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Original article

Cost-effectiveness of denosumab vs zoledronic acid for prevention of skeletal-related events in patients with solid tumors and bone metastases in the United States

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Abstract

Objective:

With increasing healthcare resource constraints, it has become important to understand the incremental cost-effectiveness of new medicines. Subcutaneous denosumab is superior to intravenous zoledronic acid (ZA) for the prevention of skeletal-related events (SREs) in patients with advanced solid tumors and bone metastases. This study sought to determine the lifetime cost-effectiveness of denosumab vs ZA in this setting, from a US managed-care perspective.

Methods:

A lifetime Markov model was developed, with relative rate reductions in SREs for denosumab vs ZA derived from three pivotal Phase 3 trials involving patients with castration-resistant prostate cancer (CRPC), breast cancer, and non-small-cell lung cancer (NSCLC), and bone metastases. The real-world SRE rates in ZA-treated patients were derived from a large commercial database. SRE and treatment administration quality-adjusted life year (QALY) decrements were estimated with time-trade-off studies. SRE costs were estimated from a nationally representative commercial claims database. Drug, drug administration, and renal monitoring costs were included. Costs and QALYs were discounted at 3% annually. One-way and probabilistic sensitivity analyses were conducted.

Results:

Across tumor types, denosumab was associated with a reduced number of SREs, increased QALYs, and increased lifetime total costs vs ZA. The costs per QALY gained for denosumab vs ZA in CRPC, breast cancer, and NSCLC were \$49,405, \$78,915, and \$67,931, respectively, commonly considered good value in the US. Costs per SRE avoided were \$8567, \$13,557, and \$10,513, respectively. Results were sensitive to drug costs and SRE rates.

Limitations:

Differences in pain severity and analgesic use favoring denosumab over ZA were not captured. Mortality was extrapolated from fitted generalized gamma function beyond the trial duration.

Conclusion:

Denosumab is a cost-effective treatment option for the prevention of SREs in patients with advanced solid tumors and bone metastases compared to ZA. The overall value of denosumab is based on superior efficacy, favorable safety, and more efficient administration.

Introduction

Bone is one of the most common sites of distant metastases among patients with cancer: up to 75% of patients with advanced prostate and breast cancers will develop metastatic bone disease, as will ~40% of patients with advanced lung cancer¹.

Bone metastases can induce bone destruction (primarily through increased osteoclast activity), which places patients at risk of skeletal-related events (SREs)^{2,3}. SREs include pathological fractures that may impair ambulation; spinal cord compressions that can result in numbness or weakness, urinary or fecal incontinence, and paralysis; the need for radiation therapy to bone to control local tumor burden and manage pain; and the need to undergo surgery to bone to prevent or treat pathologic fractures^{4,5}. SREs secondary to bone metastases can be painful and debilitating, and can result in reduced health-related quality-of-life (HRQoL)⁶. SREs are also costly to manage⁷. In the US, patients with bone metastases secondary to breast cancer who experienced an SRE incurred significantly higher total medical costs compared with those who did not experience an SRE over a 60-month period (\$115,542 vs \$67,369⁸), with most of the total economic burden—nearly 60%—relating to SREs requiring hospitalization⁸. The mean reimbursed amount per hospital admission associated with SREs across tumor types has been estimated at ~\$31,000–\$42,000 for bone surgery, \$22,000–\$27,000 for pathologic fracture, and \$44,000–\$60,000 for spinal cord compression⁹.

The bisphosphonate zoledronic acid (4 mg given intravenously [IV] once every 3–4 weeks) is frequently utilized in the US to delay or prevent SREs in patients with bone metastases secondary to advanced solid tumors¹⁰. However, a significant proportion of patients still experience SREs despite treatment with IV zoledronic acid^{11–13}. In addition, zoledronic acid is associated with renal toxicity, such that serum creatinine monitoring is required before each dose, and dose reduction or dose delay is required in patients with renal impairment¹⁴. Furthermore, zoledronic acid is specified to be infused intravenously over no less than 15 minutes¹⁴.

Denosumab (XGEVA®) is a fully human monoclonal antibody against RANK ligand that inhibits osteoclast-mediated bone destruction¹⁵. In three large, pivotal Phase 3 international clinical trials, denosumab 120 mg subcutaneously (SC) every 4 weeks demonstrated superior efficacy over IV zoledronic acid for the prevention of SREs in patients with bone metastases secondary to castration-resistant prostate cancer (CRPC)¹⁶, advanced breast cancer¹⁷, and other advanced solid tumors¹⁸. Overall, denosumab significantly delayed time to first on-study SRE (HR: 0.83; 95% CI: 0.76–0.90; $p < 0.001$) as well as time to first and subsequent on-study SREs (HR: 0.82; 95% CI: 0.75–0.89; $p < 0.001$) compared with zoledronic acid

($n = 2862$ denosumab; $n = 2861$ zoledronic acid)¹⁹. Denosumab also delayed the onset of moderate or severe pain compared with zoledronic acid^{20–22}, and maintained HRQoL in patients with solid tumors and bone metastases^{23,24}. Unlike zoledronic acid, denosumab can be used in patients regardless of renal status or concomitant use of nephrotoxic agents, with no renal monitoring or dose adjustments required²⁵.

With increasing healthcare resource constraints²⁶, it is important to understand the relative benefits and costs of new treatments²⁷, and this is particularly informative to payers when making formulary decisions. Since the approval of denosumab for the prevention of SREs by the US Food and Drug Administration in November 2010, there has been great interest in the assessment of its relative economic value^{28,29}. A recently published cost-effectiveness analysis³⁰ was intended to delineate the cost-effectiveness of denosumab vs zoledronic acid for the prevention of SREs among patients with CRPC and bone metastases. However, it was associated with a number of limitations, including the under-estimation of the true incidence of skeletal complications in oncology, thus limiting the accurate assessment of the cost-effectiveness of denosumab and zoledronic acid in this patient group³¹. Furthermore, corresponding data in other tumor types have not yet been published.

