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Subcutaneous daratumumab plus standard treatment regimens in patients with multiple myeloma across lines of therapy (PLEIADES): an open-label Phase II study

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Summary

Daratumumab is a CD38-targeting monoclonal antibody approved for intravenous (IV) infusion for multiple myeloma (MM). We describe the Phase II PLEIADES study of a subcutaneous formulation of daratumumab (DARA SC) in combination with standard-of-care regimens: DARA SC plus bortezomib/lenalidomide/dexamethasone (D-VRd) for transplant-eligible newly diagnosed MM (NDMM); DARA SC plus bortezomib/melphalan/prednisone (D-VMP) for transplant-ineligible NDMM; and DARA SC plus lenalidomide/dexamethasone (D-Rd) for relapsed/refractory MM. In total, 199 patients were treated (D-VRd, $n = 67$; D-VMP, $n = 67$; D-Rd, $n = 65$). The primary endpoints were met for all cohorts: the ≥very good partial response (VGPR) rate after four 21-day induction cycles for D-VRd was 71·6% [90% confidence interval (CI) 61·2–80·6%], and the overall response rates (ORRs) for D-VMP and D-Rd were 88·1% (90% CI 79·5–93·9%) and 90·8% (90% CI 82·6–95·9%). With longer median follow-up for D-VMP and D-Rd (14·3 and 14·7 months respectively), responses deepened (ORR: 89·6%, 93·8%; ≥VGPR: 77·6%, 78·5%), and minimal residual disease –negativity (10^{-5}) rates were 16·4% and 15·4%. Infusion-related reactions across all cohorts were infrequent (≤9·0%) and mild. The median DARA SC administration time was 5 min. DARA SC with standard-of-care regimens demonstrated comparable clinical activity to DARA IV–containing regimens, with low infusion-related reaction rates and reduced administration time.

Keywords: subcutaneous, daratumumab, NDMM, RRMM, combination therapy.

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Introduction

Daratumumab is a human immunoglobulin G kappa (IgGκ) monoclonal antibody targeting CD38 with a direct on-tumour[1-4] and immunomodulatory mechanism of action.[5–7] Daratumumab 16 mg/kg is approved for intravenous (IV) infusion in combination with standard-of-care regimens for patients with newly diagnosed multiple myeloma (NDMM) and relapsed or refractory MM (RRMM), and as monotherapy in patients with heavily pre-treated RRMM.[8]

Although daratumumab IV (DARA IV) has consistently shown efficacy and tolerability in NDMM and RRMM, the median duration of the first, second and subsequent infusions in clinical studies were approximately 7, 4 and 3 h respectively.[8] To reduce patient and provider burden without compromising safety or efficacy, a subcutaneous co-formulation of daratumumab (DARA SC) with recombinant human hyaluronidase PH20 (rHuPH20, 2000 U/ml; ENHANZE® drug delivery technology, Halozyme, Inc., San Diego, CA, USA) in a total volume of 15 ml was developed.[9,10] rHuPH20 increases subcutaneous tissue permeability and facilitates drug dispersion and absorption, enabling subcutaneous administration of large volumes.[11,12]

The Phase III COLUMBA study (ClinicalTrials.gov Identifier: NCT03277105) demonstrated that DARA SC (1800 mg flat dose) and DARA IV (16 mg/kg) monotherapy for RRMM have comparable efficacy, pharmacokinetics (PK) and safety.[13,14] In the primary analysis of COLUMBA, DARA SC monotherapy was non-inferior to DARA IV monotherapy in terms of the pre-defined non-inferiority criteria [overall response rate (ORR) and DARA maximum trough concentration (C_{trough})].[14] With longer median follow-up, responses to DARA SC monotherapy deepened; DARA SC had a similar safety profile compared with DARA IV, with a statistically significant reduction in infusion-related reaction (IRR) rates (12·7% vs. 34·5%; $P < 0·0001$). DARA SC also had a reduced treatment burden associated with a considerably shorter median administration duration of 5 min. According to a modified version of the Cancer Therapy Satisfaction Questionnaire, patients who received DARA SC were more satisfied with their cancer treatment compared with patients who received DARA IV.[13]

In the present study, we report the primary endpoint analysis and updated efficacy and safety data from the Phase II PLEIADES (ClinicalTrials.gov Identifier: NCT03412565) study investigating DARA SC with bortezomib/lenalidomide/dexamethasone (VRd) and bortezomib/melphalan/prednisone (VMP) for patients with NDMM; and DARA SC with lenalidomide/dexamethasone (Rd) for patients with RRMM.

Methods

Study design and participants

PLEIADES is a multicentre, open-label, Phase II study to investigate the safety and efficacy of DARA SC with standard-of-care regimens, including VRd (D-VRd) in patients with NDMM who are eligible for autologous stem cell transplant (ASCT), VMP (D-VMP) in ASCT-ineligible patients with NDMM and Rd (D-Rd) in patients with RRMM who received ≥1 prior line of therapy (Fig 1).

Eligible patients (aged ≥18 years) had a diagnosis of MM according to International Myeloma Working Group criteria.[15] Additional eligibility criteria are listed in Data S1.

