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Interim Safety Analysis of a Phase 2 Randomized Study of Daratumumab (Dara), Lenalidomide (R), Bortezomib (V), and Dexamethasone (d; Dara-RVd) vs. RVd in Patients (Pts) with Newly Diagnosed Multiple Myeloma (MM) Eligible for High-Dose Therapy (HDT) and Autologous Stem Cell Transplantation (ASCT) (GRIFFIN)

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INTRODUCTION

- Daratumumab is the first CD38-directed human monoclonal antibody to target tumor cells and promote an anti-tumor immune response[1]
- Daratumumab, in combination with a proteasome inhibitor (PI) or an immunomodulatory agent, delivers an unprecedented progression-free survival (PFS) benefit and rapid, deep, and durable responses in relapsed or refractory MM[2]
- RVd followed by HDT, ASCT and consolidation therapy has shown high response rates in previously untreated MM[3]
- Attainment of stringent complete response (sCR) correlates with improved long-term outcomes after ASCT for MM[4]
- The primary objective of this study is to determine if the addition of daratumumab to RVd will increase the sCR rate by the end of post-ASCT consolidation therapy

METHODS

Study Design

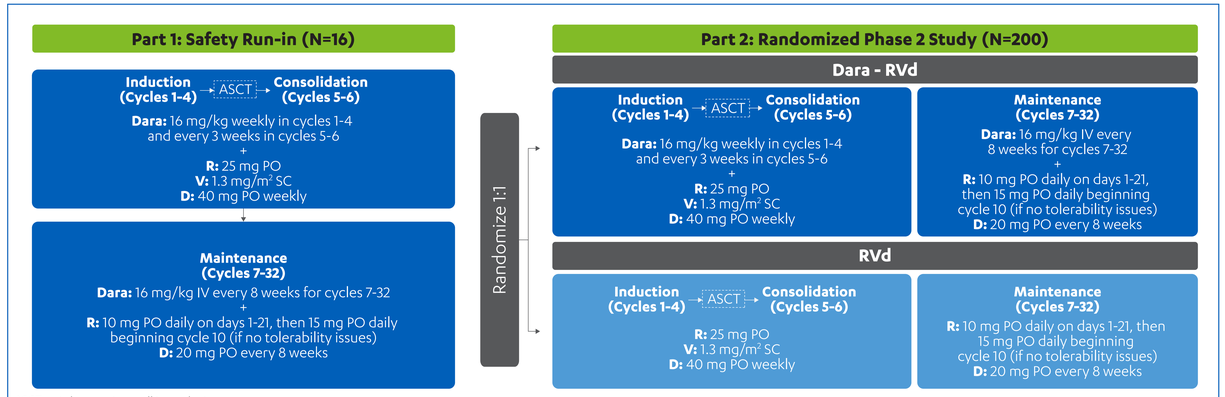
- Griffin (NCT02874742) is an ongoing multicenter, randomized, open-label, active comparator-controlled study conducted in the United States
- Safety Run-in Phase (N=16)
  - Performed in 16 pts treated with Dara-RVd in order to assess potential dose limiting toxicities (DLTs) during Cycle 1 (Figure 1)
  - One interim safety analysis was performed as planned for the safety run-in subjects after treated for at least 4 cycles or discontinued study participation
- Randomized Phase 2 Study
  - Following successful completion of the safety run-in phase, approximately 200 patients will be randomized 1:1 to Dara-RVd or RVd, followed by HDT, ASCT, consolidation therapy with Dara-Rd or Rd

Table 1. Patient Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Age 18-70 years	History of meningeal or central nervous system involvement by MM or plasma cell leukemia
Documented MM per IMWG 2015 criteria	Diagnosis or treatment for malignancy other than MM
Eligible for HDT and ASCT	COPD with FEV1<50% of predicted normal
ECOG performance score of 0-2	Moderate or severe persistent asthma within past 2 years
Adequate organ function	Clinically significant cardiac disease
No prior systemic therapy for MM	Pregnant or breastfeeding
Measurable disease	Seropositive for HIV
	Hepatitis B (surface antigen positive)
	Hepatitis C with detectable virus
	Allergies, hypersensitivity, or intolerance to monoclonal antibodies

IMWG, international myeloma working group; ECOG, eastern cooperative oncology group; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; HIV, human immunodeficiency virus.

- **DLTs were defined as reported adverse experiences of:**
  - **Grade 4** neutropenia lasting >7 days
  - **Grade 4** thrombocytopenia lasting >7 days despite transfusion support
  - **Grade 3 or higher** non-hematological toxicity, except:
    - Grade 3 nausea, vomiting or diarrhea that can be controlled within 48 hours with maximal supportive care
    - Grade 3 hyperglycemia that can be controlled within 48 hours with supportive care
    - Asymptomatic Grade 3 or higher electrolyte disturbances that can be controlled with repletion within 24 hours
    - Grade 3 maculopapular rash attributable to lenalidomide
  - **Infusion reactions (IRs):**
    - Any **Grade 4 IR** occurring within 48 hours of infusion of daratumumab
    - Any **Grade 3 IR** occurring within 48 hours of infusion of daratumumab that does not resolve with a reduced infusion rate or temporarily stopping the infusion, as well as administration of supportive care and symptomatic therapy such as a steroid and an antihistamine
- A Data Review Committee (DRC) was established to review safety data after 8, 12, and 16 subjects in the safety run-in phase completed Cycle 1, and to determine if the study should proceed to the randomized phase 2 portion or stop (Table 2)



ASCT, autologous stem cell transplant.
Cycles 1-6 = every 21 days; Cycles 7-32 = every 28 days
Induction and Consolidation:
Lenalidomide given on days 1-14; Bortezomib given on days 1, 4, 8, and 11; Dexamethasone 20 mg given on days 1, 2, 8, 9, 15, and 16.

