FAST FACTS

EAA173 - Daratumumab to Enhance Therapeutic Effectiveness of Revlimid in Smoldering Myeloma (DETER-SMM)

Eligibility criteria

Step 0 Pre-Registration Eligibility Criteria

1. Patients must be considered potential candidates for participation in EAA173.

Step 1 Randomization Eligibility Criteria

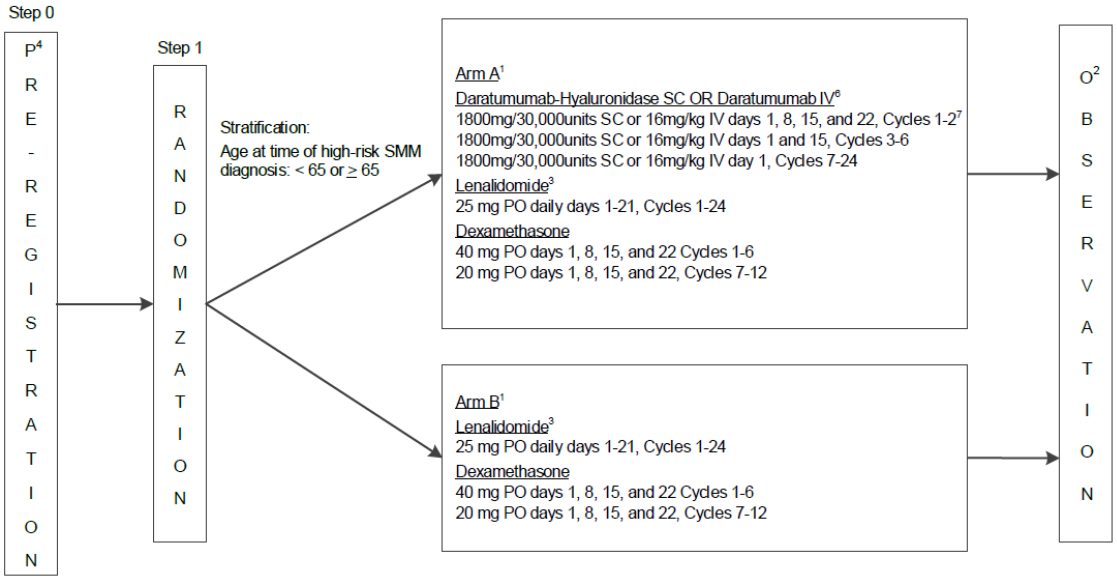
1. Patient must be ≥ 18 years of age.
2. Patient must be diagnosed with asymptomatic high-risk smoldering multiple myeloma (SMM) within the past 12 months. High-risk is defined by the presence of 2 or more of the following factors:
   - Abnormal serum free light chain (FLC) ratio of involved to uninvolved >20, but less than 100 if the involved FLC is >10 mg/dL by serum FLC assay
   - Serum M-protein level > 2 gm/dL
   - Presence of t(4;14) or del 17p, del 131q or 1q gain by conventional cytogenetics or FISH studies
   - >20% plasma cells on biopsy or aspirate
3. A bone marrow aspirate and/or biopsy is required to be performed within 42 days prior to randomization and must demonstrate 10-59% clonal plasma cells.
4. Patient must have measureable disease as defined by having one or more of the following, obtained within 28 days prior to randomization:
   • ≥ 1 g/dL on serum protein electrophoresis
   • ≥ 200 mg of monoclonal protein on a 24 hour urine protein electrophoresis
   NOTE: In the rare situation where the SPEP is felt to be unreliable, then quantitative immunoglobulin levels on nephelometry or turbidometry can be accepted. Please refer to Section 6.1.2 for more information.
5. SPEP, UPEP, and serum FLC are required to be performed within 28 days prior to randomization.
   Serum M-protein by SPEP _____ (g/dL)
   Date of Test: _____
   Urine M-protein light chain excretion by UPEP_____ (mg/24hr)
   Date of Test: _____
   NOTE: UPEP (on a 24-hour collection) is required; no substitute method is acceptable. Urine must be followed monthly if the baseline urine M-spike is ≥ 200 mg/24 hr, and urine in addition to serum must be followed in order to confirm a VGPR or higher response.
   Serum Free Light Chain
   Kappa FLC _____ (mg/dL) or _____ (mg/L);
   Lambda FLC _____ (mg/dL) or _____ (mg/L);
   Kappa/lambda ratio _____
   Date of Test: _____
6. Patient must have no lytic lesions, no known plasmacytoma, and no unexplained hypercalcemia (i.e., > 11 mg/dL or 1mg/dL above ULN). Specifically, local interpretation of MRI and PET scans will be used to exclude lytic lesions or plasmacytomas and must be obtained within 60 days prior to randomization.
7. Patient must not have known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal or known moderate or severe persistent asthma within 2 years prior to randomization.

