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Committed to Community Cancer Research & Education

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E1A11 - Randomized Phase III Trial of Bortezomib, L**EN**alidomide and Dexamethasone (VRd) Versus Carfilzomib, Lenalidomide and Dexamethasone (CRd) Followed by Limited or Indefinite **DUR**ation Lenalidomide Mainten**ANCE** in Patients with Newly Diagnosed Symptomatic Multiple Myeloma (ENDURANCE)

Selection of Patients:

Step 1 Randomization

1. Age ≥ 18 years.
2. Patients must be diagnosed with symptomatic standard-risk multiple myeloma (SR-MM) as defined by all of the following (except GEP70 status if unknown):
   - No evidence of t(14;16) by FISH testing on bone marrow or not available:
   - No evidence of t(14:20) by FISH testing on bone marrow or not available:
   - No evidence of deletion 17p by FISH testing on bone marrow;
   - FISH should be from within 90 days of registration.
     NOTE: If the FISH result states that no IgH abnormality is present, both t(14;16) and t(14;20) can be considered negative. In addition, if the patient has a t(11;14) or t(4;14) translocation present, they can be considered negative for t(14;16) and t(14;20). If testing for t(14;16) or t(14;20) could not be performed for lack of sufficient material or non-availability of the probe in the test panel, patients can be enrolled on the study.
   - Standard Risk GEP70 signature within the past 90 days (only if GEP has been done and results are available).
     NOTE: GEP testing is NOT a requirement for the study. If the test has been done, patients found to have a GEP70 status of High-Risk will not be eligible.
   - Serum LDH ≤ 2 x ULN within the past 28 days
   - No more than 20% circulating plasma cells on peripheral blood smear differential or 2,000 plasma cells/microliter on WBC differential of peripheral blood within the past 90 days

     NOTE: This is NOT the plasma cell % from the marrow aspirate.

     NOTE: If peripheral blood flow cytometry was done and no plasma cells reported, the following can be marked "0".
3. Patients must have measurable or evaluable disease as defined by having one or more of the following, obtained within 28 days prior to randomization:
   - ≥ 1g/dL monoclonal protein (M-protein) on serum protein electrophoresis
   - ≥ 200 mg/24 hrs 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)
4. SPEP, UPEP, and serum FLC assay and bone marrow biopsy and or aspirate are required to be performed within 28 days prior to randomization. A bone marrow biopsy and/or aspirate is required within 28 days if bone marrow is being followed for response.

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.

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.

5. The following laboratory levels must be obtained within 28 days prior to randomization:

   5.1 Hemoglobin ≥ 8 g/dL.

   5.2 Untransfused platelet count ≥ 75,000 cells/mm^3.

   5.3 Absolute neutrophil count ≥ 1000 cells/mm^3.

   5.4 Calculated creatinine clearance ≥ 30 mL/min

   5.5 Bilirubin ≤ 1.5 mg/dL.

   5.6 SGPT (ALT) and SGOT (AST) < 2.5 times the upper limit of normal.

6. Patients must have received no more than one cycle (4 weeks or less) of prior chemotherapy and no more than 160mg of prior dexamethasone (or equivalent dose of prednisone) for treatment of symptomatic myeloma. They should not have been exposed to lenalidomide, bortezomib or carfilzomib 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 that meet the study requirements.
7. Prior systemic glucocorticoid use for the treatment of non-malignant disorders is permitted. Prior or concurrent topical or localized glucocorticoid therapy to treat non-malignant comorbid disorders is permitted.
8. Patients must not have active, uncontrolled seizure disorder. Patients must have had no seizures in the last 6 months.
9. Patients must not have uncontrolled intercurrent illness including uncontrolled hypertension, symptomatic congestive heart failure, unstable angina, uncontrolled cardiac arrhythmia, uncontrolled psychiatric illness or social situation that would limit compliance with the study, or a prior history of Stevens Johnson Syndrome.
10. ECOG performance status 0, 1, or 2. (PS 3 allowed if secondary to pain)
11. Patients with monoclonal gammopathy of undetermined significance or asymptomatic multiple myeloma are not eligible.
12. Patients must not have Grade 2 or higher peripheral neuropathy by CTCAE 4.0.
13. Patients must not have active, uncontrolled infection.
14. Patients may have a history of current or previous deep vein thrombosis or pulmonary embolism but must be willing to take some form of anti-coagulation as prophylaxis if they are not currently on full- dose anticoagulation.
15. Patients should not have New York Heart Association classification III or IV heart failure or myocardial infarction within the previous 6 months.
16. Patients with a history of prior malignancy are eligible provided they were treated with curative intent and do not require active therapy (currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma “in situ” of the cervix or breast are not excluded).

17. Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting lenalidomide and 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 she starts taking lenalidomide, throughout the entire duration of study treatment, and for 28 days after the last dose of lenalidomide.. FCBP must also agree to ongoing pregnancy testing. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix V: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods. Female subjects must agree to use contraception or abstinence for 30 days after last dose of carfilzomib.

    † A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 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.

