Daratumumab to Enhance Therapeutic Effectiveness of Revlimid in Smoldering Myeloma

Overall EAA173 Study Objective
To examine whether the addition of daratumumab, a monoclonal antibody targeting the CD38 antigen on immune cells, to the chemotherapy regimen of lenalidomide and dexamethasone can provide a durable response in patients with high-risk smoldering multiple myeloma (SMM)

Study Objectives

Primary Objective
• Compare overall survival (OS) in patients with high-risk SMM randomized to daratumumab-hyaluronidase subcutaneous (SC)-revlimid-dexamethasone or revlimid-dexamethasone

Secondary Clinical Objectives
• Compare progression-free survival (PFS) and response rates

Exploratory Clinical Objectives
• Evaluate safety and compare toxicity rates
• Monitor incidence of infusion-related reactions over the first cycle of daratumumab
• Evaluate stem cell mobilization failure and early stem cell mobilization feasibility

Primary Patient-Reported Outcomes Objective
• Compare change in health-related quality of life (FACT-G) from baseline to end of study therapy (cycle 24)
When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.

**Eligibility Criteria**

**Main Inclusion Criteria**
- ≥ 18 years of age and diagnosed with asymptomatic high-risk SMM within the past 12 months.
- High-risk is defined by the presence of 2 or more of the following factors:
  - Abnormal serum free light chain (FLC) ratio of involved to uninvolved > 20, but less than 100 if the involved FLC is ≥ 10 mg/dL by serum FLC assay
  - Serum M-protein level > 2 g/dL
  - Presence of t(4;14) or del 17p, del 13q or 1q gain by conventional cytogenetics or FISH studies
  - > 20% plasma cells on biopsy or aspirate

- Bone marrow aspirate and/or biopsy required to be performed within 42 days prior to randomization and must demonstrate 10% to 59% clonal plasma cells
- Measurable disease as defined by one or more of the following, obtained within 28 days prior to randomization:
  - ≥ 1 g/dL on serum protein electrophoresis (SPEP)
  - ≥ 200 mg of monoclonal protein on 24-hour urine protein electrophoresis (UPEP)
- SPEP, UPEP, and serum FLC are required to be performed within 28 days prior to randomization
- ECOG performance status 0, 1, or 2
- Adequate organ and marrow function within 28 days prior to randomization
- History of current or previous deep vein thrombosis (DVT) or pulmonary embolism but required to take anticoagulant prophylaxis
- History of prior malignancy, if treated with curative intent and considered disease free
- Registered into the mandatory Risk Evaluation and Mitigation Strategy (REMS) program and willing to comply with REMS requirements
- Use of effective contraception or abstinence

**Main Exclusion Criteria**
- History of prior malignancy, if treated with curative intent and considered disease free

**Secondary Patient-Reported Outcomes Objectives**

- Compare change in FACT-G score from end of study therapy (cycle 24) or early treatment discontinuation to 6-months post-treatment end between arms
- Evaluate time to worsening of FACT-G score
- Compare MRD-positive to MRD-negative conversion rates from 12 cycles to end of treatment
- Examine patterns of change in MRD levels during therapy
- Compare minimal residual disease (MRD)–negative rates after 12 cycles of therapy
- Compare MRD-positive to MRD-negative conversion rates from 12 cycles to end of treatment
- Examine patterns of change in MRD levels during therapy

**Exploratory Laboratory Objectives**

- Evaluate agreement and discordance between methods determining disease-free status
- Assess prognostic value of MRD status at 24 cycles for PFS

**Exploratory Imaging Objectives**

- Evaluate the association of baseline FDG-PET/CT imaging with PFS
- Assess the ability of baseline FDG-PET/CT to predict MRD status after 12 cycles and end of therapy (cycle 24)
- Describe the results of subsequent FDG-PET/CT imaging studies in the subset of patients with baseline abnormal FDG-PET/CT, and associate these results with PFS

**Exploratory Patient-Reported Outcomes Objectives**

- Describe changes in FACT-G scores over study therapy and shortly after treatment discontinuation, and evaluate correlation with survival
- Evaluate attributes of select patient-reported treatment-emergent symptomatic adverse events (PRO-CTCAE) longitudinally and compare responses with reported adverse events
- Measure the likelihood of medication adherence (ASK-12) and examine the relationship with treatment exposure
- Assess correlation of treatment adherence and ASK-12 with FACT-G score
- Tabulate PRO compliance and completion rates

**Primary Laboratory Objectives**

- Compare minimal residual disease (MRD)–negative rates after 12 cycles of therapy
- Compare MRD-positive to MRD-negative conversion rates from 12 cycles to end of treatment
- Examine patterns of change in MRD levels during therapy

**Exploratory Laboratory Objectives**

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**Exploratory Imaging Objectives**

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Eligibility Criteria (cont)*

Main Exclusion Criteria

- Known lytic lesions, plasmacytoma, or unexplained hypercalcemia (ie, > 11 or 1 mg/dL above upper limit of normal)
  - Baseline FDG-PET and MRI of the spine/pelvis is required 60 days prior to randomization
- Known COPD with FEV1 < 50% of predicted normal or known moderate to severe persistent asthma within 2 years prior to randomization
- Prior or concurrent systemic or radiation therapy for treatment of myeloma, or having a contraindication to DVT prophylaxis/aspirin
- More than one focal marrow lesion on MRI of either pelvis or spine (see protocol for patients that are excused)
- Concurrent use of erythropoietin
- Prior or current glucocorticosteroid therapy for treatment of multiple myeloma, with exceptions
- Active, uncontrolled seizure disorder, or a seizure within 6 months of randomization
- Uncontrolled intercurrent illness including uncontrolled hypertension, symptomatic congestive heart failure, unstable angina, uncontrolled cardiac arrhythmia, uncontrolled psychiatric illness or social situation limiting compliance, or history of Stevens-Johnson syndrome
- Known monoclonal gammopathy of undetermined significance
- Grade 2 or higher peripheral neuropathy per CTCAE
- Active, uncontrolled infection
- NYHA classification III or IV heart failure at baseline
- History of allergic reactions attributed to compounds similar in chemical or biologic composition to daratumumab, lenalidomide, or dexamethasone
- Pregnancy or breastfeeding

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