We therefore sought to determine the cost-effectiveness of denosumab relative to zoledronic acid for the prevention of SREs among patients with bone metastases secondary to CRPC, breast cancer, or NSCLC, based on a lifetime Markov cohort model from a US managed care perspective. We aimed to obtain incremental cost-effectiveness ratios (ICERs) including cost per quality-adjusted life year (QALY) gained and cost per SRE avoided.

Methods

Design

A lifetime Markov cohort model was constructed from the US managed care perspective. It was structured identically for both treatments (denosumab and zoledronic acid) and across all tumor types (CRPC, breast cancer, and NSCLC), with treatment- and tumor-specific model inputs.

A Markov model is a type of mathematical model containing a finite number of mutually exclusive and exhaustive health states, having time periods (cycles) of uniform length and in which the probability of movement from one state to another depends on the current state and remains constant over time³².

In this analysis, the Markov model consisted of three Markov health states (On Treatment, Off Treatment, and Dead). When a patient was in the 'On Treatment' Markov

state, there was a risk for SREs, bone-modifying agent treatment-related adverse events (AEs), and death. When a patient was in the 'Off Treatment' Markov state, there was a higher risk of SREs, an unchanged risk of death, and no risk of bone-modifying agent treatment-related AEs. In the model, costs were a consequence of treatment, drug administration, SREs, and AEs; declines in utility from baseline (expressed as decrements in QALYs) were a consequence of SREs, the administration of drugs to prevent SREs, and AEs (Figure 1).

The model cycle length was 28 days (or 4 weeks), consistent with the dose frequency of the two treatments and previous published cost-effectiveness analyses of bone-modifying agents in the treatment of bone metastases³³. Given that the nature of a Markov cohort model is to predict the events for each cycle, which does not allow for multiple events within one cycle, a longer cycle length was not considered appropriate as patients are more likely to develop multiple SREs over longer periods of time.

As SREs may occur throughout the entire remaining lifespan of patients with bone metastases, the time horizon for this cost-effectiveness analysis was a lifetime, thus extending far enough into the future to capture all major health and economic outcomes³². Specifically, the model was run for 200 cycles (15.33 years), after which more than 99% of patients had transitioned to the 'Dead' health state, with more than 70% of patients transitioning to this state within the first 24–48 cycles (i.e., 2–4 years) of the model, depending on tumor type.

Model event parameters

For each Markov cycle, the model event parameters in this cost-effectiveness analysis included probabilities of SREs, probabilities of death, probabilities of drug discontinuation, and probabilities of AEs. These model probabilities

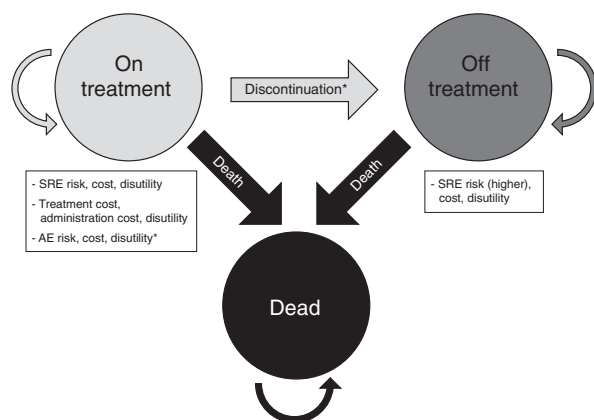


Figure 1. Depiction of Markov model states.

*Not included in the base case scenario. SRE, skeletal-related event; AE, adverse event.

were derived largely from the results of the three pivotal Phase 3 clinical trials, in which SC denosumab 120 mg every 4 weeks was compared with IV zoledronic acid 4 mg every 4 weeks for the prevention of SREs in patients with bone metastases secondary to CRPC ($n=1901$)¹⁶, advanced breast cancer ($n=2046$)¹⁷, and other advanced solid tumors (including NSCLC) or multiple myeloma ($n=1776$)¹⁸. The last of these studies included patients with multiple tumor types. We selected data from patients with NSCLC for inclusion in the model as these patients represented a significant sub-set of the overall study population (702/1776 patients; 40%)^{18,34} and a suitably homogeneous sub-population. The primary end-point in all three of these studies was time to first on-study SRE (with SREs defined as pathologic fracture, radiation or surgery to bone, or spinal cord compression)^{16–18}.

The model was based on constant rates for SREs, drug discontinuation, and AEs over the lifetime of the patient, and the corresponding probabilities in each cycle were derived from the rates by assuming an exponential relationship between rates and probabilities. This approach is consistent with other published cost-effectiveness literature in this therapeutic area³⁵. It also presents a straightforward method of extrapolating results beyond the time frame of the clinical trials^{16,17}.

Probability of skeletal-related events

To ensure that the model better reflected the US managed care perspective, SRE rates in clinical practice in each treatment group were derived by comparing published rates derived from the managed care setting as captured in a large commercial database (PharMetrics integrated claims database, a nationally-representative database of medical and pharmaceutical claims that includes 80 US health plans and covers 55 million patients)¹⁰ and SRE rates (total number of SREs divided by total patient follow-up time) reported in the denosumab Phase 3 clinical trials^{16,17}. An adjustment factor of 2.01 was derived and was used to adjust the trial-based SRE rates for zoledronic acid-treated patients in the model. The SRE rates for denosumab-treated patients were then calculated by applying the treatment effects from the Phase 3 clinical trials. The adjusted annual SRE rates in clinical practice for denosumab and zoledronic acid were 1.500 and 1.903, respectively, in the CRPC model; 0.980 and 1.267, respectively, in the breast cancer model; and 2.242 and 2.634, respectively, in the NSCLC model (Table 1).

