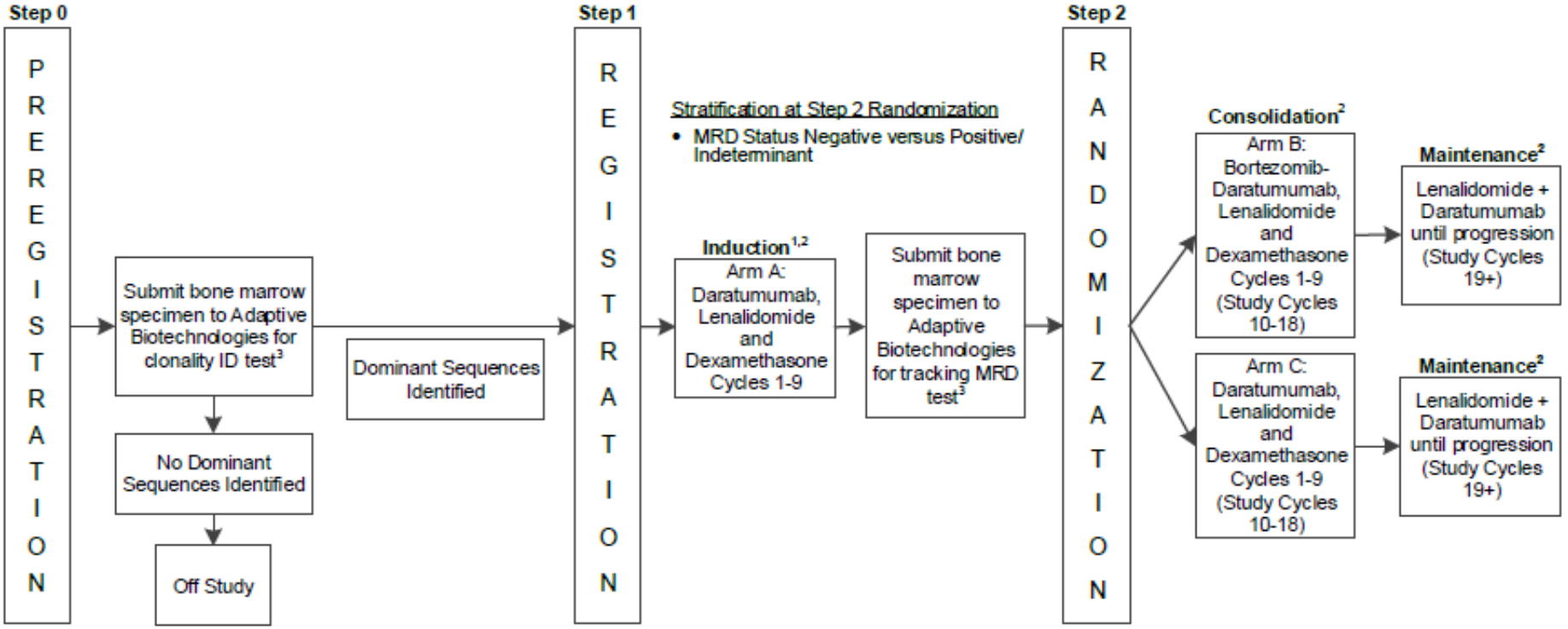
Schema



Accrual Goal:
Step 1 = 1450
Step 2 = 1232
Cycle Duration: 28 days (4 weeks)

1. 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.
2. Refer to Section 5.1 for detailed dosing instructions.
3. Institutions will be notified of the results of the Clonality ID and tracking MRD tests. Patients for whom dominant sequences were identified must submit bone marrow specimen for MRD test.

3. Selection of Patients

This study requires the submission of bone marrow aspirate to Adaptive Biotechnologies for the clonoSEQ® Assay. Bone marrow aspirates are to be submitted at preregistration and post induction as outlined in Section 10**Error! Reference source not found.**. Institutions will be notified of the results of the Clonality (ID) test and Tracking (MRD) test.

