Accrual Goal: Step 1 = 1450.
Cycle = 28 days (4 weeks).

*Institutions will be notified of the results of the Clonality ID and Tracking MRD tests. Patients must submit bone marrow specimen for MRD test.

†Patients can mobilize stem cells any time after 4 cycles of induction therapy. If stem cells are harvested, patients can be off treatment for up to 35 days for completion of stem cell collection. While stem cell collection is strongly recommended for patients who are considered eligible for transplant, it is not mandated.

See Protocol Section 5.0 for complete treatment details.

Btz = bortezomib; DRd = daratumumab-hyaluronidase, lenalidomide, and dexamethasone; MRD = minimal residual disease; R-ISS = Revised International Staging System.

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**Study Schema**

### Step 0
- Submit bone marrow specimen to Adaptive Biotechnologies for clonality ID test*.
- **Dominant Sequences Identified**
- **No Dominant Sequences Identified**
- Off Study

### Step 1
- **Induction† Cycles 1-9**
  - Arm A (DRd) Daratumumab-hyaluronidase, Lenalidomide and Dexamethasone
  - Submit bone marrow specimen to Adaptive Biotechnologies for Tracking MRD test*

### Step 2
- **Consolidation Cycles 10-18**
  - Arm B (Btz+DRd) Bortezomib-Daratumumab-hyaluronidase, Lenalidomide and Dexamethasone
  - Arm C (DRd) Daratumumab-hyaluronidase, Lenalidomide and Dexamethasone

**Stratification at Step 2 Randomization**
- Post-Induction MRD Status: Negative vs Positive/Indeterminant
- R-ISS Stage at Diagnosis/Study Entry: Stage I vs Stage II
- Treatment of Bortezomib Prior to Study Entry: Received vs Never Received

### Maintenance
- Cycles 19+ until progression

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EAA181 / EQUATE: Effective Quadruplet Utilization After Treatment Evaluation (EQUATE): A Randomized Phase 3 Trial for Newly Diagnosed Multiple Myeloma Not Intended for Early Autologous Transplantation
Overall EAA181 Study Objective
Develop a treatment approach to define the role of adding new drug classes for consolidation based on the depth of response to initial therapy for treatment of newly diagnosed multiple myeloma (MM).

Study Objectives

Primary Objective
- Determine if Btz-DRd consolidation followed by DR maintenance after standard induction therapy with DRd results in superior overall survival (OS) compared to DRd consolidation followed by DR maintenance in minimal residual disease (MRD)-positive patients.
- Determine if Btz-DRd consolidation results in superior progression-free survival in both MRD-positive and MRD-negative patients.
- Describe and compare toxicities during consolidation.
- Assess the improvement in MRD-negative rate with consolidation among patients who are MRD positive after induction.
- Assess the sustained MRD-negative rate among patients who are MRD negative after induction.
- Evaluate best response on induction, consolidation, and maintenance.

Secondary Objectives
- Determine if Btz-DRd consolidation results in superior OS in MRD-negative patients.

Patient-Reported Outcomes (PRO) Objectives
Refer to Protocol Section 2.3 for primary, secondary, and exploratory PRO objectives.

Imaging Objectives
Refer to Protocol Section 2.4 for primary, secondary, and exploratory imaging objectives.

Eligibility Criteria*

Main Inclusion Criteria
Step 0 – Preregistration
- ≥ 18 years of age with suspected or confirmed newly diagnosed MM by International Myeloma Working Group (IMWG) criteria and must not have received more than one cycle of treatment.
  - Bone marrow evaluation is not required prior to preregistration; this can be performed after preregistration step for diagnostic confirmation as per IMWG criteria and for Clonality ID sample.
- Considered ineligible for autologous stem cell transplantation by the treating physician, or willing to delay stem cell transplantation until first relapse or later.

NOTE: Stem cell collection is allowed on study.

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.
• Able to undergo diagnostic bone marrow aspirate following pre-registration if not performed previously
• ECOG performance status (PS) of 0–2 (PS 3 allowed if secondary to pain)

Step 1 - Registration
• Institution must have received Clonality ID test results from Adaptive Biotechnologies with dominant sequences identified
• Standard risk MM as defined by the Revised International Staging System (R-ISS) Stage I or II
• Measurable or evaluable disease as defined by having one or more of the following and obtained within 28 days prior to Step 1 registration:
  – ≥ 1 g/dL monoclonal protein (M-protein) on serum protein electrophoresis
  – ≥ 200 mg/24 h of M-protein on a 24-hour urine protein electrophoresis
  – Involved free light chain (FLC) ≥10 mg/dL or ≥100 mg/L AND abnormal serum immunoglobulin kappa to lambda FLC ratio (< 0.26 or > 1.65)
  – Monoclonal bone marrow plasmacytosis ≥ 30% (evaluable disease)
• SPEP, UPEP, and serum FLC assay performed within 28 days prior to Step 1 registration; bone marrow biopsy and/or aspirate is required within 28 days if bone marrow is being followed for response
• Adequate organ and marrow function obtained ≤ 14 days prior to registration and randomization
• Prior radiation therapy to symptomatic lesions is allowed provided there are no residual toxicities. Radiation must be completed at least 14 days prior to Step 1 registration
• HIV, HBV, HCV positivity with undetectable viral load and undergoing treatment per protocol

Step 2 - Randomization
• Institution received Tracking (MRD) test results from Adaptive Biotechnologies
• Completed Step 1 induction phase without experiencing progression
• Registered to Step 2 within 8 weeks of completing Step 1 induction treatment
• Any adverse event related to Step 1 induction treatment must have resolved to ≤ grade 2

Continued
**Eligibility Criteria**

**Main Exclusion Criteria**

**Step 0 - Preregistration**
- Known allergies, hypersensitivity, or intolerance to corticosteroids, monoclonal antibodies or human proteins, or their excipients, or known sensitivity to mammalian-derived products

**Step 1 - Registration**
- Received more than one cycle (28 days or less) of prior chemotherapy or more than 160 mg of prior dexamethasone (or equivalent dose of prednisone) for treatment of symptomatic myeloma. Exposed to daratumumab-hyaluronidase for the treatment of symptomatic myeloma
- Patients who have received prior treatment for smoldering multiple myeloma are eligible, except those who received prior lenalidomide with an anti-CD38 monoclonal antibody
- Prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen
- Evidence of uncontrolled cardiovascular conditions within 6 months prior to Step 1 registration
- Peripheral neuropathy ≥ grade 2 on clinical examination or grade 1 with pain at time of Step 1 registration
- Severe or moderate persistent asthma within the past 2 years or uncontrolled asthma of any classification

**Step 2 - Randomization**
- Received any non-protocol therapy outside of the assigned Step 1 induction treatment, including stem cell transplant

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