disease.[2,3] Outcomes for patients who are resistant to proteasome inhibitors (bortezomib and carfilzomib) and immunomodulatory drugs (lenalidomide, thalidomide, and pomalidomide) are especially poor. Before the availability of carfilzomib and pomalidomide, median expected overall survival in these patients was 9 months.[4] Additional treatment can be complicated by cytopenias, secondary to poor haematological reserves, and comorbidities such as renal insufficiency. Therefore, effective treatments that target novel pathways with little toxicity and favourable tolerability are needed. Monoclonal antibodies are a novel class of agents in myeloma, targeting cell surface

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Research in context

Evidence before this study

We searched PubMed on July 29, 2015, with no date restriction using the keywords "progression risk", "overall survival", "multiple myeloma", "relapsed", and "refractory". From the 45 articles identified, the evidence indicates that despite the introduction of new agents that have prolonged survival, multiple myeloma remains incurable because most patients relapse or become refractory to available treatments. Daratumumab, a human monoclonal antibody that binds CD38-expressing malignant cells, gained US Food and Drug Administration breakthrough therapy designation based on phase 1 data from a first-in-human study in patients with multiple myeloma who relapsed or were refractory to at least two previous therapies. The first-in-human study was expanded and we concurrently initiated our study to further investigate the selected dose schedule.

Added value of this study

The current study is the largest study so far of the single-agent activity of daratumumab 16 mg/kg in heavily pretreated patients with multiple myeloma who were refractory to both a proteasome inhibitor and an immunomodulatory drug. The overall response rate was 29% and responses were rapid, deep, and durable. Efficacy was consistent in subgroups based on previous therapy and patients' characteristics, including age and renal function. Side-effects of daratumumab were clinically manageable, and no patient discontinued treatment because of drug-related adverse events. These data are in accord with results from the expansion of the first-in-human study in which the overall response rate was 36% in patients given daratumumab 16 mg/kg monotherapy.

Implications of all the available evidence

As a result of this study, daratumumab was the first monoclonal antibody approved by the US Food and Drug Administration for the treatment of refractory myeloma. Daratumumab is indicated for patients who have received at least three previous lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, or who are double refractory to a proteasome inhibitor and an immunomodulatory drug. Based on its efficacy, with rapid, deep, and durable responses, and its favourable safety profile, further activity in combination regimens is being investigated.

markers, such as SLAMF7 (CS-1) and CD38, with few off-target effects.[5]

Daratumumab is a first-in-class, human IgG1 monoclonal antibody that binds CD38-expressing malignant cells with high affinity and induces tumour cell death through diverse mechanisms of action, which include complement-dependent cytotoxicity,[6,7] antibody-dependent cell-mediated cytotoxicity,[6,7] antibody-dependent cellular phagocytosis,[7,8] and induction of apoptosis.[7,9] In a first-in-human phase 1/2 study of daratumumab monotherapy (0·005–24 mg/kg) in patients with relapsed or relapsed and refractory multiple myeloma, a maximum tolerated dose was not achieved.[10] In an expansion cohort of this study, the overall response rate (ORR) was 36% with daratumumab 16 mg/kg.[10]

In the current phase 2 study, we assessed daratumumab in patients with multiple myeloma and an unmet medical need—specifically, those who were refractory to their most recent treatment regimen after receiving at least three previous lines of therapy (including proteasome inhibitors and immunomodulatory drugs), or whose disease was refractory to both the most recent proteasome inhibitors and immunomodulatory drugs they had received, irrespective of the number of previous lines of treatment.

Methods

Study design and participants

This two-part, open-label, multicentre, phase 2 study started on Sept 30, 2013, at 26 sites in Canada, Spain, and the USA, and is ongoing. Inclusion criteria for patients included age at least 18 years old, documented secretory multiple myeloma, and evidence of disease progression on or within 60 days of the last dose of the most recent previous treatment regimen, based on the International Myeloma Working Group criteria.[11,12] Eligible patients had responded to at least one previous treatment regimen, received an alkylating agent alone or in combination with other myeloma treatments, received at least three previous lines of treatment that included a proteasome inhibitor and an immunomodulatory drug, or had disease double refractory to the most recent proteasome inhibitor and immunomodulatory drug they had received, and had an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or lower.

Exclusion criteria included any antimyeloma treatment within 2 weeks, or autologous stem cell transplantation within 12 weeks, of day 1 of cycle 1, and meningeal involvement of multiple myeloma and other malignancies within 5 years. Patients with absolute neutrophil counts of 1×10^9 per L or lower, haemoglobin concentration of 75 g/L or lower, platelet counts of less than 50×10^9 per L, and creatinine clearance of 20 mL/min per 1·73 mm² or lower were excluded. Other exclusion criteria were myocardial infarction within 1 year, uncontrolled or unstable angina, congestive heart failure (New York Heart Association Class III or IV), arrhythmia (grade 2 or higher), QTcF interval that was longer than 470 ms, chronic obstructive pulmonary disease, persistent asthma, or a history of asthma within 5 years.

Ethics committees or institutional review boards at the study sites approved the study, which was done in

accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation, and the guidelines for Good Clinical Practice. All patients provided written informed consent.

Randomisation and masking

In part 1 stage 1 of the trial, patients were randomly allocated in a 1:1 ratio to the daratumumab 8 mg/kg group or 16 mg/kg group (≤20 patients per group). Central randomisation was done with an interactive web response system, and patients were randomly allocated to treatment with a computer-generated randomisation schedule prepared under the supervision of the vendor. Randomisation was balanced by use of permuted blocks, and stratification factors included International Staging System staging (I, II, or III) and refractory status (ie, refractory to either a proteasome inhibitor or an immunomodulatory drug, refractory to both a proteasome inhibitor and immunomodulatory drug, or not refractory to either). Refractory was defined as disease progression on or within 60 days of the last dose. No one was masked to treatment assignment.