Probability of death

Overall survival was not significantly different between the two treatment groups in the randomized clinical trials^{16–18}, therefore the generalized gamma functions were fitted using mortality data pooled across both

Table 1. Skeletal-related event and drug discontinuation rates included in the model.

Model input	CRPC ^{10,16}		Breast cancer ^{10,17}		NSCLC ¹⁰	
	Dmab	ZA	Dmab	ZA	Dmab	ZA
Annual SRE rate	1.500	1.903	0.980	1.267	2.242	2.634
Annual drug discontinuation rate	0.409	0.476	0.284	0.288	0.842	1.009

SRE, skeletal-related event; CRPC, castration-resistant prostate cancer; NSCLC, non-small-cell lung cancer; Dmab, denosumab; ZA, zoledronic acid.

treatment groups for each tumor type, to avoid random survival differences. The generalized gamma function was selected based on a comparison against other parametric models including: Weibull, log-logistic, log-normal, exponential, normal, logistic, and extreme value according to log likelihood or the Akaike Information Criterion (AIC).

Probability of drug discontinuation

Due to a lack of data from clinical practice, discontinuation of therapy was incorporated into the model based on the discontinuation rate from each clinical trial (excluding discontinuation due to death, which was already accounted for in the model by the mortality inputs)^{16,17} (Table 1). The model assumed that SRE rates increased after discontinuation of therapy. The placebo rates from other trials were used as a proxy for the effects of discontinuation on outcomes in the absence of published data. The SRE rate for patients who discontinued either treatment was assumed to be 1.75-times higher than the SRE rate in the zoledronic acid-treated patients^{36,37}. Drug discontinuations were not considered in the base case analyses, but were included in a separate scenario analysis.

Probability of adverse events

It is generally not feasible to include all possible AEs in cost-effectiveness models as the models would become too complex. Since most AEs are infrequent, not related to drug administration, and many have little to no effect on the results of economic models, only clinically and economically important AEs, including osteonecrosis of the jaw (ONJ), acute phase reactions, hypocalcemia, and renal toxicity, were included in the model. The rates of these four AEs were estimated for denosumab and for zoledronic acid based on the integrated safety results across all three Phase 3 clinical studies to help provide more stable rates. Rates of AEs were calculated by using the total number of patients with each AE, and dividing by the person-time on study over which patients were followed for AEs. Adverse events were not included in the base case analyses, but were included in a separate scenario analysis.

Table 2. Baseline utilities and skeletal-related event QALY decrements.

	CRPC	Breast cancer	NSCLC
Baseline utility	0.680	0.660	0.560
SRE QALY decrement ³⁸			
Pathologic fracture		0.070	
Radiation to the bone		0.100	
Surgery to the bone		0.140	
Spinal cord compression ^a		0.560	
Weighted average	0.150	0.142	0.124
SRE QALY decrement ^b			

^aSRE QALY decrement based on a 50:50 split between spinal cord compression with and without paralysis³⁹.

^bDifferences in the composite SRE QALY decrement reflect differences in the distribution of the different SRE types.

SRE, skeletal-related event; QALY, quality-adjusted life year; CRPC, castration-resistant prostate cancer; NSCLC, non-small-cell lung cancer.

Model utilities

Utility refers to the preference of a patient for a particular health outcome or health state³². In this cost-effectiveness analysis, the baseline utility for patients with advanced solid tumors and bone metastases was estimated using the EuroQoL 5-Dimensions (EQ-5D) data from the three Phase 3 trials pooled across all patients who did not have any on-study SREs (Table 2).

The QALY is a measure of health outcome, which includes both the quality and the quantity of life lived. It assigns to each period of time a weight, ranging from 0 (equivalent to death) to 1 (optimal health), corresponding to the HRQoL during that period³². The QALY decrements associated with SREs in the model were derived from a time trade-off (TTO) study conducted in 126 participants from the UK general population, who completed TTO interviews to assess the utility of hypothetical health state vignettes describing patients with cancer with bone metastases and SREs³⁸ (Table 2). Changes in QALYs were computed to estimate the decrement associated with each year in which an SRE occurred. The model calculates the expected average QALY decrement of an SRE based on the proportion distribution of each type of SRE (see 'SRE type distribution' section of the Methods).

The QALY decrements associated with administration of drugs for SRE prevention were estimated from another TTO study conducted in 121 participants from the UK general population, who were interviewed using hypothetical vignettes describing the health states of patients with cancer with bone metastases not receiving bone metastases treatments, receiving bone metastases treatments involving a less than 10 second SC injection, or receiving bone metastases treatments involving an IV infusion of at least 30 minutes. The mean disutility for receiving monthly SC injections for 1 year was 0.015 and the mean disutility for receiving monthly IV infusions for 1 year was 0.027, resulting in an annual QALY difference of 0.012. This was divided by 13 and applied in each cycle for patients who were on treatment.

The QALY decrements associated with AEs were estimated from EQ-5D data using a generalized estimating equations (GEE) regression approach. Due to the small number of these AEs, the QALY decrements were developed by pooling EQ-5D data from patients across the three trials and both treatment groups. No QALY decrement was assumed for acute phase reactions.

An annual discount rate of 3% was applied to the QALYs³².

Costs

The cost inputs included SRE costs by type, drug costs, administration costs, and AE costs.

