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CLINICAL TRIALS AND OBSERVATIONS

Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma

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Key Points

- No new safety signals were observed with daratumumab plus pomalidomide and dexamethasone, except for increased neutropenia.
- Daratumumab plus pomalidomide and dexamethasone induced rapid, deep, and durable responses in heavily treated patients with multiple myeloma.

Daratumumab plus pomalidomide and dexamethasone (pom-dex) was evaluated in patients with relapsed/refractory multiple myeloma with ≥2 prior lines of therapy who were refractory to their last treatment. Patients received daratumumab 16 mg/kg at the recommended dosing schedule, pomalidomide 4 mg daily for 21 days of each 28-day cycle, and dexamethasone 40 mg weekly. Safety was the primary end point. Overall response rate (ORR) and minimal residual disease (MRD) by next-generation sequencing were secondary end points. Patients (N = 103) received a median (range) of 4 (1-13) prior therapies; 76% received ≥3 prior therapies. The safety profile of daratumumab plus pom-dex was similar to that of pom-dex alone, with the exception of daratumumab-specific infusion-related reactions (50%) and a higher incidence of neutropenia, although without an increase in infection rate. Common grade ≥3 adverse events were neutropenia (78%), anemia (28%), and leukopenia (24%). ORR was 60% and was generally consistent across subgroups (58% in double-refractory patients). Among patients with a complete response or better, 29% were MRD negative at a threshold of 10^{-5}. Among the 62 responders, median duration of response was not estimable (NE; 95% confidence interval [CI], 13.6-NE). At a median follow-up of 13.1 months, the median progression-free survival was 8.8 (95% CI, 4.6-15.4) months and median overall survival was 17.5 (95% CI, 13.3-NE) months. The estimated 12-month survival rate was 66% (95% CI, 55.6-74.8). Aside from increased neutropenia, the safety profile of daratumumab plus pom-dex was consistent with that of the individual therapies. Deep, durable responses were observed in heavily treated patients. The study was registered at www.clinicaltrials.gov as #NCT01998971. (*Blood*. 2017;130(8):974-981)

Introduction

Despite advances in treatment options over the last decade, patients with the malignant plasma cell disorder multiple myeloma (MM) typically have recurrent relapses.[1] Although there are several treatments available for relapsed patients, they have limited efficacy. In particular, patients who have had successive relapses or who are refractory to treatment have poor survival.[1] A recent retrospective analysis of real-world survival outcomes reported a median overall survival (OS) of only 7.9 months in patients with ≥3 prior lines of therapy, including a proteasome inhibitor (PI) or an immunomodulatory drug (IMiD), or who were double refractory to a PI and an IMiD.[2] Novel effective therapies and treatment combinations are needed.

Daratumumab, a human monoclonal antibody targeting CD38, is approved as a monotherapy for the treatment of patients with heavily treated MM[3-5] and in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with MM who have received ≥1 prior treatment.[6] Daratumumab has multiple mechanisms of action, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, apoptosis, and modulation of CD38 enzyme activity.[7,8] Daratumumab may also have immunomodulatory effects that increase T-cell clonality while attenuating the immune-suppressive activity of $CD38^+$ regulatory T cells, regulatory B cells, and myeloid-derived suppressor cells.[9]

Daratumumab monotherapy produced deep and durable responses, allowing patients with heavily treated relapsed and refractory MM to achieve a median OS of 20.1 months.[2] Two phase 3 studies

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of daratumumab in combination with standard-of-care regimens in patients treated with at least 1 prior line of therapy (POLLUX and CASTOR) have demonstrated a significant benefit to progression-free survival (PFS).[10,11] The reduction in the risk of disease progression or death was more than 60% compared with active controls. In these studies, patients refractory to the standard-of-care regimens were not eligible for enrollment.

Pomalidomide plus dexamethasone (pom-dex) has been shown to confer a PFS benefit in patients with relapsed and refractory MM compared with pomalidomide alone.[12] A phase 3 study of pomalidomide plus low-dose dexamethasone vs high-dose dexamethasone alone demonstrated a significant benefit to OS, PFS, and overall response rate (ORR).[13] Notably, subgroup analyses demonstrated a benefit to OS and PFS in lenalidomide-refractory patients treated with pomalidomide plus low-dose dexamethasone vs high-dose dexamethasone.[13] In addition, single-agent pomalidomide has been shown to upregulate CD38 expression on MM cell lines,[14] and pretreatment of patient-derived effector cells with an IMiD (lenalidomide) has been shown to synergistically enhance daratumumab-mediated antibody-dependent cell-mediated cytotoxicity.[15] Finally, pom-dex has demonstrated immune modulation, via activation of T cells, that correlated with clinical response,[16] which could potentially complement the immunomodulatory effects demonstrated by daratumumab.[9] For all of these reasons, pomalidomide paired with daratumumab is a rational choice for a combination regimen.

