Safety and Efficacy of Daratumumab with Lenalidomide and Dexamethasone in Relapsed, or Relapsed and Refractory Multiple Myeloma

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INTRODUCTION

- Multiple myeloma (MM) remains incurable despite important recent advances in treatment and continues to claim over 11,000 lives a year in the United States and the European Union.[1] Relapsed/refractory MM is characterized by highly complex and heterogeneous molecular and genetic abnormalities that are further supported by the myeloma bone marrow (BM) microenvironment.
- Thus, there exists a need for novel therapies, particularly for those patients who are not candidates for autologous stem cell transplantation.
- Daratumumab (DARA) (HuMax™-CD38), a human IgG1κ monoclonal antibody effectively mediates destruction of CD38-expressing malignant plasma cells.[2]
- In a first-in-human dose-escalation study, 42% of heavily pretreated patients with relapsed, or relapsed and refractory (RR) multiple myeloma (MM) treated with DARA alone (≥4mg/kg) achieved partial response (PR) (modified IMWG guidelines[3]) and an acceptable safety profile.[2]
- Targeting MM cells by a combination therapy approach has demonstrated superior clinical response as compared with that of single agents.[4]
- DARA + Lenalidomide (LEN) enhances the NK cell-mediated killing of MM cells in vitro and is hypothesized to lead to a synergistically higher efficacy in the clinical setting.[5]

OBJECTIVES

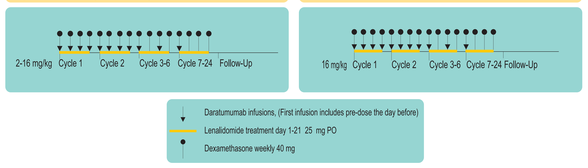
- **Primary:** To evaluate the safety profile of DARA + LEN + dexamethasone (DEX) in patients with relapsed or RR MM.
- **Secondary:** To evaluate the efficacy and pharmacokinetics of DARA + LEN + DEX in patients with relapsed or relapsed and refractory MM.

METHODS

Study Design

- Open-label, dose-escalation, multicenter, phase 1/2, safety study consisting of 2 parts.
  - ***Part 1: Dose escalation study, 3 + 3 design***
    - Evaluated DARA at doses from 2 to 16 mg/kg, in combination with LEN+DEX in 28-day treatment cycles.
    - Maximum tolerated dose (MTD) was not reached in doses which ranged from 2 to 16 mg/kg of DARA in part 1.
  - ***Part 2: Expansion cohort study***
    - 16 mg/kg was considered as the recommended part 2 dose (RP2D) based upon PK/PD, safety and efficacy evaluation.
    - Explored the safety and efficacy of RP2D.

Figure 1: Study Design



DARA: starting dose of 2 mg/kg given by IV infusion, as follows: Cycle 1: Day 0 (predose infusion); Day 1 (first full-dose infusion); Days 8, 15, and 22 of a 28-day cycle; Cycle 2: Days 1, 8, 15, and 22 of a 28-day cycle; Cycles 3-6: Days 1 and 15 of a 28-day cycle for 4 cycles; Cycles 7-24: Day 1 of a 28-day cycle for 18 cycles; treatment may continue up to 24 cycles or until the patient experiences disease progression or unacceptable toxicity, whichever comes first. LEN, 25 mg PO daily on Days 1-21 of each 28-day cycle; DEX, 40 mg weekly, given as follows: On the predose infusion day (Cycle 1 Visit 1), 20 mg IV before the infusion; 20 mg IV before the DARA infusion and 20 mg PO the day after DARA infusion during weeks when DARA infusion is administered, and 40 mg/week PO during weeks when no DARA infusion is administered
IV=intravenously; PO=orally.

Key Inclusion Criteria

- For Part 1: Relapsed and refractory MM following minimum 2 prior lines of therapy either in separate regimens or in combination and maximum 4 prior lines of therapy.
- For Part 2: Patient must have received at least 1 prior line of therapy for multiple myeloma.
  - Patient must have achieved a response (PR or better) to at least one prior regimen.
  - Patient must have documented evidence of progressive disease (PD) as defined by the IMWG criteria on or after their last regimen.
- Measurable M-component levels (≥1.0 g/dL) and/or urine M-component levels (≥200 mg/24-hour sample).
- Aged ≥18 years and with life expectancy of ≥3 months.
- Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2.

Key Exclusion Criteria

- Previously treated with an allogenic stem cell transplant or autologous stem cell transplantation (within 12 weeks before the first infusion).
- Have received antimyeloma treatment, radiotherapy, or any experimental drug or therapy within 2 weeks before the first infusion.
- Have discontinued lenalidomide due to any treatment-related adverse event or be refractory to any dose of lenalidomide.

