Results of an Early Access Program (EAP) of Daratumumab in United States Patients With Relapsed or Refractory Multiple Myeloma

A. Chari,[1] T.M. Mark,[2] A. Krishnan,[3] K. Stockerl-Goldstein,[4] S.Z. Usmani,[5] A. Londhe,[7*] D. Etheredge,[7*] H. Parros,[7*] S. Fleming,[7*] B. Liu,[8*] S. Freeman,[6*] J. Ukropec,[6*] T. Lin,[6] S. Lonial[9]

[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Weill Cornell Medical College, New York, NY; [3]City of Hope, Duarte, CA; [4]Washington University School of Medicine, Saint Louis, MO; [5]Department of Hematologic Oncology and Blood Disorders, Levine Cancer Institute/Carolinas HealthCare System, Charlotte, NC; [6]Janssen Scientific Affairs, LLC, Horsham, PA; [7]Janssen Research & Development, LLC, Titusville, NJ; [8]Janssen Research & Development, LLC, Spring House, PA; [9]Winship Cancer Institute, Emory University, Atlanta, GA

BACKGROUND

- Daratumumab is a human CD-38-directed monoclonal antibody indicated for:
  - In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with MM who have received at least one prior therapy
  - As monotherapy, for the treatment of patients with MM who have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent, or who are double-refractory to a PI and immunomodulatory agent
- A multi-center, open-label Early Access Treatment Protocol was opened in June 2015 after presentation of the MMY2002 results demonstrated the efficacy and safety profile of daratumumab in this patient population

OBJECTIVES

- To provide early access to daratumumab treatment
- To collect safety and patient-reported outcome (PRO) data in patients with MM who have received ≥3 prior lines of therapy including a PI and an IMID or are double refractory to a PI and an IMID

STUDY DESIGN

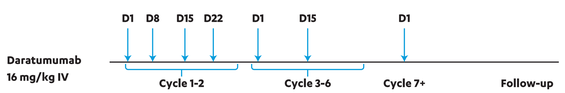
Table 1. Patient Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Age 18 years or older	Known chronic obstructive pulmonary disease
Documented MM	Persistent asthma
Progression by IMWG criteria following the most recent therapy	Ongoing MM therapy
≥3 prior lines of therapy including a PI and an IMID or disease double refractory to a PI and an IMID	Prior exposure to anti-CD38 antibody therapy
ECOG performance status score 0-2	Absolute neutrophil count <0.5 × 10^9/L
	Platelet count <50 x 10^9/L
	Creatinine clearance <20 mL/min/1.73 m^2

IMWG = International Myeloma Working Group; ECOG = Eastern Cooperative Oncology Group

- Patients received daratumumab 16 mg/kg IV weekly for 8 weeks, then every 2 weeks for 16 weeks, and then every 4 weeks until disease progression, unacceptable toxicity, or 60 days after US approval (**Figure 1**)

Figure 1. Schematic Overview of Study Treatment Administration*



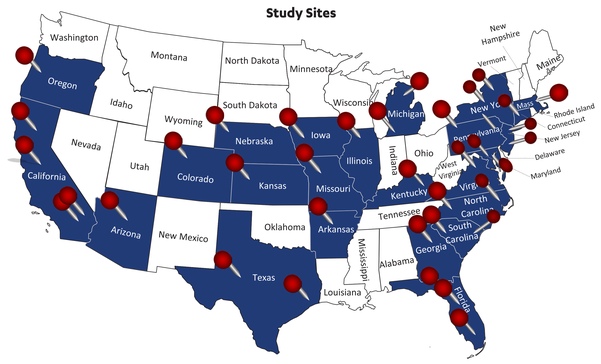
*Cycle length = 28 days

- Pre- and post-infusion medications were administered as in study MMY2002:
  - Acetaminophen (paracetamol) 650-1000 mg IV or PO 1 hour prior to infusion
  - An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent) 1 hour prior to infusion
  - Methylprednisolone 100 mg IV prior to infusions 1-2 (60 mg IV prior to subsequent infusions)
  - Methylprednisolone 20 mg or equivalent post-infusion for 2 days
- For subjects with a higher risk of respiratory complications [predicted % forced expiratory volume in 1 minute (FEV1%PRED) <75%], the following post-infusion medications were considered:
  - 25-50 mg of diphenhydramine or equivalent on the 2 days following all daratumumab infusions
  - Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
  - Inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma
  - Long-acting bronchodilators such as tiotropium or salbutamol ± inhaled corticosteroids for subjects with chronic obstructive pulmonary disease (COPD)
- Serious adverse events (SAEs), Grade 3-4 AEs, infusion related reactions (IRRs), and PRO data were collected

RESULTS

- In total, 400 patients were screened and 348 patients were enrolled and dosed (**Table 2**, **3** and **Figure 3**)
- Patients were enrolled at 39 US sites from July to November 2015 (**Figure 2**)