Procedures

A dose of daratumumab could be discontinued if the dose was deemed to be ineffective (ie, did not meet specified criteria for continuation) or poorly tolerated, or both, based on the results from the first interim analysis, which was done about 8 weeks after the last patient was enrolled in part 1 stage 1 of the study. After the first interim analysis, patients treated with an ineffective or poorly tolerated dose could crossover to the more effective dose if it was in their best interest according to the investigator treating them. A second interim analysis was done after another 25 patients were treated for at least 8 weeks in stage 2 of part 1. In part 2 of the study, an expansion cohort of 65 patients was treated at the selected dose to assess safety and efficacy. Dose reductions were not permitted. Patients were treated until disease progression or unacceptable toxicity, and long-term follow-up began after treatment discontinuation. The planned end of the study at 18 months after the last patient received the first dose of daratumumab had not been reached. The results of a prespecified efficacy analysis about 6 months after the last patient received his or her first dose of daratumumab are presented.

Patients received one of two regimens of daratumumab intravenously: daratumumab at 16 mg/kg per week for 8 weeks (cycles 1 and 2), then every 2 weeks for 16 weeks (cycles 3–6), then every 4 weeks thereafter (cycle 7 and higher); or daratumumab 8 mg/kg every 4 weeks continuously. First infusions of daratumumab were 1000 mL at 50 mL/h. If no infusion-related reactions occurred, the dose was increased in 50 mL/h increments to 200 mL/h. Second infusions were 500 mL at 50 mL/h and increased to 200 mL/h. Subsequent 500 mL infusions were at 100 mL/h and increased to 200 mL/h. Pre-infusion medications, 1 h (±0·25 h) before dosing, were methylprednisolone (100 mg intravenously for the first and second infusions and 60 mg thereafter), paracetamol (650–1000 mg), and diphenhydramine (25–50 mg) or equivalent antihistamine drug. Oral methylprednisolone (20 mg) or equivalent was administered on the 2 days after all daratumumab infusions.

Outcomes

The primary endpoint was overall response rate (ORR; partial response [PR] + very good PR + complete response [CR] + stringent CR). Secondary endpoints included duration of response, progression-free survival (PFS), overall survival, and clinical benefit rate (minimal response + ORR). Response was confirmed on two consecutive measurements, and data were assessed by an independent review committee.

Safety assessments were the monitoring of adverse events, physical examinations, electrocardiogram monitoring, clinical laboratory measurements, vital sign

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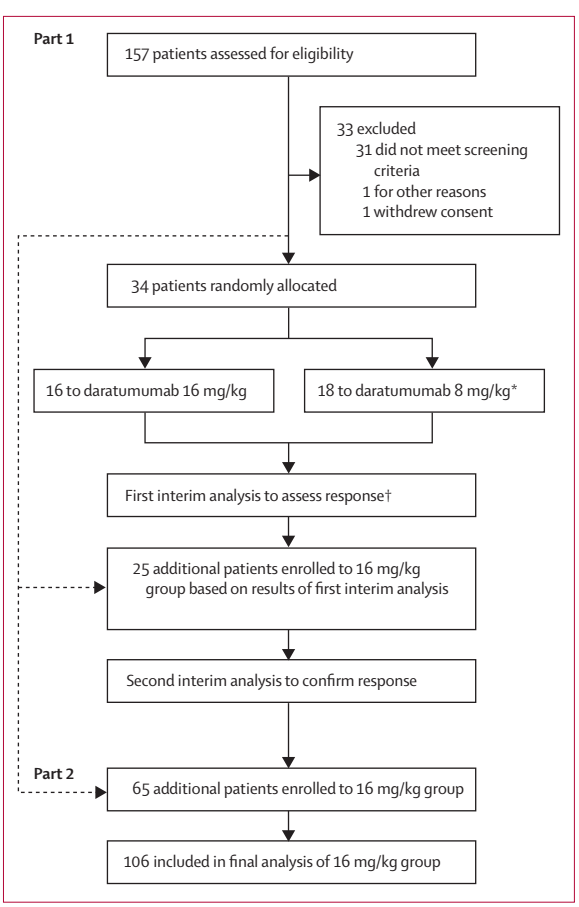

Figure 1: **Trial profile**
*Three patients were crossed over to the daratumumab 16 mg/kg group after the first interim analysis, but were not included in the efficacy analysis of the 16 mg/kg group. †Treatment with 8 mg/kg was discontinued because the overall response rate did not meet the prespecified criteria for continuation.

	Daratumumab 16 mg/kg (n=106)
Age (years)	
Median (range)	63·5 (31·0–84·0)
18 to <65	58 (55%)
65 to <75	36 (34%)
≥75	12 (11%)
Men	52 (49%)
Ethnic origin	
White	84 (79%)
Black or African American	15 (14%)
Asian	4 (4%)
Not reported, other, unknown	3 (3%)
Eastern Cooperative Oncology Group score	
0	29 (27%)
1	69 (65%)
2	8 (8%)
International Staging System staging	
I	26 (25%)
II	40 (38%)
III	40 (38%)
Cytogenetics profile*	
t (4; 14)	9 (10%)
del17p	16 (17%)
del13q	30 (32%)
amp1q21	23 (24%)
Other	43 (45%)
Renal function (baseline creatinine clearance)	
≥1·0 mL/s (≥60 mL/min)	60 (57%)
0·5 to <1·0 mL/s (30 to <60 mL/min)	42 (40%)
<0·5 mL/s (<30 mL/min)	4 (4%)
Extramedullary plasmacytomas	
≥1	14 (13%)
Time since initial diagnosis (years; median, range)	4·8 (1·1–23·8)
Lines of previous therapy	
>3	87 (82%)
Median (range)	5 (2–14)
Previous proteasome inhibitor	106 (100%)
Bortezomib	105 (99%)
Carfilzomib	53 (50%)
Previous immunomodulatory drug	106 (100%)
Lenalidomide	105 (99%)
Pomalidomide	67 (63%)
Thalidomide	47 (44%)
Previous steroids	106 (100%)
Dexamethasone	106 (100%)
Previous autologous stem cell transplantation	85 (80%)
Refractory to	
Both proteasome inhibitor and immunomodulatory drug	101 (95%)
Last line of previous therapy	103 (97%)
Bortezomib	95 (90%)
Carfilzomib	51 (48%)
Lenalidomide	93 (88%)
Pomalidomide	67 (63%)
Thalidomide	29 (27%)
Alkylating agent	82 (77%)
Bortezomib + lenalidomide	87 (82%)
Bortezomib + lenalidomide + carfilzomib	42 (40%)
Bortezomib + lenalidomide + pomalidomide	57 (54%)
Bortezomib + lenalidomide + carfilzomib + pomalidomide	33 (31%)