Refractory to LEN was defined as either:

- Patients whose disease progressed within 60 days of LEN treatment, or
- Patients whose disease was nonresponsive while on any dose of LEN.
- Nonresponsive disease was defined as either failure to achieve at least an MR or development of PD while on LEN treatment.

Safety Assessments

- Safety assessments included: incidence of treatment-emergent adverse events (TEAEs), physical examination findings, electrocardiogram results, vital sign measurements, ECOG performance status, laboratory test results, and immunogenicity assessments.

Efficacy Assessments

- Efficacy assessments included: the rate of response according to the International Uniform Response Criteria, time to progression, duration of response, and progression-free survival.

Statistical Analysis

- Analyses were performed on safety analysis set, which included all patients exposed to the trial drug; efficacy analysis set included all treated patients who had at least one post-baseline efficacy assessment.
- Demographic and baseline variables were estimated using descriptive statistics. Results were presented by cohort as well as by all participants combined.
- Number of infusions for each patient and duration of each infusion were summarized descriptively.
- Response to treatment was determined in accordance with the IMWG criteria. Time to response was summarized descriptively for all patients achieving response of PR or better.
- TEAEs were summarized descriptively for all treated patients. The number and percentage of patients with TEAEs (defined as those adverse events that started during the treatment phase, or had worsened since baseline, or were reported as related to the study treatment), were provided.

RESULTS

Table 1: Demographics and Patient Characteristics (Safety Analysis Set)

Characteristics	2mg/kg N=3	4mg/kg N=3	8 mg/kg N=4	16 mg/kg Part 1 N=3	16 mg/kg Part 2 N=9	16 mg/kg Total N=12	Total N=22
Gender, n (%)							
Men	3 (100.0%)	2 (66.7%)	4 (100.0%)	1 (33.3%)	6 (66.7%)	7 (58.3%)	16 (72.7%)
Age, years Median (range)	69.0 (48; 71)	62.0 (61; 65)	55.5 (49; 69)	71.0 (56; 76)	62.0 (56; 73)	62.5 (56; 76)	62.0 (48; 76)
Prior lines of therapy Median (range)	3.0 (2; 4)	2.0 (2; 4)	3.0 (3; 4)	3.0 (2; 4)	1.0 (1; 3)	1.5 (1; 4)	2.5 (1; 4)
LEN refractory, n							
Refractory	0	1 (33.3%)	2 (50.0%)	0	0	0	3 (13.6%)
Non-refractory	3 (100.0%)	2 (66.7%)	1 (25.0%)	1 (33.3%)	1 (11.1%)	2 (16.7%)	8 (36.4%)
LEN naïve	0	0	1 (25.0%)	2 (66.7%)	8 (88.9%)	10 (83.3%)	11 (50.0%)
Years since MM diagnosis Median (range)	3.95 (2.2; 7.6)	2.05 (1.9; 5.1)	3.17 (0.9; 5.1)	9.97 (1.1; 14.0)	6.40 (1.6; 12.7)	8.18 (1.1; 14.0)	3.84 (0.9; 14.0)
Body weight, kg Mean (SD)	92.27 (7.18)	76.47 (5.78)	90.20 (12.81)	81.93 (11.82)	80.78 (20.03)	81.07 (17.82)	83.63 (15.09)
ECOG status, n							
0	2 (66.7%)	2 (66.7%)	1 (25.0%)	3 (100.0%)	5 (55.6%)	8 (66.7%)	13 (59.1%)
1	1 (33.3%)	1 (33.3%)	3 (75.0%)	0	3 (33.3%)	3 (25.0%)	8 (36.4%)
2	0	0	0	0	1 (11.1%)	1 (8.3%)	1 (4.5%)

ECOG=Eastern cooperative oncology group; LEN=lenalidomide; MM=multiple myeloma

Table 2: Number and Duration of Daratumumab Infusions Received (Safety Analysis Set)

	2mg/kg N=3	4mg/kg N=3	8 mg/kg N=4	16 mg/kg Part 1 N=3	16 mg/kg Part 2 N=9	16 mg/kg Total N=12	Total N=22
Number of infusions per patient, Median (range)	21.0 (13; 26)	23.0 (22; 24)	20.0 (17; 21)	11.0 (10; 16)	2.0 (1; 4)	2.5 (1; 16)	12.0 (1; 26)
Duration of infusions, N Median (range), **(hours)**	60 7.25 (5.8; 11.9)	69 7.22 (5.7; 10.3)	78 5.92 (5.6; 9.3)	36 6.31 (5.8; 8.5)	19 6.92 (5.8; 12.2)	55 6.53 (5.8; 12.2)	262 6.42 (5.6; 12.2)

Safety

- Safety data from 22 patients were collected.
- No DLTs were reported in any of the dose cohorts.
- Infusion reactions (grade 1 and 2) were reported in 4 patients.
- 8 SAEs were reported, all assessed as unrelated to DARA.
- One patient (2 mg/kg dose cohort) was withdrawn due to recurrent grade 1 QT prolongation which was considered as related to underlying hypokalemia and unrelated to DARA.

