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Daratumumab (DARA) in Combination With Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Patients With Newly Diagnosed Multiple Myeloma (MMY1001): Updated Results From an Open-label, Phase 1b Study

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INTRODUCTION

- Triplet regimens with a proteasome inhibitor (PI), immunomodulatory drug, and steroids, with or without autologous stem cell transplantation (ASCT), are now established as standard of care for newly diagnosed multiple myeloma (NDMM)
- Among triplet regimens, extended treatment with carfilzomib, lenalidomide, and dexamethasone (KRd) has emerged as highly active in NDMM, and results are improved with the incorporation of ASCT[1-5]
  - In a phase 1/2 study of KRd with or without ASCT for the treatment of NDMM, KRd demonstrated efficacy and a tolerable safety profile[3]
    - At a median follow-up of 26.5 months, deep responses were observed with KRd
      - ◊ The rate of stringent complete response (sCR) was 51% without ASCT and 74% with ASCT
      - ◊ The 3-year progression-free survival (PFS) rate was 80% without ASCT and 86% with ASCT
- We hypothesized that KRd activity may be improved by adding daratumumab to the treatment regimen
- Daratumumab is a human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action[6-11]
- Daratumumab has clear single-agent activity; achieves rapid, deep, and durable responses; and provides clinical benefit in combination with standard of care regimens (lenalidomide and dexamethasone [Rd], bortezomib and dexamethasone [Vd], or pomalidomide and dexamethasone [pom-dex]) in relapsed or refractory multiple myeloma (RRMM)[12-17]
  - A pooled analysis of daratumumab monotherapy studies GEN501 and SIRIUS identified an overall response rate (ORR) of 30.4%, with a median overall survival (OS) of 20.5 months[12]
  - In POLLUX, with a median follow-up of 25.4 months, daratumumab in combination with Rd reduced the risk of disease progression or death by 59% versus Rd alone; median PFS was not reached with DRd versus 17.5 months with Rd (hazard ratio [HR], 0.41; 95% confidence interval [CI], 0.31-0.53; *P* <0.0001)[15]
  - In CASTOR, with a median follow-up of 19.4 months, daratumumab in combination with Vd reduced the risk of disease progression or death by 69% versus Vd alone; median PFS was 16.7 versus 7.1 months (HR, 0.31; 95% CI, 0.24-0.39; *P* <0.0001), respectively[16]
  - In MMY1001, with a median follow-up of 13.1 months, the ORR was 60.2% and the median OS was 17.5 months with daratumumab in combination with pom-dex[17]
  - Based on the results of daratumumab monotherapy studies (GEN501 and SIRIUS)[12] and daratumumab combination therapy studies (POLLUX and CASTOR),[13,14] daratumumab is approved in the United States, European Union, and many other countries as monotherapy in heavily pretreated RRMM patients, and in combination with the standard of care regimens Rd or Vd in patients who have received ≥1 prior therapy[18,19]
  - In the United States, daratumumab plus pom-dex is indicated for patients with ≥2 prior therapies, including lenalidomide and a PI[18]
- These studies provide rationale for the evaluation of daratumumab plus KRd in NDMM

OBJECTIVE

- The aim of this study was to determine the tolerability and efficacy of daratumumab in combination with KRd in patients with NDMM

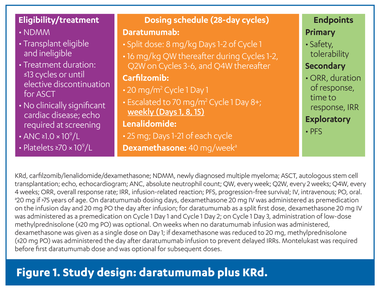
METHODS

Patients

- Key inclusion criteria were as follows:
  - NDMM, regardless of transplant eligibility
  - Measurable MM disease
  - Absolute neutrophil count ≥1.0 × 10^9/L
  - Platelet count ≥70 × 10^9/L
  - Creatinine clearance >30 mL/min/1.73 m^2
  - Bilirubin ≤1.5 times the upper limit of normal

Study Design and Treatment

- This was an open-label, nonrandomized, multicenter, phase 1b study of daratumumab in combination with KRd for the treatment of patients with NDMM, regardless of transplant eligibility (**Figure 1**)



