RESULTS (Continued)

Attrition Bias

- Discontinuation rates were as follows and unlikely to bias results as determined by a special analysis:

<table>
<thead>
<tr>
<th>Study</th>
<th>Attrition Bias (in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZA</td>
<td>Denosumab</td>
</tr>
<tr>
<td>5.8</td>
<td>2.1</td>
</tr>
<tr>
<td>20.0%</td>
<td>14.8%</td>
</tr>
<tr>
<td>27.2%</td>
<td>26.4%</td>
</tr>
<tr>
<td>27.2%</td>
<td>26.4%</td>
</tr>
</tbody>
</table>

Special Analysis: Would the efficacy results be different if subjects had not discontinued the study?

Answer: It is improbable the efficacy results would be different, as described below:

1. Results of statistical significance testing, patients in multiple outcomes, and similar outcomes across the two groups make it likely that the efficacy results are due to chance.
2. Low risk of bias overall, including no confounding treatments, makes it unlikely that efficacy results are explained by a confounding treatment.
3. Uniformity in adverse events in both groups, due to similar study procedures (e.g., blinded assessment, performance outcomes), and likelihood of similar treatment responses contained in the studies that are unlikely to bias. Therefore, it is unlikely that bias would create inter-group differences.
4. The difference in median time to first SRE was 8.2 months.
5. The risk of time to first SRE was decreased by 17% (hazard ratio: 0.83 [95% CI: 0.76–0.90]).
6. The critical appraisal confirmed that the results of the three pivotal trials and the integrated analysis were found to be of high-quality evidence and were at low risk of bias and chance effects.
7. The critical appraisal confirmed that the results of the three pivotal trials and the integrated analysis were found to be of high-quality evidence and were at low risk of bias and chance effects.
8. Neither of the two groups was at high risk of bias and chance effects.
9. The critical appraisal confirmed that the results of the three pivotal trials and the integrated analysis were found to be of high-quality evidence and were at low risk of bias and chance effects.
10. The critical appraisal confirmed that the results of the three pivotal trials and the integrated analysis were found to be of high-quality evidence and were at low risk of bias and chance effects.
11. The critical appraisal confirmed that the results of the three pivotal trials and the integrated analysis were found to be of high-quality evidence and were at low risk of bias and chance effects.

CONCLUSIONS

The critical appraisal confirmed that the results of the three pivotal trials and the integrated analysis were robust and provided clinically meaningful benefit to patients with bone metastases from advanced cancer in the prevention of SREs.

- The three pivotal trials and the integrated analysis were found to be of high-quality evidence and low risk of bias and chance effects based on:
  - Large and appropriate study populations
  - High likelihood of balanced treatment groups through effective randomization
  - No unplanned inter-group differences or biases
  - High likelihood of successful blinding including concealed allocation and blinded assessments
  - Balanced and high degree of treatment adherence, per protocol (higher than 97%)
  - Balanced and low incidence of protocol deviations (lower than 1.5%)
  - Use of protocol adherence and assessments (e.g., self-reported outcomes, blinded assessments, and primary outcomes) to minimize bias
  - Appropriate use of censoring methods
  - No confounding of outcomes from use of bone-specific agents other than study treatment
  - Appropriate use of censoring methods
  - No confounding of outcomes from use of bone-specific agents other than study treatment
  - No significant deviation from intended study design due to missing data (special analysis conducted)

DISCLOSURES

- Sheri A. Strle, Michael E. Stuart, Lidya S. Beckman, Katarina Řehůrková
- Delfini Group, LLC, Portland, OR, USA; Delfini Group, LLC, Seattle, WA, USA; Amgen Inc., Thousand Oaks, CA, USA

REFERENCES