Table 3: Incidence of Most Frequent Adverse Events Reported in >10% of Patients (Safety Analysis Set)

	2mg/kg N=3	4mg/kg N=3	8 mg/kg N=4	16 mg/kg Part 1 N=3	16 mg/kg Part 2 N=9	16 mg/kg Total N=12	Total N=22
Total number of patients with TEAE, n	3 (100.0%)	3 (100.0%)	4 (100.0%)	3 (100.0%)	3 (33.3%)	6 (50.0%)	16 (72.7%)
Neutropenia	3 (100.0%)	1 (33.3%)	1 (25.0%)	2 (66.7%)	0	2 (16.7%)	7 (31.8%)
Diarrhea	2 (66.7%)	3 (100.0%)	2 (50.0%)	0	0	0	7 (31.8%)
Fatigue	3 (100.0%)	0	2 (50.0%)	1 (33.3%)	0	1 (8.3%)	6 (27.3%)
Nasopharyngitis	1 (33.3%)	3 (100.0%)	2 (50.0%)	0	0	0	6 (27.3%)
Constipation	3 (100.0%)	1 (33.3%)	1 (25.0%)	1 (33.3%)	0	1 (8.3%)	6 (27.3%)
Muscle Spasms	1 (33.3%)	2 (66.7%)	0	2 (66.7%)	0	2 (16.7%)	5 (22.7%)
Nausea	1 (33.3%)	2 (66.7%)	2 (50.0%)	0	0	0	5 (22.7%)
Upper Respiratory Tract Infection	1 (33.3%)	2 (66.7%)	1 (25.0%)	0	0	0	4 (18.2%)
Peripheral Edema	2 (66.7%)	0	1 (25.0%)	1 (33.3%)	0	1 (8.3%)	4 (18.2%)
Cough	0	1 (33.3%)	2 (50.0%)	1 (33.3%)	0	1 (8.3%)	4 (18.2%)
Insomnia	1 (33.3%)	2 (66.7%)	1 (25.0%)	0	0	0	4 (18.2%)
Anemia	1 (33.3%)	2 (66.7%)	0	1 (33.3%)	0	1 (8.3%)	4 (18.2%)
Bone Pain	1 (33.3%)	1 (33.3%)	1 (25.0%)	0	0	0	3 (13.6%)
Musculoskeletal Chest Pain	1 (33.3%)	1 (33.3%)	1 (25.0%)	0	0	0	3 (13.6%)
Pyrexia	1 (33.3%)	1 (33.3%)	1 (25.0%)	0	0	0	3 (13.6%)
Headache	1 (33.3%)	0	1 (25.0%)	1 (33.3%)	0	1 (8.3%)	3 (13.6%)
Hypocalcemia	1 (33.3%)	2 (66.7%)	0	0	0	0	3 (13.6%)
Hypokalemia	1 (33.3%)	1 (33.3%)	0	1 (33.3%)	0	1 (8.3%)	3 (13.6%)
Cardiac Disorder	1 (33.3%)	0	1 (25.0%)	1 (33.3%)	0	1 (8.3%)	3 (13.6%)
Immune System Disorder	1 (33.3%)	1 (33.3%)	0	1 (33.3%)	0	1 (8.3%)	3 (13.6%)
Hepatic Function Abnormal	2 (66.7%)	1 (33.3%)	0	0	0	0	3 (13.6%)

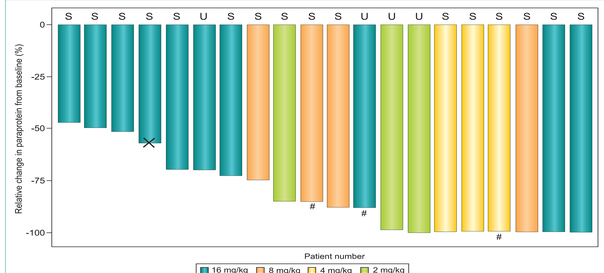
Table 4: Patients with Infusion Reaction Reported by Investigators (Safety Analysis Set)

	2mg/kg N=3	4mg/kg N=3	8 mg/kg N=4	16 mg/kg Part 1 N=3	16 mg/kg Part 2 N=9	16 mg/kg Total N=12	Total N=22
Number of patients, n	0	1 (33.3%)	1 (25.0%)	1 (33.3%)	1 (11.1%)	2 (16.7%)	4 (20.0%)

Efficacy

A total of 20 patients were included for efficacy analyses.