Data are number (%), unless otherwise indicated. *Cytogenetic abnormalities were detected by fluorescence in-situ hybridisation or karyotyping, or both at baseline (n=95).

Table 1: **Patients' demographic and baseline disease characteristics**

measurements, and ECOG performance status. Severity of adverse events was assessed with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).[13]

Statistical analysis

Briefly, about 100 patients would be treated during the study for the selected dose schedule. Response assessments were done by an independent review committee using the International Myeloma Working Group response criteria.[11,12] ORRs were reported with two-sided 95% exact CI. Additionally, the number and percentage of patients in each response category were presented. Time-to-event endpoints, including duration of response, PFS, and overall survival, were analysed descriptively with the Kaplan-Meier method. All patients who received at least one dose of daratumumab were used for efficacy and safety analyses.

The study is registered with ClinicalTrials.gov, number NCT01985126.

Role of the funding source

The clinical investigators and funder were responsible for adherence to the study design and analysis plan. The investigators and their research teams gathered the data, and the funder compiled the data for summation and analysis and confirmed its accuracy. The funder coordinated the development of the manuscript and funded writing assistance. The authors had full access to the study data, participated in the development of the manuscript, and made the final decision to submit the manuscript for publication.

Results

124 patients received at least one dose of daratumumab (18 received 8 mg/kg, 106 received 16 mg/kg; figure 1). The clinical cutoff date for primary analysis was Jan 9, 2015, 7·7 months after the last patient had received the first dose. At the first interim analysis, the

daratumumab 8 mg/kg group did not meet the criteria for expansion because of an ORR of 11·1% (95% CI 1·4–34·7). Baseline characteristics of this group are presented in the appendix. Concurrent pharmacokinetic analyses of the 8 mg/kg dose in the first-in-human study indicated that drug concentrations were probably less than the trough threshold for target saturation.[10] The results of these analyses also suggested that, although 24 mg/kg daratumumab would have been well tolerated, the gain in clinical benefit would have been small with this dose compared with 16 mg/kg. Three patients in the 8 mg/kg group crossed over to the 16 mg/kg group, and were included in the 8 mg/kg group in all analyses. At the second interim analysis, after an additional 25 patients were treated in the 16 mg/kg group, the cumulative ORR justified expansion of the study into part 2 and an additional 65 patients were enrolled.

All 106 patients in the daratumumab 16 mg/kg group had been previously treated with proteasome inhibitors and immunomodulatory drugs (bortezomib 105 [99%], carfilzomib 53 [50%], lenalidomide 105 [99%], pomalidomide 67 [63%], and thalidomide 47 [44%]; table 1). All patients had received dexamethasone previously, and 87 (82%) patients had previously received more than three lines of therapy. Patients were highly refractory, with 103 (97%) refractory to the last line of therapy before enrolment in the study and 101 (95%) refractory to the most recent proteasome inhibitors and immunomodulatory drugs (table 1). Refractoriness to specific agents included alkylating agents (82 [77%] patients), pomalidomide (67 [63%] patients), carfilzomib (51 [48%] patients), and bortezomib plus lenalidomide (double refractoriness, 87 [82%] patients; table 1). 70 (66%) patients were refractory to at least three of four drugs: bortezomib, lenalidomide, pomalidomide, and carfilzomib, and 33 (31%) patients were refractory to all four agents. Median time since initial diagnosis was 4·8 years (range 1·1–23·8), median number of lines of previous therapy was five (range 2–14), and 85 (80%) patients received previous autologous stem cell transplantation (table 1).

The median and mean numbers of treatment cycles given to patients were 4·0 (range 1–16) and 5·3 (SD 3·7), respectively, with 40 (38%) patients receiving six or more cycles of daratumumab 16 mg/kg. Median duration was 7·0 h (range 1·5–14·3) for the first infusion of daratumumab (n=106), 4·2 h (2·7–8·5) for the second infusion (n=103), and 3·4 h (1·1–6·7) for subsequent infusions (n=1105). 90 (85%) of 106 patients discontinued daratumumab 16 mg/kg: 82 (77%) because of progressive disease, five (5%) because of treatment-unrelated adverse events, and three (3%) as a result of consent withdrawal because of symptoms related to disease progression.