NOTE: Patients without an identifiable dominant sequence will not proceed to Step 1.

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.

NOTE: Prior to consenting patients and registration to Step 0, review of Step 1 criteria is recommended.

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: Before submitting specimens, physicians must first register with Adaptive Biotechnologies. Please refer to Section 10**Error! Reference source not found.** for instructions.

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.

3.1 Eligibility Criteria- Step 0 Preregistration

_____ 3.1.1 Patient must be ≥ 18 years of age.

_____ 3.1.2 Patient must have the ability to understand and the willingness to sign an informed consent document. Patients with impaired decision-making capacity (IDMC) who have a legally authorized representative (LAR) or caregiver and/or family member available will also be eligible.

_____ 3.1.3 Patient must have an ECOG performance status (PS) of 0-2 (PS 3 allowed if secondary to pain).

_____ 3.1.4 Patient must have newly diagnosed multiple myeloma (MM) by International Myeloma Working Group (IMWG) criteria.

_____ 3.1.5 Patients must be considered ineligible for autologous stem cell transplantation by the treating physician, or willing to delay stem cell transplantion until first relapse or later.

NOTE: Stem cell collection is allowed on study.

_____ 3.1.6 Patient must agree to register to the mandatory RevREMS program and be willing and able to comply with the requirements of RevREMS. See Section 8 for details.

_____ 3.1.7 Patient must not have any known allergies, hypersensitivity, or intolerance to corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to respective package inserts or Investigator's Brochure), or known sensitivity to mammalian-derived products.

_____ 3.1.8 Patient must be able to undergo diagnostic bone marrow aspirate following preregistration.

NOTE: Bone marrow aspirate specimen must be submitted to Adaptive Biotechnologies for clonoSEQ® Assay.

NOTE: Adaptive Biotechnologies will release results to the diagnostic Portal from the Clonality (ID) test within fourteen (14) days of receipt and reconciliation of fresh bone marrow specimen to the submitting institution.

3.2 Eligibility Criteria- Step 1 Registration

_____ 3.2.1 Patient must meet all eligibility criteria in Section 3.1 with exception of Section 3.1.5.

_____ 3.2.2 Institution must have received the Clonality (ID) test results from Adaptive Biotechnologies and dominant sequences must have been identified.

_____ 3.2.3 Patient must have standard risk MM as defined by the Revised International Staging System (RISS) Stage I or II.[31]

NOTE: R-ISS Stage is based on serum β2 microglobulin, albumin and LDH levels along with presence of chromosomal abnormalities (CA) detected by interphase fluorescent in situ hybridization (iFISH). Presence of del(17p), t(4;14), and/or t(14;16) is considered high risk and absence of these, including any other findings, are standard risk.

R-ISS Stage

Stage I: ISS Stage I [β2 microglobulin<3.5 mg/L, albumin>3.5 g/dL] AND standard-risk CA AND normal LDH

Stage II: Not R-ISS Stage I or III

Stage III: ISS Stage III [β2 microglobulin>5.5 mg/L] AND high-risk CA OR high LDH (>upper limit of normal) [patients with Stage III are ineligible]

_____ 3.2.4 Patient must have measurable or evaluable disease as defined by having one or more of the following, obtained within 28 days prior to registration:

- ≥ 1g/dL monoclonal protein (M-protein) on serum protein electrophoresis
- ≥ 200 mg/24 hours of monoclonal protein on a 24-hour urine protein electrophoresis
- Involved free light chain ≥ 10 mg/dL or ≥ 100 mg/L AND abnormal serum immunoglobulin kappa to lambda free light chain ratio (< 0.26 or > 1.65)
- Monoclonal bone marrow plasmacytosis ≥ 30% (evaluable disease)

_____ 3.2.5 Patients must have a SPEP UPEP, and serum FLC assay performed within 28 days prior to registration. In addition, a bone marrow biopsy and/or aspirate is required within 28 days if bone marrow is being followed for response.

