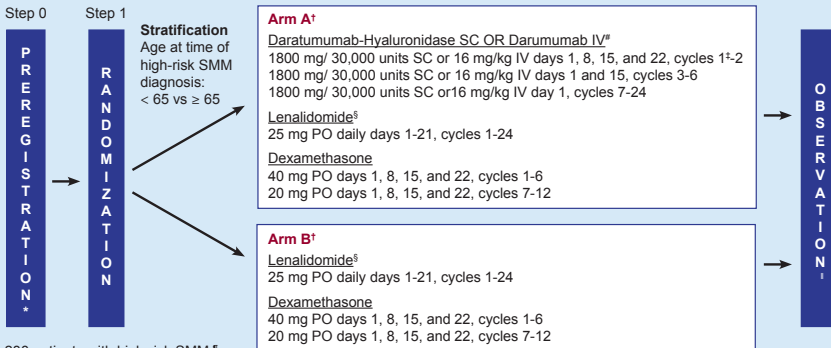


Daratumumab to Enhance Therapeutic Effectiveness of Revlimid in Smoldering Myeloma

Study Schema



Accrual goal = 288 patients with high-risk SMM.[†]

Cycle = 28 days. All doses are based on actual body weight.

*Submission of prestudy specimens per patient consent.

[†]Peripheral blood stem cells (PBSC) for future transplants should be collected during cycles 4-6 of therapy. Therapy may be interrupted for up to 6 weeks to allow for PBSC collection. Collection following 4-6 weeks of therapy is not required for protocol participation.

[‡]Note: For patients receiving IV daratumumab, "split-dosing" schedule may be used for first infusion, and will consist of 8 mg/kg given on Cycle 1, days 1 and 2 only.

[§]In patients with calculated (Cockcroft-Gault) creatinine clearance of 30-59 mL/min, starting dose of lenalidomide should be reduced to 10 mg. If clearance improves to ≥ 60 mL/min, the dose can be increased to 25 mg provided the patient has not experienced any toxicity that would require a dose reduction for lenalidomide.

[¶]All patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if nonprotocol therapy is initiated, and for survival for 15 years from date of randomization.

^{††}Patients must have been diagnosed within the past 12 months. See Section 3.2.2 for high-risk SMM definition.

^{†††}Patients currently receiving IV daratumumab should cross over to SC daratumumab-hyaluronidase (if tolerated; see protocol Section 5.1.1 for details). SMM = smoldering multiple myeloma.

EAA173/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 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
- 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

Refer to the protocol for patient-reported outcomes objectives (section 2.4), primary and exploratory laboratory objectives (sections 2.5 and 2.6), and imaging objectives (section 2.7)

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***
- Known lytic lesions, plasmacytoma, or unexplained hyper-calcemia (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

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

Continued

Eligibility Criteria (cont)*

- 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

