SWOG S1211
A Randomized Phase II Study of Optimal Induction Therapy of Bortezomib, Dexamethasone and Lenalidomide with or without Elotuzumab (NSC-764479) for Newly Diagnosed High Risk Multiple Myeloma (HRMM)

Fast Facts

Inclusion Criteria

1. **Disease Related Criteria**
   a. Patients must have newly diagnosed active MM as defined in Section 4.1. (See Sections 5.2a and 5.2b for prior therapy information.) All tests for establishing baseline disease status must be completed within 28 days prior to registration for patients with no prior therapy, or within 28 days prior to initiation of first Induction course for patients with prior therapy.

   b. For the Phase II portion only patients must have high risk MM based on one or more of the following criteria at the time of initial diagnosis (prior to any chemotherapy):
      - Poor risk genomic signature according to the University of Arkansas 70- gene model (available clinically as MyPRS score, Signal Genetics, Inc.)**AND/OR**
      - Translocation (14;16), and/or translocation (14;20), and/or deletion (17p) by florescence in-situ hybridization (FISH) or cytogenetics **AND/OR**
      - Primary plasma cell leukemia (defined by either ≥ 2,000 plasma cells/mL of peripheral blood, or 20% on a manual differential count **AND/OR**
      - Serum lactate dehydrogenase (LDH) ≥ 2 x Institutional Upper Limit of Normal (IULN)**AND/OR**
      - 1q21 amplification by FISH analysis **AND/OR**
      - High risk by the SKY92 signature

      All tests for establishing high risk status must be completed within 28 days prior to registration for patients with no prior therapy, or within 28 days prior to initiation of first Induction course for patients with prior therapy.

   c. Patients with non-secretory MM or known amyloidosis are not eligible.

   d. Patients must have measurable disease as defined by Section 10.1a within 28 days prior to registration (or prior to initiation of first induction course for patients with prior therapy).

2. **Prior Therapy Criteria**
   a. Patients on the Phase I portion may not have received ANY prior chemotherapy. Patients on the Phase II portion may have received one prior cycle of any non-investigational chemotherapy. Prior chemotherapy must have been completed within 56 days prior to registration and all toxicities must have resolved to ≤ Grade 1. Patients on either portion may have received prior treatment with dexamethasone, providing total Number of days of treatment was ≤ 14 days and total treatment dose was ≤ 360 mg.

   b. Patients may have received prior radiotherapy for symptomatic localized bone lesions or impending spinal cord compression only. Radiotherapy must be completed at least 14 days prior to registration and all toxicities must have resolved to ≤ Grade 1.

3. **Clinical/Laboratory Criteria**
   a. Patients must have adequate marrow function defined by the following within 14 days prior to registration:
      - ANC ≥ 1,000 cells/mm3 without growth factor support
        AND
      - Platelet count ≥ 70,000 cells/mm3 for patients who have bone marrow plasmacytosis < 50%; or ≥ 50,000 cells/mm3 for patients who have bone marrow plasmacytosis of ≥ 50%

   b. Patient must have adequate hepatic function defined by the following within 14 days prior to registration:
      - Total bilirubin ≤ 1.5 x IULN
        AND
      - SGOT/AST and SGPT/ALT ≤ 2.5 x IULN

c. Patients must have adequate renal function as evidenced by creatinine clearance (CrCL) ≥ 30 mL/min, measured by a 24-hour urine collection or estimated by the Cockcroft and Gault formula within 14 days prior to registration:

$$\text{CrCl} = \frac{(140 - \text{patient's age} \times \text{patient's weight in kilograms}) \times 0.85 \text{ (if female)}}{72 \times \text{patient's serum creatinine}}$$

d. Patients must not have active involvement of the central nervous system (CNS) with MM (by clinical evaluation). Patients with documentation of, or clinical signs or symptoms consistent with, CNS involvement of MM must have a lumbar puncture that is negative for CNS involvement of MM. The lumbar puncture must be completed within 14 days prior to registration. Patients with no previous history of documented CNS involvement and with no clinical signs or symptoms consistent with CNS involvement are not required to have completed a lumbar puncture prior to registration. Note that monitoring of CNS involvement and treatment with intrathecal therapy is recommended during protocol treatment.