Serum M-protein by SPEP _____ (g/dL)

Date of Test: _____

Urine M-protein measurement by 24 hr 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. Please note that if both serum and urine M-components are present, both must be followed in order to evaluate response.

Serum Free Light Chain Assay

Kappa FLC_____ (mg/dL) or _____ (mg/L);

Lambda FLC_____ (mg/dL) or _____ (mg/L);

kappa/lambda ratio_____

Date of Test: _____

NOTE: The serum free light chain test is required to be done if the patient does not have measurable disease in the serum or urine. Measurable disease in the serum is defined as having a serum M-spike ≥ 1 g/dL. Measurable disease in the urine is defined as having a urine M-spike ≥ 200mg/24 hr.

Plasma cell % on Bone Marrow _____%

Date of Test: _____

_____ 3.2.6 Patient must have adequate organ and marrow function as defined below (these must be obtained ≤ 14 days prior to Step 1 registration)

_____ Calculated creatinine clearance >30 mL/min

Creatinine clearance: _____ Date of Test: _____

_____ Absolute neutrophil count (ANC) ≥1000/mm3

ANC: _____ Date of Test: _____

_____ Untransfused Platelet count ≥75,000/mm3

Platelet: _____ Date of Test: _____

_____ Hemoglobin ≥8.0 g/dL

Hemoglobin: _____ Date of Test: _____

_____ Total bilirubin ≤ 1.5 x ULN (Institutional upper limit of normal)

Total Bilirubin: _____ ULN: _____

Date of Test: _____

_____ ALT and AST ≤ 3 x ULN

ALT: _____ ULN: _____

Date of Test: _____

AST: _____ ULN: _____

Date of Test: _____

_____ 3.2.7 Patient must have received no more than one cycle (28 days or less) of prior chemotherapy and no more than 160mg of prior dexamethasone (or equivalent dose of prednisone) for treatment of symptomatic myeloma. Patient must not have been exposed to daratumumab for treatment of symptomatic myeloma. Prior radiation therapy to symptomatic lesions is allowed provided there are no residual toxicity related to radiation and blood counts meet the study requirements. Radiation treatment must be completed at least 14 days prior to Step 1 registration.

_____ 3.2.8 Women must not be pregnant or breast-feeding due to the potential harm and teratogenic effects to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used.

All females 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 Step 1 registration to rule out pregnancy and again within 24 hours prior to the first dose of lenalidomide. Females of childbearing potential must also agree to ongoing pregnancy testing while on protocol treatment.

Please see Appendix V: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

A female of childbearing potential is defined as 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).

Female of childbearing potential? _____ (Yes or No)

Date of blood test or urine study: _____.

_____ 3.2.9 Women of childbearing potential must not expect to conceive children by using accepted and effective method(s) of contraception [for this protocol defined as the use of 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 protocol treatment; 2) while participating in the study; 3) during dose interruptions; and 4) for at least 3 months days after the last dose of protocol treatment] OR by practicing true abstinence from sexual intercourse for the duration of their participation in the study (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

Men must not expect to father children by practicing true abstinence from sexual intercourse for the duration of their participation in the study (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception] OR use a latex condom during sexual contact with a female of child bearing potential while participating in the study and for at least 3 months 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 3 months 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.

_____ 3.2.10 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of randomization are eligible for this trial.

_____ 3.2.11 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

_____ 3.2.12 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.

_____ 3.2.13 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

_____ 3.2.14 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical

risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better. Patients must not have evidence of current uncontrolled cardiovascular conditions, including hypertension, cardiac arrhythmias, congestive heart failure, unstable angina, or myocardial infarction within 6 months prior to Step 1 registration.

_____ 3.2.15 Patient must not have peripheral neuropathy ≥ Grade 2 on clinical examination or grade 1 with pain at time of Step 1 registration.