In the daratumumab 16 mg/kg group, overall response was noted in 31 of 106 patients (ORR 29·2%, 95% CI 20·8–38·9) based on assessment by an independent review committee (figure 2; table 2). Three (3%) patients achieved stringent CR, ten (9%) achieved very good PR, and 18 (17%) patients had PR (table 2). The clinical benefit rate was 34·0% (95% CI 25·0–43·8; table 2). The median time to first response was 1·0 month (range

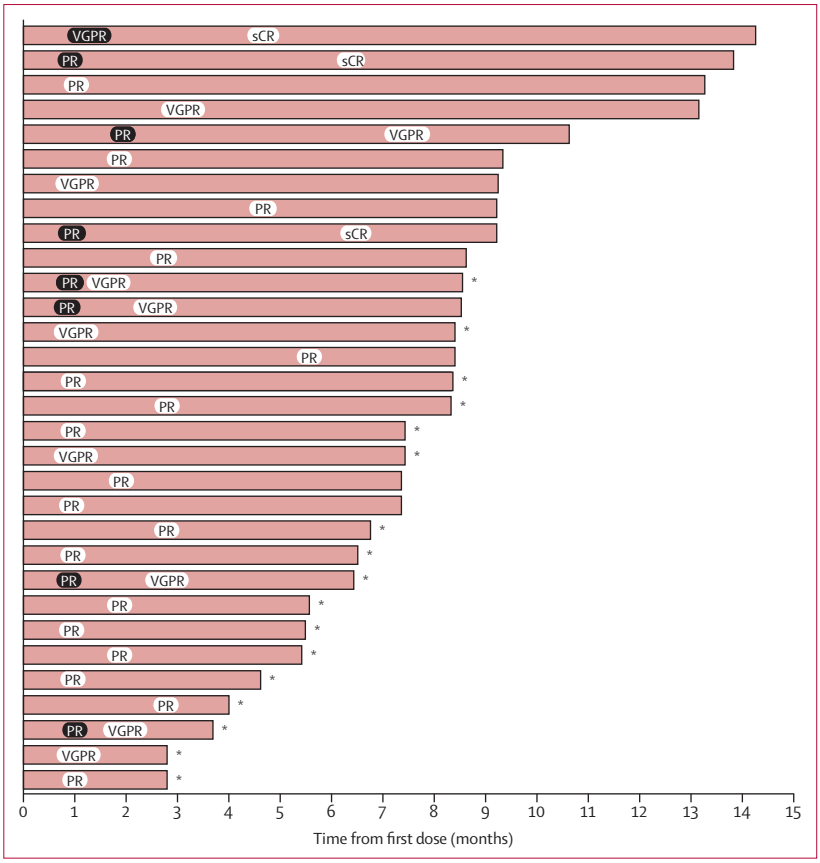

Figure 2: **Swim-lane plot of responders in the daratumumab 16 mg/kg group**
Black ovals indicate first response and white ovals indicate best response. VGPR=very good partial response. sCR=stringent complete response. PR=partial response. *Disease progression.

	Daratumumab 16 mg/kg group (n=106)
Stringent complete response	3 (2·8%, 0·6–8·0)
Complete response	0
Very good partial response	10 (9·4%, 4·6–16·7)
Partial response	18 (17·0%, 10·4–25·5)
Minimal response	5 (4·7%, 1·5–10·7)
Stable disease	46 (43·4%, 33·8–53·4)
Progressive disease	18 (17·0%, 10·4–25·5)
Not evaluable	6 (5·7%, 2·1–11·9)
Overall response rate*	31 (29·2%, 20·8–38·9)
Clinical benefit rate†	36 (34·0%, 25·0–43·8)
Very good partial response or better‡	13 (12·3%, 6·7–20·1)

Data are number (%, 95% CI). *Defined as stringent complete response, complete response, very good partial response, plus partial response. †Defined as overall response rate plus minimal response. ‡Defined as stringent complete response, complete response, plus very good partial response.

Table 2: **Overall best responses**

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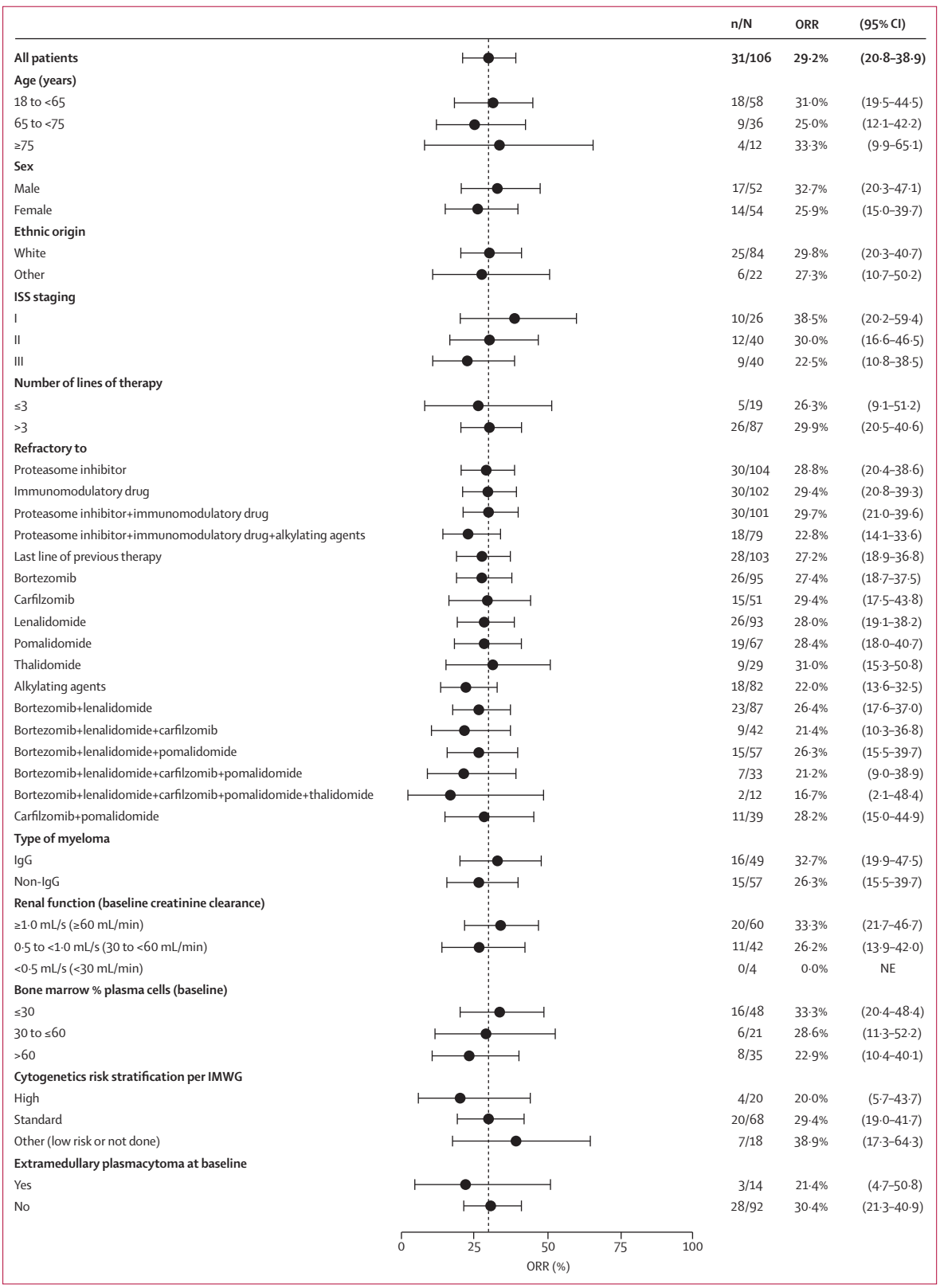