This study (EQUULEUS; MMY1001) evaluated safety and tolerability of daratumumab in combination with various treatment regimens. This report focuses on results from the daratumumab plus pom-dex treatment arm.

Methods

Eligibility criteria

Patients were ≥18 years of age and had documented myeloma, defined by ≥10% monoclonal plasma cells in the bone marrow or a proven plasmacytoma per International Myeloma Working Group (IMWG) criteria[17] and had an Eastern Cooperative Oncology Group performance status of ≤2. Patients had received ≥2 prior lines of antimyeloma therapy, including at least 2 consecutive cycles of prior treatment that included lenalidomide and bortezomib. Patients were eligible if they progressed on a regimen that combined lenalidomide and bortezomib or consecutive regimens that contained lenalidomide and bortezomib separately. Patients who were lenalidomide refractory (defined as disease progression on or within 60 days of the completion of receiving lenalidomide) were eligible. Per IMWG criteria, for patients with immunoglobulin G (IgG) disease, serum M-protein level was ≥1.0 g/dL (≥0.5 g/dL in IgA, IgD, or IgE disease) or urine M-protein was ≥200 mg/24 h. For patients with light-chain MM, serum immunoglobulin free light chain was ≥10 mg/dL, and an abnormal serum immunoglobulin κ:λ free light-chain ratio was required. Patients were required to have hemoglobin ≥8 g/dL, absolute neutrophil count ≥1.0×10^9/L, aspartate aminotransferase and alanine aminotransferase ≤2.5× upper limit of normal, total bilirubin ≤2.0 mg/dL, calculated creatinine clearance ≥45 mL/min/1.73 m^2,[13] corrected serum calcium <14 mg/dL or free ionized calcium <6.5 mg/dL, and a platelet count ≥75×10^9/L in patients for whom <50% of bone marrow nucleated cells were plasma cells (>50×10^9/L otherwise).

Patients were excluded if they had received previous treatment with daratumumab or pomalidomide, had undergone allogeneic stem cell transplantation at any time or autologous stem cell transplantation within 12 weeks of cycle 1 day 1, or had received antimyeloma therapy within 2 weeks of cycle 1 day 1. Patients with a diagnosis of monoclonal gammopathy of undetermined significance, smoldering MM, amyloidosis, or Waldenström disease were excluded. The study excluded patients with peripheral neuropathy (grade ≥2), meningeal involvement of myeloma, chronic obstructive pulmonary disease (with a forced expiratory volume in 1 second <50% of predicted normal), asthma (moderate, severe, or uncontrolled), significant heart disease, or a known hypersensitivity to thalidomide or lenalidomide.

Study design

This was an open-label, nonrandomized, multicenter, multiarm, phase 1b study in a large number of patients (N = 103). Treatment arms evaluated daratumumab in combination with a variety of backbone regimens in newly diagnosed patients and in patients who had received prior therapy. Results from the daratumumab plus pom-dex treatment arm, which only included patients with prior antimyeloma treatment, are discussed here. Initially, 6 patients were treated with daratumumab 16 mg/kg plus pom-dex. Because no more than 1 patient experienced dose-limiting toxicity, 97 additional patients were enrolled in an expansion cohort.

Cycles were 28 days in duration. Patients received daratumumab 16 mg/kg IV weekly in cycles 1 and 2 and then every 2 weeks in cycles 3 to 6 and every 4 weeks thereafter. All patients received an antihistamine and acetaminophen prior to each daratumumab infusion to reduce the risk for infusion-related reactions (IRRs). Patients received pomalidomide 4 mg per day orally on days 1 to 21. Dexamethasone 40 mg (20 mg per week in patients >75 years of age) was administered weekly and before and after the daratumumab infusions on days when daratumumab was given to further reduce the risk for IRRs. Growth factor support was provided without restriction and according to the local prescribing patterns of the treating physician. Patients received treatment until disease progression.

Study end points and analyses

The primary safety end point was the maximum tolerated dose of daratumumab, defined as the highest dose level at which ≤1 patient out of the initial 6 patients experienced a dose-limiting toxicity, as determined by the Independent Data and Safety Monitoring Board (IDSMB), when daratumumab was combined with pom-dex. Safety evaluations included adverse event (AE; occurring from consent to 30 days after last study treatment) monitoring, physical examinations, electrocardiogram monitoring, clinical laboratory tests, vital sign measurements, and Eastern Cooperative Oncology Group performance status. Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4 and coded using the *Medical Dictionary for Regulatory Activities*. For each AE, the percentage of patients who experienced ≥1 occurrence was summarized. The first 6 patients treated with daratumumab plus pom-dex were evaluated for dose-limiting toxicities. The IDSMB then evaluated aggregate safety data for these patients and recommended expansion to a further 97 patients at the same dose level.

