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Original article

Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: A cost-effectiveness analysis

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Abstract

Objective:
Denosumab has been approved in the US for skeletal-related event (SRE) prevention in bone-metastatic prostate cancer on the basis of a phase III clinical trial in which denosumab reduced SREs relative to zoledronic acid. Overall survival, disease progression, and serious adverse events did not differ significantly between groups. This analysis assessed the cost-effectiveness of denosumab vs zoledronic acid in bone-metastatic prostate cancer from a US payer perspective.

Methods:
A literature-based Markov model, wherein inputs were selected to reproduce clinical trial outcomes, was developed to estimate the survival, quality-adjusted life-years (QALYs), number and costs of SREs, and drug and administration costs for patients receiving denosumab or zoledronic acid over 27 months. QALYs were estimated by assigning health-state utilities. SRE-related costs and utilities were literature-based. Outcomes were discounted 3% per annum, and model robustness was tested via scenario, univariate, and probabilistic sensitivity analyses.

Results:
Denosumab resulted in fewer estimated SREs (−0.241; 1.036 vs 1.277), more QALYs (0.0074; 0.9306 vs 0.9232), and lower SRE-related costs (−$2340; $8824 vs $11,164), but higher drug-related costs ($10,181; $23,144 vs $12,963) and total costs ($7841; $31,968 vs $24,127) vs zoledronic acid. The base case estimated cost per QALY-gained was $1,058,741.

Conclusion:
This analysis was limited by the restricted availability of clinical data and the need to use projection methods beyond the trial time frame. However, a wide range of scenarios predicted denosumab to have an incremental cost/QALY gained above what may be considered acceptable value for money in the US. This raises important questions regarding the pharmacoeconomic value of denosumab in bone-metastatic prostate cancer.

Introduction

Approximately 70% of advanced prostate cancer patients will develop bone metastases[1]. Subsequent skeletal-related events (SREs; e.g., radiotherapy or surgery to bone, pathological fracture, and spinal cord compression) are associated with increased treatment costs[2], decreased survival[3], and impaired quality-of-life (QoL)[4].

On the basis of a phase III clinical trial wherein prostate cancer patients with bone metastases were randomized to receive monthly denosumab or zoledronic acid until first on-study SRE or death[5], denosumab was approved by the US Food and Drug Administration for SRE prevention in patients with bone-metastatic prostate cancer; an indication for which zoledronic acid had been the only approved therapy. In the trial, monthly denosumab (120 mg subcutaneously) demonstrated a primary end-point of statistical non-inferiority to monthly zoledronic acid (4 mg intravenously) for time to first SRE (HR = 0.82, 95% CI = 0.71–0.95; $p = 0.0002$; $p = 0.008$ for secondary end-point, superiority). Overall survival, disease progression, and adverse event (AE) rates were similar between treatment arms, with the exception of hypocalcemia (denosumab 121 [13%] vs zoledronic acid 55 [6%]; $p < 0.0001$)[5]. Denosumab also offers the convenience of subcutaneous injection and no requirement for routine renal monitoring (except in renally compromised patients).

In the US, the monthly wholesale acquisition cost of denosumab is $1650[6] compared to $886[7] for zoledronic acid. Thus, despite its obvious clinical benefit, concerns have been expressed regarding denosumab's cost given its clinical benefits[8–10]. The present analysis was therefore conducted to estimate the cost-effectiveness of denosumab compared with zoledronic acid in metastatic prostate cancer patients from a US payer perspective.

Methods

A Markov decision model (Figure 1), representing monthly progression through eight mutually exclusive health states, was developed to estimate the SRE incidence, survival, quality-adjusted life-years (QALYs), SRE-related costs, and drug-related costs for metastatic prostate cancer patients receiving monthly denosumab 120 mg or zoledronic acid 4 mg for up to 27 months (the maximum published duration of patient follow-up data available at the time of this analysis). In a scenario analysis, the duration of follow-up was extended to 60 months using projection methods.

Disease progression and adverse events were not considered, as they did not differ significantly between treatments (with the exception of bypocalcemia)[5]. It was assumed that including hypocalcemia would have biased the analysis against denosumab because the trial was not powered to detect significant differences for specific adverse events between treatments. Mortality was not assumed to differ between treatments as there was no significant difference reported in the clinical trial[5].