8. Patient must have adequate organ and marrow function as defined below (obtained within 28 days prior to randomization):
    a. Hemoglobin ≥ 11 g/dL
    Hemoglobin:_____ Date:_____
    b. Platelet count ≥ 100,000 cells/mm3
    Platelet:_____ Date:_____
    c. Absolute neutrophil count(ANC) ≥ 1500 cells/mm3
    ANC:_____ Date:_____
    d. Calculated creatinine clearance ≥ 30 mL/min
    Calculated creatinine clearance:_____ Date:_____
    e. Bilirubin ≤ 1.5 mg/dL (except patients with known Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dl)
    Bilirubin:_____ Date:_____
    f. SGPT (ALT) and SGOT (AST) ≤ 2.5 times the upper limit of normal (ULN)
    SGPT (ALT):_____ ULN:_____ Date:_____
    SGOT (AST):_____ ULN:_____ Date:_____
9. Patient must not have any prior or concurrent systemic or radiation therapy for the treatment of myeloma. Patient must also not have contraindication to DVT prophylaxis/aspirin.
10. Patient must not have more than one focal marrow lesion on MRI of either pelvis or spine. Patients with indwelling pacemakers and/or ICD (implantable cardioverter-defibrillator) that is known or suspected to be MRI incompatible will be excused from this test.
11. Concurrent use of erythropoietin is not allowed while on study therapy.
12. Prior or glucocorticosteroid therapy for the treatment of multiple myeloma is not permitted. Prior systemic glucocorticosteroid use for the treatment of non-malignant disorders is permitted; concurrent use after registration on the study should be restricted to the equivalent of prednisone 10 mg per day. Prior or concurrent topical or localized glucocorticosteroid therapy to treat non-malignant comorbid disorders is permitted.
13. Patient must not have active, uncontrolled seizure disorder. Patient must not have had a seizure in within the 6 months prior to randomization.
14. Patient must not have uncontrolled intercurrent illness including uncontrolled hypertension, symptomatic congestive heart failure, unstable angina, uncontrolled cardiac arrhythmia, uncontrolled psychiatric illness or social situation that would limit compliance with the study, or a prior history of Stevens Johnson Syndrome.
15. Patient must have an ECOG performance status 0, 1, or 2.
16. Patients with monoclonal gammopathy of undetermined significance are not eligible.
17. Patient must not have Grade 2 or higher peripheral neuropathy per CTCAE.
18. Patient must not have active, uncontrolled infection.
19. Patient may have a history of current or previous deep vein thrombosis or pulmonary embolism but are required to take some form of anti-coagulation as prophylaxis if they are not currently on full-dose anticoagulation.
20. Patient should not have New York Heart Association classification III or IV heart failure at baseline.
21. Patients with a history of prior malignancy are eligible provided they were treated with curative intent and have been free of disease for the time period considered appropriate for cure of the specific cancer.
22. Patient must agree to register into the mandatory REMS program and be willing and able to comply with the requirements of REMS.
23. Patients must not be pregnant due to potential harm to the fetus from Daratumumab and Lenalidomide. All patients of childbearing potential must have a blood test or urine study with a sensitivity of at least 25 mIU/mL within 10-14 days prior to the first dose of lenalidomide and again within 24 hours prior to the first dose of lenalidomide. Patients of childbearing potential must also agree to ongoing pregnancy testing while on treatment. A patient of childbearing potential is defined as anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy, or 3)

has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Please see Appendix V: Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, AND also Appendix IV: Lenalidomide Information Sheet.
Patient of childbearing potential (Y/N)? _____
Date of blood test or urine study: _____

24. Patients of childbearing potential must either abstain from sexual intercourse for the duration of their participation in the study or agree to use TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME for 1) at least 28 days before starting study treatment; 2) while participating in the study; 3) during dose interruptions; and 4) for at least 28 days after the last dose of protocol treatment. (Patients of childbearing potential who are assigned to Arm A and receive daratumumab must extend this contraception requirement to 3 months after the last dose of protocol treatment). Patients must also agree to not breastfeed during this same time period. Men must agree to either abstain from sexual intercourse for the duration of their participation in the study or use a latex condom during sexual contact with a partner of childbearing potential while participating in the study and for 28 days after the last dose of protocol treatment even if they have had a successful vasectomy (Men assigned to Arm A and receive daratumumab must extend this contraception requirement to 3 months after the last dose of protocol treatment). Patients must also agree to abstain from donating sperm, even if they have had a successful vasectomy, or eggs while on study treatment and for 28 days after the last dose of protocol treatment (patients assigned to Arm A and receiving daratumumab must extend this requirement to 3 months after the last dose of protocol treatment). Patients must agree to abstain from donating blood during study participation and for at least 28 days after the last dose of protocol treatment.
25. Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months prior to randomization are eligible for this trial.
26. Patient should not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to daratumumab, lenalidomide, or dexamethasone.
27. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
28. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

Schema


Step 0
P[4]
RE-REGISTRATION
Step 1
RANDOMIZATION
Stratification:
Age at time of high-risk SMM diagnosis: < 65 or ≥ 65
Arm A[1]
Daratumumab-Hyaluronidase SC OR Daratumumab IV[6]
1800mg/30,000units SC or 16mg/kg IV days 1, 8, 15, and 22, Cycles 1-2[7]
1800mg/30,000units SC or 16mg/kg IV days 1 and 15, Cycles 3-6
1800mg/30,000units SC or 16mg/kg IV day 1, Cycles 7-24
Lenalidomide[3]
25 mg PO daily days 1-21, Cycles 1-24
Dexamethasone
40 mg PO days 1, 8, 15, and 22 Cycles 1-6
20 mg PO days 1, 8, 15, and 22, Cycles 7-12
Arm B[1]
Lenalidomide[3]
25 mg PO daily days 1-21, Cycles 1-24
Dexamethasone
40 mg PO days 1, 8, 15, and 22 Cycles 1-6
20 mg PO days 1, 8, 15, and 22, Cycles 7-12
O[2]
OBSERVATION