The Authors Respond:

We admit that any cost-effectiveness analysis (CEA) has limitations, the details of which have been stated in the paper. However, we disagree that the flaws cited by Rader et al.1 lead to biases that will change the study conclusions. We would also like to point out that we have conducted extensive sensitivity analyses to address the limitations, such as uncertainties of data and restrictiveness of base-case assumptions. The results were robust under various scenarios, except for substantial changes in drug prices and relative efficacy between denosumab and zoledronic acid.

With respect to the flaws cited by Rader et al.,1 we have provided the following responses.

Rader et al.1 commented that the model was based on clinical trials instead of real-world rates of skeletal-related events (SREs). CEA based on clinical trials is not uncommon. For example, most of the guidance published by the National Institute for Health and Clinical Excellence is based on the technology appraisals using clinical trial data.2 The real-world comparative effectiveness between denosumab and zoledronic acid has not been reported. Using the same relative efficacy reported by Fizazi et al. (2011),3 when we artificially inflated the number of SREs of patients receiving zoledronic acid to 3.48 for the first year, as suggested by Rader et al., the incremental cost per SRE avoided increased to $78,217. Unless there is solid evidence that the real-world relative effectiveness of denosumab versus zoledronic acid is larger compared with the relative efficacy observed in the trial, using clinical trial data will not bias against denosumab.

Although we did make assumptions in the CEA, the “inappropriate assumptions” cited by Rader et al. warrant further discussion. First, we did not assume that patients entering the Markov model were SRE-naive. We specifically mentioned in the methods section that the transition probabilities were “to the first on-study SRE” instead of the first-ever SRE, and the probabilities were calculated based on the results reported by Fizazi et al.3 Second, we had a detailed discussion in the limitations section about the assumption of constant hazard and its effects on the results. We showed that it did not affect our conclusion. Third, we used the risk ratio reported by Tchekmedyian et al. (2010)4 for both first and subsequent SREs because there is no evidence that the impact of disease progression is different between first on-study SREs and subsequent SREs. We have stated this limitation in the published study.

Without further evidence, it is difficult to assess whether and how the current assumption biases the incidence of SREs.

The cycle length of 12 weeks was consistent with the mean...
time of 3 months between the first and second types of SREs in prostate cancer patients reported by a study using real-world data. Although the assumption of 1 SRE per cycle is somewhat arbitrary, as stated in the limitations, the proportion of patients with first on-study SREs and the total number of SREs in each arm match well with the numbers reported in the Phase 3 clinical trial.

In the study, we presented the results for both 1- and 3-year time horizons. The reason for not using the longer time horizon is that zoledronic acid (Zometa) is expected to be available in a less expensive generic form by March 2013. Because the model results are sensitive to zoledronic acid drug price, a longer time horizon is not meaningful in this case. With respect to the suggestion of using a lifetime model, we would like to mention that metastatic castration-resistant prostate cancer (mCRPC) patients had a poor survival (median 9-13 months). In our model, 83% of patients died by the end of 3 years. Therefore, even if we used a lifetime model, the results would not be very different compared to the 3-year model.

Regarding the cost estimate for SREs, we have provided detailed information and discussed its limitations in the published study. However, we would like to reiterate that using the 1-year cumulative costs as per event costs would not underestimate the cost of SRE because in the study by Lage et al. (2008), the 1-year costs were estimated among patients experiencing 1 or more episodes of a specific type of SRE. Barlev et al. (2010) reported inpatient costs for only 3 types of SREs: pathologic fracture, surgery to bone, and spinal cord compression. Radiation to bone, which we believe is primarily managed in an outpatient setting, was not estimated in the study, and it accounted for more than 50% of first on-study SREs in both treatment arms in the Phase 3 trial. Therefore, using the costs suggested by Rader et al. will inevitably inflate the mean costs for SREs.

Finally, SRE was the primary endpoint of the Phase 3 trial and was thus used as the effectiveness measure in this CEA. From clinical perspectives, SRE is the most relevant outcome among CRPC patients with bone metastasis. Therefore, incremental cost per SRE avoided is particularly pertinent to physicians as well as payers. The outcome has been commonly used in the previous economic analyses of treatments that prevent and delay SREs in cancer patients. Although a CEA using cost per quality-adjusted life year (QALY) as the outcome has not been published, another independent study by Snedecor et al. has been presented at the 2011 American Society of Clinical Oncology meeting. Both the current study and the study by Snedecor et al. estimated that the incremental cost per QALY comparing denosumab versus zoledronic acid was more than $1 million.

Overall, despite the limitations, we feel that the results of our study are robust and the conclusion is valid. Denosumab does have better efficacy in preventing and delaying SREs in CRPC patients with bone metastases compared with zoledronic acid but at considerable costs.

Jipan Xie, MD, PhD
Analysis Group, Inc., Boston, MA
jxie@analysisgroup.com

Madhav Namjoshi, PhD
Novartis Pharmaceuticals Corporation, East Hanover, NJ

Kejal Parikh, MSc, and Eric Q. Wu, PhD
Analysis Group, Inc., Boston, MA

DISCLOSURES
Namjoshi is employed by Novartis Pharmaceuticals Corporation, the manufacturer of zoledronic acid intravenous infusion. Xie, Parikh, and Wu are employees of Analysis Group, Inc., which received consulting fees from Novartis for this research.

REFERENCES