SRE costs by type of event and by tumor type were estimated using the reimbursed amount from a large representative US commercial claims database⁹, weighting the inpatient and outpatient costs, and were inflated from 2009 to 2011 costs using the medical component of the Consumer Price Index (CPI)⁴⁰ (Table 3). The model calculates the expected average costs of an SRE based on the proportion distribution of each type of SRE.

The 2011 wholesale acquisition cost (WAC) was used for drug costs, with costs of denosumab of \$1650 per 120 mg administration and zoledronic acid of \$895.61 per administration⁴¹. A \$35.42 administration fee for an SC injection of denosumab and a \$154.64 administration fee for an IV infusion of zoledronic acid were included for each administration. In addition, a \$21.43 renal monitoring fee was also included for each zoledronic acid administration⁴².

Due to a lack of data from clinical practice, compliance was assumed to be balanced between the two treatments (10% of doses would be missed for both drugs), consistent with the trial data. In the base case, patients were assumed to continue treatment for their lifetime. Adverse event costs were based on published data, where available (the cost of pyrexia was used for acute phase reactions)^{30,43}. An annual discount rate of 3% was applied to the costs³².

Table 3. Costs of skeletal-related events (2011 USD)⁹.

Cost inputs	CRPC	Breast cancer	NSCLC
SRE by type			
Pathologic fracture	\$8382	\$9854	\$9118
Radiation to the bone	\$9027	\$11,512	\$10,269
Surgery to the bone	\$35,834	\$29,792	\$32,813
Spinal cord compression	\$25,983	\$22,845	\$24,414

Note: No SRE costs were available for NSCLC so the average cost of CRPC and breast was used.

Costs were inflated from 2009 to 2011 prices using Medical Care Services Consumer Price Index³⁹.

Table 4. Real-world skeletal-related event type distribution^{44,45}.

	CRPC	Breast cancer	NSCLC
Pathologic fracture events	19%	29%	14%
Radiation to the bone events	68%	59%	79%
Surgery to the bone events	1%	1%	1%
Spinal cord compression events	12%	11%	6%

CRPC, castration-resistant prostate cancer; NSCLC, non-small-cell lung cancer.

SRE type distribution

The SRE type distributions by tumor type as occur in clinical practice were estimated from published studies of a SEER-Medicare database of patients with prostate, breast, or lung cancer and bone metastases^{44,45} (Table 4).

Cost-effectiveness analyses

The outcome measures for the cost-effectiveness analyses included QALY and number of SREs. The ICERs included cost per QALY gained and cost per SRE avoided. The ICER is the ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives³². Cost per QALY gained is one of the most frequently used ICERs to compare the economic interventions across disease areas. It is also a standard and internationally recognized method to assess the value for money of a medical intervention⁴⁶.

In this cost-effectiveness analysis, ICERs were obtained by calculating the difference in total cost (ΔC) between denosumab (C_{dmab}) and zoledronic acid (C_{zol}) and dividing that value by the difference in outcomes (ΔE) between denosumab (E_{dmab}) and zoledronic acid (E_{zol})³², where the outcomes are cumulative lifetime QALYs and number of SREs.

$$\text{ICER} = \frac{\Delta C}{\Delta E} = \frac{C_{\text{dmab}} - C_{\text{zol}}}{E_{\text{dmab}} - E_{\text{zol}}}$$

The base case analysis used a lifetime time horizon, a 3% per year discount rate for costs and QALYs, and did not

Table 5. Cost-effectiveness of denosumab vs zoledronic acid base case results.

	CRPC			Breast cancer			NSCLC		
	Dmab	ZA	Diff	Dmab	ZA	Diff	Dmab	ZA	Diff
Total lifetime number of SREs	3.23	4.04	−0.81	3.56	4.55	−0.99	2.46	2.84	−0.39
Total lifetime QALYs	0.97	0.83	0.14	1.76	1.59	0.17	0.33	0.27	0.06
Total lifetime costs (\$)	76,486	69,577	6910	108,538	95,087	13,451	49,068	44,993	4076
Cost per QALY gained (\$)		49,405			78,915			67,931	
Cost per SRE avoided (\$)		8567			13,557			10,513	

CRPC, castration-resistant prostate cancer; NSCLC, non-small-cell lung cancer; Dmab, denosumab; ZA, zoledronic acid; Diff, difference; SRE, skeletal-related event; QALY, quality-adjusted life year.

incorporate drug discontinuation or AEs. For all three tumor types, two additional scenarios with drug discontinuation and AEs were analyzed.

One-way deterministic and probabilistic sensitivity analyses (PSA) were conducted for key model probability-related, utility-related, and cost-related inputs to test the robustness of the results. In the one-way deterministic sensitivity analyses, plausible values of parameter inputs in the model were varied one at a time and ICERs were recalculated accordingly. In PSA, probability distributions were specified for each uncertain parameter, and a simulation was performed whereby values of each parameter were randomly drawn from the corresponding distribution, and the resulting probability distribution of expected outcomes was displayed³².

In this cost-effectiveness analysis, individual model variables were intentionally ranged $\pm 50\%$ in one-way deterministic sensitivity analyses to test the robustness of the individual values to large variations. The results are presented in tornado diagrams, where the bars represent the value of ICERs as results of varying the model variables by $\pm 50\%$. The variable with the largest impact on ICERs appears at the top of the chart, the second largest appears second from the top, and so on. To incorporate the cumulative effect of uncertainty across multiple model inputs, a multivariate PSA was conducted using a Monte Carlo simulation of 1000 iterations for each tumor type. Where possible, the PSA input uncertainties were derived from the confidence intervals, or other measures of uncertainty, available for each parameter (Appendix). The cost-effectiveness acceptability curves (CEACs) for each tumor type were derived to present the probability of denosumab being cost-effective compared with zoledronic acid based on different willingness-to-pay (WTP) thresholds for cost per QALY gained.

