**Patient Population:**
See Protocol Section 3 for Complete Eligibility Details

**Step 0 Pre-Registration:**
- Age ≥ 18 years; ECOG PS 0-2 (PS 3 allowed if secondary to pain); able to have a diagnostic bone marrow aspirate
- Must have suspected/confirmed newly diagnosed MM (IMWG); no more than 1 cycle of treatment
- Must be ineligible for autologous stem cell transplantation/willing to delay stem cell transplantation until first relapse or later (stem cell collection is allowed)
- Must agree to register to Celgene Revlimid REMS/ comply with requirements
- No known allergies/hypersensitivity/intolerance to corticosteroids, monoclonal antibodies/human proteins, or their excipients, or known sensitivity to mammalian-derived products

**Step 1 Registration:**
- Dominant sequences must have been identified
- Must have standard risk MM (R-ISS) Stage I/II and measurable/evaluable disease defined per protocol; adequate lab values
- Must have received no more than 1 cycle (28 days or less) of prior chemotherapy and no more than 160 mg of prior dexamethasone (or equivalent dose of prednisone) for treatment of symptomatic myeloma; must not have been exposed to daratumumab for treatment of symptomatic myeloma; prior RT to symptomatic lesions is allowed per protocol (see protocol for SMM treatment)
- HIV, HBV, HCV patients permitted per protocol
- Must be NYHA class 2B or better/meet cardiac criteria per protocol; DVT or PE patients are permitted if they are on anti-coagulation
- No peripheral neuropathy ≥ Gr 2 (or Gr 1 with pain)
- Must not have moderate/severe persistent asthma within the past 2 years/uncontrolled asthma of any classification

**Step 2 Randomization:**
- Institution must have received MRD test results; adequate lab values
- Must have completed Step 1 without experiencing progression

**Treatment Plan:**
See Protocol Section 5 for Complete Treatment Details

**Cycle= 28 days**

**Step 1—Induction (9 cycles):**
- **Arm A:**
  - Daratumumab-hyaluronidase 1800 mg/30,000 units SC days 1, 8, 15, 22 cycles 1-2; days 1 and 15 cycles 3-6; day 1 cycles 7-9
  - Lenalidomide 25 mg PO daily days 1-21 cycles 1-9
  - Dexamethasone 40 mg PO days 1, 8, 15, 22 cycles 1-4; 20 mg PO days 1, 8, 15, 22 cycles 5-9

**Step 2—Consolidation (9 cycles) and Maintenance (until disease progression):**
- **Arm B:**
  - Bortezomib 1.3 mg/m² SC (or IV per protocol) days 1, 8, 15 cycles 1-9
  - Daratumumab-hyaluronidase 1800 mg/30,000 units SC once every 28 days (day 1) cycles 1-9
  - Lenalidomide 15 mg PO daily days 1-21 cycles 1-9 (or dose tolerated in cycle 9)
  - Dexamethasone 12 mg PO days 1, 8, 15, 22 cycles 1-9 (or dose tolerated in cycle 9)
  - Maintenance (study cycles 19+):
    - Daratumumab-hyaluronidase 1800 mg/30,000 units SC once every 28 days (day 1)
    - Lenalidomide 10 mg PO daily days 1-21
- **Arm C:**
  - Consolidation (9 cycles/ study cycles 10-18): same as Arm B
  - Maintenance (study cycles 19+): same as Arm B

**Notes:**
- See protocol for pre-medication/daratumumab injection information, and dose modifications
- Patients should complete a medication diary for lenalidomide and dexamethasone each cycle; see protocol for fertility instructions
- Stem cells can be mobilized after 4 cycles of induction

**Patient Enrollment**
All Sites: Oncology Patient Enrollment Network (OPEN) [https://open.ctsu.org/open](https://open.ctsu.org/open)

**Protocol Information**
ECOG-ACRIN Operations-Boston: 857-504-2900, [http://ecog-acrin.org](http://ecog-acrin.org) (Member Login)

Please Enroll Your Eligible Patients!