Clinical inputs and transition probabilities

Health state transition probabilities were selected to replicate SRE incidence (first and subsequent) and overall

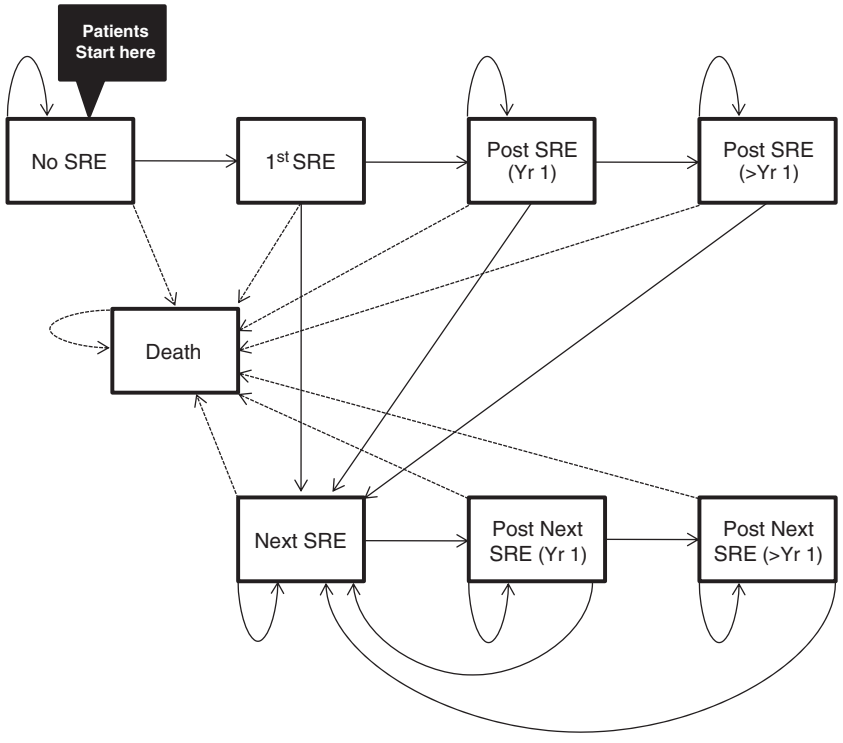

Figure 1. Model structure. Patients occupied one health state at a time and transited monthly according to transition probabilities. 'No SRE' makes no assumption whether a patient has had any SRE before model initiation.

survival shown in the Kaplan-Meier curves of the clinical trial (Clinical Trial Number: NCT00321620)[5], which displayed data for 27 months (Table 1). These curves were approximated using Weibull survival models which allowed for the calculation of absolute SRE/Death risks at any given time point for either treatment arm[11]. This absolute risk, or hazard (r), at any given month was calculated as follows:

$$r = \lambda * (\text{month}^{\alpha} - (\text{month} - 1)^{\alpha})$$

where λ and α represent the shape and scale of the curve, respectively. To obtain the transition probability, P, from the hazard for each model month, the following transformation was used[12]:

$$P = 1 - e^{-r}$$

SRE inputs

Quality-of-life

SREs were expected to negatively impact QoL proportionally to their severity. The calculation of QALYs, a measure of the quality-adjusted duration of life, is the standard approach to quantifying QoL in cost-effectiveness analysis[13]. QALYs were calculated by multiplying the QoL score (i.e., utility; ranging from 0 = death to 1 = best possible health) assigned to a given health state, by the duration of time spent in that state. Because patients in this analysis had bone-metastatic prostate cancer, their pre-SRE baseline utility was assigned 0.70, equal to the baseline utility value elicited in a previous metastatic prostate cancer patient sample[14].

The decreases in utility for each SRE type (Table 1), which vary in severity and level of impairment, were obtained from the same study by Weinfurt *et al.*[14]. In this study, a change in utility score (measured in patients who experienced an SRE) reflected the difference between predicted (in absence of SRE) and actual scores reported after the SRE. The changes in utility were −0.07 for radiation to the bone ($n = 121$, 95% CI: −0.13, −0.02), −0.13 for pathologic fractures ($n = 76$, 95% CI: −0.20, −0.07), and −0.02 for a combination of events including surgery to the bone, spinal cord compression, and change in antineoplastic therapy to treat bone pain ($n = 42$, 95% CI: −0.17, +0.13). Since it is likely that spinal cord compression and surgery to the bone would be associated with worse decrease in utility than fractures or radiation to the bone, it was assumed that the disutility for both surgery to the bone and spinal cord compression would be −0.17 (the lowest end of the confidence interval reported by Weinfurt *et al.*). The use of SRE-related utilities reported

Table 1. Model inputs for this cost-effectiveness analysis.