Results

Base case

Denosumab was associated with a reduction in the number of SREs compared with zoledronic acid and an

improvement in patients' quality-of-life (thereby increasing QALYs) compared with zoledronic acid across all three tumor types (Table 5). Over a patient's lifetime, the number of SREs avoided per patient taking denosumab was 0.81 for CRPC (median survival = 1.7 years, 56% death in 2 years), 0.99 for breast cancer (median survival = 3.1 years, 34% death in 2 years), and 0.39 for NSCLC (median survival = 9 months, 83% death in 2 years). The lifetime QALYs gained were 0.14 for CRPC, 0.17 for breast cancer, and 0.06 for NSCLC.

The total lifetime incremental costs of denosumab vs zoledronic acid were \$6910 for CRPC (incremental drug costs: \$18,967; drug administration costs reduction: \$3536; SRE costs reduction: \$8522), \$13,451 for breast cancer (incremental drug costs: \$30,431; drug administration costs reduction: \$5674; SRE costs reduction: \$11,306), and \$4076 for NSCLC (incremental drug costs: \$10,136; drug administration costs reduction: \$1890; SRE costs reduction: \$4171). The cost per QALY gained for denosumab compared to zoledronic acid in CRPC, breast cancer, and NSCLC were \$49,405, \$78,915, and \$67,931, respectively. Cost per SRE avoided was \$8567, \$13,557, and \$10,513, respectively (Table 5).

Additional scenarios

Table 6 shows the results for the additional scenarios. When drug discontinuation was considered, the cost per QALY gained for CRPC and NSCLC were reduced to \$42,526, and \$49,781, respectively, whereas it remained almost constant for breast cancer (Table 6).

The results were not sensitive to the incorporation of ONJ, acute phase reaction, hypocalcemia or renal toxicities (Table 6), with the costs per QALY gained and costs per SRE avoided being similar to the base case scenario for each tumor type.

Sensitivity analyses

In one-way sensitivity analyses, the most influential variables were drug costs and SRE rates (Figure 2a–c).

Table 6. Cost-effectiveness of denosumab vs zoledronic acid scenario analyses results.

	CRPC	Breast cancer	NSCLC
With drug discontinuation			
Cost per QALY gained	\$42,526	\$78,175	\$49,781
Cost per SRE avoided	\$7120	\$13,818	\$7130
With ONJ, acute phase reactions, hypocalcemia and renal toxicity considered			
Cost per QALY gained	\$49,428	\$78,935	\$67,959
Cost per SRE avoided	\$8571	\$13,562	\$10,518

CRPC, castration-resistant prostate cancer; NSCLC, non-small-cell lung cancer; QALY, quality-adjusted life year; SRE, skeletal-related event.

In the multivariate probabilistic sensitivity analysis (PSA), the probabilities of denosumab being cost-effective vs zoledronic acid in patients with CRPC and bone metastases were ~0.83, 0.94, and 0.98 with ICER thresholds of \$100,000, \$150,000, and \$200,000, respectively (Figure 3). For patients with breast cancer and bone metastases, the corresponding probabilities were 0.62, 0.79, and 0.91, respectively, and they were 0.60, 0.72, and 0.78 for patients with NSCLC and bone metastases.

Discussion

Cost-effectiveness analyses help to inform payers and formulary decisions by quantifying the comparative value of treatments. We determined the lifetime cost-effectiveness of denosumab vs zoledronic acid in preventing SREs among patients with CRPC, breast cancer, or NSCLC and bone metastases, from a US managed care perspective.

In the base case analyses, the costs per QALY gained of denosumab vs zoledronic acid were \$49,405 for CRPC, \$78,915 for breast cancer, and \$67,931 for NSCLC, and the corresponding costs per SRE avoided in patients treated with denosumab vs zoledronic acid were \$8567, \$13,557, and \$10,513, respectively. When the rate of drug discontinuation associated with denosumab or zoledronic acid (as reported in the Phase 3 trials) was included in the analyses, cost per QALY gained in CRPC and NSCLC were reduced substantially (to \$42,526 and \$49,781, respectively), due to the non-trivial difference in this rate, which was higher for zoledronic acid than for denosumab^{16,34}. The results were robust to the incorporation of ONJ, acute phase reactions, hypocalcemia, and renal toxicity across all three tumor types. By assuming no QALY decrement associated with treatment administration, the cost per QALY gained ranged from ~\$60,000–\$105,000, which reflects the non-trivial impact of differences in mode of administration on the cost-effectiveness of denosumab vs zoledronic acid. In fact, previous time and motion studies have demonstrated notably increased time burden associated with zoledronic acid infusions^{47,48}.

