Daratumumab to Enhance Therapeutic Effectiveness of Revlimid in Smoldering Myeloma (DETER-SMM)

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 smoldering multiple myeloma (SMM)

Study Objectives
Primary Objective
- Compare overall survival (OS) in patients with high-risk SMM randomized to daratumumab-revlimid-dexamethasone or revlimid-dexamethasone

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

Patient-Reported Outcomes 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

Exploratory Clinical Objectives
- Measure treatment exposure and adherence
- Estimate treatment duration and time to progression

Continued
Patient-Reported Outcomes
Objectives (cont)
- 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
- Derive an overall PRO-CTCAE score at each assessment time point
- Measure the likelihood of medication adherence (ASK-12) at 6-month intervals
- Assess the association of overall PRO-CTCAE score with FACT-G score
- Compare select PRO-CTCAE items and related provider-reported CTCAEs
- Evaluate association between treatment adherence and ASK-12 score
- Assess correlation of treatment adherence and ASK-12 with FACT-G score
- Tabulate PRO compliance and completion rates

Laboratory Objectives
- Compare minimal residual disease (MRD)–negative rates after 12 cycles of therapy
- Compare MRD-positive to-negative conversion rates from 12 cycles to end of treatment
- Examine patterns of change in MRD levels during therapy
- Evaluate agreement and discordance between methods determining disease-free status

Assess prognostic value of MRD status at 12 cycles for OS and PFS

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
- 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

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 any one of the following:
  - Abnormal serum free light chain (FLC) ratio (≤ 0.125 or ≥ 8.0 and involved chain < 100 mg/L) by serum FLC assay
  - Serum M-protein level ≥ 3 mg/dL
  - Presence of t(4;14) or del 17p or 1q gain by conventional cytogenetics or FISH studies
- Bone marrow aspirate and/or biopsy required to be performed within 28 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 marrow, renal, and hepatic 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
- HIV+ with undetectable HIV viral loads tested within 6 months
- Use of effective contraception or abstinence

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.
Eligibility Criteria (cont)*

Main Exclusion Criteria
- Known lytic lesions, plasmacytoma, or unexplained hypercalcemia (ie, > 11 or 1 mg/dL above upper limit of normal)
- 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
- Concurrent use of erythropoietin
- Prior or current glucocorticosteroid therapy for treatment of multiple myeloma, with exceptions
- Active, uncontrolled seizure disorder, or a seizure in the past 6 months

- 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

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.