KRd, carfilzomib/lenalidomide/dexamethasone; NDMM, newly diagnosed multiple myeloma; ASCT, autologous stem cell transplantation; echo, echocardiogram; ANC, absolute neutrophil count; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; ORR, overall response rate; IRR, infusion-related reaction; PFS, progression-free survival; IV, intravenous; PO, oral. [a]20 mg if >75 years of age. On daratumumab dosing days, dexamethasone 20 mg IV was administered as premedication on the infusion day and 20 mg PO the day after infusion; for daratumumab as a split first dose, dexamethasone 20 mg IV was administered as a premedication on Cycle 1 Day 1 and Cycle 1 Day 2; on Cycle 1 Day 3, administration of low-dose methylprednisolone (40 mg PO) was optional. On weeks when no daratumumab infusion was administered, dexamethasone was given as a single dose on Day 1; if dexamethasone was reduced to 20 mg, methylprednisolone (40 mg PO) was administered the day after daratumumab infusion to prevent delayed IRRs. Montelukast was required before first daratumumab dose and was optional for subsequent doses.

Figure 1. Study design: daratumumab plus KRd.

- All patients were treated for up to 13 cycles (28 days/cycle) or until elective discontinuation for ASCT
  - Daratumumab 16 mg/kg (intravenous) was administered weekly (Days 1, 8, 15, and 22) during Cycles 1 and 2, every 2 weeks (Days 1 and 15) during Cycles 3 to 6, and every 4 weeks thereafter
    - All patients received the first dose of daratumumab as a split dose over 2 days: 8 mg/kg on Days 1 and 2 of Cycle 1
  - Carfilzomib was administered weekly on Days 1, 8, and 15 of each 28-day cycle as a 30-minute infusion
    - Patients received an initial dose of 20 mg/m^2 on Cycle 1 Day 1 and escalated to 70 mg/m^2 at Cycle 1 Day 8+ if deemed tolerable
  - Lenalidomide was given at a dose of 25 mg on Days 1 through 21 of each cycle
  - Dexamethasone was administered at a dose of 40 mg per week in patients aged ≤75 years and at a dose of 20 mg per week in patients >75 years of age
- Pre-infusion medications included dexamethasone 20 mg, diphenhydramine 25 mg to 50 mg, paracetamol 650 mg to 1,000 mg, and montelukast 10 mg
  - Montelukast was required before the first dose and was optional for subsequent doses
  - Patients received diphenhydramine and paracetamol on Cycle 1 Day 2
- Post-infusion medications included dexamethasone 20 mg or methylprednisolone 20 mg
- All patients received aspirin prophylaxis
- Growth factors were permitted for patients experiencing neutropenia

Minimal Residual Disease (MRD) Evaluation

- MRD was assessed at the time of suspected complete response and at 12 months following the first treatment dose
- MRD was assessed on bone marrow aspirate or whole blood samples that were ficolled and evaluated by the clonoSEQ™ assay V2.0 (Adaptive Biotechnologies, Seattle, WA) at sensitivity thresholds of 10^{-4} (1 cancer cell per 10,000 nucleated cells), 10^{-5}, and 10^{-6}
- The rate of MRD negativity was determined as the proportion of all treated patients with MRD-negative status at any time point following the first treatment dose
- Patients with positive, ambiguous, missing, or unevaluable MRD status were considered as MRD positive

Statistical Analyses and Assessments

- Patients who received ≥1 administration of study treatment were included in the safety analysis (N = 22)
- PFS was estimated using the Kaplan-Meier method based on all treated patients
- Response rates were based on the response-evaluable population
  - Patients in the response-evaluable population had a confirmed diagnosis of MM and had measurable disease at the baseline or screening visit, received ≥1 study treatment, and had adequate post-baseline disease assessment or discontinued treatment due to progressive disease
  - Response was assessed by a computerized algorithm,[20] based on International Myeloma Working Group consensus criteria
  - For daratumumab interference on serum immunofixation (IFE), a second reflex assay using an anti-idiotype monoclonal antibody was used to confirm daratumumab migration on the IFE[21]

RESULTS

Patients and Treatments

- Twenty-two patients were enrolled and treated in the study
  - Median (range) age was 59.5 (34-74) years, and 95% of patients had an Eastern Cooperative Oncology Group score of ≤1 (**Table 1**)

Table 1. Patient Demographics and Baseline Clinical Characteristics

Characteristic	DARA + KRd (N = 22)
Age, y, n (%)	
Median (range)	59.5 (34-74)
<65	15 (68)
Sex, n (%)	
Male	12 (55)
Female	10 (45)
Race, n (%)	
White	19 (86)
African American	1 (5)
American Indian or Alaska Native	1 (5)
Not reported	1 (5)
ECOG score, n (%)	
0	12 (55)
1	9 (41)
2	1 (5)

DARA, daratumumab; KRd, carfilzomib/lenalidomide/dexamethasone; ECOG, Eastern Cooperative Oncology Group.