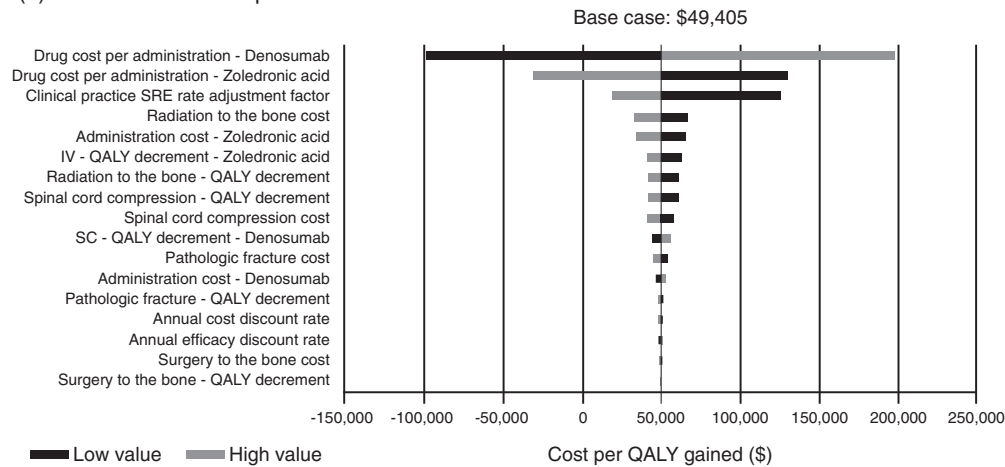
It is worth noting that, among all the important inputs, the model results were most sensitive to drug costs and SRE rates. The Phase 3 trials tended to enroll patients with a better performance status (eligibility criteria required all patients to have an Eastern Cooperative Oncology Group [ECOG] performance status ≤ 2 , with more than 80% of patients randomized having an ECOG of 0 or 1) and longer life expectancies^{16–18} than patients in the real world setting, such that the trial-based SRE rates were likely to under-estimate the expected SRE rates in clinical practice. From a payer's perspective, under-estimating real world SRE rates will under-estimate the economic burden of SREs. A previously reported economic evaluation of denosumab vs zoledronic acid in patients with CRPC and bone metastases³⁰ used SRE rates from the Phase 3 trial of patients with CRPC, and thus is likely to have under-estimated the economic value of denosumab. Given the importance of SRE rates in the model (Figure 2a–c), we believe that use of an adjusted rate of SREs that reflects clinical practice (as per our analyses) provides a more accurate assessment of the relative value of these treatments to payers.

In addition, the previously published economic evaluation of denosumab vs zoledronic acid in patients with CRPC and bone metastases³⁰ made several inappropriate assumptions to derive the transition probabilities between Markov health states, which yield downwardly biased estimates of the incidence of SREs³¹. This evaluation applied 1-year cumulative costs associated with SREs in aggregate⁴⁹, which is also not justified and leads to under-estimation of the SRE costs³¹.

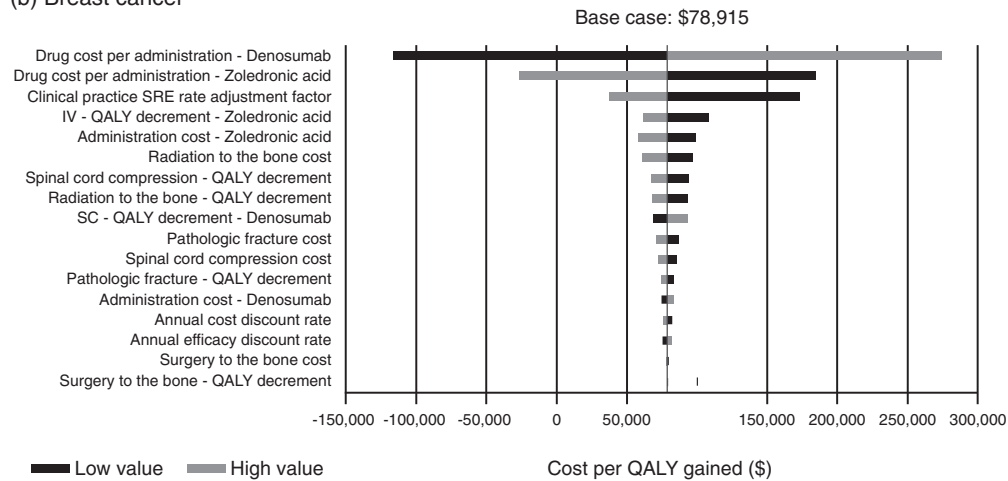
Our Markov model was validated against the clinical trial results by comparing the number of SREs predicted by the model with the number of SREs observed from the trials. By setting the clinical practice SRE rate adjustment factor to one, the model predicted almost the same number of SREs as observed from the trials over the same time duration and for the same number of patients, for both treatment groups in each tumor type.

As noted in the methods, the SRE and drug administration QALY decrement inputs in this cost-effectiveness evaluation were based on TTO studies rather than the EQ-5D data from the Phase 3 clinical trials. Although widely used for the assessment of health state utilities, there are known limitations of the EQ-5D such as ceiling effects^{50–53}, a limited ability to capture mild burdens of morbidity, and a limited ability to reflect small differences in health states that are particularly important to specific groups of patients^{53–55}. Therefore, it is unlikely that differences among the SRE types would be captured using the five items of EQ-5D (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with only three response options (no problems, some problems, and severe problems). In addition, due to the clinical characteristics of SREs (i.e., as acute events), it has become very

(a) Castration-resistant prostate cancer



(b) Breast cancer



(c) Non-small-cell lung cancer

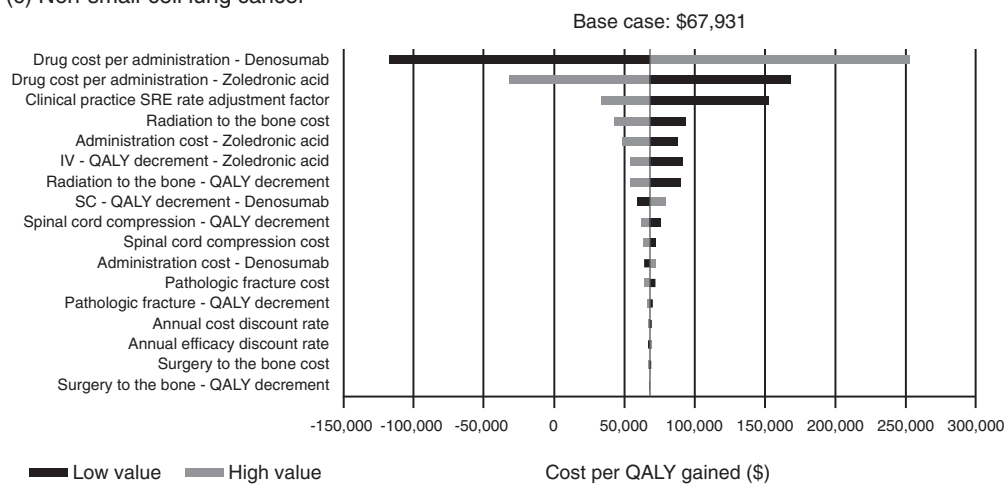


Figure 2. One-way sensitivity analyses of the effect of the input parameters on cost per QALY gained. SRE, skeletal-related events; IV, intravenous; QALY, quality-adjusted life year; SC, subcutaneous.

