

FAST FACTS

S1803 - PHASE III STUDY OF DARATUMUMAB/rHuPH20 (NSC- 810307) + LENALIDOMIDE OR LENALIDOMIDE AS POST-AUTOLOGOUS STEM CELL TRANSPLANT MAINTENANCE THERAPY IN PATIENTS WITH MULTIPLE MYELOMA (MM) USING MINIMAL RESIDUAL DISEASE TO DIRECT THERAPY DURATION (DRAMMATIC STUDY)

Eligibility criteria

Except where otherwise indicated below that test is required in a shorter timeframe, all tests for establishing baseline disease status must be completed prior to registration. All diagnostic test results must be documented on the Baseline Tumor Assessment Form for Multiple Myeloma and the Onstudy Form.

Registration Step 1

Disease Related Criteria

1. Patients must have had a confirmed diagnosis of symptomatic multiple myeloma (See Section 4.1) with measurable disease at the time of myeloma diagnosis that required systemic induction therapy prior to autologous stem cell transplantation (ASCT).
Measurable disease is defined as measurable M protein in the serum ($\geq 0.5\text{g/dL}$) or urine ($\geq 200\text{ mg/24h}$) or serum free light chain assay (defined as $\geq 10\text{ mg/dL}$ [$\geq 100\text{ mg/L}$] on involved light chain) at the time of diagnosis.
Patients with smoldering myeloma are not eligible until they have progressed to symptomatic myeloma. Patients with purely non-secretory MM at the time of diagnosis as measured by electrophoresis and immunofixation and the absence of Bence Jones proteins in the urine are not eligible. Patients with plasma cell
2. leukemia are not eligible. Patients must not have any organ involvement by amyloidosis or evidence of amyloidosis related organ dysfunction.
3. Patients must not have progressive disease at any time prior to registration.

Prior/Concurrent Therapy Criteria

1. Patients must not be refractory to either lenalidomide or daratumumab/rHuPH20.
2. Patients must not be intolerant to the starting dose of either lenalidomide (10 mg) or daratumumab/rHuPH20. Patients intolerant to the 25 mg starting dose of lenalidomide are eligible.
3. Patients who have already received transplant must have initiated induction therapy within 18 months prior to transplant and received at least two cycles of induction therapy before transplant. Patients who have not already received transplant must have begun induction therapy within 18 months prior to the planned date of transplant and must receive at least two cycles of induction therapy before transplant. Note that patients who receive tandem transplant will not be eligible for Step 2 registration.
4. Patients must be registered to Step 1 prior to registration to Step 2. Registration to Step 1 may take place prior to or after autologous stem cell transplant (ASCT), but after completion of induction therapy. Patients who have completed ASCT may be registered to Step 1 and Step 2 on the same day, provided all eligibility criteria are met.

5. Patients must not have received any investigational agents within 14 days prior to registration.
6. Patients must be willing and able to take DVT prophylaxis (aspirin, low molecular weight heparin, warfarin, or equivalent oral anticoagulation).

Clinical/Laboratory Criteria

1. Patients must be ≥ 18 and ≤ 75 years of age at time of registration to Step 1.
2. Patients must have history and physical exam within 28 days prior to registration.
3. Patients must have Zubrod Performance Status ≤ 2 .
4. Patients must have evidence of adequate renal function, as defined by (1) creatinine clearance (CrCl) ≥ 30 mL/min., as measured by a 24-hour urine collection, or estimated by the Cockcroft and Gault formula, or (2) serum creatinine < 2.5 mg/dL. Values must be obtained within 28 days prior to registration.
5. Estimated creatinine clearance =

Calculate ideal body weight (IBW):

If SEX = M:

$$IBW = 50 + (2.3 \times (\frac{HT-152}{2.54}))$$

If SEX = F:

$$IBW = 45.5 + (2.3 \times (\frac{HT-152}{2.54}))$$

If $WT > IBW \times 140\%$ (1.4), use $WT = IBW \times 1.4$ in the CALCCREAT formula.

