**SWOG 1211: A RANDOMIZED PHASE I/II STUDY OF OPTIMAL INDUCTION THERAPY FOR NEWLY DIAGNOSED HIGH RISK MULTIPLE MYELOMA (HRMM)**

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**SCIENTIFIC BACKGROUND:**

- The introduction of immunomodulatory agents and proteasome inhibitors, and advances in high dose therapy administration have made an impact on progression free survival (PFS) and overall survival (OS) for multiple myeloma (MM) patients.
- Patients with HRMM still have a poor long-term prognosis, with a 2-year PFS of ~50% even with aggressive treatments like the Total Therapy 3 trials (Barlogie et al Br J Haematol 2007; Nair et al Blood 2010).
- Therefore, it is imperative to develop novel therapeutic regimens that will extend PFS and OS in this group.
- The SWOG 1211 is the first national and inter-group study targeting the HRMM population.

**ELIGIBILITY & TRIAL DESIGN:**

- A randomized phase I/II trial was designed to evaluate the efficacy of incorporating novel agents into first line therapy for HRMM patients comparing lenalidomide, bortezomib and dexamethasone (RVD) with or without addition of elotuzumab (Elo).
- Eligible patients must have a documented history of HRMM defined by one or more of the following:
  - Poor risk genomics defined by Arkansas 70-gene model or HOVON 92-gene model
  - Translocation (14;16), translocation (14;20), deletion (17p), and/or chromosome 1q21 amplification (3 or more copies) by fluorescent in-situ hybridization (FISH)
  - Primary plasma cell leukemia
  - Serum LDH > 2 times of institutional normal levels
- Patients must be either transplant ineligible OR have deferred transplant for first relapse.
- Patients will receive either RVD (standard of care arm) or RVD-Elo (experimental arm) for 8 induction cycles.
- Patients can receive 1 prior cycle of therapy before study enrollment, in which case they will receive 7 cycles of planned induction therapy.
- After completion of induction, patients will remain on a dose-attenuated RVD or RVD-Elo schedule until relapse, disease progression or treatment intolerance.

**OBJECTIVES:**

- Phase I: To determine the maximum tolerated dose (MTD) of RVD-Elo.
- Phase II: To assess whether incorporation of the novel agent Elo into treatment algorithm of HRMM will improve PFS.

**STATISTICAL METHODS:**

- The phase I study enrolled 6 DLT evaluable patients; no DLTs were observed.
- The phase II study is now open and will accrue 100 eligible patients (50 per arm).
- An additional 10 patients (5 per arm) will be accrued to account for ineligibility/patients withdrawing consent.
- The median expected PFS in the control arm (RVD) is 2.2 years, based on the experience in Total Therapy 3 studies (high risk genomics defined by 70-gene model).
- Assuming uniform accrual of 25 patients per year, four years of accrual and an additional 2 years of follow-up yields a study with 82% power and a one-sided significance level alpha of 0.1 to detect a hazard ratio of 1.75 between two treatment arms, or an increase in median PFS from 2 years to 3.5 years in the RVD-Elo arm versus the RVD arm.

**PHASE I PORTION**

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<thead>
<tr>
<th>Induction</th>
<th>Maintenance</th>
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<tr>
<td>RVD + Elotuzumab 8 cycles of Induction Therapy followed by Maintenance until progression or relapse n=6</td>
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**RANDOMIZED PHASE II PORTION**

<table>
<thead>
<tr>
<th>Induction</th>
<th>Maintenance</th>
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<tr>
<td>RVD × 8 Cycles¹,² n=50</td>
<td>RVD Dose reduced</td>
</tr>
<tr>
<td>RVD-Elo × 8 Cycles¹,² n=50</td>
<td>RVD-Elo Dose reduced</td>
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1. ONE CYCLE OF PRIOR THERAPY ALLOWED PRIOR TO ENROLLMENT
2. STEM CELL COLLECTION ALLOWED AFTER CYCLE 2 ON PROTOCOL
3. ASCT ALLOWED OFF-PROTOCOL AT PROGRESSION/RELAPSE

Phase I complete, no DLTs observed

Phase II open for accrual: Open to all National Clinical Trials Network members

**CONFLICT OF INTEREST:** S.Z.U. is a consultant for Celgene, research funding from Celgene, Onyx & Millennium; M.D is a consultant for Bristol Myers Squibb, research funding from Celgene; P.G.R is a consultant for Celgene, Bristol Myers Squibb & Millennium; R.Z.O. is a consultant and has received research funding for BMS, Celgene, Onyx & Millennium; S.A received honorarium from Millennium