Figure 3: **Overall response rate in patient subgroups in the daratumumab 16 mg/kg group**
Exact 95% CIs are provided. ORR=overall response rate. ISS=International Staging System. IMWG=International Myeloma Working Group. NE=not estimable.

0·9–5·6), and responses improved in eight (25·8%) of 31 patients over time (figure 2). Responses were noted in prespecified subgroups irrespective of previous lines of therapy and refractory status (figure 3). Overall responses were noted in 30 of 101 patients (29·7%, 21·0–39·6) who were refractory to both proteasome inhibitors and immunomodulatory drugs (figure 3), and in 20 of 70 patients (28·6%, 18·4–40·6) who were refractory to at least three of four agents (bortezomib, lenalidomide, carfilzomib, and pomalidomide). Of 12 patients who were refractory to five agents (bortezomib, lenalidomide, carfilzomib, pomalidomide, and thalidomide), two (16·7%, 2·1–48·4) achieved responses after daratumumab treatment. Overall responses occurred in the non-treatment-based subgroups: three of 14 patients (21·4%, 4·7–50·8) with extramedullary disease, four of 20 patients (20%, 5·7–43·7) with baseline high-risk cytogenetics, 11 of 42 patients (26·2%, 13·9–42·0) with moderate renal impairment (0·5–1·0 mL/s [30–60 mL/min]), and four of 12 patients (33·3%, 9·9–65·1) older than 75 years (figure 3).

The median follow-up of patients was 9·3 months (range 0·5–14·4), and median duration of response was 7·4 months (95% CI 5·5–not estimable [NE]). Median PFS was 3·7 months (95% CI 2·8–4·6; figure 4A), and the median overall survival was not reached (13·7–NE; figure 4B). The 12-month overall survival was 64·8% (95% CI 51·2–75·5). Median overall survival was not reached in responders and was 13·7 months (95% CI, 8·6–NE) in non-responders (appendix). 29 (94%) of 31 responders treated with daratumumab 16 mg/kg were still alive, compared with 45 (60%) of 75 non-responders. A subsequent clinical cutoff for a safety update to meet regulatory requirements was June 30, 2015. With this update, the median overall survival was 17·5 months (13·7–NE).

Daratumumab was well tolerated, and no patients discontinued because of drug-related treatment-emergent adverse events, infusion-related reactions, or death. The safety profile in the 8 mg/kg group was similar to that in the 16 mg/kg group (appendix). In the 16 mg/kg group, the most common haematological treatment-emergent adverse events of any grade (≥20%) were anaemia (35 [33%] patients), thrombocytopenia (27 [25%]), and neutropenia (24 [23%]; table 3). Grade 3 or higher anaemia and thrombocytopenia occurred more frequently in non-responders (24 [32%] and 18 [24%] of 75 patients, respectively) than in responders (one [3%] and two [6%] of 31 patients, respectively). Grade 3 or higher neutropenia rates were similar in non-responders (nine [12%]) and responders (four [13%]). Few patients required additional supportive care: 40 (38%) of 106 received red blood cell transfusions, 14 (13%) had platelet transfusions, and eight (8%) needed granulocyte colony-stimulating factor. Blood transfusions were unaffected by previously reported daratumumab interference with blood typing assays.[14] Fatigue (42 [40%] of 106 patients) and nausea (31 [29%] patients) of any grade were the most prevalent non-haematological treatment-emergent adverse events in the 16 mg/kg daratumumab group (table 3). 32 (30%) patients had serious treatment-emergent adverse events, and 24 (23%) had grade 3 or 4 serious treatment-emergent adverse events. Infusion-related reactions occurred in