e. Patients who are known to be HIV+ are eligible providing they meet all of the following additional criteria within 28 days prior to registration:
   - CD4 cells ≥ 500/mm3
   - Viral load of < 50 copies HIV mRNA/mm3 if on cART or < 25,000 copies HIV mRNA if not on cART
   - No zidovudine or stavudine as part of cART

   Patients who are HIV+ and do not meet all of these criteria are not eligible for this study.

f. Patients must have baseline skeletal survey (whole body x-ray) to document lytic lesions, osteopenia or compression fracture.

g. Patients must have Zubrod Performance Status ≤ 2 (see Section 10.6).

h. Patients must be ≥ 18 years of age.

i. Patients with known Hepatitis B or Hepatitis C infection may be eligible providing they have viral load < 800,000 IU/L within 28 days prior to registration.

j. Patients must not have POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

k. Patients must not have clinically significant illness including uncontrolled, active infection requiring intravenous antibiotics, New York Heart Association (NYHA) Class III or Class IV heart failure (see Appendix 19.2), unstable angina pectoris, myocardial infarction within the past 6 months, uncontrolled ≥ Grade 3 cardiac arrhythmias, uncontrolled hypertension, or uncontrolled diabetes mellitus. Patients must have undergone an EKG within 28 days prior to registration.

   Uncontrolled diabetes: An Hg A1C > 7% within 14 days prior to registration. The same criterion will be used in patients with confirmed diagnosis of diabetes mellitus who have been on a stable dietary or therapeutic regimen for this condition in the last three months.
   Uncontrolled blood pressure and hypertension: SBP > 140 mm Hg or DBP > 90 mm Hg within 14 days prior to registration. Patients are permitted to be receiving multiple anti-hypertensive medications (unless otherwise indicated in the study). All blood pressure measurements within the 14 days prior to registration and on Day 1 of Cycle 1 must be SBP ≤ 1 40 and D BP ≤ 9 0. An exception can be made by a healthcare provider for a patient with a single blood pressure elevation who upon rechecking has a normal blood pressure.
   - See ACCF/AHA.AMA-PCPI joint statement.

l. Patients must have history and physical examination within 28 days prior to registration.
m. Patients must not have any psychiatric illness that could potentially interfere with the completion of treatment according to this protocol.

n. 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. (Note: that pregnancy testing is also required within 24 hours prior to treatment on Cycle 1, Day 1.) Furthermore, they 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. Men must agree to use a latex condom during sexual contact with a FCBP, even if they have had a successful vasectomy. A FCBP is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

See Appendix 18.4: Elotuzumab Reproductive Warnings, for additional elotuzumab related pregnancy and contraception information, including instructions to investigators.

o. 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 five years.

4. Specimen Submission Criteria

a. Patients must be offered participation in banking of specimens for future research. With the patient's consent, specimens (serum and bone marrow biopsy core) must be submitted to the repository. Patient consent must be obtained before specimens are submitted. See Section 15.1 for further information, including specimen submission time-points.

Pre-Study Parameters

1. History and physical including weight, ECOG PS, toxicity assessment
2. Bone marrow aspirate/biopsy
3. FISH and cytogentics (optional)
4. Labs including CBC, CMP, LDH, β2-microglobulin, CRP, HIV/Hep B/HepC (if indicated),
5. Serum protein electrophoresis, 24 hr urine for total protein, protein electrophoresis, immunofixation electrophoresis
6. Pregnancy testing
7. EKG
8. Skeletal survey
9. Risk Assessment per section 5.1b
10. Lenalidomide Education and Counseling
11. Optional serum /biopsy for banking
12. Patients must be registered to the mandatory Revlimid REMS program.

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