If $CREATSV < 0.7$, use $CREATSV = 0.7$ in the CALCCREAT formula.

CALCCREAT formula:

If SEX = M:

$$\frac{(140 - \text{patient's age}) \times WT}{72 \times CREATSV}$$

If SEX = F:

$$\frac{(140 - \text{patient's age}) \times WT \times .85}{72 \times CREATSV}$$

Patients must have

adequate hepatic function defined by the following within 42 days prior to registration:

- a. Total bilirubin $\leq 1.5 \times$ IULN (institutional upper limit of the norm)
- b. AST and ALT $\leq 3.0 \times$ IULN
6. Patients with a known history of asthma or chronic obstructive pulmonary disease must not have had forced expiratory volume in 1 second (FEV1) $< 50\%$ of predicted normal.
7. Patients must not have moderate or severe persistent asthma within the past 2 years and must not have currently uncontrolled asthma of any classification.
8. Patients must meet one of the following criteria:
 - a. Be acceptable for transplant per institutional guidelines and the criteria evidencing this must be documented on the **S1803** Onstudy Form. (See Appendix 18.3 for standard transplant eligibility guidelines. Note that these are guidelines and not required criteria.)
 - b. Have completed autologous stem cell transplant within 180 days prior to registration (see also Section 5.2a).
9. Patients must not have had prior autograft or allograft, or prior organ transplant requiring immunosuppressive therapy.
10. Patient's with human immunodeficiency virus (HIV) are eligible providing they are on effective antiretroviral therapy and have undetectable viral load at their most previous viral load test and within 6 months prior to registration.
11. Patients must not have known allergy to any of the study drugs.
12. Patients with uncontrolled bacterial, viral or fungal infections (currently taking medication and with progression or no clinical improvement) at time of enrollment are not eligible.

13. Patients must not have known central nervous system (CNS) involvement with multiple myeloma, defined as CSF positivity for plasma cells at any time or a parenchymal CNS plasmacytoma at time of enrollment. Lumbar puncture is not required.
14. Patients must not be seropositive for hepatitis C (except in the setting of sustained virologic response, defined as undetectable viral load at least 12 weeks after completion of antiviral therapy). HCV testing is only required if clinically indicated or if the patient has a history of HCV.
15. Patients must be able to take and swallow oral medication (capsules) whole. Patients may not have any known impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of study drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
16. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for three years.
17. Patients must not have any uncontrolled intercurrent illness including (not limited to): Symptomatic CHF (NYHA III/IV), unstable angina pectoris or coronary angioplasty, or stenting within 6 months prior to registration, Unstable cardiac arrhythmia (ongoing cardiac dysrhythmias of NCI CTCAE v5.0 Grade ≥ 2), intra-cardiac defibrillators, known cardiac metastases, or abnormal cardiac valve morphology (\geq Grade 3), or known psychiatric illness that would limit study compliance.
18. Patients must not be seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (i.e., subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (antiHBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.
19. For patients who have not yet received transplant: Patients must be willing and able to return to a participating treatment center for their assigned treatment after randomization. Note that patients need not have a direct relationship with the transplant center in order to register.
20. Patient-Reported Outcomes Criterion
Patients who can complete patient-reported outcomes instruments in English or Spanish must agree to complete the assessments described in Section 15.3 at the protocol-specified time points.

Registration Step 2 – First Randomization (Post-ASCT, Pre-Maintenance)

Prior/Concurrent Therapy Criteria

1. Patients must have completed ASCT within 180 days prior to registering to Step 2. Patients who enroll after ASCT may be registered to Step 1 and Step 2 concurrently.
2. Patients must not have received tandem transplant.
3. Patients must not have received any other maintenance therapy post-ASCT and prior to Step 2 registration.
4. Patients must not have had progressive disease between induction and registration to Registration Step 2. (See Section 10.1b).
5. Patients must have the following performed within 60 days prior to Registration Step 2 for disease assessment:

- a. myeloma-specific tests for establishing baseline disease status (SPEP, Serum Immunofixation, Serum free light chains, 24-hour UPEP, Urine immunofixation, bone marrow aspirate/biopsy, and quantitative immunoglobulins);
AND
- b. One of the following diagnostic quality skeletal survey, whole body CT scan, MRI, or PET.