Major secondary end points included evaluating the efficacy of daratumumab plus pom-dex, including ORR and rate of complete response (CR). Response to treatment and disease progression were evaluated according to the IMWG response criteria at the end of each treatment cycle.[18,19] Paraproteins were assessed by a central laboratory. Cytogenetic risk was assessed at the individual study centers and risk was adjudicated per local protocols. Disease progression was confirmed by ≥1 repeated test performed 1-3 weeks after the initial test showing progression. Serum and urine immunofixation electrophoresis (IFE) were performed at screening and when CR was suspected. A daratumumab-specific IFE assay was used to confirm CR for patient samples in which daratumumab interference with IFE was suspected.[20] Minimal residual disease (MRD) was evaluated in bone marrow aspirate samples from patients who achieved a CR or better. Samples were prepared with Ficoll using the ClonoSEQ assay (Version 1.3; Adaptive Biotechnologies, Seattle, WA) at sensitivities of 0.01% (1 cancer cell per 10 000 nucleated cells or 10^{-4}), 0.001% (10^{-5}), and 0.0001% (10^{-6}).

Study oversight

This study was registered at www.clinicaltrials.gov as #NCT01998971 and was sponsored by Janssen Research & Development. The research was approved by the clinical study sites' institutional review boards or ethics committees, and all patients gave written informed consent. The study design and analyses were devised by the investigators and sponsor. Study data were collected by the investigators and their research teams. Final data analysis and verification of accuracy were conducted by Janssen. The investigators were not restricted by

confidentiality agreements and had full accessibility to all the data. Writing assistance was funded by Janssen Global Services.

Statistical analyses

Sample size was not determined based on formal hypothesis testing. Descriptive statistics for treatment-emergent AEs (TEAEs) were summarized, including AEs of clinical interest: IRRs, infections, and neutropenia. Efficacy assessment was performed per IMWG criteria, and response assessment was based on investigator assessment, IDSMB assessment, and a validated computer algorithm. Responses were categorized per IMWG criteria, and, for each response category, a 2-sided 95% exact confidence interval (CI) was calculated. ORR was analyzed for all treated patients and defined as the proportion of patients with stringent CR, CR, very good partial response (VGPR), or partial response (PR). Predefined subgroup analyses were performed to determine whether clinical characteristics were associated with selected efficacy and safety end points. Sensitivity analyses per IDSMB were performed for ORR using the response-evaluable population. Duration of response, PFS, OS, and time to response were estimated using the Kaplan-Meier method per IDSMB assessment.

Results

Patients

One hundred and three patients received ≥1 dose of daratumumab plus pom-dex. Demographics and baseline disease characteristics are presented in Table 1. The median (range) age was 64.0 (35-86) years, and 49% of patients were >65 years of age. All patients had received prior antimyeloma treatment, and 74% of patients had received a prior autologous stem cell transplant. The majority of patients (76%) had received ≥3 prior lines of therapy. The median (range) number of prior therapies was 4 (1-13), and the median time since diagnosis was 5.1 (0.4-16.0) years. All patients had received prior treatment with lenalidomide, 98% of patients had previously received bortezomib, 98% of patients had prior exposure to both lenalidomide and bortezomib, and a third (33%) of patients had been treated with carfilzomib. The majority of patients were refractory to prior therapies; 30% were refractory to carfilzomib, 89% and 71% were refractory to lenalidomide and bortezomib, respectively, and 71% were double refractory to a PI (typically bortezomib) and an IMiD (typically lenalidomide). Of the 87 patients with available cytogenetic data, 25% had a high-risk cytogenetic anomaly at baseline, most commonly del17p (18%).

Disposition and drug exposure

Of the 103 patients treated with daratumumab plus pom-dex, 67% discontinued treatment: 39% due to progressive disease; 16% due to AEs; 4% each due to a physician's decision, withdrawal of consent, and death; and 1% due to other considerations. All 4 patients died before completing the first treatment cycle. The median (range) duration of study treatment was 6.7 (0.0-20.0) months, and the median (range) number of daratumumab infusions received was 16 (1-30). Median relative dose intensities of daratumumab, pomalidomide, and dexamethasone were 97%, 74%, and 89%, respectively. Daratumumab dose modifications (skipped or delayed) occurred in 49% of patients; the most common reasons for dose modifications of daratumumab were neutropenia (23%) and thrombocytopenia (9%). Dose reductions or skipped doses of pomalidomide due to neutropenia occurred in 47 (46%) patients.

