Comparing the Efficacy of Denosumab Versus Zoledronic Acid for Prevention of Skeletal-Related Events: A Critical Appraisal of Three Pivotal Trials

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BACKGROUND AND OBJECTIVES

- Bias, defined as anything that is likely to lead away from the truth other than random chance, and chance effects can distort reported results in clinical trials
- Rigorous critical appraisal of clinical trials is important:
  - Assessments of bias or chance findings are conducted to ensure that reported study results are internally valid (ie, reliable)
- Patients with skeletal complications from metastatic cancer to bone often experience loss of mobility, independence, and social functioning as well as reductions in physical well-being (eg, severe pain), emotional well-being, and health-related quality of life[1-9]
- In a prespecified integrated analysis of three double-blinded phase 3 trials in patients with bone metastases secondary to breast cancer, prostate cancer, and other solid tumors or multiple myeloma (N = 5,723), denosumab was found to be superior to zoledronic acid (ZA) in delaying time to first on-study skeletal-related event (SRE), defined as pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression[10]
  - The difference in median time to first SRE was 8.2 months
  - The risk of time to first SRE was decreased by 17% (hazard ratio: 0.83 [95% CI: 0.76–0.90]; $P < 0.001$)
  - Efficacy was demonstrated for first and multiple events and across patient subgroups (ie, prior SRE status, age, etc)
- Delfini Group critically appraised the prespecified integrated analysis of the three pivotal trials comparing denosumab to ZA for the prevention of SREs[10]

METHODOLOGY

- Published trials (Lipton, et al[10]; Stopeck, et al[11]; Henry, et al[12]; Fizazi, et al[13]) were analyzed along with supplementary information from study protocols, clinical study reports, and prescribing information
- The risk of bias for each area listed below was rated as low, medium, high, or uncertain
  - Combinability of studies
    - Heterogeneity
  - Selection bias
    - Study size
    - Random allocation of study subjects to treatment groups
    - Concealment of allocation (blinding subjects and investigators to treatment group assignment)
    - Balanced distribution of prognostic variables as assessed through review of baseline characteristics
  - Performance bias
    - Blinding of subjects and all people working with subjects and their data
    - Treatment adherence
    - Inter-group differences in treatment or care of subjects, except for the interventions of interest (Denosumab and ZA)
  - Attrition bias
    - Distortion of study results due to missing data, eg, subject dropout [subjected to special analysis]
  - Assessment bias
    - Blinded assessment
    - Analysis methods, eg, same method for assessing results in each group, method used for imputing missing data
    - Assumptions for modeling
  - Safety assessment
  - Other threats to validity

RESULTS

Overview: Internal Validity Assessment

- The three pivotal trials and the integrated analysis were found to be of high-quality evidence ie, were at low risk for bias and chance effects

Area of Consideration	Low Risk of Bias
Combinability	●
Selection Bias	●
Performance Bias	●
Attrition Bias	●
Assessment Bias	●
Other Threats to Validity	●

Details: Internal Validity Assessment

Combinability

- Heterogeneity testing: $P > 0.4$, supports combining the studies

Selection Bias

- 5732 randomized patients = large study population
- Randomization was based on a computer-generated schedule prepared before the start of the trials by an individual not involved with the trials and with no access to study data
- Interactive voice response systems (IVRS) was used to conceal allocation of subjects to their study groups. Subjects were randomized (1:1 ratio) to receive:
  - Denosumab 120 mg subcutaneously (SC) plus intravenous (IV) placebo or
  - Zoledronic acid (ZA) 4 mg IV plus placebo SC
- Balance in baseline characteristics between groups supports the conclusion that randomization was effective

Baseline Characteristic	Integrated Analysis ZA Arm	Integrated Analysis Denosumab Arm
N	2,861	2,862
Median Age, years	63	63
ECOG 0 or 1, n (%)	2,546 (89)	2,585 (90)
Previous SRE, n (%)	1,157 (40)	1,112 (39)
Presence of Visceral Metastases, n (%)	1,154 (40)	1,187 (42)
Median Time From Initial Cancer Diagnosis to First Bone Metastasis, months	16.5	16.6
Median Time From First Bone Metastasis to Randomization, months	2.3	2.2

ECOG = Eastern Cooperative Oncology Group; SRE = skeletal-related event; ZA = zoledronic acid