Patients in the D-VRd cohort had NDMM and were eligible for high-dose chemotherapy and ASCT. In the D-VMP cohort, patients had previously untreated NDMM and were ineligible for high-dose chemotherapy and ASCT due to age (≥65 years) or comorbid conditions that would make ASCT intolerable; patients with Grade ≥2 neuropathy or neuropathic pain were also ineligible. The D-Rd cohort consisted of patients with RRMM who had ≥1 prior line of therapy and a ≥partial response (PR) to ≥1 prior line of therapy; patients refractory or intolerant to lenalidomide were not eligible. Patients with any prior or concurrent exposure to anti-CD38 therapies were excluded.

All patients provided written informed consent according to local requirements and principles of the Declaration of Helsinki, International Conference on Harmonisation and Good Clinical Practice guidelines, applicable regulatory requirements and sponsor policy.

Procedures

For all cohorts, DARA SC (1800 mg flat dose in a 15 ml solution; Janssen Biotech, Inc., Horsham, PA, USA) was

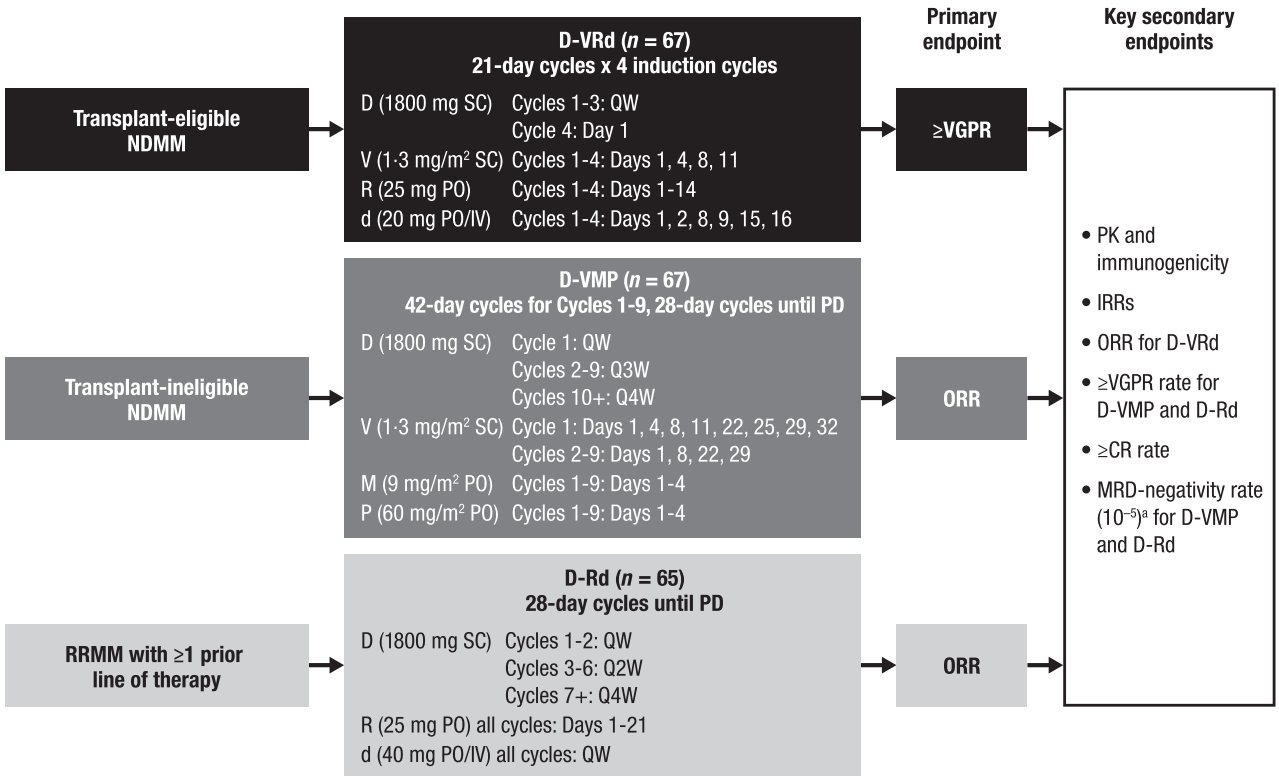

Fig 1. PLEIADES study design. [a]Assessed using next-generation sequencing. CR, complete response; D-Rd, daratumumab plus lenalidomide/dexamethasone; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; IRR, infusion-related reaction; IV, intravenous administration; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; PD, progressive disease; PK, pharmacokinetics; PO, oral administration; QW, weekly; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous administration; VGPR, very good partial response.

administered by manual injection over 3–5 min at left or right abdominal sites, alternating between individual doses. For patients receiving DARA SC and bortezomib on the same day, bortezomib was administered after DARA SC. Granulocyte-colony stimulating factor, bisphosphonates, denosumab, growth factors and antibiotic prophylaxis could be administered as supportive therapy. Dose regimen details are provided in Data S1.

Outcomes

Primary endpoints were the ≥very good PR (VGPR) rate after four induction cycles for the D-VRd cohort and ORR (≥PR) for the D-VMP and D-Rd cohorts. Secondary endpoints included ORR for the D-VRd cohort and rates of ≥VGPR and minimal residual disease (MRD) negativity for the D-VMP and D-Rd cohorts. Secondary endpoints for all cohorts included IRR rate, ≥complete response (CR) rate, PK (serum concentrations of daratumumab) and immunogenicity (anti-daratumumab and anti-rHPH20 antibodies). Response evaluation details are presented in Data S1.