Table 1. Demographics, baseline disease characteristics, and prior treatment history

	Daratumumab plus pom-dex (N = 103)
Age, median (range), y	64.0 (35-86)
<65	52 (51)
65 to <75	43 (42)
≥75	8 (8)
Sex	
Male	57 (55)
Female	46 (45)
Race	
White	79 (77)
Other	24 (23)
ECOG performance status	
0	28 (27)
1	63 (61)
2	12 (12)
>2	0 (0)
Type of myeloma	
IgG	63 (61)
IgA	18 (18)
IgD	2 (2)
Light chain	20 (19)
Time since initial diagnosis (y), median (range)	5.1 (0.4-16.0)
Number of prior lines, median (range)	4.0 (1-13)
Prior lines of therapy	
1*	3 (3)
2	22 (21)
3	25 (24)
>3	53 (52)
Prior ASCT	76 (74)
Prior therapy	
PI + IMiD	102 (99)
PI	102 (99)
BORT	101 (98)
CARF	34 (33)
IXA	2 (2)
LEN	103 (100)
THAL	29 (28)
BORT + LEN	101 (98)
BORT + LEN + CARF	34 (33)
Steroids	103 (100)
Chemotherapy	103 (100)
Refractory to	
PI only	9 (9)
IMiD only	21 (20)
PI + IMiD	73 (71)
Cytogenetic abnormality†	
Standard risk	65 (75)
High risk‡	22 (25)
del17p	16 (18)
t(4;14)	6 (7)
t(14;16)	1 (1)

Values represent n (%) of patients unless otherwise indicated. Total percentages within categories may not equal 100% due to rounding.

ASCT, autologous stem cell transplantation; BORT, bortezomib; CARF, carfilzomib; ECOG, Eastern Cooperative Oncology Group; IXA, ixazomib; LEN, lenalidomide; THAL, thalidomide.

*Three patients were identified by investigators as having ≥2 prior lines of therapy, but, per IMWG criteria, they were later determined to have received only 1 prior line that included both bortezomib and lenalidomide.

†N = 87.

‡The presence of high-risk cytogenetic abnormalities was adjudicated locally per individual center practices.

Table 2. Most common (>25%) TEAEs

	Daratumumab plus pom-dex (N = 103)	
	Any grade	Grade 3/4
Total AEs	103 (100)	102 (99)
Neutropenia	82 (80)	79 (77)
Anemia	56 (54)	29 (28)
Fatigue	54 (52)	12 (12)
Diarrhea	44 (43)	4 (4)
Thrombocytopenia	43 (42)	20 (19)
Cough	39 (38)	1* (1)
Leukopenia	38 (37)	25 (24)
Constipation	35 (34)	0 (0)
Dyspnea	33 (32)	8 (8)
Nausea	32 (31)	0 (0)
Pyrexia	31 (30)	2 (2)
Back pain	29 (28)	6 (6)
Upper respiratory tract infection	29 (28)	3 (3)
Muscle spasms	28 (27)	1 (1)

Values represent n (%) of patients.
*Reported as "productive cough."

Safety

The most common (>25%) TEAEs (Table 2) included neutropenia (80%), anemia (54%), fatigue (52%), diarrhea (43%), thrombocytopenia (42%), cough (38%), leukopenia (37%), constipation (34%), dyspnea (32%), nausea (31%), pyrexia (30%), back pain and upper respiratory tract infection (28% each), and muscle spasms (27%). The most common (>5%) grade 3/4 TEAEs were neutropenia (77%); anemia (28%); leukopenia (24%); thrombocytopenia (19%); lymphopenia (14%); fatigue (12%); pneumonia (10%); febrile neutropenia and dyspnea (8% each); and hyperglycemia, back pain, and fall (6% each). Other than neutropenia, rates of grade 3/4 TEAEs were similar to those observed historically with pom-dex alone.[13]

Neutropenia and febrile neutropenia were managed using growth factors or dose modifications. Growth factors were administered to 57% of patients, including filgrastim (49%) and pegfilgrastim (13%). The majority of grade 3/4 neutropenia events occurred within 2 months of the first study dose, which may be due in part to preexisting grade 1/2 neutropenia in 44% of patients at enrollment. Despite higher rates of neutropenia, rates of grade 3/4 infection (32%) and febrile neutropenia (8%) were comparable with the safety profile of pom-dex alone.[13] Thirty-two percent of patients received transfusions (predominantly packed red blood cells [27%] and platelets [13%]). No transfusion-related hemolysis occurred, a finding that is consistent with the clinical trial experience with daratumumab.[21]

Serious TEAEs occurred in 53% of patients, 25% of which were considered related to a study drug and 18% of which were deemed related to daratumumab. Pneumonia (9%), sepsis and febrile neutropenia (5% each), falls (4%), and anemia and dyspnea (3% each) were the most common (occurring in >2 patients) serious TEAEs. There were no reports of secondary primary malignancies.

Sixteen percent of patients experienced TEAEs that led to discontinuation of study treatment; 8% of discontinuations were considered related to a study drug, and 3% were considered related to daratumumab. None of the TEAEs that resulted in discontinuation occurred in >1 patient. No patient discontinued the study due to neutropenia, and no patient discontinued treatment as a result of febrile neutropenia.

