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Results of an Interim Safety Analysis of a Phase 2 Study of Daratumumab (Dara) plus Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) in Previously Untreated and Relapsed Patients (Pts) with Multiple Myeloma (MM) (LYRA)

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INTRODUCTION

- Daratumumab is a human monoclonal antibody targeting CD38 that is indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy[1]
  - In clinical trials (monotherapy and combination treatments; N=820) the incidence of any grade infusion reactions was 46% with the first infusion of daratumumab, 2% with the second infusion, and 3% with subsequent infusions. Median durations of infusion for the 1st, 2nd and subsequent infusions were 7.0, 4.3, and 3.5 hours respectively.
- Daratumumab, in combination with a proteasome inhibitor (PI), delivers rapid, deep, and durable responses, and significantly improves progression free survival (PFS)[2]
- CyBorD is a commonly used PI (bortezomib) based regimen for MM
- The LYRA study (NCT02951819) is being conducted in patients with MM who are previously untreated or have relapsed following only one line of therapy and was designed to evaluate:
  - Efficacy and safety of the combination of daratumumab and CyBorD
  - Administration of the first daratumumab infusion as a divided dose over 2 days
- We report results from a planned interim analysis of the first 48 patients who completed Cycle 1 of study treatment, focusing on the safety and infusion reaction profile of daratumumab

METHODS

Study Design

- This is a multicenter, single-arm, open-label, Phase 2 study conducted at US community oncology centers (Figure 1)

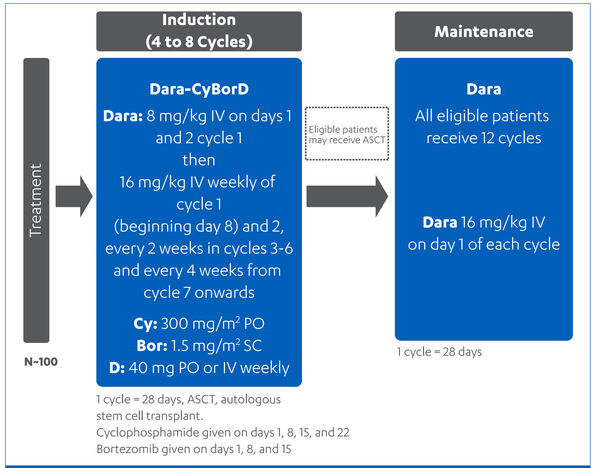

Figure 1. Study Design for Patients Treated with Dara-CyBorD

- The primary objective of this study is to evaluate the VGPR or better rate following 4 cycles of daratumumab + CyBorD
- Secondary objectives include overall response rate, time to response, duration of response, PFS, overall survival, safety and the infusion reaction profile
- Required pre-infusion medications are dexamethasone, acetaminophen and diphenhydramine; montelukast is allowed at the investigator's discretion

Table 1. Patient Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Age ≥18 years	Refractory to any PI or combination of PI and IMiD agents
Documented MM per IMWG 2015 criteria	History of meningeal or central nervous system involvement by MM
ECOG score of 0-2	COPD with FEV1<50% of predicted normal
Previously untreated MM or relapsed MM with one prior line of therapy*	Moderate or severe persistent asthma within past 2 years
Measurable disease	Seropositive for HIV
	Hepatitis B surface antigen positivity
	History of Hepatitis C (untreated)
	Clinically significant cardiac disease

IMWG, international myeloma working group; PI, protease inhibitor; IMiD, immunomodulatory drug; COPD, chronic obstructive pulmonary disease; ECOG, eastern cooperative oncology group; FEV1, forced expiratory volume in 1 second.
*Inclusion criteria modified (Amendment 2) to only include previously untreated patients due to physicians not opting to enroll patients in the relapsed MM arm after approval of daratumumab in combination with bortezomib + dexamethasone in subjects with MM after 1 prior line of therapy

RESULTS

- The first 48 patients included 39 previously untreated and 9 relapsed patients (Table 2)

Table 2. Patient Demographics and Baseline Characteristics

	N=48
Age, median (range), years	62.5 (41-80)
Male, n (%)	31 (65)
ISS staging, n (%)	
Stage 1	15 (33)
Stage 2	23 (50)
Stage 3	8 (17)
ECOG performance status, n (%)	
0	20 (42)
1	25 (52)
2	3 (6)
Previous treatments, n (%)	
Untreated	39 (81)
1 prior therapy	9 (19)

ISS, international staging system; ECOG, eastern cooperative oncology group.