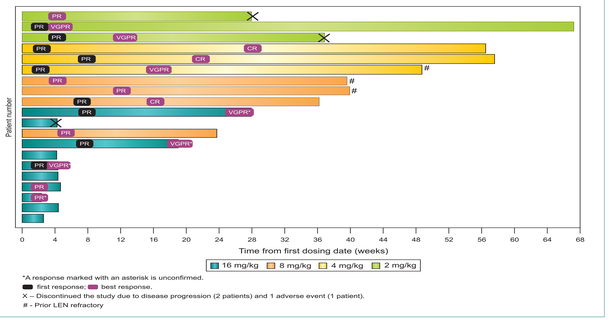
Figure 2: Maximum Percent Change in Para-protein from Baseline (Efficacy Analysis Set)



Patients followed at least for 2 cycles (weekly dosing)
S = serum M-protein; U = urine M-protein
X – Discontinued the study due to disease progression (2 patients) and 1 adverse event (1 patient).
- Prior LEN refractory

- All patients had a marked decrease in M-protein.

Figure 3: Best Response and Duration of Follow-up (Efficacy Analysis Set)



*A response marked with an asterisk is unconfirmed.
first response; best response.
X – Discontinued the study due to disease progression (2 patients) and 1 adverse event (1 patient).
- Prior LEN refractory

Table 5: Time to Response* (Responders in Efficacy Analysis Set)

	2mg/kg N=3	4mg/kg N=3	8 mg/kg N=4	16 mg/kg* Part 1 N=2	16 mg/kg* Part 2 N=3	16 mg/kg* Total N=5	Total N=15
Weeks, Median (range)	4.3 (2.3, 4.3)	2.4 (2.3, 8.1)	7.65 (4.3, 12.3)	9.8 (8.3, 11.3)	2.3 (2.1, 2.3)	2.3 (2.1, 11.3)	4.3 (2.1, 11.3)

*Including responses to be confirmed. Only includes patients achieving response of PR or better. Response evaluated according to IMWG criteria. Time to response in weeks is defined as (first documented response date – first dosing date + 1)/7.

- Median time to achieve PR was 4.3 weeks (2.1-11.3).

Table 6: Response Rate# (Efficacy Analysis Set)

	2mg/kg N=3	4mg/kg N=3	8 mg/kg N=4	16 mg/kg* Part 1 N=3	16 mg/kg* Part 2 N=7	16 mg/kg* Total N=10	Total N=20
CR	0	2	1	0	0	0	3
VGPR	2	1	3	2	1	3	9
PR	1	0	0	0	2	2	3
MR	0	0	0	0	1	1	1
SD	0	0	0	1	3	4	4

# Evaluated using IMWG criteria; * Including responses to be confirmed.
CR=complete response; MR=minimal response; PR=partial response; SD= stable disease; VGPR=very good partial response

CONCLUSIONS

- DARA+LEN+DEX treatment demonstrated a favorable safety profile with manageable toxicities in relapsed and RR MM patients.
- The MTD was not reached in part 1; RP2D was determined by PK/PD, safety and efficacy evaluation.
- All patients were followed up for at least 2 weeks.
- ORR was 75% (15/20) combining all patients in part 1 and 2; ORR was 92.3% (12/13) for part 1 patients, who had at least 2 months of follow-up or discontinued earlier.
- Encouraging early activity is seen with marked reduction in M-protein and 15/20 patients achieving PR or better.
  - Among them, 3 were CR and 6 were VGPR in this heavily pretreated population.
  - Most patients were previously treated with bortezomib and lenalidomide.
  - Among the 3 patients refractory to prior lenalidomide, all achieved a response (2 PR, 1 VGPR).
- Further clinical development of DARA in combination with LEN+DEX is merited. A phase 3 study evaluating DARA in combination with LEN+DEX in comparison with LEN+DEX has been initiated (clinical trial number: NCT02076009).

References

1. American Cancer Society. Cancer Facts and Figures 2010. ; 2. Lokhorst et al. EHA 2013 abstract #8512; 3. Rajkumar et al. Blood 2011;117:4691-5; 4. Lonial et al. J Clin Oncol 2010;28(15s); 5. van der Veer et al. Haematologica 2011;96(2):284-90.

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Disclosures & Author Contributions

Drs. TP, HL, AP and GR: Consultancy. Drs. TA, PG, JK, CL, MM and UL: No relevant conflicts of interest to disclose. Drs. HY, MG, TA, SL, NB and LB: Employment. Drs. HY, MG, TA, SL, NB and LB were involved in study design, data collection and data analysis. Drs. TP, HL, AP, GR, TA, PG, JK, CL, MM and UL were the principal investigators for the study. All authors meet ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors had access to the study data and made the final decision about where to present these data.

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