Daratumumab, bortezomib, cyclophosphamide and dexamethasone in newly diagnosed and relapsed multiple myeloma: LYRA study

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Summary

This United States community study evaluated the combination of daratumumab, bortezomib, cyclophosphamide and dexamethasone (D-VCd) in newly diagnosed multiple myeloma (NDMM) and relapsed multiple myeloma (RMM). Patients received 4–8 induction cycles of bortezomib 1·5 mg/m^2, cyclophosphamide 300 mg/m^2 and dexamethasone 40 mg weekly. Intravenous daratumumab 16 mg/kg was administered as approved except for a split-first dose in Cycle 1. Eligible patients underwent autologous stem cell transplantation. All patients received ≤12 daratumumab maintenance doses monthly. Eighty-six NDMM and 14 RMM patients received ≥1 treatment dose. In NDMM patients, very good partial response or better (≥VGPR) and overall response rates after 4 induction cycles were 44% (primary endpoint) and 79%, respectively, and 56% and 81% at end of induction. The 12-month progression-free survival (PFS) rate was 87%. Efficacy was also observed in RMM patients. Fatigue (59%) and neutropenia (13%) were the most frequent treatment-emergent adverse event (TEAE) and grade 3/4 TEAE, respectively. Infusion reactions occurred in 54% of patients, primarily during the first dose, and were mild (2% grade 3). The first 2 daratumumab infusions were 4·5 and 3·8 h (median). Overall, D-VCd was well tolerated, split-first daratumumab dosing was feasible, the ≥VGPR rate after 4 cycles was 44% and the 1-year PFS rate was 87%.

Keywords: daratumumab, multiple myeloma, cyclophosphamide, bortezomib, LYRA.

Over the past decade, advances in treatment options have improved clinical outcomes for patients with multiple myeloma (MM); however, despite these advances, patients eventually relapse and require subsequent therapy (Kumar *et al*, 2012a; Ocio *et al*, 2014). The duration and depth of response is reduced with each relapse, resulting from lower sensitivity of heavily treated patients to subsequent therapy (Borrello, 2012; Kurtin, 2013). Therefore, the treatment with the most effective regimen in the frontline setting may provide the best approach to achieve deep and durable clinical responses.

Proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) are commonly used to treat MM and have demonstrated improved efficacy when administered in combination with other agents (e.g., monoclonal antibodies, alkylating drugs, corticosteroids) *versus* monotherapy (Reeder *et al*, 2014). Triplet combinations are commonly used as induction therapy in MM (Moreau *et al*, 2017). Bortezomib, cyclophosphamide and dexamethasone (VCd) is an IMiD-sparing regimen that has demonstrated high response rates and a tolerable safety profile in newly diagnosed MM

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(NDMM), leading to its widespread use as induction therapy in transplant-eligible and ineligible patients (Reeder *et al*, 2009, 2010; Khan *et al*, 2012; Kumar *et al*, 2012b; Jimenez Zepeda *et al*, 2014; Areethamsirikul *et al*, 2015). However, a standard VCd dosing protocol has not been implemented across studies or in clinical practice, contributing in part to different response rates reported in clinical trials (Reeder *et al*, 2009, 2010; Khan *et al*, 2012; Kumar *et al*, 2012b; Mai *et al*, 2015). In clinical studies of VCd in NDMM patients, rates of very good partial response (VGPR) or better ranged from 13% to 70% during induction therapy (Reeder *et al*, 2009, 2010; Kumar *et al*, 2012b; Jimenez Zepeda *et al*, 2014; Mai *et al*, 2015).

Daratumumab, a human monoclonal antibody targeting CD38, provides superior clinical benefit across lines of MM therapy when combined with other regimens. In combination with an IMiD [lenalidomide (R); plus dexamethasone (d)] or with bortezomib [plus dexamethasone (Vd) or plus prednisone and melphalan (VMP)], daratumumab-containing regimens induce deep and durable responses, reduce the risk of disease progression or death by ≥50%, and have tolerable safety profiles (Dimopoulos *et al*, 2016; Palumbo *et al*, 2016; Mateos *et al*, 2018). These findings led to the approval of daratumumab-based treatment for MM across multiple lines of therapy. Daratumumab is approved in combination with Rd or Vd for relapsed MM (RMM) patients who received ≥1 prior therapy, and in combination with pomalidomide and dexamethasone for RMM patients with ≥2 prior therapies, including lenalidomide and a PI (http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX-pi.pdf). Most recently, daratumumab in combination with the PI/alkylator/steroid regimen VMP (D-VMP) reduced the risk of disease progression or death by 50% compared with VMP alone in NDMM patients ineligible for autologous stem cell transplantation (ASCT), leading to the first approval of daratumumab in the frontline setting (http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX-pi.pdf; Mateos *et al*, 2018). The VMP regimen is not commonly used in some countries, especially the United States (US); thus, there is an unmet need to evaluate other daratumumab-based combination regimens, especially in newly diagnosed patients. As VCd is commonly used in the treatment of MM, we conducted a multicentre, single-arm, phase 2 study (LYRA; MMY2012) to evaluate the efficacy and safety of daratumumab in combination with VCd (D-VCd) in patients with newly diagnosed and RMM. This US community practice–based study also evaluated split-dosing of the first daratumumab infusion over 2 days to determine if such a schedule is well tolerated and reduces infusion time on the first day of treatment.