Analyses of disposition, demographic and baseline disease characteristics, treatment exposure, safety and efficacy were conducted in the all-treated population, which included all patients who received ≥1 dose of study treatment. PK and immunogenicity analyses were conducted in PK- and immunogenicity-evaluable populations, which included patients who received ≥1 dose of study treatment and had ≥1 PK sample concentration value or immunogenicity sample after the first dose.

Statistical analysis

For the primary analysis, 60 patients in the D-VRd cohort were required to achieve a ≥93% power to test the null hypothesis that the ≥VGPR rate was ≤50% against the alternative hypothesis that the ≥VGPR rate was ≥70% (one-sided $\alpha = 0{\cdot}05$). In the D-VMP cohort, 60 patients were required to achieve a ≥98% power to test the null hypothesis that the ORR was ≤70% against the alternative hypothesis that the ORR was ≥90% (one-sided $\alpha = 0{\cdot}05$). In the D-Rd cohort, 60 patients were needed to achieve a ≥90% power to test the null hypothesis that the ORR was ≤75% against the alternative hypothesis that the ORR was ≥90% (one-sided $\alpha = 0{\cdot}05$).

The pre-specified analysis of primary endpoints occurred approximately 6 months after the 60th patient enrolled in the last treatment cohort (D-VRd, D-VMP or D-Rd). For

Table I. Baseline demographic and clinical characteristics.*

	D-VRd (n = 67) Transplant-eligible NDMM	D-VMP (n = 67) Transplant-ineligible NDMM	D-Rd (n = 65) RRMM with ≥1 prior line of therapy
Age, years			
Median (range)	59·0 (33–76)	75·0 (66–86)	69·0 (33–82)
18 to <65, *n* (%)	54 (80·6)	0 (0)	22 (33·8)
65 to <75, *n* (%)	12 (17·9)	33 (49·3)	29 (44·6)
≥75, *n* (%)	1 (1·5)	34 (50·7)	14 (21·5)
Male, *n* (%)	48 (71·6)	31 (46·3)	45 (69·2)
Body weight, kg, median (range)	77·0 (43–148)	66·0 (45–100)	80·6 (54–143)
Race, *n* (%)			
White	38 (56·7)	46 (68·7)	45 (69·2)
Black or African American	5 (7·5)	1 (1·5)	2 (3·1)
Asian	0 (0)	5 (7·5)	0 (0)
Not reported	24 (35·8)	15 (22·4)	18 (27·7)
ECOG PS score, *n* (%)			
0	40 (59·7)	25 (37·3)	36 (55·4)
1	26 (38·8)	38 (56·7)	29 (44·6)
2	1 (1·5)	4 (6·0)	0 (0)
ISS disease stage, *n* (%)†			
I	30 (44·8)	22 (32·8)	27 (41·5)
II	23 (34·3)	30 (44·8)	19 (29·2)
III	14 (20·9)	15 (22·4)	18 (27·7)
Unknown	0	0	1 (1·5)
Time since initial diagnosis, median (range), months	1·2 (0·3–14·5)	1·2 (0·5–5·3)	35·0 (3·6–384·5)
Prior ASCT, *n* (%)	–	–	34 (52·3)
Prior lines of therapy, median (range)	–	–	1 (1–5)
Refractory to, *n* (%)			
Last prior line of therapy	–	–	20 (30·8)
PI and IMiD	–	–	1 (1·5)
Bone marrow % plasma cells, *n* (%)			
<10	0 (0)	3 (4·5)	15 (23·1)
10–30	29 (43·3)	31 (46·3)	28 (43·1)
>30	38 (56·7)	33 (49·3)	22 (33·8)
Cytogenetic risk profile‡			
n	53	41	31
Standard risk, *n* (%)	40 (75·5)	33 (80·5)	20 (64·5)
High risk, n (%)§	13 (24·5)	8 (19·5)	11 (35·5)
t(4;14)	9 (17·0)	2 (4·9)	6 (19·4)
t(14;16)	1 (1·9)	2 (4·9)	3 (9·7)
del17p	5 (9·4)	4 (9·8)	4 (12·9)

ASCT, autologous stem cell transplant; D-Rd, daratumumab subcutaneous plus lenalidomide/dexamethasone; D-VMP, daratumumab subcutaneous plus bortezomib/melphalan/prednisone; D-VRd, daratumumab subcutaneous plus bortezomib/lenalidomide/dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; ISS, International Staging System; NDMM, newly diagnosed multiple myeloma; PI, proteasome inhibitor; RRMM, relapsed or refractory multiple myeloma.

*All-treated population, defined as patients who received ≥1 dose of study treatment.

†Derived based on the combination of serum β_2-microglobulin and albumin at screening.

‡Based on fluorescence *in situ* hybridisation/karyotype testing conducted locally.

§High cytogenetic risk was defined as having ≥1 of t(4;14), t(14;16) or del17p abnormalities.

the primary analysis, response rates were provided with two-sided 90% exact confidence intervals (CIs). No formal comparisons between the treatment cohorts were performed; descriptive statistics were used to summarise data. For continuous parameters, the number of observations, mean, standard deviation (SD), median and range were used. For discrete parameters, frequency was summarised. For evaluation of the MRD-negativity rate and additional response endpoints, the two-sided 90% exact CIs were also provided.