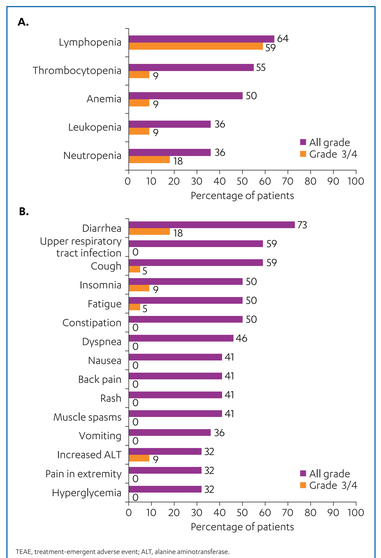
- The clinical cutoff date was October 12, 2017, with a median (range) follow-up of 16.1 (5.7-18.3) months
  - Patients received a median (range) of 13 (1.0-13.0) treatment cycles
- Nineteen (86%) patients escalated to carfilzomib 70 mg/m^2 by Cycle 2 Day 1
  - Treatment discontinuation occurred at Cycle 2 Day 1 in 1 (5%) patient
  - Dose reduction to 56 mg/m^2 occurred at Cycle 2 Day 1 in 1 (5%) patient
  - Escalation to carfilzomib 70 mg/m^2 occurred at Cycle 3 Day 8 in 1 (5%) patient

Patient Disposition

- Eight (36%) patients discontinued study treatment
  - Six (27%) patients discontinued treatment due to elective ASCT
  - Treatment discontinuation due to progressive disease and a treatment-emergent adverse event (TEAE; pulmonary embolism; unrelated to daratumumab or carfilzomib) occurred in 1 (5%) patient each

Adverse Events

- The most common hematologic TEAE was lymphopenia, occurring in 14 (64%) patients (**Figure 2A**)
  - The lymphopenia rate is consistent with previous findings for KRd[2]
- Diarrhea was the most common nonhematologic TEAE, occurring in 16 (73%) patients (**Figure 2B**)
- Serious adverse events (SAEs) were reported in 10 (46%) patients, with pulmonary embolism (3 [14%] patients) being the most common SAE
  - Bilateral deep vein thrombosis and pulmonary embolism were reported in 1 of these 3 patients
- Among patients with SAEs, 3 (14%) events were reasonably related to daratumumab, 5 (23%) to carfilzomib, 5 (23%) to lenalidomide, and 2 (9%) to dexamethasone



TEAE, treatment-emergent adverse event; ALT, alanine aminotransferase.

Figure 2. Most common (≥30%) (A) hematologic and (B) nonhematologic TEAEs.

Cardiac Function

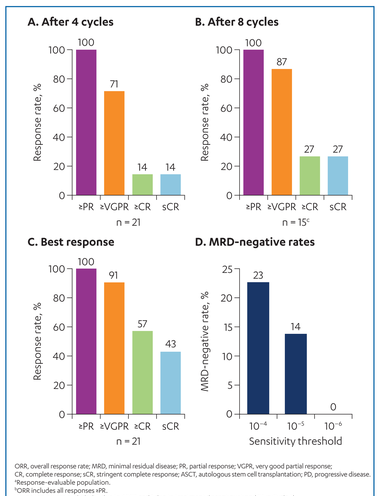
- No notable change from baseline over time was observed for median left ventricular ejection fraction (median change from baseline to Cycles 3, 6, 9, and 12 [per protocol] was <2 at all time points)
- A transient grade 3 cardiac failure was reported in 1 (5%) patient
  - The patient resumed treatment on Cycle 2 Day 1 with reduced carfilzomib dose (56 mg/m^2) and elected ASCT on Day 113, ending treatment with a very good partial response (VGPR)

Infusion Times and Related Reactions

- Median (range) infusion time for the first split-dose infusion was 4.15 (4.0-6.0) hours on Cycle 1 Day 1 and 4.15 (3.9-6.0) hours on Cycle 1 Day 2
  - Median infusion durations were similar for the second (4.18 [3.6-7.1] hours) and subsequent (3.38 [1.4-6.1] hours) infusions
- Infusion-related reactions (IRRs) occurred in 6 (27%) patients, occurring primarily during the first infusion (5 [23%] patients)
  - IRRs occurred in 1 (5%) patient each in the second and subsequent infusions
- IRRs were mild, with no grade 3/4 events

