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

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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 lymphoplasma cell proliferative disorder
- 60% progression [SPB] within 3 years

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Objective

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)

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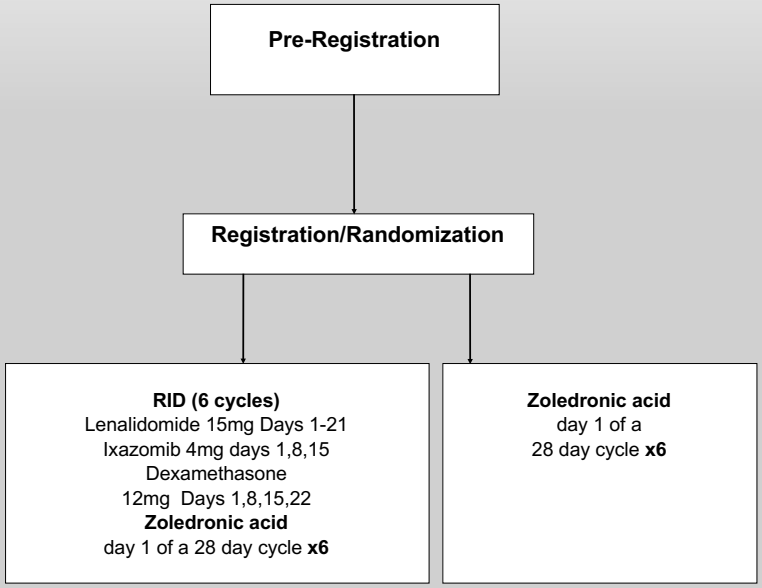
Study Schema



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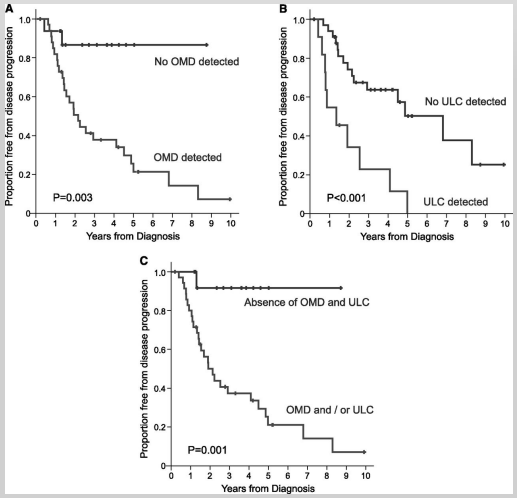
Background / Rationale

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



Blood 2014;124:1296-1299
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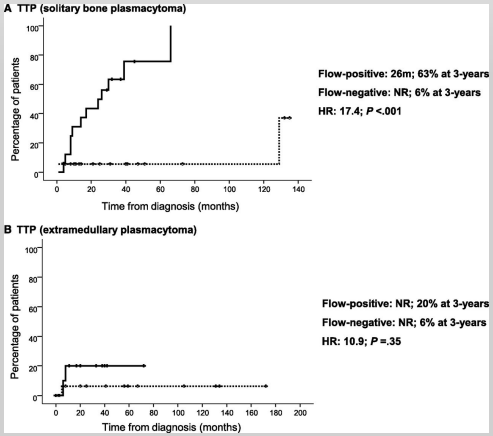
TTP to MM according to sensitive MFC immunophenotypic evaluation of the BMPC compartment



Paiva B et al. Blood 2014;124:1300-1303
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Key Eligibility Criteria

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.

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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 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+

- 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.

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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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