Methods

Eligibility criteria

Patients were ≥18 years of age, had documented MM defined by International Myeloma Working Group (IMWG) criteria (Kumar *et al*, 2016), measurable disease, previously untreated myeloma or relapsed myeloma with 1 prior line of therapy (including an induction regimen that may have been followed by ASCT and single-agent maintenance therapy), and an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2. RMM patients must have achieved a partial response (PR) or better with initial therapy before disease progression. For patients with previously untreated MM, an emergency steroid course (≤40 mg dexamethasone, or equivalent, per day for ≤4 days) was permitted. Radiation therapy for lytic bone disease was permitted prior to study entry, during screening, and during Cycles 1–2. Per IMWG criteria (Kumar *et al*, 2016), patients with measurable disease had a serum M-protein level ≥10 g/l (≥5·0 g/l in IgA, IgD, IgE or IgM disease) or urine M-protein ≥200 mg/24 h. For patients with light chain MM, serum immunoglobulin free light chain (FLC) ≥0·1 g/l and an abnormal serum immunoglobulin κ:λ FLC ratio was required. Eligible patients had haemoglobin >75 g/l; absolute neutrophil count $>1{\cdot}0 \times 10^9$/l; alanine aminotransferase and aspartate aminotransferase <2·5× upper limit of normal; total bilirubin <1·5× upper limit of normal; creatinine clearance >20 ml/min/1·73 m^2; corrected serum calcium ≤3·5 mmol/l or free ionized calcium ≤1·625 mmol/l; and a platelet count $\geq 75 \times 10^9$/l in patients in whom <50% of bone marrow nucleated cells were plasma cells ($>50 \times 10^9$/l, otherwise).

Patients were excluded if they were refractory to a PI or a PI and IMiD combination, defined as failure to respond or progression within 60 days of the end of PI therapy. Other exclusion criteria included clinical signs or a history of meningeal or central nervous system involvement by MM, chronic obstructive pulmonary disease (forced expiratory volume in 1 s <50% of predicted normal), clinically significant cardiac disease {including myocardial infarction within 6 months of Cycle 1 Day 1, New York Heart Association Class III–IV congestive heart failure, uncontrolled cardiac arrhythmia [National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03, https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf; grade ≥2]}, baseline QT interval (QTc) >470 ms for 12-lead electrocardiogram (ECG) at screening, moderate or severe persistent asthma within the past 2 years, plasma cell leukaemia ($>2{\cdot}0 \times 10^9$/l circulating plasma cells by standard differential), Waldenström macroglobulinaemia, POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes), amyloid light chain amyloidosis, human immunodeficiency virus seropositivity, hepatitis B surface antigen positivity, or a history of hepatitis C.

Study design

This was a multicentre, single-arm, open-label phase 2 study of D-VCd in patients with NDMM, irrespective of eligibility for high-dose chemotherapy and ASCT, or RMM following

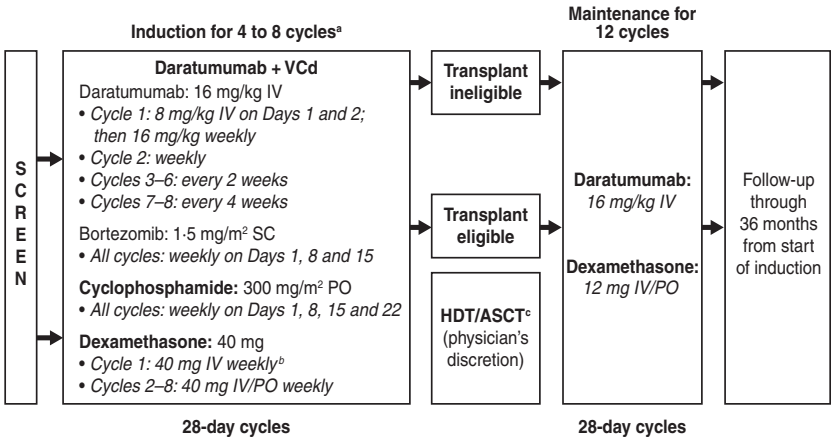

Fig 1. LYRA study design. [a]Range of 4–8 induction cycles due to differences in local standard of care across study sites and enrolment of both transplant eligible, transplant ineligible and relapsed patients. [b]In Cycle 1, 20 mg dexamethasone was given on Days 1 and 2 and weekly thereafter. [c]In patients who underwent ASCT, maintenance therapy was to begin approximately 90 days after ASCT. ASCT, autologous stem cell transplantation; HDT, high-dose therapy; IV, intravenously; PO, orally; SC, subcutaneously; VCd, bortezomib, cyclophosphamide and dexamethasone.

1 prior line of therapy (Fig 1). Planned enrolment was 100 patients with ≥40 previously untreated patients. Due to slow recruitment of RMM patients, this cohort was subsequently closed to enrolment. Patients received 4–8 cycles of induction therapy with bortezomib 1·5 mg/m^2 (subcutaneous) on Days 1, 8 and 15; cyclophosphamide 300 mg/m^2 (oral) on Days 1, 8, 15 and 22 of each 28-day cycle; and weekly dexamethasone 40 mg [oral or intravenous (IV)]. In Cycle 1 only, dexamethasone 20 mg was administered on Days 1 and 2, resulting in a total weekly dose of 40 mg. Patients received daratumumab 8 mg/kg IV on Days 1 and 2 of Cycle 1. Daratumumab 16 mg/kg was administered weekly from Cycle 1 Day 8 to the end of Cycle 2, every 2 weeks in Cycles 3–6, and every 4 weeks thereafter. The allowable range of 4–8 induction cycles was permitted due to differences in local standard of care across US community settings and due to the enrolment of both transplant eligible and ineligible patients. After induction therapy, eligible patients could receive a transplant conditioning regimen and ASCT at the discretion of the investigator. Following induction and/or conditioning/ASCT, patients received ≤12 cycles of daratumumab 16 mg/kg maintenance therapy every 4 weeks. Daratumumab maintenance therapy commenced approximately 90 days after ASCT when appropriate. Follow-up will continue through 36 months from the start of induction.