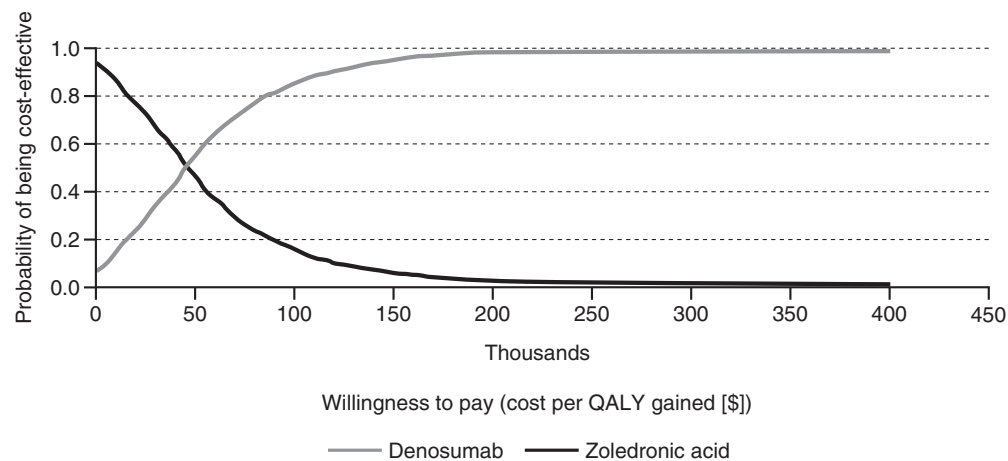


Figure 3. Cost-effectiveness acceptability curves (CEACs) of denosumab vs zoledronic acid in the prevention of skeletal-related events in patients with castration-resistant prostate cancer and bone metastases. The curves illustrate the probability of denosumab being cost-effective relative to zoledronic acid and vice-versa based on different thresholds of willingness to pay. The probability of denosumab being cost-effective relative to zoledronic acid increases as the willingness to pay threshold increases. QALY, quality-adjusted life year.

challenging to prospectively capture the accurate impact of SREs on QALY within an observational research design. Regarding the impact on QALY of different modes of administrations, due to the double-blinded, double dummy design of the Phase 3 trials of denosumab vs zoledronic acid^{16–18}, the trial-based quality-of-life measures were not designed to be able to capture the different QALY decrements associated with IV infusions (zoledronic acid) vs SC injections (denosumab). Most reimbursement authorities prefer utilities derived from general population values (e.g., National Institute for Health and Clinical Excellence [NICE], Pharmaceutical Benefits Advisory Committee [PBAC]). The general population approach has the theoretical advantage of ensuring that societal values are represented when making decisions about the levels of public funding for medical treatment^{54,56}. Thus, we believe the SRE and IV vs SC QALY decrements assessed with a time trade-off approach in the general population are appropriate for application in the CEA model.

As with all cost-effectiveness models, these analyses also have limitations. For example, the model does not capture pain management costs, even though the clinical studies have demonstrated a difference in pain severity and analgesic use between the two treatments in favor of denosumab^{20–22}. The inclusion of pain management costs would therefore be anticipated to provide lower costs per QALY gained for denosumab vs zoledronic acid than the current estimates. A further limitation is that, due to the lack of empirical data, the mortality rate beyond the clinical study durations were extrapolated from the generalized gamma functions, which may or may not accurately reflect actual outcomes. However, given that, overall, there was no significant difference in mortality between the two treatment groups^{16–18}, it is very unlikely that the

cost-effectiveness results are biased because of this. As there are limited data on compliance with denosumab in the oncology setting, the current model assumed the same drug compliance rate for both treatment groups. Since denosumab does not require dose adjustment or dose withholding based on renal status and is associated with fewer acute phase reactions compared with zoledronic acid¹⁹, compliance with denosumab is expected to be higher than with zoledronic acid in clinical practice. However, further studies are needed to investigate the compliance rates and usage of these two drugs in clinical practice. The SRE costs in patients with NSCLC were assumed to be the average of SRE costs in breast cancer and CRPC. The direction of bias due to this assumption is not clear; however, the model results were robust to the SRE costs. Finally, costs and QALY decrements associated with the AEs, such as ONJ and hypocalcemia, are not well documented in the literature. Although these inputs in this model are very unlikely to bias the results substantially, this suggests the need for further research in costs and patient utilities in this area.