IRRs occurred in 50% of patients, all of which occurred during the first infusion, except for 1 case of laryngeal edema, which occurred during the second infusion. The most common IRRs (>5%) were chills (15%), cough and dyspnea (11% each), nausea (9%), and throat irritation and nasal congestion (7% each). Four (4%) patients had grade 3 IRRs (hypertension/increased blood pressure [n = 3] and hypoxia [n = 1]); no grade 4 or 5 IRRs occurred. One patient discontinued daratumumab treatment due to an IRR (grade 3 hypoxia). The majority of IRRs were managed by interrupting the daratumumab infusion or slowing the infusion rate.

Nine (9%) patients died during treatment or within 30 days of receiving their last dose of study drug. Causes of death included progressive multifocal leukoencephalopathy, sepsis, general physical health deterioration, interstitial lung disease, pleural effusion, respiratory failure, cerebrovascular accident, cardiac arrest, and sudden death (n = 1 each). Neither of the latter 2 patients had a prior history of cardiac disease, and both died 19 days after their last dose of daratumumab; neither death was deemed related to daratumumab. The case of sudden death occurred in the patient's home. Four patients died within the first cycle of treatment (general physical health deterioration, cerebrovascular accident, sepsis, and progressive multifocal leukoencephalopathy); none were considered related to daratumumab. The case of progressive multifocal leukoencephalopathy was in a subject who previously received a single dose of rituximab as a conditioning regimen prior to earlier tandem autologous stem cell transplantations. The patient died after only 1 dose of daratumumab was received. Overall, no deaths were considered to be related to daratumumab.

Efficacy

The daratumumab plus pom-dex–treated analysis set, which included patients who received ≥1 dose of study drug, was used to calculate ORR and time-to-event variables such as PFS, time to progression, and OS. The response-evaluable analysis set included 103 patients who received ≥1 dose of study drug and had ≥1 postbaseline disease assessment and was used for sensitivity analysis of ORR and for duration of response and time to response. Ninety-nine patients had evaluable paraprotein (supplemental Figure 1, available on the *Blood* Web site).

The ORR was 60% (95% CI, 50.1% to 69.7%; Figure 1A); 8%, 9%, 25%, and 18% of patients had a best response of stringent CR, CR, VGPR, or PR, respectively. The clinical benefit rate was 62%, with 2% of patients with a minimal response. Twenty-five percent of patients had stable disease, and 3% had progressive disease. Overall, 7%, 6%, and 2% of patients became negative for MRD at thresholds of 10^{-4}, 10^{-5}, and 10^{-6}, respectively. Among the 17 patients with a CR or better, 35%, 29%, and 6% of patients were negative for MRD at thresholds of 10^{-4}, 10^{-5}, and 10^{-6}, respectively.

ORR was generally consistent across prespecified subgroups stratified by age, race, renal function, refractory status, type of myeloma, and cytogenetic risk (Figure 1B). When stratified by number of prior lines of therapy, ORRs were 64%, 65%, and 55% in patients with 2, 3, and >3 prior lines of therapy, respectively. ORRs were similar for patients with standard or high cytogenetic risk (both 59%). Given that the patient numbers were small and no formal statistical tests were performed, these results should be interpreted with caution.

Figure 2 represents the time to first response, time to best response, and duration of response for the 62 responders. The median duration of response was not estimable (NE; 95% CI, 13.6-NE months). Among responders, the 6- and 12-month disease-progression–free rates in these patients were 85% (95% CI, 72.4-91.7) and 68% (53.2-78.8), respectively. Median (range) time to first response was 1.0 (0.9-2.9) month, and time to best response was 2.3 (0.9-12.5) months. The