Table II. Patient drug exposure with D-VRd, D-VMP and D-Rd therapies at clinical cut-off.*

	D-VRd (n = 67) Transplant-eligible NDMM	D-VMP (n = 67) Transplant-ineligible NDMM	D-Rd (n = 65) RRMM with ≥1 prior line of therapy
Number of treatment cycles, median (range)	4·0 (1–4)	12·0 (1–14)	16·0 (1–19)
Duration of treatment, months, median (range)	2·6 (0–4)	14·3 (0–17)	14·9 (0–17)
Median relative dose intensity, %			
Daratumumab	100·0	100·0	100·0
Bortezomib	97·9	95·2	–
Melphalan	–	97·5	–
Prednisone	–	98·4	–
Lenalidomide	100·0	–	81·9
Dexamethasone	100·0	–	65·6

D-Rd, daratumumab subcutaneous plus lenalidomide/dexamethasone; D-VMP, daratumumab subcutaneous plus bortezomib/melphalan/prednisone; D-VRd, daratumumab subcutaneous plus bortezomib/lenalidomide/dexamethasone; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed or refractory multiple myeloma.

*All-treated population, defined as patients who received ≥1 dose of study treatment.

Results

PLEIADES was initiated on 2 May 2018; 199 patients from 43 sites in eight countries were enrolled and treated in all cohorts (D-VRd, n = 67; D-VMP, n = 67; D-Rd, n = 65). Baseline demographics and clinical characteristics of patients in each cohort are presented in Table I. The median (range) age was 59 (33–76) years for D-VRd, 75 (66–86) years for D-VMP and 69 (33–82) years for D-Rd cohorts. The median time since diagnosis was 1·2 months for patients with NDMM in the D-VRd and D-VMP cohorts, and 35·0 months for patients with RRMM in the D-Rd cohort. Patients in the D-Rd cohort received a median (range) of 1 (1–5) prior lines of therapy. Most of the patients in all cohorts had baseline Eastern Cooperative Oncology performance status (ECOG PS) scores of ≤1. Among evaluable patients, 20·9%, 22·4% and 28·1% in the D-VRd, D-VMP and D-Rd cohorts had International Staging System disease Stage III, and 24·5%, 19·5% and 35·5% had high cytogenetic risk respectively.

All patients in the D-VRd cohort either completed four 21-day cycles of D-VRd induction [65 (97·0%) patients] or discontinued treatment [two (3·0%)]. In the D-VMP and D-Rd cohorts, 12 (17·9%) and 17 (26·2%) patients discontinued treatment, respectively, and the rest remain on study treatment. The most common reasons for treatment discontinuation with D-VRd, D-VMP and D-Rd, respectively, were progressive disease [one patient (1·5%), seven (10·4%) and 10 (15·4%)] and adverse events [AEs; one patient (1·5%), three (4·5%) and six (9·2%)]. Patients in the D-VRd, D-VMP and D-Rd cohorts had a median relative daratumumab dose intensity of 100% (Table II). The median (range) duration of treatment in the D-VRd, D-VMP and D-Rd arms was 2·6 (0–4), 14·3 (0–17) and 14·9 (0–17) months respectively. The median duration of treatment administration of DARA SC was 5 min during the first, second and all subsequent infusions across all cohorts.

The pre-specified primary analysis occurred on 4 March 2019, with a median follow-up of 3·9 months for D-VRd, 6·9 months for D-VMP and 7·1 months for D-Rd. At the primary analysis date, the primary endpoints were met for all cohorts. In the D-VRd cohort (n = 67), the ≥VGPR rate was 71·6% (90% CI 61·2–80·6); in the D-VMP (n = 67) and D-Rd (n = 65) cohorts, the ORR was 88·1% (90% CI 79·5–93·9) and 90·8% (90% CI 82·6–95·9; Table III).

At a subsequent clinical cut-off (11 November 2019), the median duration of follow-up in the D-VMP and D-Rd cohorts was 14·3 and 14·7 months respectively. With longer follow-up, the ORR in the D-VMP cohort was 89·6% (90% CI 81·3–95·0), the ≥VGPR rate was 77·6% (90% CI 67·6–85·7) and the ≥CR rate was 47·8% (90% CI 37·2–58·5; Table III). For D-Rd, the ORR was 93·8% (90% CI 86·5–97·9), the ≥VGPR rate was 78·5% (90% CI 68·4–86·5) and the ≥CR rate was 38·5% (90% CI 28·3–49·4). MRD negativity (10^{-5} threshold; clinical cut-off: 30 September 2019) assessed by next-generation sequencing was achieved by 11 patients (16·4%, 90% CI 9·4–25·7) in the D-VMP cohort and 10 patients (15·4%, 90% CI 8·6–24·7) in the D-Rd cohort.