Interpretation of the cost per QALY gained of denosumab vs zoledronic acid leads to the question of what is considered an acceptable ICER threshold in the US healthcare sector, specifically, in US oncology settings. Unlike European countries (UK NICE recommends an ICER threshold of £20,000–£30,000 per QALY gained⁴⁶; other European countries generally recommend €50,000), there is no generally accepted cost per QALY gained threshold in the US, and the implied thresholds likely vary by disease area. The recently enacted Patient Protection and Affordable Care Act states: ‘... the Patient Centered Outcomes Research Institute... shall not develop or employ a dollars per quality adjusted life year (or similar measure that discounts the value of a life

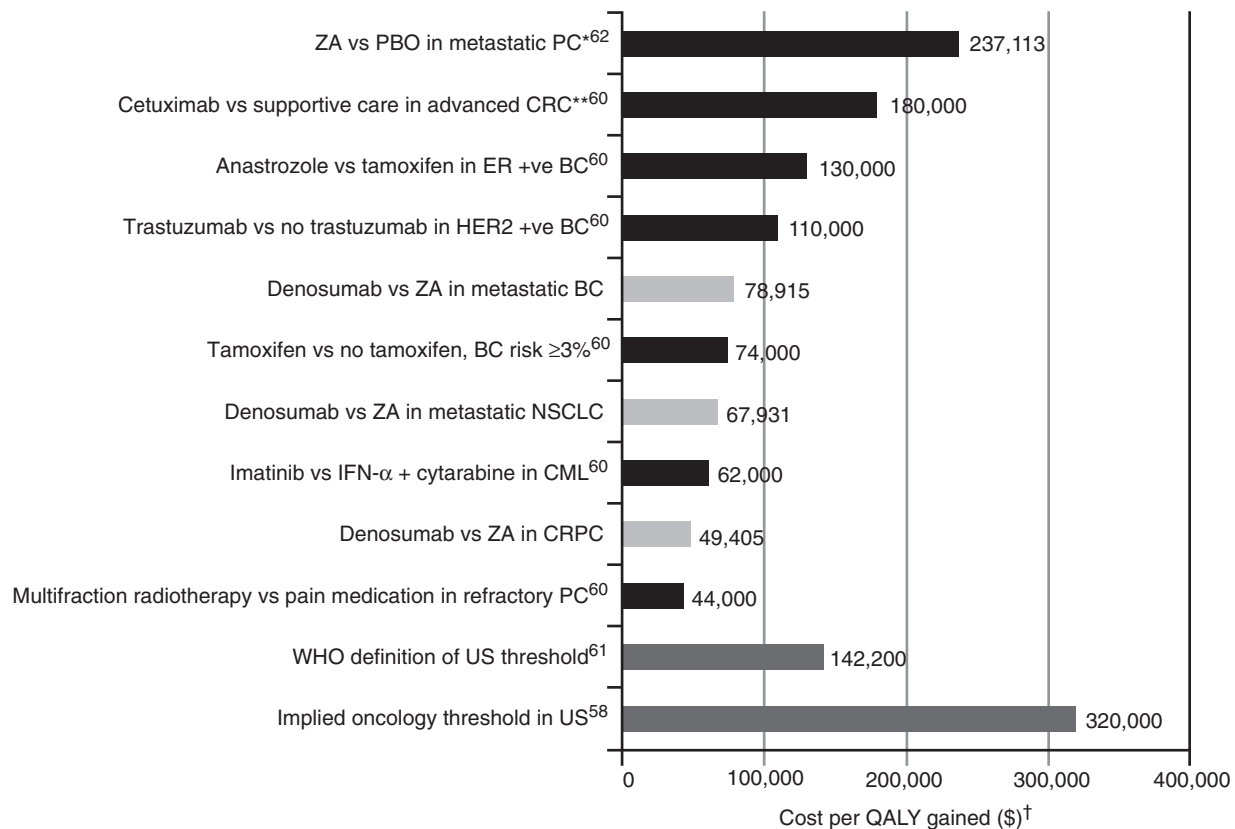


Figure 4. Cost-effectiveness of denosumab vs zoledronic acid relative to other select innovative oncology therapies^{58,60–62}. *Costs inflated to 2010 using proportional increase in US consumer price index from 2000 to 2010 (<http://www.bls.gov/data>). **In patients with wild-type *KRAS*. †Costs in 2010 USD for historical data. ZA, zoledronic acid; PBO, placebo; PC, prostate cancer; CRC, colorectal cancer; ER + ve, estrogen receptor positive; BC, breast cancer; HER2 + ve, HER2-receptor positive; NSCLC, non-small-cell lung cancer; CML, chronic myeloid leukemia; CRPC, castration resistant prostate cancer; WHO, World Health Organization.

because of an individual's disability) as a threshold to establish what type of health care is cost-effective or recommended...'. In addition, although several instances were identified where cost-effectiveness evidence was cited in National Coverage Decisions, no clear evidence was found indicating an implicit threshold from the Centers for Medicare and Medicaid Services (CMS)⁵⁷. A survey study of US oncologists suggested an average cost per QALY gained threshold of \$320,000⁵⁸. Another simulation model study estimated the value of a statistical year of life implied by dialysis practice at \$129,090 per QALY⁵⁹. However, the costs per QALY gained of denosumab vs zoledronic acid for all the three tumor types from this analysis (\$49,405 for CRPC, \$78,915 for breast cancer and \$67,931 for NSCLC) are within the range of other innovative oncology therapies available on the US market (Figure 4).

Conclusions

In conclusion, from the US managed care perspective, denosumab is cost-effective in preventing SREs in patients

with bone metastases secondary to advanced solid tumors compared with zoledronic acid. The overall value of denosumab is based on superior efficacy, a favorable safety profile, and more efficient administration.

Transparency

Declaration of funding

This study was funded by Amgen Inc.

Declaration of financial/other relationships

KC, ZC, RD, and YQ are employees of Amgen Inc. MD and MH received funding from Amgen Inc in order to perform cost-effectiveness analyses. DH has received research funding from Amgen. DH and MR have received consultancy/speaker fees from Amgen. AS has acted as a paid consultant/advisor to Amgen and Novartis.

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