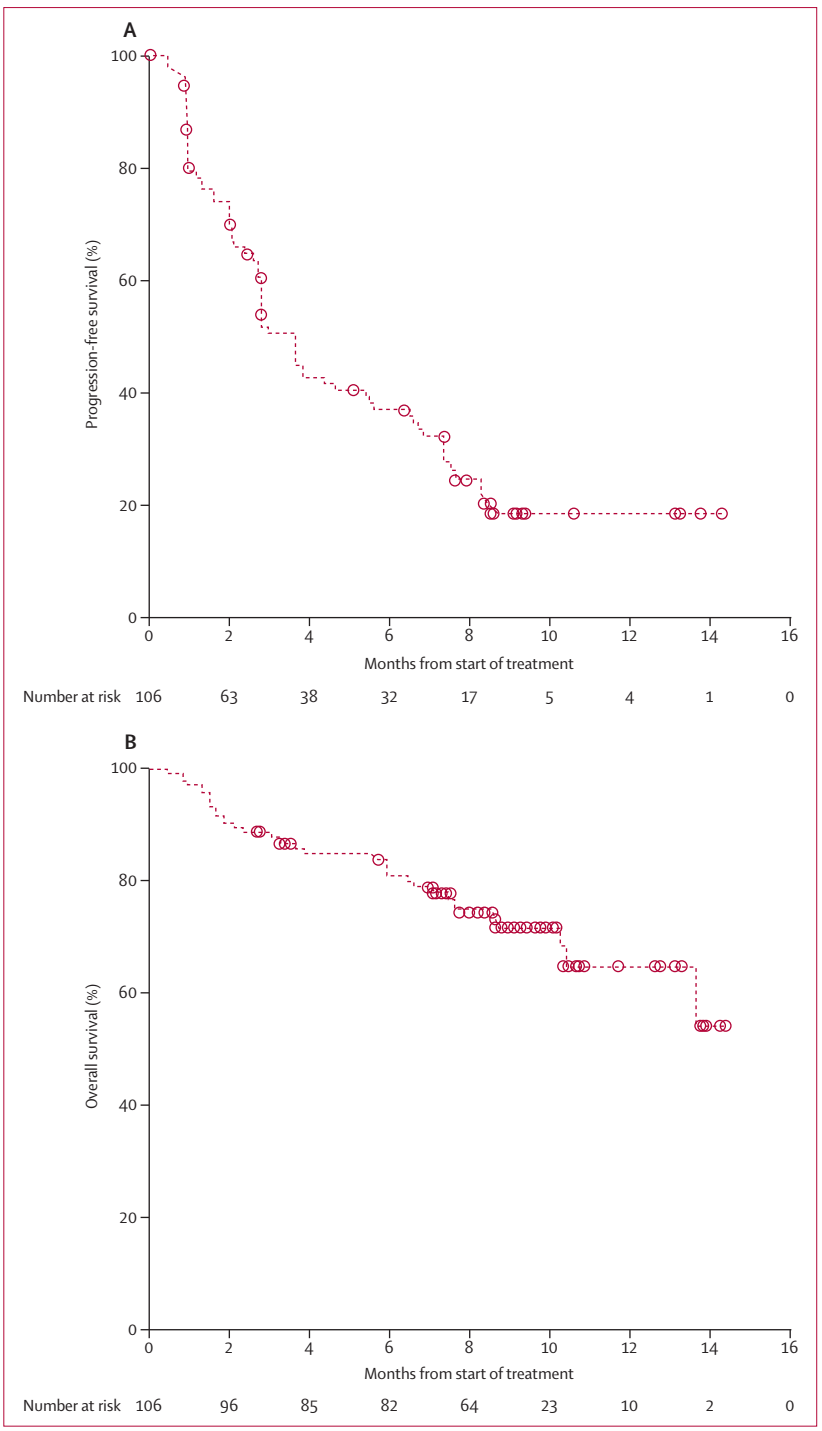

Figure 4: **Progression-free survival (A) and overall survival (B) in the daratumumab 16 mg/kg group**

	Daratumumab 16 mg/kg (n=106)	
	Any grade	Grade 3 or 4
Fatigue	42 (40%)	3 (3%)
Anaemia	35 (33%)	25 (24%)
Nausea	31 (29%)	0
Thrombocytopenia	27 (25%)	20 (19%)
Neutropenia	24 (23%)	13 (12%)
Back pain	23 (22%)	3 (3%)
Cough	22 (21%)	0 (0%)

Data are number (%).

Table 3: **Most common (≥20%) treatment-emergent adverse events**

45 (42%) patients and were predominantly grade 1 or 2 (grade 3 occurred in five [5%] patients; no grade 4 infusion-related reactions were reported). 39 (37%) patients experienced infusion-related reactions during the first infusion and only six (6%) patients had more than one infusion-related reaction. The most common (≥5%) infusion-related reactions included nasal congestion (13 [12%]), throat irritation (seven [7%]), and cough, dyspnoea, chills, and vomiting (six [6%] each; appendix). No patient discontinued daratumumab because of an infusion-related reaction. No immunogenicity was reported.

Five (5%) patients discontinued treatment because of treatment-emergent adverse events (two with general physical health deterioration (ie, progressive disease), and one each with H1N1 influenza, hypercalcaemia, and spinal cord compression). 31 (29%) patients died after treatment with daratumumab 16 mg/kg: 29 (27%) because of progressive disease and two (2%) because of adverse events (cardiorespiratory failure secondary to H1N1 influenza complications, and general health deterioration secondary to complications of aspiration pneumonia).

Discussion

Daratumumab monotherapy showed substantial clinical activity, with an ORR of 29%, and was well tolerated in patients with multiple myeloma who had been heavily treated; most patients were double refractory to bortezomib and lenalidomide, and many were refractory to pomalidomide or carfilzomib. Resistance to any previous therapy had no effect on the activity of daratumumab, lending support to a novel mechanism of action, but these findings need to be confirmed in larger studies. Similar response rates were also noted in patients with moderate renal impairment, older than 75 years of age, and with extramedullary disease or high-risk baseline cytogenetic characteristics.[15] Although this study did not have a control arm, patients with the degree of treatment refractoriness in our study historically have poor outcomes.[4] Follow-up is ongoing and thus more complete survival data will become available.