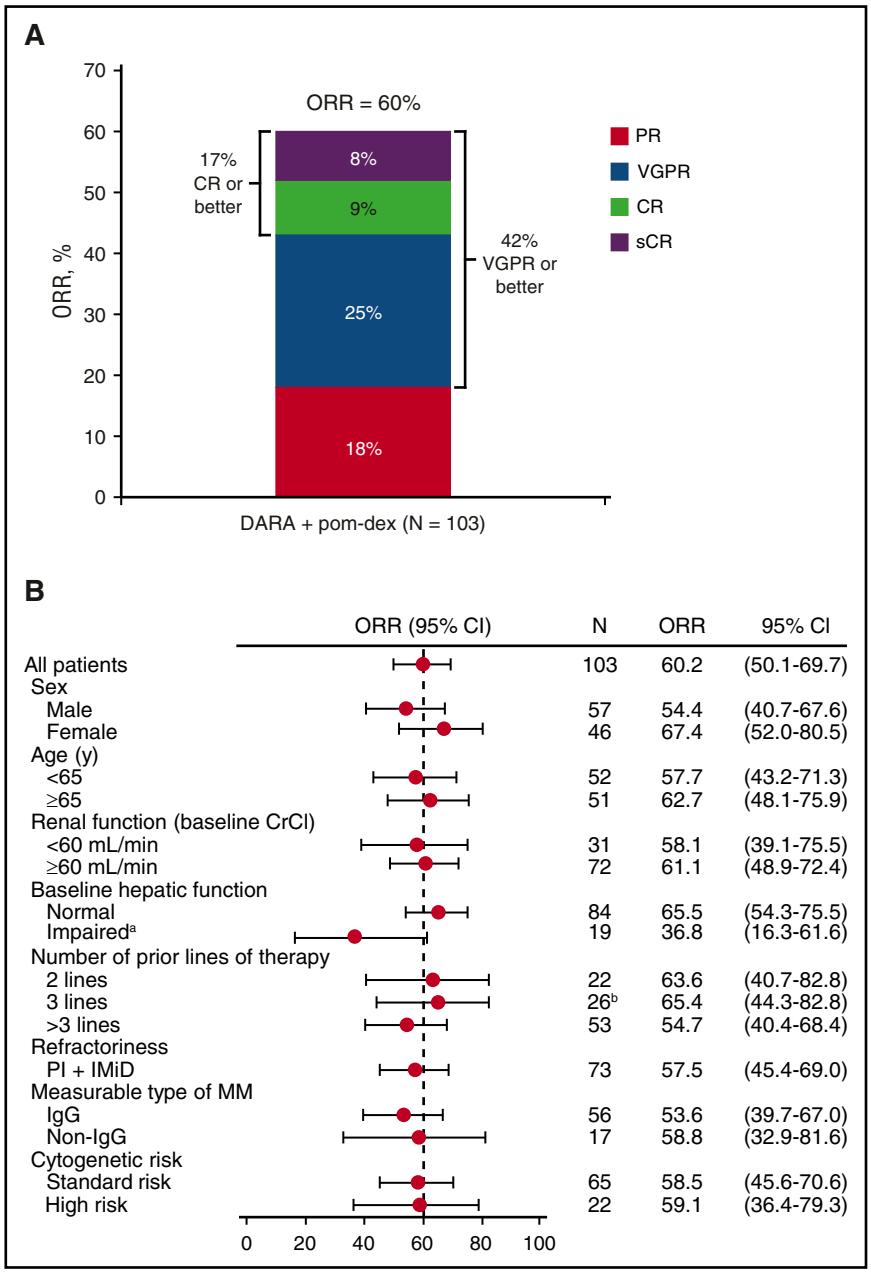

Figure 1. Response rate in patients treated with daratumumab plus pom-dex. (A) Overall response rate. (B) Subgroup analysis of the overall best response. The dashed vertical line indicates 60.2%, which was the ORR in the total patient cohort. Exact 95% CIs are provided. [a]Classified as mild (total bilirubin 1.0-1.5× upper limit of normal or aspartate aminotransferase above upper limit of normal), moderate (total bilirubin >1.5-3.0× upper limit of normal), or severe (total bilirubin >3.0× upper limit of normal); 17% had mild impairment; 1% had moderate impairment; 0% had severe impairment. Patients with impaired hepatic function received fewer doses of daratumumab vs patients with normal hepatic function. [b]The discrepancy with the demographics table is due to updated concomitant medication data. CrCl, creatinine clearance; DARA, daratumumab; sCR, stringent complete response.

median (range) time to CR or better was longer (5.9 [2.8-12.5] months), consistent with prior studies of daratumumab monotherapy in heavily treated patients.[2]

Median PFS was 8.8 (95% CI, 4.6-15.4) months, and the 12-month PFS rate was 42% (31.5-51.9; Figure 3A). Median time to progression was 10.4 months (95% CI, 6.7-NE). At a median (range) follow-up of 13.1 (0.2-25.8) months, median OS was 17.5 (13.3-NE) months (Figure 3B). Estimated survival rates at 3, 6, and 12 months were 89% (95% CI, 81.2-93.8), 79% (69.3-85.6), and 66% (55.6-74.8), respectively.

In an exploratory analysis of PFS based on cytogenetic risk classification at baseline, median PFS was 10.3 (95% CI, 4.6-NE) months in patients with standard risk and 3.9 (95% CI, 2.3-NE) months in those with high-risk status. An exploratory analysis of OS revealed that 12-month survival rates were similar in standard-risk (66%; 95% CI, 52.8% to 77.0%) and high-risk (61%; 95% CI, 36.0% to 78.2%) patients; however, the median OS was NE (95% CI, 12.8-NE) vs 12.6 (95% CI, 5.4-NE) months, respectively.