_____ 3.2.16 Patient must not have any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

_____ 3.2.17 Patient may have a history of current or previous deep vein thrombosis (DVT) or pulmonary embolism (PE) but must be willing to take some form of anti-coagulation as prophylaxis if they are not currently on full-dose anticoagulation.

_____ 3.2.18 Patients with a history of chronic obstructive pulmonary disease (COPD) must have FEV1 testing done within 28 days prior to Step 1 registration and the forced expiratory volume in 1 second (FEV1) must be > 50% of predicted normal.

_____ 3.2.19 Patient must not have moderate or severe persistent asthma within the past 2 years, or uncontrolled asthma of any classification.

NOTE: Patients who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to register.

_____ 3.2.20 Patient must not receive any other concurrent chemotherapy, or any ancillary therapy considered investigational while on this protocol.

NOTE: Bisphosphonates are considered to be supportive care rather than therapy, and are thus allowed while on protocol treatment.

_____ _____

Physician Signature Date

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

3.3 Eligibility Criteria- Step 2 Randomization

_____ 3.3.1 Institution must have received Tracking (MRD) test results from Adaptive Biotechnologies.

_____ 3.3.2 Patient must have completed the Step 1 Induction phase of this protocol without experiencing progression.

_____ 3.3.3 Patient must be registered to Step 2 within 8 weeks of completing Step 1 Induction Treatment, counting from last day of completion of last cycle.

Date Step 1 Induction Treatment Completed: _____

_____ 3.3.4 Patient must not have received any non-protocol therapy outside of the assigned Step 1 Induction treatment including stem cell transplant.

_____ 3.3.5 Patient must have an ECOG performance status (PS) of 0-2. (PS 3 allowed if secondary to pain).

_____ 3.3.6 Any adverse event(s) related to Step 1 Induction Treatment must have resolved to grade 2 or less.

_____ 3.3.7 Patient must have adequate organ and marrow functions as defined below (these must be obtained within 14 days prior to Step 2 randomization).

_____ 3.3.7.1 Hemoglobin ≥ 8 g/dL.

Hemoglobin: _____Date of Test: _____

_____ 3.3.7.2 Platelet count ≥ 50,000/mm3.

Platelet: _____ Date of Test: _____

_____ 3.3.7.3 Absolute neutrophil count (ANC) ≥ 1000/mm3.

ANC: _____ Date of Test: _____

_____ 3.3.7.4 Calculated creatinine clearance ≥ 30 mL/min.

Creatinine clearance: _____ Date of Test: _____

_____ 3.3.7.5 Total bilirubin ≤ 1.5 x ULN (Institutional upper limit of normal).

Total bilirubin: _____ ULN: _____

Date of Test: _____

_____ 3.3.7.6 ALT and AST < 3 X ULN

ALT: _____ ULN: _____

Date of Test: _____

AST: _____ ULN: _____

Date of Test: _____

_____ 3.3.8 Women must not be pregnant or breast-feeding due to the potential harm and teratogenic effects to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used.

All females 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 Step 2 randomization to rule out pregnancy and again within 24 hours prior to the first dose of lenalidomide. Females of childbearing potential must also agree to ongoing pregnancy testing while on protocol treatment.

Please see Appendix V: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

A female of childbearing potential is defined as 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).

Female of childbearing potential? _____ (Yes or No)

Date of blood test or urine study: _____.

_____ 3.3.9 Women of childbearing potential must not expect to conceive children by using accepted and effective method(s) of contraception [for this protocol defined as the use of 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 protocol treatment; 2) while participating in the study; 3) during dose interruptions; and 4) for at least 3 months days after the last dose of protocol treatment] OR by practicing true abstinence from sexual intercourse for the duration of their participation in the study (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

Men must not expect to father children by practicing true abstinence from sexual intercourse for the duration of their participation in the study (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception] OR use a latex condom during sexual contact with a female of child bearing potential while participating in the study and for at least 3 months 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 3 months 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.

_____ _____

Physician Signature Date

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