All patients received pre-infusion medication on daratumumab dosing days (≤3 h before dosing) comprising oral dexamethasone 40 mg (20 mg IV on Days 1, 2, 8, 15 and 22 of Cycle 1; 12 mg during maintenance cycles), acetaminophen 650–1000 mg IV or oral, diphenhydramine 25–50 mg IV or oral (or equivalent), and an optional leukotriene inhibitor (montelukast 10 mg oral or equivalent). Post-infusion medication included oral dexamethasone 4 mg on Cycle 1 Day 3 and 20 mg on Cycle 1 Day 9, 16 and 23. Additional medications, including an antihistamine, leukotriene inhibitor, short-acting β2 adrenergic receptor agonist, or control medications for lung disease, were administered for patients with a higher risk of respiratory complications.

Study endpoints and analyses

The primary endpoint was the rate of complete response + very good partial response (CR + VGPR) following 4 cycles of induction therapy with D-VCd in patients with newly diagnosed or RMM. The primary endpoint was measured after all enrolled patients had completed 4 cycles of induction therapy or had discontinued by the time of analysis. The primary hypothesis was that >60% of patients with NDMM and >30% of patients with RMM would achieve either CR or VGPR following 4 cycles of induction therapy. Disease response and progression were evaluated according to IMWG criteria (Kumar *et al*, 2016). Efficacy assessments included serum and urine M-protein measurements, serum and urine immunofixation electrophoresis, serum FLC, serum calcium corrected for albumin, serum immunoglobulins, and examination of bone marrow aspirate or biopsy. Extramedullary plasmacytomas present at screening or as clinically indicated were assessed by clinical examination or radiological imaging.

Major secondary efficacy endpoints included overall response rate (ORR), time to VGPR or better, time to PR or better, duration of response, progression-free survival (PFS) and overall survival (OS). ORR was measured following 4 cycles of induction therapy, at the end of 4–8 cycles of induction therapy and after all 12 cycles of maintenance therapy. The rate of CR + VGPR at the end of induction, following 4–8 cycles of therapy, was also assessed. Time to response was measured from the start of induction therapy to the date of initial response documentation, confirmed by a repeated measurement. Duration of response was defined as the time from the initial documentation of a response (PR

or better) to the first documented evidence of progressive disease.

Patients with a response of VGPR who had negative M-protein by serum M-protein quantitation by electrophoresis (SPEP) received a reflex serum immunofixation (IFE) test to confirm the presence of daratumumab on IFE. Patients with positive serum IFE and confirmed daratumumab IFE interference who met all other clinical criteria for CR or stringent CR (sCR) were considered to have responses of CR/sCR.

Safety and tolerability were assessed by laboratory test abnormalities and the incidence of adverse events (AEs), including infusion reactions (IRs). Safety evaluations included AE monitoring, clinical laboratory parameters (haematology and serum chemistry), ECG monitoring (at screening only), vital sign measurements, physical examinations and ECOG performance status. AEs were reported for the duration of the study. Vital signs were monitored regularly during the split-dose infusion and other doses of daratumumab. Toxicities were graded using the NCI-CTCAE Version 4.03 (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). An Internal Data Review Committee evaluated 3 prespecified interim safety analyses after ≥20 patients received ≥1 induction cycle, after ≥50 patients completed Cycle 1 (with a focus on IRs during Cycle 1), and after ≥50 patients received ≥4 induction cycles. Exploratory endpoints included efficacy in high-risk molecular subgroups, including del(17p), t(4;14) and t(14;16).

Stem cell collection

Eligible patients could undergo stem cell collection, high-dose therapy and ASCT following 4–8 cycles of induction. Criteria, testing and treatment for patients undergoing ASCT followed the standard operating procedures of the transplant centre.

Study oversight

The study was sponsored by Janssen Scientific Affairs, LLC and registered at ClinicalTrials.gov (identification number: NCT02951819). The research was approved by the clinical study sites' institutional review boards or ethics committees, and all patients gave written informed consent. Janssen Scientific Affairs, LLC funded writing assistance.

Statistical analyses

Responses to treatment and disease progression were evaluated by a validated computer algorithm to calculate IMWG response. For each response category, a 2-sided 95% confidence interval (CI) was calculated. In a study of VCd, a VGPR or better rate of 61% was reported (Reeder *et al*, 2009). This response rate was the basis for the assumption used for the present study. With a planned enrolment of 100 patients (minimum of 40 NDMM patients), ≥80% power was needed to detect an absolute 20% increase in the untreated cohort at the 5% 1-sided significance level. Time-to-event efficacy evaluations, including duration of response (PR or better), time to progression, PFS and OS, were summarized with descriptive statistics using the Kaplan–Meier method. Due to slow recruitment of patients with RMM, the protocol was amended to close this cohort. Therefore, no inferential statistics were performed on the relapsed cohort. Treatment-emergent adverse events (TEAEs) and clinical laboratory test results were summarized.