No new safety concerns were identified with DARA SC combination therapies. At the subsequent clinical cut-off, all patients experienced ≥1 any-grade treatment-emergent AE (TEAE; Table IV). In the D-VRd, D-VMP and D-Rd cohorts, Grade 3/4 TEAEs occurred in 39 (58·2%), 50 (74·6%) and 58 (89·2%) patients respectively. The most common haematological Grade 3/4 TEAE was neutropenia in the D-VRd and D-Rd cohorts [19 (28·4%) and 32 (49·2%)] and thrombocytopenia in the D-VMP cohort [29 (43·3%)]. The most common (≥5%) non-haematological Grade 3/4 TEAEs were pneumonia [D-VRd, two (3·0%); D-VMP, five (7·5%); D-Rd, eight (12·3%)], hyperglycaemia [one (1·5%); one (1·5%); six (9·2%)], hypertension [one (1·5%); six (9·0%); one (1·5%)] and hypokalaemia [0 (0%); two (3·0%); four (6·2%)]. Serious TEAEs were reported in 19 (28·4%), 28

Table III. Summary of responses* with D-VRd therapy at primary analysis and D-VMP and D-Rd therapies at clinical cut-off.†

	D-VRd (n = 67)		D-VMP (n = 67)		D-Rd (n = 65)	
	Transplant-eligible NDMM		Transplant-ineligible NDMM		RRMM with ≥1 prior line of therapy	
	Primary analysis Median follow-up, 3·9 months		Clinical cut-off Median follow-up, 14·3 months		Clinical cut-off Median follow-up, 14·7 months	
Response	n (%)	90% CI	n (%)	90% CI	n (%)	90% CI
Overall response	65 (97·0)	90·9–99·5	60 (89·6)	81·3–95·0	61 (93·8)	86·5–97·9
Stringent CR	6 (9·0)	4·0–16·9	13 (19·4)	11·9–29·1	12 (18·5)	11·0–28·2
CR	5 (7·5)	3·0–15·1	19 (28·4)	19·4–38·8	13 (20·0)	12·3–29·9
VGPR	37 (55·2)	44·5–65·6	20 (29·9)	20·7–40·4	26 (40·0)	29·8–51·0
PR	17 (25·4)	16·9–35·6	8 (11·9)	6·1–20·5	10 (15·4)	8·6–24·7
MR‡	–	–	–	–	1 (1·5)	0·1–7·1
Stable disease	1 (1·5)	0·1–6·9	5 (7·5)	3·0–15·1	1 (1·5)	0·1–7·1
Response could not be evaluated	1 (1·5)	0·1–6·9	2 (3·0)	0·5–9·1	2 (3·1)	0·5–9·4
≥CR	11 (16·4)	9·5–25·7	32 (47·8)	37·2–58·5	25 (38·5)	28·3–49·4
≥VGPR	48 (71·6)	61·2–80·6	52 (77·6)	67·6–85·7	51 (78·5)	68·4–86·5

CI, confidence interval; CR, complete response; D-Rd, daratumumab subcutaneous plus lenalidomide/dexamethasone; D-VMP, daratumumab subcutaneous plus bortezomib/melphalan/prednisone; D-VRd, daratumumab subcutaneous plus bortezomib/lenalidomide/dexamethasone; MR, minimal response; NDMM, newly diagnosed multiple myeloma; PR, partial response; RRMM, relapsed or refractory multiple myeloma; VGPR, very good partial response.

*All-treated population, defined as patients who received ≥1 dose of study treatment.

†Clinical cut-off was 11 November 2019.

‡For previously untreated patients in the D-VRd and D-VMP cohorts, the MR category was not assigned/not applicable.

Table IV. Summary of TEAEs across D-VRd, D-VMP and D-Rd cohorts.*

TEAE, n (%)	D-VRd (n = 67) Transplant-eligible NDMM	D-VMP (n = 67) Transplant-ineligible NDMM	D-Rd (n = 65) RRMM with ≥1 prior line of therapy
Any-Grade	67 (100)	67 (100)	65 (100)
Grade 3/4	39 (58·2)	50 (74·6)	58 (89·2)
Grade 5	1 (1·5)	2 (3·0)	2 (3·1)
Serious	19 (28·4)	28 (41·8)	34 (52·3)
TEAEs leading to treatment discontinuation	1 (1·5)	3 (4·5)	5 (7·7)
Most common Grade 3/4 (≥5% in any cohort)			
Neutropenia	19 (28·4)	25 (37·3)	32 (49·2)
Lymphopenia	11 (16·4)	15 (22·4)	7 (10·8)
Thrombocytopenia	10 (14·9)	29 (43·3)	9 (13·8)
Leukopenia	5 (7·5)	4 (6·0)	6 (9·2)
Anaemia	3 (4·5)	12 (17·9)	6 (9·2)
Pneumonia	2 (3·0)	5 (7·5)	8 (12·3)
Hypertension	1 (1·5)	6 (9·0)	1 (1·5)
Hyperglycaemia	1 (1·5)	1 (1·5)	6 (9·2)
Hypokalaemia	0 (0·0)	2 (3·0)	4 (6·2)
Any-Grade IRR	6 (9·0)	6 (9·0)	3 (4·6)

D-Rd, daratumumab subcutaneous plus lenalidomide/dexamethasone; D-VMP, daratumumab subcutaneous plus bortezomib/melphalan/prednisone; D-VRd, daratumumab subcutaneous plus bortezomib/lenalidomide/dexamethasone; IRR, infusion-related reaction; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed or refractory multiple myeloma; TEAE, treatment-emergent adverse event.

*All-treated population, defined as patients who received ≥1 dose of study treatment.

(41·8%) and 34 (52·3%) patients in the D-VRd, D-VMP and D-Rd cohorts respectively. A low proportion of patients discontinued study treatment due to TEAEs [D-VRd, one (1·5%); D-VMP, three (4·5%); D-Rd, five (7·7%)] or had a TEAE leading to death [one (1·5%); two (3·0%); two (3·1%)].