Efficacy Results

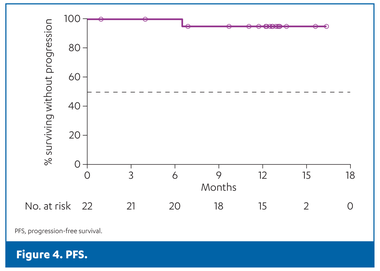
- Responses deepened with time, including an increased rate of ≥CR from 14% after 4 cycles to 27% after 8 cycles and a higher rate of ≥VGPR from 71% after 4 cycles to 87% after 8 cycles (**Figures 3A** and **3B**)
- After a median follow-up of 16 months, the ORR was 100%, including 57% ≥CR and 91% ≥VGPR (**Figure 3C**)
- MRD-negative rate was:
  - 23% for 10^{-4} sensitivity threshold (**Figure 3D**)
  - 14% for 10^{-5} sensitivity threshold (**Figure 3D**)
  - 0% for 10^{-6} sensitivity threshold (**Figure 3D**)



ORR, overall response rate; MRD, minimal residual disease; PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; ASCT, autologous stem cell transplantation; PD, progressive disease. [a]Response-evaluable population. [b]ORR includes all responses ≥PR. [c]Six patients were excluded: 5 due to ASCT and 1 due to treatment discontinuation (PD in Cycle 7).

Figure 3. (A, B) Response rates by treatment cycle[a]; (C) ORR[a,b]; and (D) MRD-negative rates.

- Only 1 patient had progressed at the clinical cutoff date (**Figure 4**)
  - At 12 months, the estimated PFS rate was 95%
  - All patients remain alive, and follow-up is ongoing



PFS, progression-free survival.

Figure 4. PFS.

Stem Cell Harvest

- Six patients discontinued study treatment for elective ASCT
- The median number of CD34+ cells collected from eligible patients (n = 20) was 10.6 × 10^6 cells/kg
- Patients received a median (range) of 5 (4-9) treatment cycles prior to stem cell harvest
- Among eligible patients (n = 20), 15 (75%) had a best response of ≥VGPR prior to stem cell harvest
  - Among 6 patients who underwent ASCT, 3 (50.0%) had a best response of sCR, and 3 (50.0%) had a best response of VGPR (**Table 2**)
  - Patient 3 and Patient 4 upgraded their previous confirmed responses from VGPRs to sCRs

Table 2. Stem Cell Harvest and ASCT

Patient	Stem cell mobilization	Total CD34+ cells (×10^6/kg body weight)	Treatment cycle at ASCT	Best response[a]
1	Plerixafor and filgrastim	30	9	sCR
2	Plerixafor and filgrastim	12	5	VGPR
3	Plerixafor and filgrastim	28	4	sCR
4	Filgrastim	38	4	sCR
5	Plerixafor and filgrastim	10.4	5	VGPR
6	Filgrastim	6.5	4	VGPR

ASCT, autologous stem cell transplantation; sCR, stringent complete response; VGPR, very good partial response. [a]Best response prior to ASCT.

CONCLUSIONS

- **Daratumumab in combination with KRd was well tolerated**
  - **The safety profile is consistent with previous reports of daratumumab and KRd**
- **Daratumumab plus KRd is highly effective, with a 100% ORR, including 91% of patients with ≥VGPR and 57% of patients with ≥CR**
  - **Depth of response continued to deepen with longer follow-up**
  - **MRD-negative rate at 10^{-5} was 14%**
- **There was no adverse impact on stem cell collection (median CD34+ 10.6 × 10^6 cells/kg)**
  - **Daratumumab is feasible as part of induction therapy**
  - **Deep responses (3 sCRs; 3 VGPRs) were achieved prior to stem cell harvest**
  - **As responses were not assessed following stem cell transplantation, further deepening of responses induced by daratumumab plus KRd could not be captured in patients electing ASCT**
- **Ongoing phase 3 studies with daratumumab in novel combinations include:**
  - **Daratumumab plus bortezomib, melphalan, and prednisone (ALCYONE) and daratumumab plus Rd (MAIA) for patients with transplant-ineligible NDMM**
  - **Daratumumab plus bortezomib, thalidomide, and dexamethasone (CASSIOPEIA) for patients with transplant-eligible NDMM**
  - **Daratumumab in combination with Kd (CANDOR) or pomalidomide and dexamethasone (APOLLO) for patients with RRMM**

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