Data sharing statement

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Results

Patients

A total of 101 patients were enrolled, including 87 patients with NDMM and 14 patients with RMM. Patient demographics and baseline disease characteristics in all treated patients are presented in Table I. The median (range) age in the combined study population was 64 (41–82) years with 14 (14·0%) patients aged ≥75 years; 81·0% were white. Ninety-four percent of patients had a baseline ECOG performance status of 0 or 1. Among patients evaluated for biomarkers (n = 96), 34 (35·4%) had high-risk cytogenetic abnormalities, including 30 (36·6%) with NDMM and 4 (28·6%) with RMM. Median (range) time from diagnosis was 0·08 (0·0–3·1) years among patients with NDMM and 2·22 (0·0–5·8) years for those with RMM. Median follow-up time for patients with newly diagnosed or RMM was 7·9 and 8·8 months, respectively.

Disposition and drug exposure

At the clinical cut-off date of 10 January 2018, 14 patients had discontinued treatment resulting from progressive disease (n = 5), other reasons (n = 4), AEs (n = 2), patient withdrawal (n = 1), refusal of further treatment (n = 1) and death (n = 1; Table II). One hundred patients received ≥1 dose of D-VCd and were included in the safety analysis set, including 86 patients with NDMM and all 14 patients with RMM. At the time of the analysis, the median (range) duration of study treatment was 225 (50–441) days, including a median of 225 (50–441) days for NDMM patients and a median of 235·5 (71–394) days in patients with RMM. The total treated population received a median (range) of 8 (2–15) treatment cycles, with 95 (95·0%) patients having completed ≥4 cycles. Patients with NDMM received a median (range) of 8 (2–15) treatment cycles *versus* 9 (3–15)

Table I. Demographics and baseline disease characteristics of treated patients.*

	NDMM (n = 86)	RMM (n = 14)	Total (n = 100)
Age, median (range), years	63 (41–82)	68 (48–78)	64 (41–82)
<65 years, *n* (%)	45 (52·3)	6 (42·9)	51 (51·0)
65 to <75 years, *n* (%)	31 (36·0)	4 (28·6)	35 (35·0)
≥75 years, *n* (%)	10 (11·6)	4 (28·6)	14 (14·0)
Sex, *n* (%)			
Male	54 (62·8)	10 (71·4)	64 (64·0)
Female	32 (37·2)	4 (28·6)	36 (36·0)
Race, *n* (%)			
White	67 (77·9)	14 (100·0)	81 (81·0)
Black or African American	11 (12·8)	0 (0)	11 (11·0)
Unknown	6 (7·0)	0 (0)	6 (6·0)
Asian	2 (2·3)	0 (0)	2 (2·0)
ECOG performance status, *n* (%)			
0	40 (46·5)	6 (42·9)	46 (46·0)
1	41 (47·7)	7 (50·0)	48 (48·0)
2	5 (5·8)	1 (7·1)	6 (6·0)
Type of myeloma, *n* (%)			
IgG	52 (60·5)	5 (35·7)	57 (57·0)
IgA	15 (17·4)	2 (14·3)	17 (17·0)
IgM	1 (1·2)	0 (0)	1 (1·0)
IgD	2 (2·3)	0 (0)	2 (2·0)
Light chain	13 (15·1)	6 (42·9)	19 (19·0)
ISS staging, *n* (%)†			
I	29 (33·7)	2 (14·3)	31 (31·0)
II	31 (36·0)	3 (21·4)	34 (34·0)
III	26 (30·2)	9 (64·3)	35 (35·0)
Time since initial diagnosis, median (range), years	0·08 (0·0–3·1)	2·22 (0·4–5·8)	0·09 (0·0–5·8)
Cytogenetic abnormality, *n* (%)	(n = 82)	(n = 14)	(n = 96)
Standard risk	52 (63·4)	10 (71·4)	62 (64·6)
High risk‡	30 (36·6)	4 (28·6)	34 (35·4)
del17p§	6 (7·3)	0 (0)	6 (6·3)
t(4;14)	19 (23·2)	3 (21·4)	22 (22·9)
t(14;16)	26 (31·7)	3 (21·4)	29 (30·2)

ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence *in situ* hybridisation; Ig, immunoglobulin; ISS, International Staging System; NDMM, newly diagnosed multiple myeloma; RMM, relapsed multiple myeloma.

*Percentages may not add up to 100% due to rounding.

†ISS staging was captured in the case report form.

‡Any of del(17p), t(4:14) or t(14:16).

§del(17p) was detected by a *TP53* FISH probe.

cycles in patients with RMM. Patients with NDMM received a median (range) of 6·0 (2–8) treatment cycles during induction *versus* a median (range) of 7·5 (3–8) induction cycles for patients with RMM. The median cumulative dose of daratumumab and bortezomib received during induction Cycles 1–4 was 192·0 mg/kg (192·0 mg/kg expected per protocol) and 18·0 mg/m^2 (18·0 mg/m^2 expected per protocol), respectively, and was similar in the newly diagnosed and RMM cohorts. For cyclophosphamide exposure, 6 (6·0%) patients had a reduced dose of the drug during Cycles 1–4. Among all treated patients, the median (range) infusion time for daratumumab was 4·5 (1–25) h on Cycle 1 Day 1 and 3·8 (3–5) h on Cycle 1 Day 2. Median (range) infusion durations were similar (3·5 [0–6] h) for subsequent infusions.

