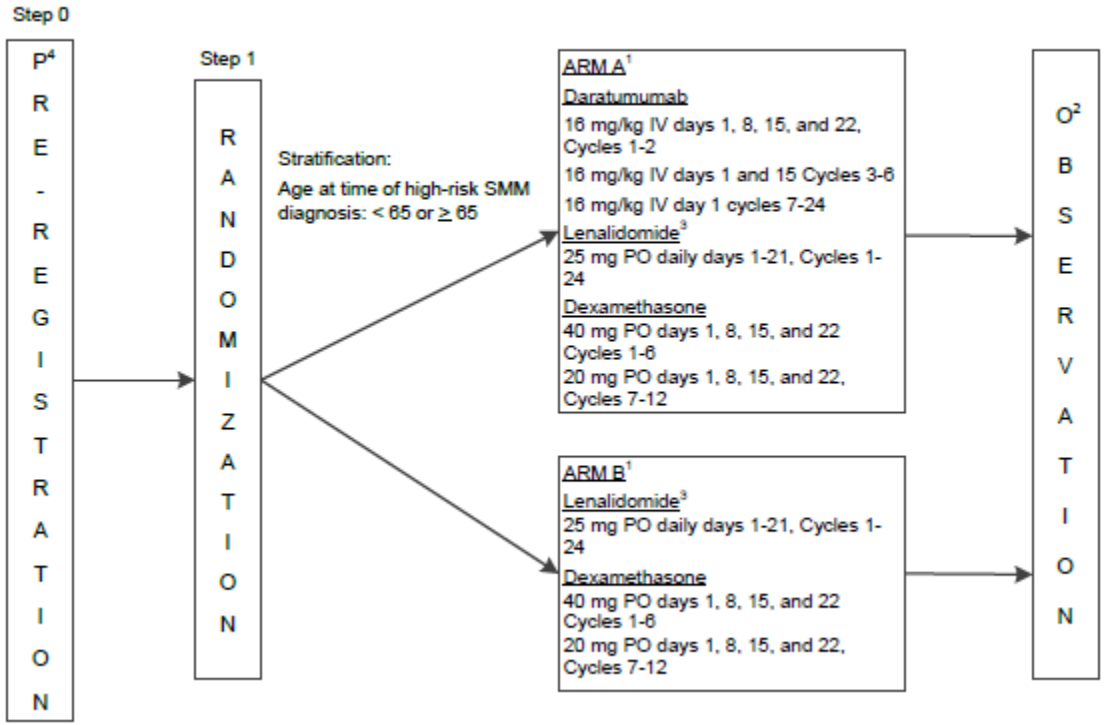
Schema



Accrual Goal: 288 patients with high-risk smoldering multiple myeloma[5]

Cycle: 28 days

1. Peripheral blood stem cells for future transplants should be collected between cycles 4-6 of therapy. Therapy may be interrupted for up to 6 weeks to allow for PBSC collection. While collection following 4-6 weeks of therapy is strongly suggested, it is not required for protocol participation.
2. All patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 15 years from the date of randomization.
3. In patients with creatinine clearance of 30-59 ml/min, starting dose of lenalidomide should be reduced to 10 mg. If the clearance improves to ≥ 60 ml/min, the dose can be increased to 25 mg provided the patient has not experienced any of the toxicities that would require a dose reduction for lenalidomide.
4. Submission of pre-study specimens per patient consent.
5. Patients must be diagnosed within the past 12 months. See Section 3.1.2 for the definition of high-risk SMM.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

NOTE: This study involves preregistration (see Section 4). Bone marrow specimens must be submitted for defined laboratory research studies as indicated in Section 10.