The results of our study corroborate the previously reported efficacy of daratumumab 16 mg/kg monotherapy in relapsed or refractory patients with multiple myeloma.[10] Elotuzumab, a monoclonal antibody in development that targets SLAMF7,[5] but lacks single-agent activity,[16] increased median PFS by 4·5 months compared with the control arm in combination with lenalidomide and dexamethasone in a population of patients who were less heavily pretreated than those in the our study.[17]

Deep responses of very good PR or better, particularly stringent CR, are associated with improved long-term outcomes in patients with newly diagnosed multiple myeloma.[18,19] Whether the same trend occurs in patients with relapsed and refractory multiple myeloma remains to be seen, although many patients treated in our study had responses to daratumumab that improved over time and might contribute to prolonged overall survival. These high-quality responses (9% very good PR, 3% stringent CR) are notable in treatment-refractory patients with multiple myeloma. The rate of high-quality responses with single-agent daratumumab were higher than those with pomalidomide monotherapy in the mm-002 clinical trial (2% of patients with at least a very good PR).[20] 61% of 108 patients in the pomalidomide monotherapy group were refractory to lenalidomide and bortezomib, and had received a median of five previous lines of therapy. In the PX-171-003-A1 study[21] of carfilzomib monotherapy in 266 patients, responses of very good PR or better were noted in 6% of patients. Similar to the present study and mm-002,[20] the patients were heavily pretreated with a median of five lines of therapy and 64% were refractory to lenalidomide and bortezomib. Peri-infusion doses of corticosteroids were used in our study to manage infusion-related reactions, and were thought to be substantially lower than the therapeutic use of dexamethasone in earlier lines of therapies to treat multiple myeloma. Thus, daratumumab can be regarded as a monotherapy in these patients who were refractory to dexamethasone.

When considering daratumumab monotherapy for treatment of refractory multiple myeloma, it should be placed in the context of other combination regimens that are in use in these patients. In the pomalidomide alone versus pomalidomide plus low-dose dexamethasone treatment groups of the mm-002 phase 2 study, 61% and 62% of 108 and 113 patients, respectively, were refractory to both bortezomib and lenalidomide, and in these double-refractory patients the ORR was 21% and 31%, median PFS was 2·0 and 3·8 months, median duration of response was 11·4 and 6·5 months, and median overall survival was 12·5 and 13·4 months, respectively.[20] In the PX-171-003-A1 study, in those treated with carfilzomib monotherapy who were refractory to both bortezomib and lenalidomide, the ORR was 15%, median duration of response was 7·8 months, and median overall survival was 11·9 months.[21] Thus, the ORR of 29%, median PFS of 3·7 months, and median

duration of response of 7·4 months in our ongoing study of daratumumab monotherapy compare favourably with these agents, particularly because most of the patients were refractory to both proteasome inhibitors and immunomodulatory drugs (95%), and many were refractory to pomalidomide (63%) or carfilzomib (48%; table 1).

Daratumumab has a favourable safety profile compared with other available agents, and results in clinically manageable side-effects. No patient treated with 16 mg/kg discontinued daratumumab treatment because of a treatment-related adverse event. This result compares favourably with the substantial risk of neutropenia, febrile neutropenia, and infections with pomalidomide and dexamethasone reported in other studies. Additionally, non-haematological toxicities, such as cardiopulmonary and renal side-effects, are an important consideration with carfilzomib, particularly in patients with advanced disease.[21,22] Lower rates of neutropenia were reported with single-agent daratumumab, and patients only routinely received steroids during the peri-infusion period and there was low use of granulocyte colony stimulating factor. Infusion-related reactions were easily managed, were usually grade 1 or 2, and did not lead to discontinuation. The overall favourable toxicity profile of daratumumab makes it an attractive drug for use in combination regimens, and it has shown early promising activity in combination with lenalidomide and dexamethasone.[23]

In conclusion, daratumumab seems to be an effective option for patients with relapsed and refractory multiple myeloma for whom available treatments have been exhausted. Based on deep and durable responses and a favourable safety profile, daratumumab 16 mg/kg seems suitable for treatment of patients with multiple myeloma. The tolerability of daratumumab in combination with other backbone agents is being assessed in early phase studies.[24] Patients with early to late stages of multiple myeloma are being enrolled in randomised phase 3 studies of daratumumab in combination with bortezomib, or lenalidomide and dexamethasone, and other combinations, for the assessment of efficacy and safety, including patient-reported outcomes.[25]

Contributors

Janssen Research & Development and PGR designed the study. SLo, BMW, SZU, SS, AC, NJB, AB, AK, RAV, MVM, AM, RZO, HJS, JBl, ECS, AO, JBe, MG, DAS, RL, MS, NC, AJ, DW, JdlR, and PMV gathered the data. SLi, HF, CMU, IK, and TA analysed the data. All authors interpreted the data. SLo wrote the preliminary draft of the manuscript. All authors wrote and reviewed subsequent drafts of the manuscript and approved the final version.