Efficacy

Analyses of primary and secondary efficacy variables were based on the response-evaluable population, which included patients with measurable disease at baseline or screening who received ≥1 dose of study treatment and had ≥1 post-baseline disease assessment. In the 86 response-evaluable patients with NDMM, the rate of CR + VGPR (primary endpoint) after 4 cycles of induction therapy was 44·2% (95% CI, 33·5–55·3%), including 4 [4·7% (95% CI, 1·3–11·5%)] patients who achieved CR. The ORR after 4 cycles of induction therapy was 79·1% (95% CI, 69·0–87·1%; Fig 2A). At the end of induction, the ORR was 81·4% (95% CI, 71·6–89·0%), with 48 [55·8% (95% CI, 44·7–66·5%)] patients achieving

Table II. Patient disposition.

	NDMM (n = 87)	RMM (n = 14)	Total (N = 101)
Treatment discontinuation, n (%)	10 (11·5)	4 (28·6)	14 (13·9)
Other	4 (4·6)*	0 (0)	4 (4·0)*
Adverse event	2 (2·3)	0 (0)	2 (2·0)
Progressive disease	2 (2·3)	3 (21·4)	5 (5·0)
Patient refused further study treatment	1 (1·1)	0 (0)	1 (1·0)
Withdrawal by patient	1 (1·1)	0 (0)	1 (1·0)
Death	0 (0)	1 (7·1)†	1 (1·0)

In the NDMM cohort, 1 patient discontinued prior to receiving study treatment.
AE, adverse event; NDMM, newly diagnosed multiple myeloma; PR, partial response; RMM, relapsed multiple myeloma.
*"Other" included lack of response to study regimen (n = 1), PR not achieved after 6 cycles (n = 1), investigator decision (patient did not respond to study treatment; n = 1), and patient not treated (n = 1).
†Patient permanently discontinued all study treatment due to the AE of sudden death.

VGPR + CR and 8 [9·3% (95% CI, 4·1–17·5%)] patients achieving CR. Responses continued to deepen in patients who had entered the maintenance phase (data not shown).

In patients with NDMM, median time to PR or better was 1·0 (95% CI, 1·0–1·0) month and median time to VGPR or better was 4·6 (95% CI, 2·8–6·4) months. Median duration of response was not reached. Among enrolled patients with NDMM (n = 87), median PFS was not reached [95% CI, not evaluable (NE)-NE], and the 12-month PFS rate was 87·0% (95% CI, 57·1–96·6%; Fig 2B). At the time of clinical cut-off, the 12-month OS rate was 98·8% (95% CI, 92·0–99·8%) for patients with NDMM.

Among patients in the small cohort with RMM (n = 14), the rate of CR + VGPR (primary endpoint) after 4 cycles of induction therapy was 57·1% (95% CI, 28·9–82·3%). The ORR after 4 induction cycles was 71·4% (95% CI, 41·9–91·6%), including 2 [14·3% (95% CI, 1·8–42·8%)] patients with CR. At the end of induction, the ORR was 71·4% (95% CI, 41·9–91·6%), with 9 [64·3% (95% CI, 35·1–87·2%)] patients achieving VGPR + CR and 3 [21·4% (95% CI, 4·7–50·8%)] patients achieving CR. Median time to PR or better was 1·0 (95% CI, 0·9–NE) month, median time to VGPR or better was 1·8 (95% CI, 1·0–NE) months, and median duration of response was 12·4 (95% CI, 3·7–12·4) months. Median PFS was 13·3 (95% CI, 6·8–13·3) months and the 12-month PFS rate was 66·2% (95% CI, 32·4–86·0%). At the time of clinical cut-off, the 12-month OS rate was 54·5% (95% CI, 8·6–86·1%).

Safety

Among patients with NDMM, the most frequent any-grade TEAE was fatigue (61·6%), and the most frequent grade 3/4 TEAE was neutropenia (11·6%; Table III). Serious TEAEs occurred in 19 (22·1%) patients with NDMM, and the most frequent (≥2 patients) included atrial fibrillation (3·5%),

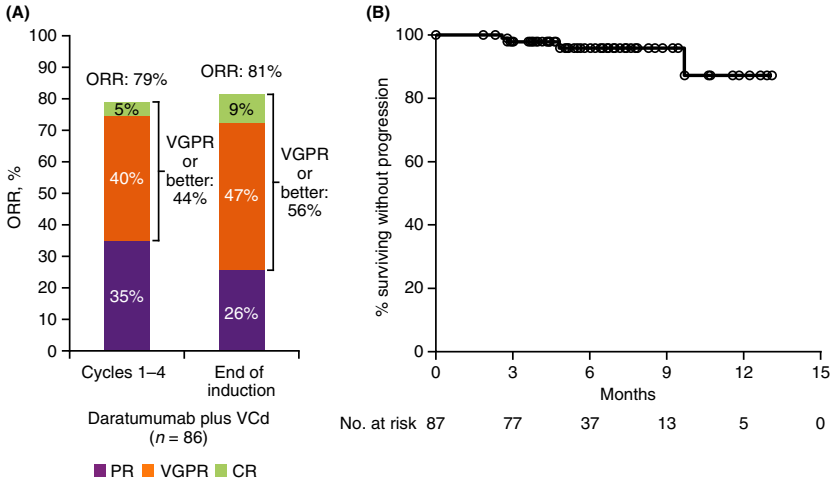

Fig 2. ORR in Cycles 1–4 and end of induction (A) and progression-free survival (B) in newly diagnosed multiple myeloma patients treated with daratumumab plus VCd. Responses may not add up to the total response rates due to rounding. CR, complete response; ORR, overall response rate; PR, partial response; VCd, bortezomib, cyclophosphamide and dexamethasone; VGPR, very good partial response.