- All patients completed Cycle 1 with no treatment discontinuations
- Five (10%) patients experienced a serious adverse event (SAE) during Cycle 1 that was not related to daratumumab according to the investigator's assessment
  - SAEs included atrial fibrillation, pyrexia, bone lesion, syncope, and deep vein thrombosis (1 each)
- 47 (98%) patients experienced at least 1 treatment emergent adverse event (TEAE) during Cycle 1 (Table 3)

Table 3. Overall Safety Profile of Patients Treated During Cycle 1

	N=48
At least 1 treatment emergent adverse event (TEAE), n (%)	47 (98)
Related to daratumumab	35 (73)
Most common TEAEs (all grades) occurring in ≥15% of patients, n (%)	
Nausea	14 (29)
Fatigue	12 (25)
Diarrhea	11 (23)
Headache	8 (17)
Chills	7 (15)
Most common TEAEs (grade 3-4) occurring in ≥5% of patients, n (%)	
Neutropenia	4 (8)

No Grade 5 adverse event was reported during cycle 1

- 21 (44%) patients experienced infusion reactions (IRs) during Cycle 1 (Table 4)
- All infusion reactions were grade ≤2

Table 4. Infusion Reactions (IRs) in Patients During Cycle 1

	N=48
Infusion reactions (IRs) (all grade ≤2) occurring in ≥5% of patients, n (%)	
Chills	6 (13)
Cough	3 (6)
Nausea	3 (6)
Pruritus	3 (6)
Respiratory symptoms of IRs, n (%)	6 (13)
Cough	3 (6)
Dyspnea	2 (4)
Bronchospasm	1 (2)
Throat irritation	1 (2)
Oropharyngeal pain	1 (2)

- Infusion reactions (all grade ≤2) occurred in 38% of patients on day 1 and in 4% of patients on day 2 of cycle 1 (Figure 2)

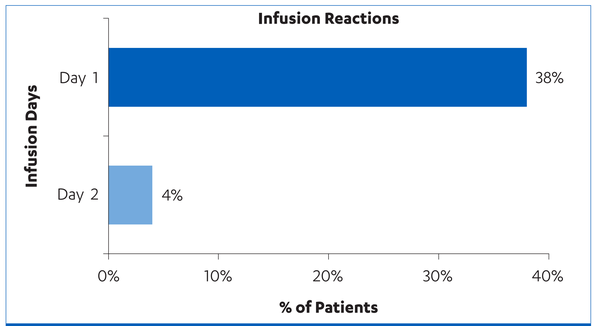

Figure 2. Infusion Reactions (grade ≤2) on Day 1 and Day 2

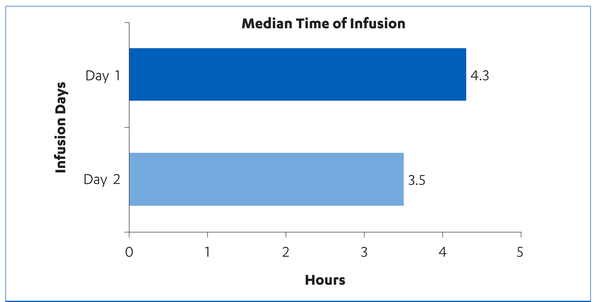

Figure 3. Median Infusion Time for Day 1 and Day 2

CONCLUSIONS

- **The first cycle of daratumumab and CyBorD was well tolerated, with a manageable safety profile and no treatment discontinuations**
- **No new safety signals were identified with the addition of daratumumab to CyBorD**
- **Split dose of 8 mg/kg/day of daratumumab over 2 days decreased the median infusion time for day 1 of Cycle 1 (4.3 vs 7.0 hours) and resulted in a similar IR rate as previous clinical trials administering 16 mg/kg on Cycle 1 day 1**
- **No Grade ≥3 IRs were observed**
- **These findings demonstrate that splitting of the first daratumumab infusion in the community setting:**
  - **Is feasible**
  - **Results in a similar infusion reaction rate with no observed Grade ≥ 3 IRs**
  - **Reduces the median time for the first day of the first daratumumab infusion (4.3 vs 7.0 hours)**
- **As of 6 November 2017, 100 patients (86 previously untreated, 14 relapsed) have been treated:**
  - **Patients have received a median of 5 cycles**
  - **11 patients have undergone autologous stem cell transplantation**
  - **10 patients dicontinued therapy due to progression of disease (5), lack of response (3), adverse event (1), and death (1)**
  - **90 continue therapy**

REFERENCES

1. DARZALEX® [package insert]. Janssen Biotech, Inc., Horsham, PA; June 2017.
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DISCLOSURES

HY holds equity in Juno pharma and Bellucum pharma. JM is a member on an entity's of directors or advisory committees for Janssen. EF served as a consultant and a member on an entity's board of directors or advisory committees for Millenium, Celgene, Onyx, Sanofi Aventis, and Gilead. EF is also on speakers bureau for Celgene and Onyx. WIB served as a member on an entity's board of directors or advisory committees for Janssen. JB served as a consultant for Incyte, Celgene, Bayer, Genentech, and Gilead; and received travel grant from Celgene. SG, SM, HP, YL, MD, AL, MQ, JU, and TL are employees of Janssen. SM, MD, and AL hold equity in Janssen. MQ holds equity in Johnson & Johnson. RMR is an employee of McKesson Specialty Health and served as a consultant and a member on an entity's board of directors or advisory committees for Amgen, Celgene, Takeda, and Janssen.

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