Figure 2. Location of Participating Sites*



*Study sites shown here are the updated locations as of October 2016

Table 2. Patient Baseline Characteristics (N=348)

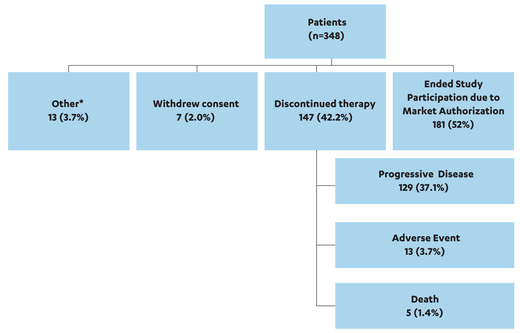
Median age, (range)	65 (27-94)
Male	59%
White/ African American / Other	72% / 17% / 11%
Performance Status	
ECOG Score of 1	58%
ECOG Score of 2	16%

Table 3. Treatment Delivery of Investigational Supply of Daratumumab*

Median number of doses, (range)	8 (1-17)
Median treatment exposure, (range)	1.9 (0.03-6.0) months
Duration of infusions, hours	
First infusion	
Mean (SD)	7.95 (2.397)
Median	7.37
Range	(1.0; 24.0)
Second infusion	
Mean (SD)	5.22 (1.490)
Median	4.42
Range	(2.9; 16.3)
All subsequent infusions	
Mean (SD)	3.56 (0.661)
Median	3.45
Range	(0.8; 26.1)

*Not including any daratumuamb administered as part of compassionate supply.

Figure 3. Patient Disposition From the EAP



***Remaining patient dispositions:** 5 (1.4%) discontinued due to other reason, 4 (1.1%) discontinued due to physician decision, 2 (0.6%) discontinued due to disease relapse, and 1 subject (0.3%) each discontinued due to adverse event-other and lost to follow-up.

Safety

- Total number of patients who experienced an AE was 281 (80.7%). AEs Grade ≥3 were reported in 50% of patients. The most common grade 3-4 AEs were thrombocytopenia (15%) and anemia (14%). Total number of patients who discontinued treatment due to an AE was 13 (3.7%) (**Table 4**).
- SAEs occurred in 35% of patients, including 12% of patients with SAEs that were determined by the investigator to be drug-related. Grade 3/4 SAEs occurred in 29.0% of subjects (**Table 5**).
- A total of 195 (56%) patients experienced IRRs during the study, and all 195 subjects experienced IRRs during their first infusion. 2% of subjects experienced additional IRRs during later infusions. The most common IRRs, across all infusions, were respiratory or thoracic symptoms which occurred in 31% of patients. No subjects discontinued the study due to an infusion related reaction (**Table 6**).

Table 4. Most Common Grade 3/4 Adverse Events

	Patients (N=348)
Total Grade 3 or 4 TEAEs	**50%**
Blood and Lymphatic System Disorders	30%
Thrombocytopenia	15%
Anemia	14%
Respiratory, Thoracic and Mediastinal Disorders	6%
General Disorders and Administration Site Conditions	4%
Dyspnea	3%

Table 5. Most Common Grade 3/4 Serious Adverse Events

	Patients (N=348)
Total Grade 3 or 4 SAEs	**29.0%**
Pneumonia	2.9%
Hypercalcemia	2.9%
Thrombocytopenia	2.3%
Urinary Tract Infection	1.7%
Febrile neutropenia	1.7%
Dyspnea	1.7%

Table 6. Infusion Related Reactions

	Infusion Related Reactions (N=348)
Percentage of Patients With IRRs	
First infusion	56%
Second infusion	2%
All subsequent infusions	2%
Respiratory or thoracic symptoms	31%
Cough	14%
Dyspnea	9%
Throat irritation	6%
Nasal congestion	5%
Bronchospasm	2%

Patient Reported Outcomes

- The median change from baseline in all the domains of the EuroQol five dimensions questionnaire (EQ5D5L) and European Organization for Research and Treatment of Cancer (EORTC) QLQC30 scales after 1 and 2 cycles as well as at patients' last assessment was 0, with the exception of EQ5D5L visual analog scale (VAS), which showed a median increase of 1 and 2 units after 1 and 2 cycles, respectively (**Table 7**)

Table 7. Summary of EQ-5D-5L and EORTC QLQ-C30: Value and Change From Baseline by Visit