Table III. Most frequent any grade (>25%) and grade 3/4 (≥10%) TEAEs.

	NDMM (n = 86)		RMM (n = 14)		Total (N = 100)	
Event, n (%)	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Total TEAEs	86 (100·0)	48 (55·8)	14 (100·0)	8 (57·1)	100 (100·0)	56 (56·0)
Fatigue	53 (61·6)	6 (7·0)	6 (42·9)	0 (0)	59 (59·0)	6 (6·0)
Nausea	38 (44·2)	1 (1·2)	3 (21·4)	0 (0)	41 (41·0)	1 (1·0)
Diarrhoea	31 (36·0)	3 (3·5)	6 (42·9)	1 (7·1)	37 (37·0)	4 (4·0)
Insomnia	26 (30·2)	0 (0)	2 (14·3)	0 (0)	28 (28·0)	0 (0)
Cough	25 (29·1)	0 (0)	5 (35·7)	0 (0)	30 (30·0)	0 (0)
Constipation	24 (27·9)	0 (0)	0 (0)	0 (0)	24 (24·0)	0 (0)
Vomiting	22 (25·6)	2 (2·3)	5 (35·7)	0 (0)	27 (27·0)	2 (2·0)
Upper respiratory tract infection	18 (20·9)	0 (0)	6 (42·9)	0 (0)	24 (24·0)	0 (0)
Back pain	16 (18·6)	0 (0)	4 (28·6)	1 (7·1)	20 (20·0)	1 (1·0)
Neutropenia	11 (12·8)	10 (11·6)	3 (21·4)	3 (21·4)	14 (14·0)	13 (13·0)
Myalgia	9 (10·5)	0 (0)	5 (35·7)	0 (0)	14 (14·0)	0 (0)
Viral upper respiratory tract infection	7 (8·1)	1 (1·2)	5 (35·7)	0 (0)	12 (12·0)	1 (1·0)

NDMM, newly diagnosed multiple myeloma; RMM, relapsed multiple myeloma; TEAE, treatment-emergent adverse event.

Table IV. Most frequent (>3 patients) IRs.

	NDMM (n = 86)		RMM (n = 14)		Total (N = 100)	
Event, n (%)	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Total IRs	46 (53·5)	2 (2·3)	8 (57·1)	0 (0)	54 (54·0)	2 (2·0)
Chills	12 (14·0)	0 (0)	1 (7·1)	0 (0)	13 (13·0)	0 (0)
Cough	6 (7·0)	0 (0)	3 (21·4)	0 (0)	9 (9·0)	0 (0)
Dyspnoea	7 (8·1)	0 (0)	1 (7·1)	0 (0)	8 (8·0)	0 (0)
Pruritus	7 (8·1)	0 (0)	0 (0)	0 (0)	7 (7·0)	0 (0)
Nausea	7 (8·1)	0 (0)	0 (0)	0 (0)	7 (7·0)	0 (0)
Flushing	5 (5·8)	0 (0)	0 (0)	0 (0)	5 (5·0)	0 (0)
Vomiting	4 (4·7)	0 (0)	0 (0)	0 (0)	4 (4·0)	0 (0)
Pyrexia	4 (4·7)	0 (0)	0 (0)	0 (0)	4 (4·0)	0 (0)
Hyperhidrosis	3 (3·5)	0 (0)	1 (7·1)	0 (0)	4 (4·0)	0 (0)

IR, infusion reaction; NDMM, newly diagnosed multiple myeloma; RMM, relapsed multiple myeloma.

pulmonary embolism (2·3%), bacteraemia (2·3%) and mental status changes (2·3%). Three patients experienced a serious TEAE related to daratumumab, including bacteraemia, viral upper respiratory tract infection and vomiting (1 each).

Among patients with RMM, the most frequent TEAEs included fatigue, diarrhoea and upper respiratory tract infection (42·9% each), whereas the most frequent grade 3/4 TEAE was neutropenia (21·4%). Serious TEAEs occurred in 2 patients with RMM, which were not considered to be daratumumab-related.

A total of 54·0% of patients experienced IRs (Table IV). In the combined study population, IRs occurred in 49 (49·0%) patients on Cycle 1 Day 1 and in 4 (4·0%) patients on Cycle 1 Day 2. The most frequent IRs (>5%) were chills (13·0%), cough (9·0%), dyspnoea (8·0%), pruritus (7·0%) and nausea (7·0%). Less frequent events, including hypertension, hypersensitivity, chest discomfort, fatigue, nasal congestion, rash and decreased oxygen saturation, were each reported in 3 (3·0%) patients. IRs were generally mild; in all patients only 2 (2·0%), both with NDMM, developed grade 3 IRs (hypertension and anaphylactic reaction). No grade 4 or 5 IRs were reported, and no patients discontinued daratumumab treatment due to an IR.

