Definition

**Solitary Plasmacytoma**
- Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells
- Normal bone marrow with no evidence of clonal plasma cells
- Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion)
- Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lymphoplasmacytic cell disorder

**Solitary Plasmacytoma with Minimal Marrow Involvement**
- Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells
- Clonal bone marrow plasma cells <10%
- Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion)
- Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lymphoplasmacytic cell proliferative disorder
- 60% progression [SPB] within 3 years
Primary

• To assess whether ixazomib, lenalidomide, dexamethasone with zoledronic acid is more promising than zoledronic acid alone in increasing the time before progression to multiple myeloma

Secondary

• To assess changes in minimal residual disease [MRD] by flow cytometry from study entry, at the completion of treatment, and at 1 year post registration

• To assess whether ixazomib, lenalidomide, dexamethasone with zoledronic acid is more promising than zoledronic acid alone in extending overall survival

• To examine the pharmacodynamics effects of treatment on biochemical markers of bone formation (osteocalcin bone-specific alkaline phosphatase), resorption (serum CTX), and metabolism (OPG)
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

Anuj Mahindra, MD
Scripps Cancer Center, La Jolla, CA

Study Schema

Pre-Registration

Registration/Randomization

RID (6 cycles)
Lenalidomide 15mg Days 1-21
Ixazomib 4mg days 1,8,15
Dexamethasone 12mg Days 1,8,15,22
Zoledronic acid day 1 of a 28 day cycle ×6

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Background / Rationale

Progression in solitary plasmacytoma of bone: impact of occult marrow disease (OMD) and urinary light chains (ULC) on outcome

TTP to MM according to sensitive MFC immunophenotypic evaluation of the BMPC compartment

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Key Inclusion Criteria

- Histologically confirmed solitary bone plasmacytoma.
- Bone marrow aspirate and biopsy containing <10% clonal cells done within 4 weeks prior to start of radiation therapy.
- Measurable disease at registration –
  - serum M protein > 0.5 G/DL, or
  - urine M protein >200 MG/24H, and/or
  - serum FLC assay: involved FLC level > 10 MG/DL with abnormal serum FLC ratio.
- ≥ 50 Plasma cells detectable by multicolor flow cytometry, at a sensitive level of 10-4.
Stratification Factors / Statistical Section

- **% 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 **MRD+**
- **Sample size of 50 patients per arm** (100 patients), a **two-sided alpha=0.05 test** of difference in two independent proportions would have a 85% chance of **detecting at least a 30% difference** proportion of patients who have documented progression to multiple myeloma or died within 5 years between those randomized to zoledronic acid, ixazomib, lenalidomide, dexamethasone compared and those randomized to zoledronic acid alone, when the 5 yr. PFS rate with the ‘poorer’ regimen is 45%.
- **To account for loss of power due to censoring** our sample size will be increased to **55 per arm**.
- **All patients will be followed for progression to multiple myeloma and death for a minimum of 5 years** post randomization.
**Correlative Studies**

**Minimal Residual Disease Monitoring**
- Prognostic value of MRD detection by sequencing and the concordance between MRD levels measured by MFC and high-throughput sequencing.
- For those patients who have not progressed to MM after 6 cycles of treatment, association between the presence of MRD at 6 months and time to MM progression having completed 6 cycles of treatment will be explored.

**Markers of Bone Turnover**
- Bone formation (osteocalcin, bone-specific alk phos)
- Resorption (serum CTX)
- Metabolism (OPG)

**Cytogenetics of Plasmacytoma [by GEP]**
- Pathways related to bone metabolism in particular will be analyzed at time of diagnosis and progression.

**Evaluation of Bone Mineral Density by DXA Scan**
- To explore the incidence of shifts in bone mineral density classification after 12 months of treatment.
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Scripps Cancer Center, La Jolla, CA

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Contact Us

Study Chair: Anuj Mahindra, MD
E-mail: mahindra.anuj@scrippshealth.org
Phone: 800-995-4200

Statistician: Vera Jean Suman, PhD
E-mail: suman@Mayo.edu
Phone: 507-284-8803

Protocol Coordinator: Destin Carlisle
E-mail: dcarlisle@uchicago.edu
Phone: 773-702-8824

Data Manager: Brandon Bright
E-mail: bright.brandon@mayo.edu
Phone: 507-538-1484

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