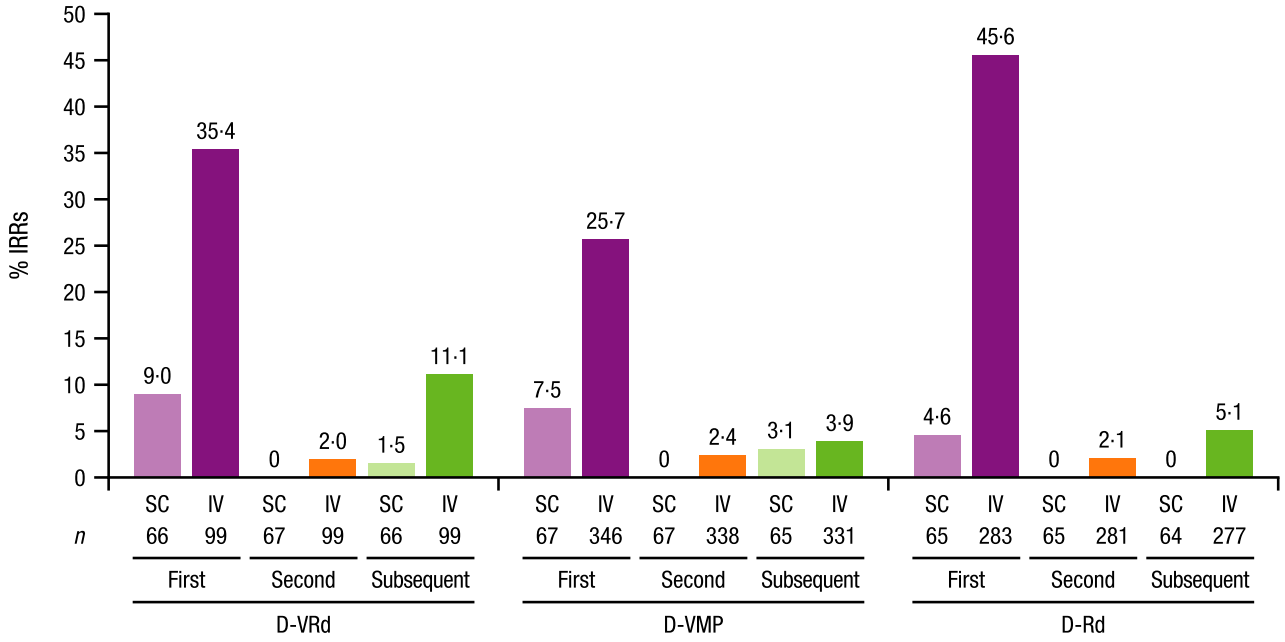

Fig 2. Infusion-related reactions in D-VRd, D-VMP and D-Rd in PLEIADES DARA SC cohorts *versus* studies using DARA IV. Proportions of IRRs at the first, second and subsequent daratumumab infusions are shown for the DARA SC cohorts from PLEIADES *versus* DARA IV cohorts from the GRIFFIN (D-VRd), ALCYONE (D-VMP) and POLLUX (D-Rd) studies. DARA IV, daratumumab administered intravenously; DARA SC, daratumumab administered subcutaneously; D-Rd, daratumumab plus lenalidomide/dexamethasone; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; IRR, infusion-related reaction.

Any-grade IRRs occurred in 7·5% (15/199) of patients across all cohorts (Table IV). Among patients who had ≥1 IRRs, most were reported with the first DARA SC administration [D-VRd, 9·0% (six of 67); D-VMP, 7·5% (five of 67); D-Rd, 4·6% (three of 65)]; no patients reported IRRs with the second infusion, and few patients reported IRRs with subsequent infusions [1·5% (one of 66); 3·1% (two of 65); 0% (none of 64); Fig 2]. Most IRRs were Grade 1/2; only one patient had a Grade 3 IRR (decreased oxygen saturation in the D-VRd cohort), and no patients had a Grade 4 IRR. The median time to onset of IRRs was 4·4, 6·9 and 5·5 h in the D-VRd, D-VMP and D-Rd cohorts respectively. Patients were not required to stay for observation beyond the first administration of DARA SC. Local injection-site reactions occurred in 7·5% (15/199) of patients across all cohorts (all Grade 1/2).

PK analyses of daratumumab were performed at the primary endpoint analysis date. On Cycle 1 Day 4 (C1D4; after the first DARA SC dose in all cohorts), maximum serum concentrations were comparable for D-VRd, D-VMP and D-Rd [mean (SD) 100·0 (48.5) μg/ml, 98·6 (51.6) μg/ml and 108·0 (49.9) μg/ml respectively]. As expected with SC administration, the highest daratumumab C_{trough} occurred at the end of weekly dosing [mean (SD) D-VRd, 635 (253) μg/ml pre-dose C4D1 (after nine weekly doses); D-VMP, 482 (217) μg/ml pre-dose C2D1 (after six weekly doses); D-Rd, 526 (226) μg/ml pre-dose C3D1 (after eight weekly doses)]. Due to its long half-life, daratumumab concentrations remained detectable at 8 weeks after the last dose. There was considerable overlap in exposure between body weight–based subgroups, with the highest exposure in patients ≤65 kg and the lowest exposure in patients >85 kg (Table SI). No patients developed treatment-emergent anti-daratumumab antibodies. Across cohorts, 11/187 (5·9%) patients developed treatment-emergent rHuPH20 antibodies; none were neutralising.

