Phase III Intergroup Study of Lenalidomide Versus Placebo Maintenance Therapy Following Single Autologous Hematopoietic Stem Cell Transplantation (AHSCT) for Multiple Myeloma: CALGB100104


Abstract #37
Patient stratification based on diagnostic $\beta$2M and thalidomide and lenalidomide therapy during induction

Objectives

• **Primary Objective:**
  – Determine the efficacy of lenalidomide in prolonging time to progression (TTP) in myeloma patients following ASCT
  – Powered to determine a prolongation of TTP from 24 months to 33.6 months (9.6 months)

• **Secondary Objectives:**
  – CR rate post-ASCT
  – PFS and OS
  – Feasibility of long-term lenalidomide administration

Accrual

- **Target Accrual**: Register 538 with a goal of 462 randomized based on 10% drop out rate.
- **First enrollment in April of 2005**
  - CALGB: n = 376; ECOG: n = 133; BMT CTN: n = 59
- **Closed in July of 2009**: 568 registered pts from 47 centers
- **Drop out rate before randomization is 19%**
  - PD/NR (16%), AEs (5%), Died during Rx (2%), Refusal (26%), Other disease (1%), Other Rx (4%), Other reasons (33%), Unknown (14%)
- **Patients continued on therapy until progression**

CALGB DSMB Reports

- CALGB DSMB report (the 2\textsuperscript{nd} analysis) analyzed outcomes up to September of 2009 for 418 pts: 210 on lenalidomide and 208 on placebo and approximately 28\% of required events observed (progression or death due to any cause)
- The DSMB released the study results on 12/17/09
- The study was unblinded allowing patients to cross over to open-label lenalidomide with MD support
- This report is the 3\textsuperscript{rd} intent to treat (ITT) analysis for TTP and includes events up to 12/17/09 for 460 pts: 231 on lenalidomide and 229 on placebo with approximately 33\% of required events observed
- The \textit{P} values in this analysis have not been adjusted for sequential setting (unadjusted \textit{P} values)

# Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Lenalidomide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>231</td>
<td>229</td>
</tr>
<tr>
<td><strong>Median age (range)</strong></td>
<td>58 (29-70)</td>
<td>57 (39-70)</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>48%</td>
<td>52%</td>
</tr>
<tr>
<td><strong>β2M &gt;2.5 mg/L</strong></td>
<td>28%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Median follow-up has increased from 12.5 to 17.5 months with this analysis

## Induction Regimens: Preliminary Results

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide-based (no bortez or len)</td>
<td>152</td>
<td>27</td>
</tr>
<tr>
<td>Lenalidomide-based (no bortez or thal)</td>
<td>122</td>
<td>22</td>
</tr>
<tr>
<td>Bortezomib-based (no len or thal)</td>
<td>109</td>
<td>20</td>
</tr>
<tr>
<td>Bortezomib+thalidomide-based (no len)</td>
<td>68</td>
<td>12</td>
</tr>
<tr>
<td>Bortezomib+dex+lenalidomide (no thal)</td>
<td>52</td>
<td>9</td>
</tr>
<tr>
<td>Dexamethasone-based (no bortez, len or thal)</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Thalidomide and lenalidomide treatment</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Bortezomib, lenalidomide, and thalidomide treatment</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Missing</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>554</td>
<td>100</td>
</tr>
</tbody>
</table>

74% of patients received either lenalidomide or thalidomide prior to enrollment

Adverse Events During Maintenance for 405 of 460 Randomized Patients

<table>
<thead>
<tr>
<th>Max Adv Events</th>
<th>3- Severe (n, %)</th>
<th>4- Life Threat (n, %)</th>
<th>5- Lethal (n, %)</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P &lt; .001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>64 (31)</td>
<td>29 (14)</td>
<td>0 (0)</td>
<td>208</td>
</tr>
<tr>
<td>Placebo</td>
<td>14 (7)</td>
<td>8 (4)</td>
<td>0 (0)</td>
<td>197</td>
</tr>
<tr>
<td><strong>Nonhematologic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P = .035</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>61 (29)</td>
<td>7 (3)</td>
<td>3 (1)</td>
<td>208</td>
</tr>
<tr>
<td>Placebo</td>
<td>37 (19)</td>
<td>8 (4)</td>
<td>3 (2)</td>
<td>197</td>
</tr>
</tbody>
</table>

## Grade 3-5 Adverse Events During Maintenance for 405 of 460 Randomized Patients

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Lenalidomide (n = 208)</th>
<th>Placebo (n = 197)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>26 (13)</td>
<td>7 (4)</td>
<td>.0009</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>89 (43)</td>
<td>17 (9)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Anemia</td>
<td>9 (4)</td>
<td>2 (1)</td>
<td>.0629</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (5)</td>
<td>7 (4)</td>
<td>.4736</td>
</tr>
<tr>
<td>Rash</td>
<td>9 (4)</td>
<td>3 (2)</td>
<td>.1418</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (4)</td>
<td>5 (3)</td>
<td>.4182</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>12 (6)</td>
<td>3 (2)</td>
<td>.0329</td>
</tr>
<tr>
<td>All other infections</td>
<td>33 (16)</td>
<td>11 (5)</td>
<td>.0012</td>
</tr>
</tbody>
</table>

Excluding PD, 12% (27 of 231) on lenalidomide and 1% on placebo (2 of 208) came off therapy due to AEs; 20% (46 of 231) on lenalidomide and 7% (14 of 208) on placebo came off therapy for other reasons.