Discussion

This study demonstrates that daratumumab can be safely combined with pom-dex. Aside from higher rates of neutropenia, the safety profiles of daratumumab plus pom-dex and pom-dex alone were similar.[13] A substantial number of patients (44%) had grade 1/2 neutropenia at baseline, which is likely to have contributed to the high rate of neutropenia observed in this study. Despite the neutropenia rate, the incidence of febrile neutropenia and infection, including grade 3/4 pneumonia, observed with daratumumab plus

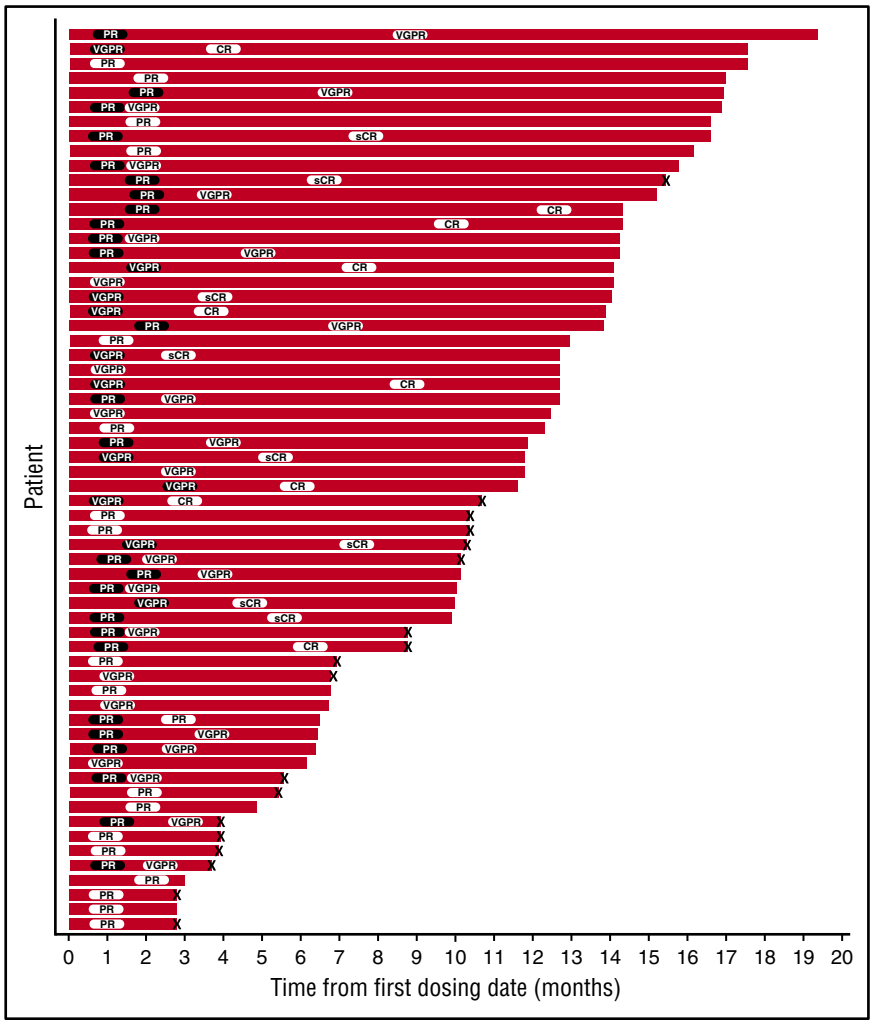

Figure 2. Response and duration of response. Responders from the response-evaluable population are represented. Black ovals indicate first response, white ovals indicate best response, and X indicates disease progression. sCR, stringent complete response.

pom-dex was comparable to that seen in the phase 3 MM-003 study with pom-dex alone.[13]

The findings from this clinical study complement the results of the POLLUX phase 3 study, in which a combination of daratumumab with lenalidomide and dexamethasone induced a high ORR and significantly reduced the risk for disease progression and death in patients with relapsed or refractory MM compared with lenalidomide and dexamethasone.[10] In the present study, the addition of daratumumab to another IMiD, pomalidomide, resulted in deep and durable responses, including MRD negativity, in heavily treated patients with relapsed or refractory disease.

The patient population reported here resembles that of MM-003 more closely. In both studies, patients were required to have experienced ≥2 prior consecutive cycles of bortezomib and lenalidomide, and patients were pomalidomide naïve.[13] In the MM-003 study, pom-dex resulted in an ORR of 31% and a median PFS of 3.8 months in patients with relapsed and refractory MM,[13] whereas here, the addition of daratumumab to pom-dex resulted in an ORR of 60% and a median PFS of 8.8 months. The high ORR of 60% may also have contributed to the prolonged median OS of 17.5 months compared with 12.7 months observed in MM-003.[22]

In comparison with other studies of primary single-arm (ie, nonrandomized) triplet regimens containing pom-dex in relapsed and refractory MM, the ORR observed here is similar. Early-phase studies of carfilzomib, pembrolizumab, isatuximab, or cyclophosphamide in combination with pom-dex reported ORRs ranging from 50% to 65%.[23-26] While ORR was slightly higher in a phase 1 study of bortezomib plus pom-dex (72%), only 13 patients had been evaluated for response, and the study population was bortezomib naïve.[27] Larger, randomized, controlled studies will be required to determine the potential benefit of these regimens, overall and in high-risk patients. As triplet regimens tend to have greater efficacy in earlier lines of treatment, it is likely that these regimens will provide more benefit at first relapse.