Clinical/Laboratory Criteria

1. Patients must have Zubrod Performance Status ≤ 2
2. Patients must have adequate bone marrow function as evidenced by platelets $\geq 75,000/\text{mm}^3$ and ANC $\geq 1,000/\text{mm}^3$ within 28 days prior to first randomization:
3. Patients must have adequate hepatic function defined by the following within 28 days prior to first randomization:
 - a. Total bilirubin $\leq 1.5 \times \text{IULN}$ (institutional upper limit of the norm)
 - b. AST and ALT $\leq 3.0 \times \text{IULN}$
4. Patients must have evidence of adequate renal function, as defined by creatinine clearance (CrCl) $\geq 30 \text{ mL/min.}$, as measured by a 24-hour urine collection, or estimated by the Cockcroft and Gault formula, or have a serum creatinine $< 2.5 \text{ mg/dL}$ within 28 days prior to first randomization.
5. Estimated creatinine clearance =

Calculate ideal body weight (IBW):

If SEX = M:

$$\text{IBW} = 50 + \left(2.3 \times \left(\frac{\text{HT} - 152}{2.54} \right) \right)$$

If SEX = F:

$$\text{IBW} = 45.5 + \left(2.3 \times \left(\frac{\text{HT} - 152}{2.54} \right) \right)$$

If $\text{WT} > \text{IBW} \times 140\%$ (1.4), use $\text{WT} = \text{IBW} \times 1.4$ in the CALCCREAT formula.

If $\text{CREATSV} < 0.7$, use $\text{CREATSV} = 0.7$ in the CALCCREAT formula.

CALCCREAT formula:

If SEX = M:

$$\frac{(140 - \text{patient's age}) \times \text{WT}}{72 \times \text{CREATSV}}$$

If SEX = F:

$$\frac{(140 - \text{patient's age}) \times \text{WT} \times .85}{72 \times \text{CREATSV}}$$

All ASCT-related toxicities must have recovered to \leq Grade 1 (except for alopecia, fatigue and amenorrhea) prior to first randomization.

6. Mucositis and gastrointestinal symptoms must have resolved to \leq Grade 1.
7. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10-14 days prior to registration. FCBP must agree to have a second pregnancy test within 24 hours prior to starting Cycle 1. Further, FCBP must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control: one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before starting lenalidomide. FCBP must also agree to ongoing pregnancy testing and must agree to not become pregnant for at least 3 months after the last dose of study treatment.

A FCBP is a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) 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 during the preceding 24 consecutive months).