Declaration of interests

SLo reports consulting for Bristol-Myers Squibb, Celgene, Janssen, Millennium, Novartis, and Onyx and research funding from Janssen for this study. BMW reports consulting for Janssen and Millennium and research funding from Janssen and Prothena. SZU reports consulting for Celgene, Millennium Takeda, Onyx, and Sanofi, speaker's fees for Celgene, Millennium Takeda, and Onyx, and research funding from Array Biopharma, Celgene, Janssen Oncology, Onyx, Pharmacyclics, and Sanofi. AC reports consulting for Array Biopharma, Celgene, Millennium Takeda, Novartis, and Onyx and research funding from Array Biopharma, Celgene, Janssen Pharmaceuticals, Millennium Takeda, Novartis, Onyx, and Pharmacyclics. NJB reports honoraria from Amgen, Celgene, and Johnson & Johnson, speaker's fees from Celgene and Johnson & Johnson, and research funding from Celgene and Johnson & Johnson. AK reports consulting for Celgene, Onyx, and Bristol-Myers Squibb, speaker's fees from Celgene, Millennium, and Onyx and immediate family ownership of stock and other interests in Celgene and Infiniti. MVM reports consulting for Amgen, Celgene, Janssen, and Takeda, honoraria from Bristol-Myers Squibb, Celgene, and Janssen, and other from Celgene and Janssen. AM reports speaker's fees from Celgene, Millennium, and Onyx. RZO reports consulting for Array BioPharma, Bristol-Myers Squibb, Celgene, FORMA Therapeutics, Janssen, Millennium, and Onyx, research funding from Bristol-Myers Squibb, Celgene, Janssen, Onyx, and Spectrum Pharmaceuticals. HJS reports consulting for Celgene and Janssen and research funding from GlaxoSmithKline and Novartis. JBl reports honoraria from Binding Site, Celgene, Janssen, and Onyx and research funding from Janssen. AO reports consultancy from Janssen, Amgen, and Celgene. JBe reports research funding from Abbvie, Acetylon, Bristol-Myers Squibb, Calithera, Celgene, Constellation, Epizyme, Karyopharm, Novartis, Onyx, Takeda, and Tragara. MG reports speaker's fees from Takeda. MS reports honoraria from Novartis, Janssen, and Celgene. AJ reports honoraria and consulting for Bristol-Myers Squibb, Celgene, Janssen, Millennium, Onyx, Amgen, Skyline Diagnostics, Karyopharm Therapeutics, and Sanofi, and research funding from Karyopharm. DW reports research funding and personal fees from Celgene and Janssen. PGR reports being a member of the advisory committee for Genmab. SLi is an employee of Genmab. HF, IK, CMU, and TA are employees of Janssen Research & Development. PMV reports honoraria from Millennium Takeda and Novartis, consulting for Array BioPharma, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, and Oncopeptides, and research funding from Celgene, GlaxoSmithKline, and Oncopeptides. The other authors declare no competing interests.

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References

1 Rollig C, Knop S, Bornhauser M. Multiple myeloma. *Lancet* 2015; **385:** 2197–208.

2 Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 2008; **111:** 2516–20.

3 Turesson I, Velez R, Kristinsson SY, Landgren O. Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study. *J Clin Oncol* 2010; **28:** 830–34.

4 Kumar SK, Lee JH, Lahuerta JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. *Leukemia* 2012; **26:** 149–57.

5 Kuroda J, Nagoshi H, Shimura Y, Taniwaki M. Elotuzumab and daratumumab: emerging new monoclonal antibodies for multiple myeloma. *Expert Rev Anticancer Ther* 2013; **13:** 1081–88.

6 de Weers M, Tai YT, van der Veer MS, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol* 2011; **186:** 1840–48.

7 Lammerts van Bueren J, Jakobs D, Kaldenhoven N, et al. Direct in vitro comparison of daratumumab with surrogate analogs of CD38 antibodies MOR03087, SAR650984 and Ab79. 56th ASH Annual Meeting and Exposition; San Francisco, CA, USA; Dec 6–9, 2014. Abstract 3474.

8 Overdijk MB, Verploegen S, Bogels M, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. *MAbs* 2015; **7:** 311–21.

9 Jansen JHM, Boross P, Overdijk MB, Lammerts van Bueren JJ, Parren PWHI, Leusen HHW. Daratumumab, a human CD38 antibody induces apoptosis of myeloma tumor cells via Fc receptor-mediated crosslinking. *Blood* 2012; **120:** 2974 (abstr).

10 Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. *N Engl J Med* 2015; **373:** 1207–19.

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

12 Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood* 2011; **117:** 4691–95.

13 US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (accessed Nov 5, 2014).

14 Chapuy CI, Nicholson RT, Aguad MD, et al. Resolving the daratumumab interference with blood compatibility testing. *Transfusion* 2015; published online March 12. DOI:10.1111/trf.13069.

15 Chng WJ, Dispenzieri A, Chim CS, et al. IMWG consensus on risk stratification in multiple myeloma. *Leukemia* 2014; **28:** 269–77.

16 Zonder JA, Mohrbacher AF, Singhal S, et al. A phase 1, multicenter, open-label, dose escalation study of elotuzumab in patients with advanced multiple myeloma. *Blood* 2012; **120:** 552–59.

17 Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med* 2015; **373:** 621–31.

18 Harousseau JL, vet-Loiseau H, Attal M, et al. Achievement of at least very good partial response is a simple and robust prognostic factor in patients with multiple myeloma treated with high-dose therapy: long-term analysis of the IFM 99-02 and 99-04 Trials. *J Clin Oncol* 2009; **27:** 5720–26.

19 Kapoor P, Kumar SK, Dispenzieri A, et al. Importance of achieving stringent complete response after autologous stem-cell transplantation in multiple myeloma. *J Clin Oncol* 2013; **31:** 4529–35.

20 Richardson PG, Siegel DS, Vij R, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. *Blood* 2014; **123:** 1826–32.

21 Siegel DS, Martin T, Wang M, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. *Blood* 2012; **120:** 2817–25.

22 San Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2013; **14:** 1055–66.

23 Plesner T, Arkenau HT, Lokhorst HM, et al. Safety and efficacy of daratumumab with lenalidomide and dexamethasone in relapsed or relapsed, refractory multiple myeloma. *Blood* 2014; **124:** 84 (abstr).

24 Moreau P, Mateos MV, Bladé J, et al. An open-label, multicenter, phase 1b study of daratumumab in combination with backbone regimens in patients with multiple myeloma. *Blood* 2014; **124:** 176 (abstr).

25 Laubach JP, Richardson PG. CD38-targeted immunochemotherapy in refractory multiple myeloma: a new horizon. *Clin Cancer Res* 2015; **21:** 2660–62.