Discussion

In this Phase II study, the pre-specified primary endpoints for each cohort were met with DARA SC plus VRd, VMP or Rd. Continued clinical activity was demonstrated with longer follow-up; no new safety concerns were identified, and IRR rates were low (≤9% for any cohort). Importantly, the median duration of administration of DARA SC was only 5 min for all infusions across all cohorts.

The response rates observed for DARA SC with standard-of-care regimens were comparable to previous clinical studies of DARA IV combination therapies in generally similar patient populations.[16-18] Among transplant-eligible patients with NDMM, DARA SC plus VRd as induction therapy led to response rates in PLEIADES that were nearly identical to those for DARA IV plus VRd induction in the Phase II GRIFFIN study[16] (ClinicalTrials.gov Identifier: NCT02874742; ≥VGPR: 71·6% and 71·7%, respectively, ≥CR: 16·4% and 19·2%). The D-VMP cohort in PLEIADES

included patients with transplant-ineligible NDMM; responses were again similar to those from the Phase III ALCYONE study (ClinicalTrials.gov Identifier: NCT02195479) of DARA IV plus VMP (median follow-up, 16·5 months).[17] ORR rates were 89·6% and 90·9%, respectively, ≥VGPR: 77·6% and 71·1%; ≥CR: 47·8% and 42·6%. In the D-Rd cohort (patients with RRMM), response rates were comparable to those in the Phase III POLLUX study (ClinicalTrials.gov Identifier: NCT02076009) of DARA IV plus Rd (median follow-up, 13·5 months).[18] ORR rates were 93·8% and 92·9%, ≥VGPR: 78·5% and 75·8%; ≥CR: 38·5% and 43·1%. Comparable response rates were supported by consistent relative dose intensities of daratumumab between DARA SC combination therapies in PLEIADES and those previously reported for DARA IV.[17-19]

While care should be taken with direct comparisons of clinical trials, these data suggest equivalent clinical activity of DARA SC and DARA IV combination therapies with standard-of-care regimens, including an immunomodulatory drug, proteasome inhibitor and/or alkylating agent. Equivalence is also supported by the Phase III COLUMBA study demonstrating non-inferiority of DARA SC monotherapy compared with DARA IV monotherapy.[14] The ongoing Phase III PERSEUS (ClinicalTrials.gov NCT03710603) study of DARA SC plus VRd *versus* VRd in transplant-eligible NDMM will assess response and long-term outcomes before and after ASCT.

The MRD-negativity (10^{-5}) rates for the DARA SC cohorts in PLEIADES were generally comparable with previous data from the corresponding DARA IV regimens. DARA SC plus VMP was associated with 16·4% MRD negativity compared with 22·3% for D-VMP in ALCYONE,[17] and DARA SC plus Rd was associated with 15·4% MRD negativity compared with 26·2% for D-Rd in POLLUX.[20] The slight variations seen in the MRD-negativity rates between the DARA IV studies and PLEIADES DARA SC cohorts should be considered within the context that the DARA IV studies had fewer patients with high-risk cytogenetics, and had longer follow-up, allowing clinical responses to daratumumab (including MRD negativity) to deepen over time. MRD negativity was not assessed in the DARA SC plus VRd cohort because patients only received four 21-day cycles of induction therapy before proceeding to ASCT, which was performed off study. Due to the short duration of the study and follow-up, the study protocol did not require patients in the VRd cohort to undergo an invasive bone marrow procedure for MRD analysis. Overall, the efficacy of DARA SC combination therapies in PLEIADES was similar to data from previous studies of DARA IV combination therapies, which have consistently shown superior outcomes for patients with MM across lines of therapy.

The addition of DARA SC to all three backbone regimens was generally well tolerated, with clinically manageable side-effects consistent with known safety profiles of daratumumab and components of each combination therapy.[16-18] No new safety concerns were identified; however, injection-site reactions did occur infrequently. Grade 3/4 neutropenia was observed in patients in the PLEIADES cohorts at rates comparable to those of DARA IV studies of similar patient populations and treatment regimens.[16-18]

Any-grade IRRs rates were notably lower among all DARA SC cohorts (≤9·0%) compared with previously published data from corresponding DARA IV regimens in similar patient populations (D-VRd, 42%; D-VMP, 27·7%; D-Rd, 47·7%).[16–18] Reduced IRR rates for DARA SC cohorts in PLEIADES *versus* DARA IV is consistent with lower IRR rates seen for DARA SC monotherapy in COLUMBA: DARA SC, 12·7% *versus* DARA IV, 34·5% ($P < 0·0001$).[13] In PLEIADES, no IRRs resulted in interruption during the injection and no patients discontinued treatment due to an IRR. Thus, the DARA SC combination therapies in PLEIADES exhibit similar safety profiles as corresponding DARA IV regimens, with a reduced duration of treatment administration and low incidence of IRRs.