In our study, the depth of response reached in heavily treated patients was remarkable, with 42% of patients achieving a VGPR or better and some patients becoming free of MRD. ORR was generally consistent across patient subgroups, including patients who were double refractory to a PI and an IMiD or who had high-risk cytogenetic anomalies, although it should be noted that PFS was, not surprisingly, shorter in high-risk patients. Response rates were also comparable regardless of the number of prior lines of therapy patients had received. However, the number of patients included in these subgroup analyses was small, and thus statistical analyses were not performed.

The major limitations of this study are the small sample size and lack of a control or active-comparator arm. In addition, the median follow-up time was ~13 months. Longer-term follow-up is required to support any benefit to PFS, and, ultimately, a phase 3, randomized, controlled study is needed to confirm the benefits of a daratumumab plus pom-dex regimen. However, taken together, the apparent benefit to PFS and OS

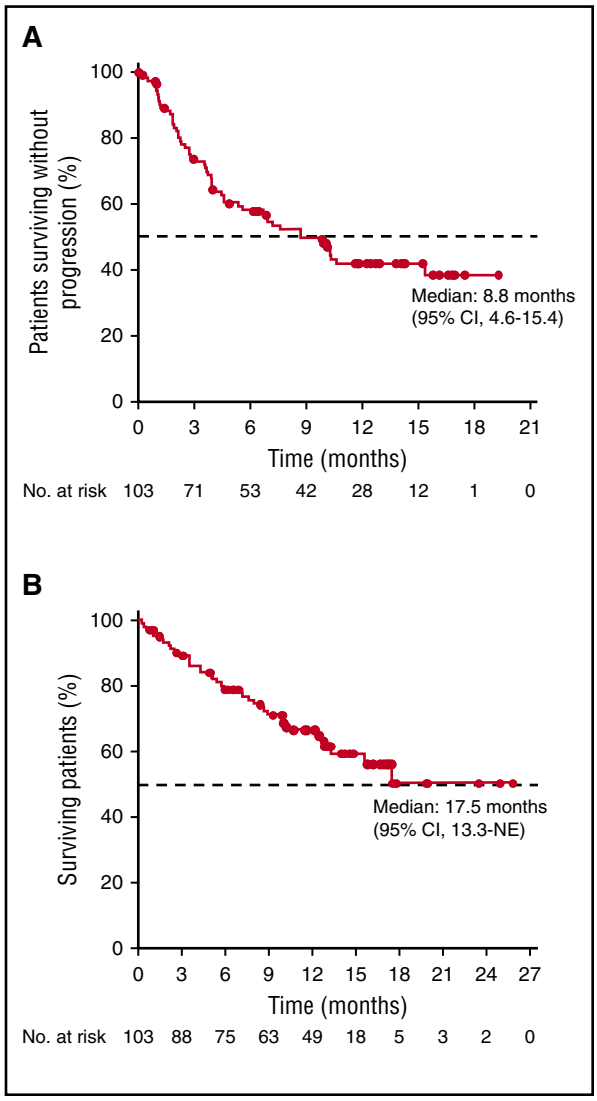

Figure 3. PFS and OS in patients treated with daratumumab plus pom-dex. At a median follow-up of 13.1 months, the median PFS (A) and median OS (B) are shown.

in comparison with MM-003 and the depth of response in a heavily treated and refractory population and the previously established single-agent efficacy of daratumumab[2,28,29] provide a compelling rationale for further investigation.

In summary, compared with studies of single-agent daratumumab or pom-dex alone, no additional safety signals were observed when daratumumab was combined with pom-dex, except for higher rates of neutropenia. There was no apparent increase in the rate of infections, despite increased neutropenia. Daratumumab plus pom-dex induced rapid, deep, and durable responses in a heavily treated patient population. Further evaluation of daratumumab plus pom-dex is underway in the ongoing APOLLO study conducted by the European Myeloma Network. APOLLO is a phase 3 randomized clinical trial in 302 patients previously treated with a PI and an IMiD (www.clinicaltrials.gov #NCT03180736).

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Authorship

Contribution: A.C., A.S., J.W.F., B.A., J.L.K., J.J.I., B.M.W., A.K., S. Lentzsch, R.C., and S. Lonial contributed to the accrual and treatment of patients and data acquisition, interpretation, and analysis; J.W., K.N., C.C., N.Z.K., and T.A. contributed to data acquisition, interpretation, and analysis; and all authors drafted and reviewed the manuscript, approved the final version, decided to publish this report, and vouch for data accuracy and completeness.

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