Figure 1. Study Design for Dara-RVd and RVd Treatment Groups

Table 2. Safety Run-in Stopping Criteria: Number of Total DLTs to Stop Study

Number of Subjects (in complete cohorts of 4)	Number of Toxicities
8	≥5
12	≥6
16	≥8

RESULTS

- 16 patients were enrolled in the safety run-in, and all patients had completed at least 4 cycles of Dara-RVd as of the clinical cutoff date of 5 July 2017 (Table 3)

Table 3. Patient Demographics in the Safety Run-in Phase

	N=16
Age, median (range), years	62.5 (46-65)
Male, n (%)	8 (50)
ISS, n (%)	
Stage I	12 (75)
Stage II	2 (13)
Stage III	2 (13)
ECOG performance status, n (%)	
0	3 (19)
1	10 (63)
2	3 (19)

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

Safety Analysis

- Among 16 treated patients, 3 patients experienced adverse events that met sponsor pre-defined DLT criteria during Cycle 1. All DLTs resolved and none of these events were determined by the investigator to require treatment discontinuation.
  - Grade 3 fatigue on Day 15
  - Grade 3 gastroenteritis on Day 21
  - Grade 3 pneumonitis (due to infection) and Grade 3 hypotension on Day 5
- The DRC recommended the study proceed to the randomized phase 2 stage
- 100% of patients experienced at least 1 treatment emergent adverse event (TEAE) (Table 4) and 8 (50%) of patients experienced Grade 3-4 TEAEs (Table 5)
- 3 (19%) patients experienced serious adverse events (SAEs) that included 2 (13%) SAEs (gastroenteritis and pneumonitis) related to daratumumab according to investigator's assessment

Table 4. Safety Profile of Patients Treated During Cycles 1-4

	N=16
At least 1 treatment emergent adverse event (TEAE), n (%)	16 (100)
Related to daratumumab	14 (88)
Most Common TEAEs (all grades) occurring in ≥20% of patients, n (%)	
Neutropenia	8 (50)
Lymphopenia	7 (44)
Thrombocytopenia	7 (44)
Fatigue	6 (38)
Oedema peripheral	6 (38)
Anemia	5 (31)
Constipation	5 (31)
Leukopenia	4 (25)
Hypoalbuminemia	4 (25)
Hypocalcemia	4 (25)
Insomnia	4 (25)

Table 5. Most Common Grade 3-4 TEAEs in Patients Treated During Cycles 1-4

	N=16
Grade 3-4 TEAEs, n (%)	8 (50)
Related to daratumumab	6 (38)
Grade 3-4 TEAEs occurring in ≥10% of patients, n (%)	
Neutropenia	3 (19)
Thrombocytopenia	3 (19)
Lymphopenia	2 (13)
Leukopenia	2 (13)

- 5 (31%) patients experienced grade ≤2 infusion reactions (Table 6)
- Six (38%) patients experienced infections, including 1 patient with a Grade 3 SAE of gastroenteritis. There were no events of febrile neutropenia.
- Two (12.5%) patients experienced grade 1 peripheral neuropathy
- Six (38%) patients had dose delay due to adverse event
- Dose of the following medications was adjusted due to AE: bortezomib (3 patients), dexamethasone (2 patients), daratumumab and lenalidomide (1 patient each)
- There were no deaths, and no patients discontinued treatment due to TEAEs
- All 16 patients have undergone mobilization as of the clinical cutoff date with a median stem cell yield of 6.05 (range 3.5-10.6) x10^6 CD34+ cells/kg
- All 16 patients in the safety run-in phase continue to be on study treatment

CONCLUSIONS

- **Daratumumab, in combination with RVd, was well tolerated, with clinically manageable side effects consistent with the known toxicities of RVd and the known adverse event profile of daratumumab**
- **No new safety signals were identified with the addition of Dara to RVd during the first 4 cycles of Dara-RVd in 16 safety run-in patients with newly diagnosed MM**
- **All 16 patients in the safety run-in have undergone successful stem cell mobilization**
- **The first 4 cycles of the safety run-in phase were completed, and all 16 patients continue on therapy**
- **Enrollment to the randomized phase 2 study is ongoing, with 106 patients randomized as of 8 November 2017**

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ACKNOWLEDGMENTS

The authors would like to thank Alliance Foundation Trials (AFT) and other participating sites for their ongoing support. This study (ClinicalTrials.gov Identifier: NCT02874742) was sponsored by Janssen Research & Development, LLC and was conducted with the support of AFT.

ALLIANCE FOUNDATION TRIALS, LLC

DISCLOSURES

PV served as a consultant for Celgene, Janssen, Bristol-Myers Squibb, Novartis, Takeda, and Oncopeptides; and is on speakers bureau for Amgen, Celgene, and Janssen. BR and NN have no relevant financial relationships to disclose. CR is on advisory board for Celgene and on speakers bureau for Takeda and Celgene. YL, LH, HP, JU, MQ, and TL are employees of Janssen. MQ holds an equity in Johnson & Johnson. LJC received research funding from Janssen, Amgen, and Celgene; and received honoraria from Celgene and Sanofi. LJC is on speakers bureau for Amgen and Sanofi. PGR served as a consultant for Jazz Pharmaceuticals, Takeda, and Celgene; received research funding from Takeda and Celgene and holds a membership on an entity's Board of Directors or advisory committees for Jazz Pharmaceuticals and Oncopeptides AB.

POSTER PRESENTED AT THE AMERICAN SOCIETY OF HEMATOLOGY (ASH) ANNUAL MEETING, DECEMBER 9–12, 2017, ATLANTA, GA