18. Sexually active males must be willing to use a condom (even if they have undergone a prior vasectomy) while having intercourse, while taking lenalidomide and for 28 days after stopping lenalidomide. Male subjects must also agree to abstain from donating blood, semen, or sperm during study participation and for at least 28 days after discontinuation from lenalidomide. Male subjects must be willing to use condoms for 90 days after discontinuation of carfilzomib.

19. The following patients will be excluded as this study involves an agent that may have genotoxic, mutagenic and teratogenic effects.

    19.1 Pregnant women

    19.2 Nursing women

20. HIV infection is not excluded. Known HIV positive patients must meet the following criteria:

    - CD4 cell count $\geq 350/mm^3$
    - No history of AIDS-related illness
    - Not currently prescribed zidovudine or stavudine

    21. Patient enrolling to this study must agree to register to the mandatory RevAssist® program, and be willing and able to comply with the requirements of RevAssist®.

Step 2 Randomization

1. Patients must have completed induction without experiencing progression or patients must have received at least 6 cycles on Arm A and 4 cycles on Arm B but stopped induction therapy due to adverse events.
2. Step 2 registration must be within 6 weeks of completing Step 1 therapy.
3. Patients must not have received any non-protocol therapy outside of the assigned induction therapy including stem cell transplant.
4. ECOG performance status 0, 1, or 2. (PS 3 allowed if secondary to pain).
5. Any adverse event related to Step 1 therapy must have resolved to grade 2 or less.
6. Patient must have adequate laboratory levels as follows (within 28 days prior to randomization to Step 2)
    - Hemoglobin ≥ 8 g/dL.

- Platelet count ≥ 75,000 cells/mm^3.
- Absolute neutrophil count ≥ 1000 cells/mm^3.
- Calculated creatinine clearance ≥ 30 mL/min.
- Bilirubin ≤ 1.5 mg/dL.
- SGPT (ALT) and SGOT (AST) < 2.5 times the upper limit of normal.

7. Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting lenalidomide and 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 she starts taking lenalidomide, throughout the entire duration of study treatment, and for 28 days after the last dose of lenalidomide. FCBP must also agree to ongoing pregnancy testing. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix V: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

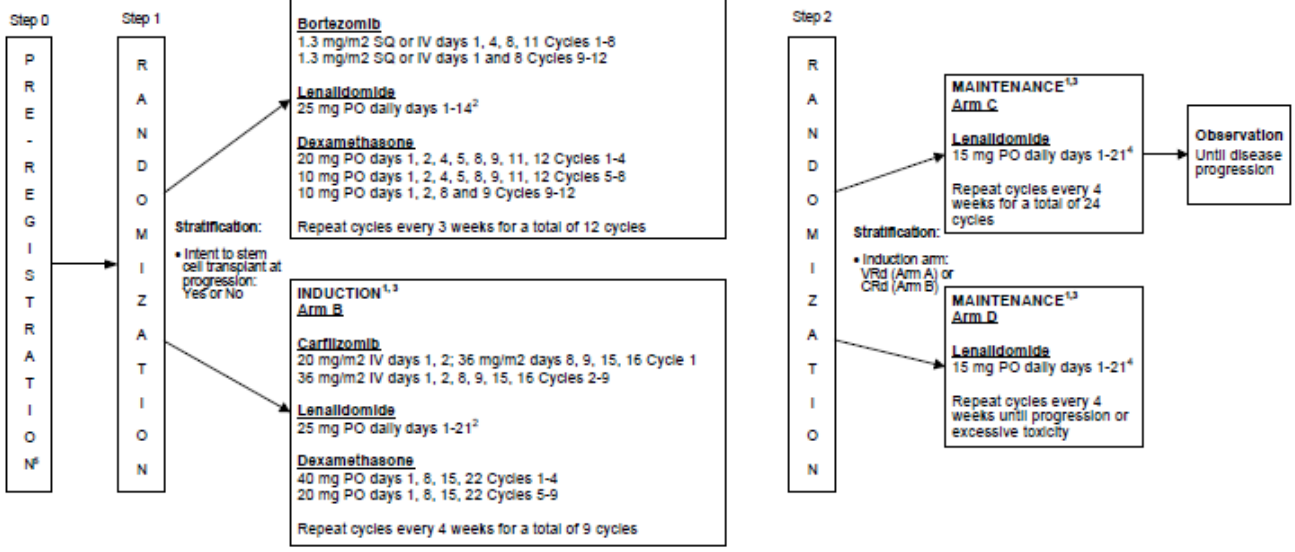
   † A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months.

8. Sexually active males must be willing to use a condom (even if they have undergone a prior vasectomy) while having intercourse, while taking lenalidomide and for 28 days after stopping lenalidomide. Male subjects must also agree to abstain from donating blood, semen, or sperm during study participation and for at least 28 days after discontinuation from lenalidomide. Males must agree to use contraception and agree to not donate sperm for at least 90 days after the last day of carfilzomib.

9. The following patients will be excluded as this study involves an agent that may have genotoxic, mutagenic and teratogenic effects.
   - Pregnant women
   - Nursing women

10. Patient enrolling to this study must agree to register to the mandatory RevAssist® program and be willing and able to comply with the requirements of RevAssist®.

Schema



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