The PK profiles of each DARA SC cohort showed that DARA serum concentrations remained above the previously recommended target saturation for DARA IV of 274 μg/ml.[21] The 90% maximal effect of DARA IV monotherapy on ORR was achieved at this target saturation, above which limited additional benefit to ORR could be obtained. Consistent with monotherapy results by body-weight subgroups,[14] the lower body-weight subgroup (≤65 kg) had higher $C_{troughs}$ and the higher body-weight subgroup (>85 kg) had lower $C_{troughs}$. Given the large therapeutic window, a flat dose-response relationship for safety, and target saturation–driven efficacy, any differences in mean exposure between body-weight subgroups are unlikely to be clinically meaningful. In support of this postulate, the mean C_{trough} at the end of weekly dosing was >274 μg/ml for all body-weight subgroups (≤65 kg, >65 kg to 85 kg and >85 kg) in all treatment cohorts. With the exception of maximum peak concentration, which was expectedly lower with DARA SC, the PK profile of daratumumab for each treatment cohort was consistent with historical data for the respective treatments and with DARA SC in other studies. At the end of weekly dosing, the mean (SD) peak C_{trough} was similar between DARA SC cohorts and other DARA IV regimens [D-VMP: 482 (217) μg/ml in the present study vs. 588 (161) μg/ml in MMY1001; D-Rd: 526 (226) μg/ml vs. 500 (85.9) μg/ml in GEN503 and 608 (232) μg/ml in MMY3003; data on file]. Given the inter-patient and inter-study variability, we considered these values comparable. No patients developed anti-daratumumab antibodies, which is consistent with that reported for DARA IV,[22,23] immunogenicity to rHuPH20 was consistent with that reported for the enzyme.[24]

In conclusion, the addition of DARA SC to VRd, VMP and Rd is efficacious, generally safe and well tolerated, and had a lower IRR incidence compared to DARA IV combination therapies. DARA SC combination therapy has a favourable benefit/risk profile, while allowing considerably shorter

administration time compared with DARA IV, thus reducing treatment burden for patients and providers. These results support the use of DARA SC 1800 mg flat dose in combination with standard treatment regimens across lines of therapy in MM.

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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.

Conflict of interest

Ajai Chari served as a consultant for, was a member of a board of directors or advisory committees for, and received research funding from Janssen, Celgene, Novartis, Amgen, Bristol-Myers Squibb, Pharmacyclics, Karyopharm, Sanofi, Seattle Genetics, OncoPeptides and Millennium/Takeda. Paula Rodriguez-Otero served as a consultant for and received honoraria from Celgene/Bristol-Myers Squibb, Janssen, Amgen, Kite, Sanofi, Abbvie, OncoPeptides, and GlaxoSmithKline. Helen McCarthy received honoraria and an education grant to attend meetings from Janssen. Kenshi Suzuki received honoraria from Takeda, Janssen and Celgene; received research funding from Ono; and received honoraria and research funding from Bristol-Myers Squibb. Vania Hungria served as a consultant for, received honoraria from, was a member of a board of directors or advisory committees for, and served on a speakers bureau for Amgen, Celgene, Janssen and Takeda; served as a consultant and was a member of a board of directors or advisory committees for AbbVie; and served as a consultant for, received honoraria from, and served on a speakers bureau for Bristol-Myers Squibb. Anna Sureda Balari received honoraria from Bristol-Myers Squibb, Roche, Sanofi, Gilead and Novartis; served as a consultant for, received honoraria from and served on a speakers bureau for Takeda; received honoraria from, was a member of a board of directors or advisory committees for and received travel support from Janssen; received honoraria from and was a member of a board of directors or advisory committees for Celgene; and was a member of a board of directors or advisory committees for Amgen. Aurore Perrot received honoraria from Janssen and reimbursement for travel and lectures from Takeda. Cyrille Hulin served as a consultant for and received honoraria from Celgene and received honoraria from Janssen, AbbVie, Celgene and Amgen. Shinsuke Iida received honoraria and research funding from Janssen. Vladimir Maisnar served as a consultant for and received honoraria from Janssen, Amgen, Celgene, Takeda and Bristol-Myers Squibb. Dolly A. Parasrampuria, Tara Masterson, Michele Kosh, Shiyi Yang, Maria Delioukina and Robin Carson are employed by and own equity in Janssen. Ming Qi is employed by Janssen. Hila Magen, Lionel Karlin, Ludek Pour and Cyrille Touzeau had no conflicts of interest to disclose. Medical writing and editorial support were provided by J. Matthew Kuczmarski, PhD, of MedErgy, and were funded by Janssen Global Services, LLC.

Author contributions

Ajai Chari, Helen McCarthy, Tara Masterson, Michele Kosh, Ming Qi and Robin Carson contributed to study design; Ajai Chari, Paula Rodriguez-Otero, Helen McCarthy, Kenshi Suzuki, Vania Hungria, Anna Sureda Balari, Aurore Perrot, Cyrille Hulin, Hila Magen, Shinsuke Iida, Vladimir Maisnar, Lionel Karlin, Ludek Pour, Dolly A. Parasrampuria, Tara Masterson, Maria Delioukina, Robin Carson and Cyrille Touzeau acquired the data; Ajai Chari, Paula Rodriguez-Otero, Helen McCarthy, Kenshi Suzuki, Vania Hungria, Anna Sureda Balari, Cyrille Hulin, Dolly A. Parasrampuria, Tara Masterson, Michele Kosh, Shiyi Yang, Maria Delioukina, Ming Qi and Robin Carson analysed or interpreted the data; and all authors contributed to the manuscript and approved it for submission. Medical writing and editorial support were provided by J. Matthew Kuczmarski, PhD, of MedErgy, and were funded by Janssen Global Services, LLC.

Supporting Information

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

Table SI. DARA maximum trough concentrations at the end of weekly dosing in body-weight subgroups across D-VRd, D-VMP and D-Rd cohorts[a].

Data S1. Supplementary methods.

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