A total of 3 (3·0%) patients experienced TEAEs that led to permanent discontinuation of all study treatment. Among the 3 patients who permanently discontinued treatment, 2 patients died due to AEs unrelated to study treatment (nephrotic syndrome and sudden death) and 1 patient experienced worsening of atrial fibrillation. Two additional patients, both with RMM, died due to progressive disease.

Stem cell transplant

At the time of clinical cut-off, 28 (32·6%) patients with NDMM had undergone ASCT. In the 26 patients for whom data were available, 25 received a transplant conditioning

regimen of full dose melphalan 200 mg/m^2, and 1 received a reduced dose of melphalan 140 mg/m^2. The median number of CD34$^+$ cells collected from eligible patients in whom stem cell data were available was 5·0 (range: 2–13) × 10^6 cells/kg.

Discussion

These results demonstrate that D-VCd can be safely administered and induces VGPR or better in the community setting, providing an IMiD-sparing regimen for patients with NDMM. Additionally, this study indicates that dividing the first daratumumab dose over 2 days is feasible, results in a reduced duration of the first infusion without an increase in IRs, and facilitates administration of the first weekly daratumumab dose in the community setting.

After 4 cycles of induction therapy, CR + VGPR was achieved in 44·2% (4·7% CR) of patients with NDMM, which increased to 55·8% (9·3% CR) at the end of induction, demonstrating that longer treatment with daratumumab provides additional benefit by increasing the depth of response. This finding is consistent with other clinical studies of daratumumab (Dimopoulos *et al*, 2016, 2017; Palumbo *et al*, 2016; Chari *et al*, 2017a,b; Facon *et al*, 2017; Spencer *et al*, 2017), in which responses deepened with longer treatment duration. Similar response rates were observed in the small number of patients with RMM enrolled in LYRA, but additional patients are needed to evaluate the efficacy and safety of D-VCd in this population.

The rate of CR + VGPR was less than the hypothesized rate of 60% for patients with NDMM. The estimated 60% rate was based on a small study conducted in 33 transplant-eligible patients at 2 academic centres (Reeder *et al*, 2009), while our study enrolled patients with transplant-eligible and ineligible MM, mostly at community-based sites. Indeed, the LYRA clinical trial is the second largest study of VCd, and the only larger study reported a 37% rate of VGPR or better (Mai *et al*, 2015). Furthermore, the lack of a consensus VCd regimen makes cross-study comparisons challenging. We utilized the regimen of Jimenez-Zepeda *et al* (2015) because this regimen administered weekly bortezomib using a schedule (Days 1, 8 and 15 every 28 days) utilized in routine clinical practice by most of the centres participating in this study. The weekly scheduling was also more convenient and less burdensome for the community-based patients. However, this regimen uses a lower dose intensity of bortezomib and dexamethasone than older VCd regimens, and it is unknown whether the relatively low bortezomib and dexamethasone dose intensities negatively impacted the rate of VGPR or better, especially after only 4 treatment cycles.

The importance of chemotherapy dose intensity in treatment with VCd was suggested by the phase 2 EVOLUTION study. The rate of VGPR or better was 13% after 4 cycles of induction therapy for patients who received cyclophosphamide 500 mg/m^2 on Days 1 and 8 of each 21-day cycle (Kumar *et al*, 2012b). An amendment that added a Day 15 dose of cyclophosphamide resulted in a 41% rate of VGPR or better, suggesting that modifying the VCd regimen to increase chemotherapy dose intensity may improve efficacy (Kumar *et al*, 2012b). In line with these findings, an Intergroupe Francophone du Myelome study administered bortezomib 1·3 mg/m^2 on Days 1, 4, 8 and 11; cyclophosphamide 500 mg/m^2 on Days 1, 8 and 15; and dexamethasone 40 mg on Days 1–4 and 9–12 of each 21-day cycle to 169 patients with NDMM. The ORR was 83·4%, including a 56·2% rate of VGPR or better, after 4 induction cycles (Moreau *et al*, 2016). These findings indicate that the lower cyclophosphamide, bortezomib and dexamethasone doses administered in the LYRA study may have adversely impacted the response rates.

Differences in disease characteristics in this study, *versus* other VCd studies and the phase 3 ALCYONE study of D-VMP in NDMM, may have also affected response rates. For example, we enrolled many more newly diagnosed patients with high cytogenetic risk (36·6%) *versus* only 16·9% of patients in ALCYONE (Mateos *et al*, 2018). Conversely, ECOG performance status scores were better than for patients in ALCYONE. Despite the observed differences in response rates, the 12-month PFS rates in the LYRA and ALCYONE studies were comparable (87·0% vs. 86·7%, respectively). This finding indicates that early response may not directly correlate with PFS. As the depth of response with daratumumab improved over time, early response to treatment may not be as important as best response after completion of induction or maintenance therapy. Follow-up for efficacy is ongoing.

The patient demographics and disease characteristics were consistent with those observed in NDMM patients in a community setting (Jagannath *et al*, 2018). However, the conduct of this study in a community setting may have impacted the observed response rates. For example, in a study conducted at a single academic centre evaluating 224 patients with previously untreated chronic lymphocytic leukaemia (CLL), a fludarabine, cyclophosphamide and rituximab (FCR) regimen demonstrated CR and ORR rates of 70% and 95%, respectively (Keating *et al*, 2005). However, a study of FCR in 86 evaluable, previously untreated or minimally treated CLL patients in a community setting reported CR and ORR rates of 14% and 59%, respectively (Reynolds *et al*, 2012). The authors concluded that the use of an alternative FCR regimen, differences in patient characteristics compared with academic studies, and challenges related to obtaining all assessments needed for full evaluations contributed to the lower than expected response rates (Reynolds *et al*, 2012). Our study highlights the need to evaluate treatment regimens in community patients to better understand the true efficacy and safety in a real-world setting.