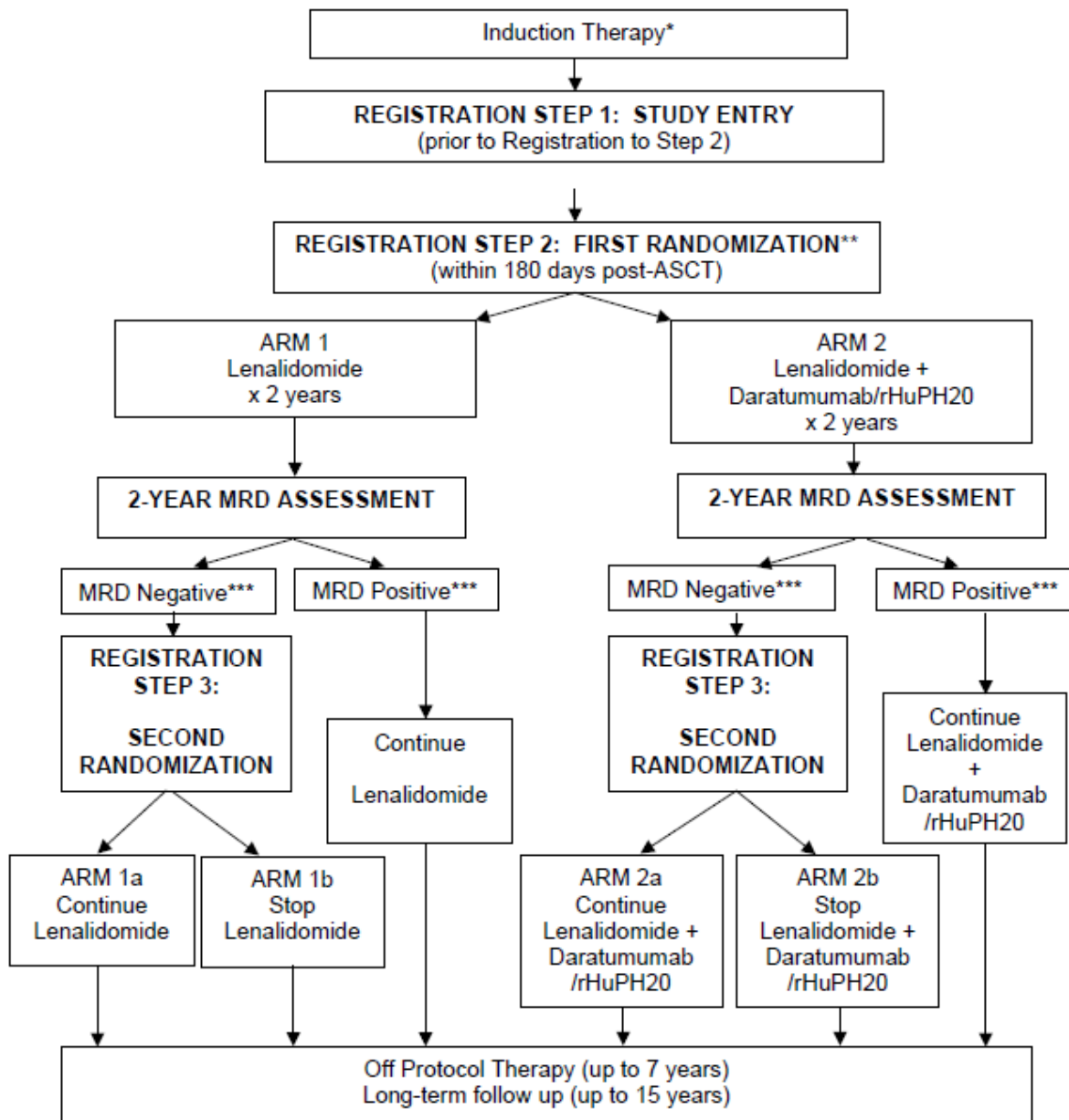
Men must agree to use a latex condom during sexual contact with a FCBP, even if they have had a successful vasectomy, during the study treatment and for 3 months after the last dose of study treatment.

Registration Step 3 – Second Randomization (Post 24 Months Maintenance)

Clinical/Laboratory Criteria

1. Patients must have been enrolled on Registration Step 2, must have 24-month MRD by NGS test results available and must be MRD negative. Patients whose PCR results are indeterminable will be considered to have positive results.
2. Patients must be in very good partial remission (VGPR) or better by IMWG response criteria (see Section 10.1b).

SCHEMA



* Therapy is given prior to protocol registration and is not part of protocol-prescribed treatment.

** Accrual goal is assessed at Registration Step 2: First Randomization.

*** Minimal residual disease (MRD)-negative includes only patients who are MRD-negative *and* in VGPR or better; MRD-positive includes all other patients, specifically, those patients who are either MRD-positive or not in VGPR or better, or who have an inconclusive or unknown response or MRD status at 24-months.