		Change From Baseline		
	Baseline	Cycle 2 Day 1	Cycle 3 Day 1	Last Assessment
	Mean, Median (N: Min, Max)	Mean, Median (N: Min, Max)	Mean, Median (N: Min, Max)	Mean, Median (N: Min, Max)
EQ-5D-5L Utility Score				
EQ-5D-5L utility score	0.75, 0.79 (324: 0.1, 1.0)	-0.01, 0.00 (223: -0.6, 0.3)	0.00, 0.00 (142: -0.6, 0.3)	-0.02, 0.00 (269: -0.6, 0.4)
Visual analogue scale (VAS)	63.06, 66.00 (324: 9.0, 100.0)	0.71, 1.00 (223: -70.0, 60.0)	3.35, 2.00 (142: -72.0, 58.0)	-0.16, 0.00 (269: -80.0, 58.0)
EORTC QLQ-C30				
Appetite loss	19.94, 0.00 (326: 0.0, 100.0)	5.04, 0.00 (225: -66.7, 100.0)	0.93, 0.00 (144: -66.7, 100.0)	4.57, 0.00 (270: -66.7, 100.0)
Cognitive functioning	76.89, 83.33 (326: 0.0, 100.0)	0.89, 0.00 (225: -83.3, 83.3)	0.93, 0.00 (144: -66.7, 83.3)	-0.74, 0.00 (270: -66.7, 66.7)
Constipation	15.54, 0.00 (326: 0.0, 100.0)	0.44, 0.00 (225: -100.0, 100.0)	-1.16, 0.00 (144: -100.0, 66.7)	-0.49, 0.00 (270: -100.0, 66.7)
Diarrhea	17.48, 0.00 (326: 0.0, 100.0)	0.44, 0.00 (225: -66.7, 100.0)	1.62, 0.00 (144: -66.7, 100.0)	1.48, 0.00 (270: -100.0, 100.0)
Dyspnoea	22.60, 33.33 (326: 0.0, 100.0)	-0.15, 0.00 (225: -66.7, 66.7)	-3.01, 0.00 (144: -100.0, 66.7)	3.21, 0.00 (270: -100.0, 66.7)
Emotional functioning	77.53, 83.33 (326: 8.3,100.0)	1.11, 0.00 (225: -75.0, 66.7)	2.49, 0.00 (144: -33.3, 41.7)	-1.42, 0.00 (270: -66.7, 66.7)
Fatigue	42.26, 33.33 (326: 0.0, 100.0)	3.01, 0.00 (225: -55.6, 66.7)	-0.54, 0.00 (144: -55.6, 55.6)	2.55, 0.00 (270: -66.7, 88.9)
Financial difficulties	24.34, 0.00 (326: 0.0, 100.0)	-4.74, 0.00 (225 -100.0, 66.7)	-0.93, 0.00 (144: -66.7, 100.0)	-2.35, 0.00 (270: -100.0, 66.7)
Global health status	58.61, 58.33 (326: 0.0, 100.0)	1.11, 0.00 (225: -58.3, 66.7)	4.69, 0.00 (144: -50.0, 66.7)	-1.48, 0.00 (270: -58.3, 66.7)
Nausea and vomiting	7.31, 0.00 (326: 0.0, 83.3)	1.04, 0.00 (225: -50.0, 100.0)	0.58, 0.00 (144: -33.3, 50.0)	3.46, 0.00 (270: -50.0, 100.0)
Pain score	39.11, 33.33 (326: 0.0, 100.0)	-1.41, 0.00 (225: -66.7, 83.3)	-2.55, 0.00 (144: -66.7, 66.7)	0.74, 0.00 (270: -66.7, 83.3)
Physical functioning	68.68, 73.33 (326: 6.7, 100.0)	-1.73, 0.00 (225: -80.0, 40.0)	0.83, 0.00 (144: -46.7, 46.7)	-3.40, 0.00 (270: -80.0, 53.3)
Role functioning	64.37, 66.67 (326: 0.0, 100.0)	0.07, 0.00 (225: -83.3, 66.7)	0.81, 0.00 (144: -83.3, 66.7)	-3.70, 0.00 (270: -100.0, 66.7)
Sleep disturbance	29.86, 33.33 (326: 0.0, 100.0)	1.48, 0.00 (225: -100.0, 100.0)	-1.39, 0.00 (144: -66.7, 100.0)	-0.12, 0.00 (270: -100.0, 100.0)
Social functioning	65.13, 66.67 (326: 0.0, 100.0)	2.67, 0.00 (225: -50.0, 66.7)	1.50, 0.00 (144: -83.3, 66.7)	-0.99, 0.00 (270: -100.0, 66.7)

CONCLUSIONS

- Adverse events in the US EAP were consistent with the previously described AE profile of daratumumab in MM patients with >3 prior therapies including a PI and IMID or who were refractory to both a PI and IMID. No new safety signals were observed.
- SAEs occurred in one-third of patients, including 12% of patients who experienced a drug-related SAE
- More than half of patients experienced IRRs, which primarily occurred during the first infusion and were mostly grade 1-2 in severity
- Patients maintained their health related quality of life during a median duration of 2 months of therapy

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