Use of Montelukast to Reduce Infusion Reactions in an Early Access Program (EAP) of Daratumumab in United States Patients With Relapsed or Refractory Multiple Myeloma

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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
- CD38 is expressed on airway smooth muscle cells, and infusion related reactions (IRRs) in registration studies were marked by symptoms (cough, wheezing, rhinorrhea) similar to those of allergic rhinitis
- Anecdotal reports indicated that premedication with montelukast, a leukotriene receptor antagonist, may reduce the IRR rate associated with daratumumab therapy

OBJECTIVES

- To provide early access to daratumumab treatment
- To collect safety data including IRRs from a multicenter, open-label EAP
- To allow the use of montelukast as a premedication for daratumumab therapy

STUDY DESIGN

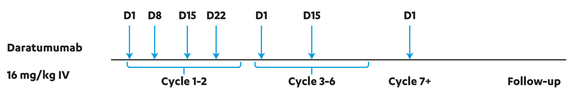
Table 1. Patient Eligibility Criteria

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
	Absolute neutrophil count ≤0.5 × 10^9/L
	Platelet count <50 x 10^9/L
ECOG performance status score 0-2	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*



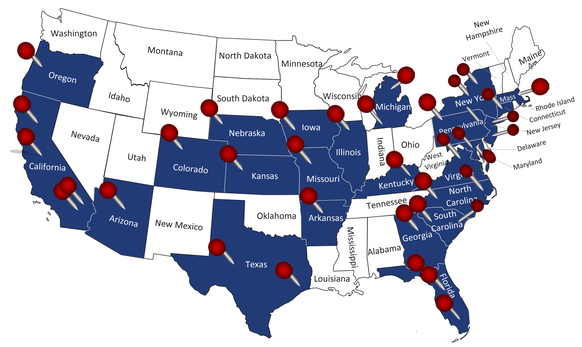
*Cycle length = 28 days

- Pre- and post-infusion medications were administered as in study MMY2002. Pre-medications administered 1 hour (±15 minutes) prior to the daratumumab infusion included:
  - Methylprednisolone 100 mg (or equivalent) intravenously for the first 2 infusions, and 60 mg with subsequent infusions
  - Acetaminophen 650-1000 mg
  - Diphenhydramine 25-50 mg (or equivalent antihistamine drug)
- Post-medication included a corticosteroid (methylprednisolone 20 mg or equivalent) and was given on the 2 consecutive days following daratumumab infusions[1]
- Montelukast was not recommended but was allowed at the investigator's discretion
- 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)

RESULTS

- In total, 400 patients were screened and 348 patients were enrolled and dosed (**Tables 2** and **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	72% / 17%
Performance Status	
ECOG Score of 1	58%
ECOG Score of 2	16%

Table 3. Treatment Delivery (N=348)

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)

- 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 (**Table 4**).

Table 4. Treatment Delivery of Investigational Supply of Daratumumab*

Infusion Related Reactions (N=348)	
Grade >3 IRRs	8%
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%

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

- Sixty patients received montelukast during therapy, including 50 patients who received montelukast 10 mg given >30 minutes prior to the first infusion (**Table 5**)
- Median time for first infusion was 6.7 and 7.6 hours for patients who did or did not receive montelukast, respectively, while times for the second and all subsequent infusions were similar in both groups

Table 5. Observed IRRs in Patients With and Without Montelukast Therapy

	Montelukast 10 mg as Pre-Infusion (n=50)	No Montelukast Given as Pre-Infusion (n=298)
IRR rate at first infusion	38.0%	58.5%
Respiratory symptoms	20%	32%
Gastrointestinal symptoms	4%	11%
Chills	14%	14%
Median time for first infusion (hours)	6.7	7.6

- A total of 24 subjects experienced infusion related reactions that were considered SAEs but no subject discontinued the study due to an infusion related reaction

CONCLUSIONS

- The findings of the EAP study in US patients with MM who had received >3 prior therapies including a PI and IMID or were double-refractory observed an IRR rate and median infusion times that were similar to what were observed in the pivotal registration study MMY2002 in this patient population
- The observed IRR rate during the first daratumumab infusion was one-third lower in patients who received 10 mg of montelukast >30 min prior to the first daratumumab infusion than in patients who did not receive montelukast
- Respiratory and gastrointestinal symptoms were lower in patients who received montelukast, whereas chills were observed at a similar rate in both groups
- The median time for the first infusion was 0.9 hours shorter in patients who received montelukast
- Because the use of montelukast was limited to a small number of centers, the role of montelukast in reducing IRRs can not be determined from these uncontrolled observations
- Additional studies to determine if montelukast mitigates the IRRs associated with the first infusion of daratumumab are indicated

REFERENCE

1. Lonial S, et al. *Lancet*. 2016; 387: 1551-1560.

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