Results

• TTP was defined as disease progression or death due to any cause
• TTP was calculated from day 0 of ASCT
• Of 231 lenalidomide patients, 46 have experienced an event (progression or death)
• Of 229 placebo patients, 95 have experienced an event ($P<.0001$)
• Estimated hazard ratio of 0.40, thus a 60% reduction in the risk of disease progression with lenalidomide

CALGB 100104, follow up to 12/17/2009

ITT analysis with a median follow-up from transplant of 17.5 months ($P<.0001$)
13 deaths in lenalidomide arm and 24 deaths in the placebo arm ($P < 0.052$) There may have been a difference between the 2 arms which may no longer be present due to crossover.

**ITT Analysis: OS based on follow-up forms submitted on or before 12/17/2009**

**Overall Survival**

**Lenalidomide**

**Placebo**

Calculated probabilities for overall survival over time since ASCT (days) with the lenalidomide and placebo arms shown.
OS based on all follow-up forms to Nov 2010 on an ITT basis ($P<.078$)

CALGB 100104

Results

• There was a benefit between lenalidomide over placebo in each stratification
• 86 of ~110 eligible placebo patients started lenalidomide therapy
• As of November 2010, 122 lenalidomide patients and 86 placebo patients remain on lenalidomide
• 25 new malignancies reported so far
  – 4 before randomization
  – 15 of 231 on lenalidomide arm
  – 6 of 229 on the placebo arm
• Of the 25 new malignancies, there are 5 cases of AML/MDS
  – 2 MDS cases did not receive lenalidomide
  – Of 3 MDS/AML lenalidomide pts, 1 received breast cancer therapy in the past

TTP Stratified by Arm and β2 Microglobulin Elevation

CALGB 100104, Dec 17 2009
TTP Stratified by Arm and Prior Thalidomide

CALGB 100104, Dec 17 2009
Conclusions

• Maintenance therapy with lenalidomide when compared to placebo will significantly prolong time to disease progression.

• Currently, there is no difference in OS at a median follow-up of 1.5 years post-ASCT.

• Lenalidomide prolonged TTP within patient stratification by high and low β2M, and prior thalidomide or lenalidomide induction therapy.

• Lenalidomide maintenance produced some hematologic toxicity, but this was not severe with dropouts due to all AEs at 12%.

Participating Centers

• **CALGB:** Dana Farber Cancer Inst, Illinois Onc Res Assoc, Memorial Sloan Kettering Cancer Ctr, Mt Sinai School of Med, North Shore Univ Hosp, Roswell Park Cancer Inst, State Univ NY, Upstate Med Univ, Ohio State Univ Med Ctr, Univ California San Diego, Univ California San Francisco, Univ Chicago, Univ Illinois Chicago, Univ Minnesota, Univ Nebraska, Univ North Carolina Chapel Hill, BMT Group Georgia, Virginia Commonwealth Univ, Univ of Vermont, Wake Forest Univ School Medicine, Walter Reed Army Med Ctr, Washington Univ School Medicine, Weill Med College Cornell Univ, Western Pennsylvania Hosp

• **ECOG:** Cancer Inst of New Jersey, Case Western Metro Health Med Ctr, Columbia Presbyterian, St Lukes Hsp, Univ of Florida Gainesville, Fox Chase Cancer Ctr, Geisinger Med Ctr, Indiana Univ Medical Ctr, Jewish Hospital, Marshfield Clinic, Med College Georgia, Univ Miami, Univ Pennsylvania, Univ Pittsburgh, Scottsdale, Univ Hospital Cleveland, Vanderbilt Univ, Med College of Wisconsin, Univ of Wisconsin

• **BMT-CTN:** City of Hope, LDS Hosp, MD Anderson, Oregon Health Sciences Univ, Univ of Mississippi Med Ctr
CALGB 100104 Cooperative Effort


**ECOG:** Stadtmauer E, Wingard J, Callandar N


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Ongoing Statistical Center Analyses

- Evaluating other induction regimens (bortezomib, other agents)
- Evaluating detailed AEs
  - Relationship to lenalidomide or placebo dose
- Response data
  - Prior to ASCT, at randomization, following maintenance
- Ability to continue therapy
- Dose modification
- Other patient risk factors, eg, cytogenetics, LDH
- Therapy after progression
- Long term follow-up