This study demonstrates that daratumumab can be safely combined with VCd in the community setting. Early findings from prespecified interim safety analyses of this study warranted its continuation as planned, and the tolerability

profile was consistent with previous reports of VCd and daratumumab. TEAEs were largely manageable, with only 3 patients experiencing a TEAE resulting in permanent discontinuation of all study treatment. While the incidence of TEAEs was largely similar between patient groups, those with RMM had a numerically higher rate of infections and neutropenia *versus* patients with NDMM.

In clinical trials of daratumumab (1166 patients) the incidence of IRs was 40%, 2% and 4% with the first, second and subsequent infusions, respectively (http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX-pi.pdf). Consistent with these findings, the overall IR rate in the present study was 54·0%, and events were predominantly mild (no grade ≥4 IRs) and occurred largely during the first infusion (49·0%). While the IR rates with the first split-dose infusion of daratumumab were numerically higher (49·0%) in this study compared to the rates observed in a phase 1 study of daratumumab-containing regimens [MMY1001; daratumumab plus carfilzomib, lenalidomide and dexamethasone (23%) or daratumumab plus carfilzomib and dexamethasone (36%)], further investigation is warranted to determine if differences in sample size or patient characteristics impacted the rate of IRs (Chari *et al*, 2017b, 2018). Early evidence in clinical trials suggests that splitting the first dose of daratumumab over 2 days may improve convenience for patients and health care providers by reducing infusion duration without affecting the pharmacokinetic profile of daratumumab (Chari *et al*, 2017b, 2018; Lonial *et al*, 2017). Here, splitting the first dose of daratumumab reduced the infusion time on Cycle 1 Day 1 to 4·5 h compared with 7·0 h for a full dose (http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX-pi.pdf), supporting the feasibility of split-first dosing of daratumumab in patients with MM. As the duration of the daratumumab first full infusion may be prolonged by the addition of pre- and post-infusion medications, patient monitoring and mitigation of IRs as needed, the ability to split the first dose of daratumumab over 2 days provides patients and health care providers with a safe and feasible option to reduce the duration of the first daratumumab infusion.

Adding daratumumab to VCd resulted in no adverse impact on stem cell collection or engraftment, confirming that daratumumab combination therapy is feasible as part of induction therapy for transplant-eligible NDMM patients. These findings were consistent with those observed with daratumumab in combination with carfilzomib, lenalidomide and dexamethasone (EQUULEUS study) in NDMM (Chari *et al*, 2017b), further supporting the use of daratumumab in induction regimens. In the phase 3 CASSIOPEIA study (NCT02541383), daratumumab in combination with bortezomib, thalidomide and dexamethasone is under investigation as induction and consolidation therapy in patients with transplant-eligible NDMM.

In summary, D-VCd induces very good partial responses in many patients and is a tolerable frontline regimen in NDMM patients, regardless of transplant eligibility. The regimen provides an alternative to using IMiD-based treatments as initial interventions when patient compliance with daily oral therapy may be a factor. Depth of response improved with additional cycles of therapy, indicating that longer treatment with daratumumab provides additional clinical benefit. Splitting the first daratumumab dose over 2 days was feasible, did not increase IRs, and reduced the time of the first daratumumab infusion. While the LYRA study is limited by the relatively small sample size, the lack of a control or active-comparator arm, and a primary endpoint that, in retrospect, may not have allowed time for deeper responses to develop, these results demonstrate the feasibility of adding daratumumab to VCd. These data also warrant investigation of alternative VCd dosing regimens that may improve the depth of response in patients with MM.

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Authorship contributions

JB and RMR contributed to the accrual and treatment of patients, data acquisition, interpretation and analysis. TSL contributed to study concept and protocol development, oversight of study conduct, and data interpretation and analysis. SG contributed to oversight of study conduct and data interpretation and analysis. All authors drafted and reviewed the manuscript, approved the final version and decided to publish this report, and they all vouch for data accuracy and completeness.

Disclosure of conflicts of interest

HY served on advisory boards for Seattle Genetics and Celgene; served as a speaker for Janssen, AstraZeneca and Seattle Genetics; owns stock in Epizyme, Clovis Oncology and Puma Biotechnology. JM served on a speakers' bureau for Janssen. EF served on advisory boards for and received honoraria from Amgen, Cardinal Health, Celgene and Kite. WIB served on speakers' bureaus for Janssen and Takeda and served on advisory boards for Janssen. JMB served as a consultant for Celgene, Bayer, Genentech, Gilead, AbbVie, Seattle Genetics and Tempus Labs, and served on a speakers' bureau for Seattle Genetics. MN received speaker fees or honoraria from Janssen and Celgene and served as a consultant for

Celgene. DS is a member on an entity's board of directors or advisory committee for Bayer and served as a consultant for Bayer. SG, YL, KQ, JU, MQ and TSL are employees of Janssen. RMR served as a consultant for Amgen, Boehringer Ingelheim, Celgene, EMD Serono, Sandoz and Takeda, and holds equity in McKesson.

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