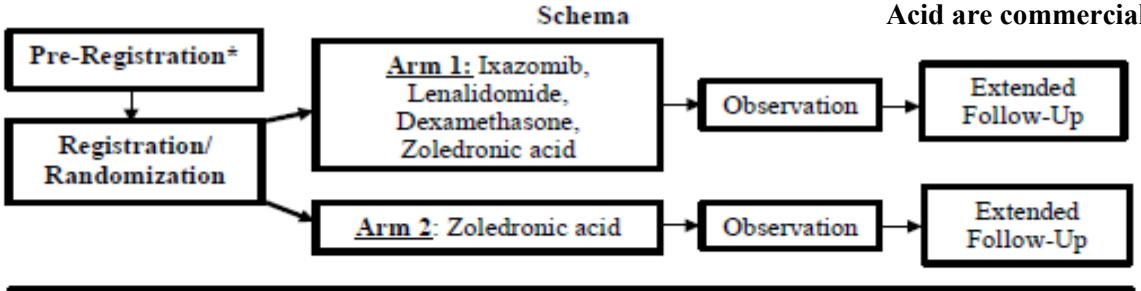
Cancer Research Consortium of West Michigan
P: 616.391.1230 | 800.336.6299 | www.crcwm.org

Fast Facts

Alliance A061402: Solitary Plasmacytoma of Bone: Randomized Phase III Trial to Evaluate Treatment with Adjuvant Systemic Treatment and Zoledronic Acid Versus Zoledronic Acid after Definite Radiation Therapy

- **Ixazomib and Lenalidomide are provided**
- **Dexamethasone and Zoledronic Acid are commercially available**

Schema



Stratification Factors:

- % of abnormal plasma cells in the bone marrow: 5-9%
- age < 60; % of abnormal plasma cells in the bone marrow < 5%; and monoclonal protein/clonal light chains present in the blood or urine
- age < 60; % of abnormal plasma cells in the bone marrow < 5%, and no monoclonal protein/clonal light chains present in the blood or urine, MRD+
- age ≥ 60; % of abnormal plasma cells in the bone marrow < 5%; and monoclonal protein/clonal light chains present in the blood or urine
- age ≥ 60; % of abnormal plasma cells in the bone marrow < 5%, and no monoclonal protein/clonal light chains present in the blood or urine, MRD+

* Patients diagnosed with solitary bone plasmacytoma may pre-register prior to the start of radiation therapy or at most 90 days after the completion of radiation therapy.

Arm 1: The 4-drug combination will be given for a maximum of six 28 day cycles as follows:
Ixazomib 4 mg on Days 1,8,15
Lenalidomide 15 mg Days 1-21
Dexamethasone 12mg PO Days 1,8,15, 22
Zoledronic acid dose based on creatinine clearance over 15 minutes on day 1

Arm 2: Zoledronic acid dose based on creatinine clearance over 15 minutes on day 1 of a 28 day cycle for a maximum of 6 cycles.

Pre-registration eligibility criteria (Step 0)

1. **Documentation of Disease:**
   - No lytic lesions on skeletal survey and whole body PET/CT other than single lesion associated with solitary bone plasmacytoma.
   - For patients pre-registering after the completion of radiation therapy, documentation of a bone marrow aspirate and biopsy containing <10% clonal plasma cells prior to start of radiation therapy.
   - For patients pre-registering before the start of radiation therapy documentation of bone marrow aspirate and biopsy containing <10% clonal plasma cells. Radiation therapy should preferably begin within 28 days after bone marrow biopsy.
2. **Age ≥ 18 years**
3. **ECOG Performance Status 0-2**
4. **Specimen submission for central review**

   - All patients are required to be pre-registered to A061402 in order to submit post-RT bone

marrow aspirate specimens to Roswell Park for occult marrow disease (OMD) detection by flow cytometry. This submission is required prior to registration to confirm eligibility. See section 6.2 for specimen collection and submission procedures.

Registration Eligibility Criteria (Step 1)

1. Documentation of Disease:

- No lytic lesions on skeletal survey and whole body PET/CT other than a single lesion associated with solitary bone plasmacytoma within 28 days prior to registration.
- Bone marrow aspirate and biopsy containing <10% clonal plasma cells performed after completion of RT and within 28 days prior to registration.
- Participants must have disease that is detectable after radiation by one of the three measures below:
  - Elevated serum M protein or
  - Abnormal serum FLC assay: involved FLC level > upper limits of normal with abnormal serum FLC ratio and/or
  - ≥ 50 Plasma cells detectable by multicolor flow cytometry, at a sensitive level of 10-4 (determined by central review).