Performance Bias

- Appropriate comparator and dosing
- Study drugs were identical in appearance
  - Denosumab and the matching placebo were provided in identical boxes, with each single-use vial labeled with a unique code assigned to the subject by the IVRS before each dose. Zoledronic acid and the matching placebo were also supplied in a blinded manner
- All involved in the study were blinded during the treatment phase
- Unlikely breaking of the blind due to adverse events
- Treatment adherence was high in all trials (higher than 97%)
- Use of concomitant medication (chemotherapy or hormonal therapy for metastatic disease and supportive care treatments) other than bone-targeted agents was balanced between treatment groups across studies

RESULTS (Continued)

Attrition Bias

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

n (%)	Integrated Analysis ZA Arm N = 2,861	Integrated Analysis Denosumab Arm N = 2,862
Discontinued Prior to Primary Data Analysis Cut-Off Date	2,014 (70.4)	1,986 (69.4)
Death	754 (26.4)	778 (27.2)
Consent Withdrawn*	424 (14.8)	389 (13.6)
Disease Progression	341 (11.9)	367 (12.8)
Subject Request†	163 (5.7)	135 (4.7)
Adverse Event	134 (4.7)	120 (4.2)
Other	99 (3.5)	95 (3.3)
Lost to Follow-Up	36 (1.3)	39 (1.4)
Noncompliance	33 (1.2)	34 (1.2)
Administrative Decision	20 (0.7)	17 (0.6)
Protocol Deviation	4 (0.1)	7 (0.2)
Ineligibility Determined	6 (0.2)	5 (0.2)

*Subject withdrew full consent to participate in study, including long term follow-up. †Subject did not wish to attend any further Q4W assessments, but agreed to be contacted for survival follow-up
Percentages based on number of subjects randomized; Q4W = once every 4 weeks; ZA = zoledronic acid

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, patterns in multiple outcomes, and similar outcomes across the studies make it improbable 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. Unlikely imbalance in undetected SREs between groups, due to quality study procedures (ie, blind assessment), performance outcomes (ie, high adherence rates), and likelihood of successful blinding. Therefore, it is unlikely that bias would create inter-group differences (ie, that subjects who would have responded to ZA were selectively removed or encouraged to withdraw from the study)
4. Balance in numbers and reasons for discontinuation is highly suggestive that subjects who discontinued the study in each treatment group were similar
5. It is unlikely that subjects in either the ZA or denosumab groups who discontinued would have had a better treatment response than subjects who remained on study in each group. Even if subjects who discontinued would have had a better treatment response than those who remained on study, the rates would likely be similar due to balance in numbers and reasons for discontinuation. This would result in no change to the reported differences between the treatment groups
6. A detailed analysis was conducted to assess the effects of missing data in the study by Stopeck, et al.[11] This study was used as a proxy for all the studies, as they are similar in study design, methods, performance outcomes, etc. For denosumab not to be superior to ZA, subjects in the ZA group who discontinued the study would have had to experience an improbable decrease in SRE rates compared with subjects in the ZA group who remained on study

Assessment Bias

- All people involved in the study were blinded during the blinded treatment phase of each study
- SRE is a composite endpoint, where all components are clinically important. SREs consist of pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression
- Endpoints were prespecified
- A Kaplan-Meier model was used for assessment of primary outcome measures and censoring rules appear reasonable
- Early stopping: The primary analysis was planned when approximately 745 patients had experienced at least one on-study SRE

Other Threats to Validity

- None identified

Safety Assessment

- The safety population consisted of patients who received ≥ 1 dose of study drug
- Consistency in results in the three individual clinical trials

CONCLUSIONS

The critical appraisal confirmed that the results of the three pivotal trials and the integrated analysis were robust, with denosumab providing clinically meaningful benefit in 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 at low risk of bias and chance effects based on:
  - Large and appropriate study populations
  - High likelihood of balanced groups through effective randomization
  - No planned intergroup differences other than study agents
  - 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%)
  - Low likelihood of any differences between groups, except for study agents, because of effective randomization, likely successful blinding, and other quality study procedures
  - Balanced use of concomitant medications
  - No confounding of outcomes from use of bone-specific agents other than study agents
  - Appropriate use of censoring in the time-to-event analyses unlikely to bias results
  - No evidence of selective reporting
  - Unlikely bias resulting from attrition (distortion of study results due to missing data) [special analysis conducted]

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DISCLOSURES

- Sheri A. Strite and Michael E. Stuart of Delfini Group, LLC received funding from Amgen Inc. for conduct of the critical appraisal.
- Vidya S. Beckman and Katarina Öhrling are employees of Amgen Inc. and may own stock or stock options in Amgen Inc.

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