3.1 Step 1 Randomization Eligibility Criteria

_____ 3.1.1 Age ≥ 18 years.

_____ 3.1.2 Patients must be diagnosed with asymptomatic high-risk smoldering multiple myeloma (SMM) within the past 12 months. High-risk is defined by any one of the following factors:

- Abnormal serum free light chain ratio (≤ 0.125 or ≥ 8.0 and involved chain < 100 mg/L) by serum FLC assay
- Serum M-protein level ≥ 3 gm/dL
- Presence of t(4;14) or del 17p or 1q gain by conventional cytogenetics or FISH studies

_____ 3.1.3 Bone marrow aspirate and/or biopsy is required to be performed within 28 days prior to randomization and must demonstrate 10-59% clonal plasma cells.

_____ 3.1.4 Patients 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.

_____3.1.5 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: _____

_____3.1.6 Patients must have no lytic lesions, no known plasmacytoma, and no unexplained hypercalcemia (i.e., > 11 mg/dL or 1mg/dL above ULN).

_____3.1.7 The following laboratory levels must be obtained within 28 days prior to randomization:

_____3.1.7.1 Hemoglobin ≥ 11 g/dL
Hemoglobin:_____Date:_____

_____3.1.7.2 Platelet count ≥ 100,000 cells/mm^3
Platelet:_____ Date:_____

_____3.1.7.3 Absolute neutrophil count ≥ 1500 cells/mm^3
ANC:_____ Date:_____

_____3.1.7.4 Calculated creatinine clearance ≥ 30 mL/min
Creatinine clearance:_____ Date:_____

_____3.1.7.5 Bilirubin ≤ 1.5 mg/dL
Bilirubin:_____ Date:_____

_____ 3.1.7.6 SGPT (ALT) and SGOT (AST) ≤ 2.5 times the upper limit of normal
SGPT (ALT):_____ULN:_____Date:_____

SGOT (AST):_____ULN:_____ Date:_____

_____ 3.1.8 Patients must not have any prior or concurrent systemic or radiation therapy for the treatment of myeloma. Patients must also not have contraindication to DVT prophylaxis/aspirin.

_____ 3.1.9 Patients must not have more than one focal marrow lesion on MRI of either pelvis or spine.

_____ 3.1.10 Concurrent use of erythropoietin is not allowed while on study therapy.

_____ 3.1.11 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.

_____ 3.1.12 Patients must not have active, uncontrolled seizure disorder. Patients must not have had a seizure in the last 6 months.

_____3.1.13 Patients 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.

_____3.1.14 Patient must have an ECOG performance status 0, 1, or 2.

_____3.1.15 Patients with monoclonal gammopathy of undetermined significance are not eligible.

_____3.1.16 Patients must not have Grade 2 or higher peripheral neuropathy per CTCAE.

_____3.1.17 Patients must not have active, uncontrolled infection.

_____3.1.18 Patients 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.

_____3.1.19 Patients should not have New York Heart Association classification III or IV heart failure at baseline.

_____3.1.20 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. For most diseases this time frame is 5 years.

_____ 3.1.21 Patients must agree to register into the mandatory REMS program and be willing and able to comply with the requirements of REMS.

_____3.1.22 Women must not be pregnant due to potential harm to the fetus from Daratumumab and Lenalidomide. All females of childbearing potential (FCBP) 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. FCBP must also agree to ongoing pregnancy testing while on treatment. A female of childbearing potential is any woman,

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: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, AND also Appendix IV: Lenalidomide Information Sheet.

Female of childbearing potential (Y/N)? _____

Date of blood test or urine study: _____

_____ 3.1.23 Females of childbearing potential (FCBP) 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 (FCBP who are assigned to Arm A and receive daratumumab must extend this contraception requirement to 3 months after the last dose of protocol treatment). Women 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 FCBP 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 must also agree to abstain from donating sperm while on study treatment and for 28 days after the last dose of protocol treatment even if they have had a successful vasectomy. Both women and men must both agree to abstain from donating blood during study participation and for at least 28 days after the last dose of protocol treatment.

_____ 3.1.24 HIV+ patients with undetectable HIV viral loads tested within 6 months are eligible.

_____ 3.1.25 Patients should not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to daratumumab, lenalidomide, or dexamethasone.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.