2. Prior Treatment

- No major surgery within 21 days of registration with stabilization or resolution of surgical adverse events.
- No investigational agent within 21 days prior to registration
- No ongoing therapy with corticosteroids greater than 10 mg of prednisone or its equivalent per day. Please note: Inhaled and topical steroids are per`mitted.
- No prior proteasome inhibitor or IMiD use.
- Prior bisphosphonate use is permitted.
- For all patients:
  - Radiation dose should range from 4500 cGy to 6000 cGy
  - No treatment for this disease following radiation therapy

3. Not pregnant and not nursing, because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown and an agent that has known genotoxic, mutagenic and teratogenic effects.

a. Females of childbearing potential (FCBP), defined as 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):

- must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to registration and again within 24 hours of starting lenalidomide.
- 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.
- must agree to ongoing pregnancy testing.

b. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a vasectomy.

See Appendix III: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

4. ECOG Performance Status 0-2

5. Required Initial Laboratory Values within 14 days of registration:

- Absolute Neutrophil Count (ANC) ≥ 1,500/mm3
- Platelet Count ≥ 75,000/mm3
- Hemoglobin ≥ 10 g/dL
- Serum Creatinine < 2.0 mg/dL [176.8 μmol/liter]
- Serum calcium ≤ 11.5 mg/dL
- Calc. Creatinine Clearance > 50 mL/min
- Bilirubin ≤ 1.5 x upper limits of normal (ULN)
- AST ≤ 2.5 x upper limits of normal (ULN)

6. Intercurrent or Recent Illness

- If history of prior malignancy, subject should be in complete remission for ≥ 5 years at the time of registration (with the exception of basal cell or squamous cell carcinoma of the skin treated with local resection).
    - HIV + patients are eligible provided they meet the other eligibility criteria and:
    - CD4+ cells are ≥ 250/mm3
    - There is no history of AIDS defining conditions other than historically low CD4+ cell count.
    - The following antiretroviral agents are not allowed: zidovudine, stavudine, protease inhibitors, non-nucleoside reverse transcriptase inhibitors, combination pills with pharmacologic boosters.
    - Recommended antiretroviral regimens to avoid PK interactions include strand integrase inhibitors with nucleoside and non-nucleoside reverse transcriptase inhibitors (for example, dolutegravir given with tenofovir and emtricitabine).

  Specific follow-up should be performed by HIV physicians at regular intervals to make sure that there is no adverse impact on the disease control.
- Patients with HBV infection are eligible provided they meet the other eligibility criteria and:
    - There is no evidence of hepatic damage related to HBV infection.
    - They have had consistently suppressed HBV viral load to undetectable levels by PCR for a minimum of 12 months.
- Patients with HCV infection are eligible provided they meet the other eligibility criteria and:
    - They have previously undergone curative therapy and have no evidence of active HCV infection.
    - They have no evidence of liver damage owing to prior HCV infection.
- Patients with active HCV infection should be referred for HCV treatment and standard radiotherapy for the plasmacytoma.

Patients cannot have:

- Known allergy to boron or excipients in the formulation.
- Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of study drugs including difficulty swallowing.

- Infection requiring systemic antibiotic therapy or other serious infection within 14 days before registration.
- Diarrhea ≥ Grade 1, based on the NCI CTCAE categorization within 14 days of registration
- Life-threatening illness unrelated to cancer
- The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide, pomalidomide, or similar drugs.

7. Peripheral Neuropathy

- ≤ Grade 2 Peripheral Neuropathy. Patients with Grade 1 peripheral neuropathy with pain will be excluded.

8. Adequate cardiac function, defined as:

- No cardiac arrhythmias within 182 days of registration.
- No congestive heart failure (CHF) within 182 days of registration.
- No angina or myocardial infarction within 182 days of registration. In view of potential cardiac risk with lenalidomide, patients with stable angina will be excluded.

9. Concomitant Treatment

- Patients cannot be on systemic treatment with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital) or use Ginkgo biloba or St. John's wort within 14 days of registration (see Appendix IV).

10. QT c< 470 milliseconds (msec) on a 12-lead ECG ≤ 28 days before registration (see section 4.4).

11. Dental evaluation within 35 days of registration

- Complete dental exam; complete elimination of dental and periodontal pathology including crowns on teeth susceptible to fracture, extraction of non-restorable or periodontally uncorrectable teeth; creation of an oral environment that the patient can efficiently maintain in a high state of health; and oral hygiene instruction to maintain excellent oral health.