	Denosumab		Zoledronic acid	
Overall survival				
% Surviving at 27 months	34.2%			
Monthly hazard of death	Mo 1–5: 0.0233/(1–0.0233 × (Mo–1)); Mo 6+: 0.0423			
First SRE				
% w/ ≥1 SRE at 27 months[a]	40.3%		45.5%	
Monthly Hazard of 1st SRE[b]	0.0513 × 0.8598 × mo^(0.8598–1)		0.0668 × 0.8324 × mo^(0.8324–1)	
Subsequent SRE				
SREs/patient at 27 Mo[a]	1.04		1.29	
Hazard/Mo. of subsequent SRE[b]	0.0284 × 1.4561 × mo^(1.4561–1)		0.0370 × 1.4206 × mo^(1.4206–1)	
	Distribution (D/Z)	SRE utility change[14]	Utility value	Cost
SRE type				
No SRE	–	–	0.70[14]	–
Pathological	40.2%/37.0%	–	–	–
Vertebral	13.9%/12.9%	−0.13	0.57	7876[20]
Non-vertebral	26.2%/24.2%	−0.13	0.57	7876[20]
Spinal cord compression	7.6%/9.3%	−0.17	0.53	13,761[20]
Bone surgery	0.3%/1.0%	−0.17	0.53	24,799[20]
Bone radiation	51.9%/52.6%	−0.07	0.63	8471[20]
		Description		Cost
Drug and admin cost				
Denosumab acquisition	WAC per month			$1650[6]
Zoledronic acid acquisition	WAC per month			$886[7]
Denosumab injection	HCPCS J code 96369; median reimbursement per admin			$32[21]
Zoledronic acid infusion	HCPCS J code 96365; median reimbursement per admin			$154[21]
Renal monitoring (Z only)[c]	CPT code 82570 (50th Percentile) per admin			$35[21]

Overall survival, first, and subsequent SRE were estimated from Fizazi *et al.*[5].

by Weinfurt *et al.* is consistent with a previous cost-effectiveness analysis comparing denosumab vs zoledronic acid in bone-metastatic prostate cancer conducted by an independent assessment group associated with the National Institute of Health and Clinical Excellence (NICE) in the United Kingdom[15]. SRE-related disutility was permanently maintained following an SRE. This assumption was varied in scenario analysis.

Distribution of SREs

The denosumab package insert[16] and trial results reported by Fizazi *et al.*[5] list the rates and distribution of first SRE types observed in the trial and the cumulative number of SREs. Neither provided information regarding the type of subsequent SREs. Thus, it was assumed that the distribution of subsequent SRE types was identical to the distribution of first SREs (Table 1).

Likewise, no information was reported on the type and severity of pathological fractures, which include vertebral and non-vertebral fractures. A pooled analysis of published bisphosphonate trials in cancer patients reporting the distribution of these fractures[17,18] resulted in an estimate of 34.7% for the proportion of vertebral pathological fractures. The effects of vertebral fractures (via costs and quality-of-life) were varied in scenario analysis.

Treatment persistence

Fizazi *et al.*[5] reported that that the median number of doses administered were 13.0 and 10.5 for the denosumab and zoledronic acid groups, respectively. Because patients received treatment approximately once every month, these data acted as proxy measures of median time on study. It was assumed that discontinuations followed an exponential decay function with the constraint that 50% of patients in the denosumab and zoledronic acid groups remained on treatment at 13.0 and 10.5 months, respectively; an assumption consistent with the recent literature[19]. Patients who discontinued were assumed not to be on second line therapy of any kind (and no costing of a second line was included. Given the uncertainty regarding the exact nature of treatment discontinuations, an alternate assumption was used for scenario analysis in which patients continued therapy until death.

Costs

SRE costs (Table 1) and cost ranges for sensitivity analysis (Table 2) by Barlev *et al.*[20] reporting on the patterns of healthcare utilization and inpatient and outpatient costs associated with SRE episodes in patients with prostate cancer that has metastasized to bone. Administration and renal monitoring costs were drawn from the Ingenix National Fee Analyser[21].

Wholesale acquisition costs were used for baseline drug acquisition costs. In sensitivity analysis, average wholesale price (equal to wholesale acquisition cost +20%) was also examined. In scenario analysis, the price of zoledronic acid was assumed to be 50% less than its current price to reflect the availability of a generic version in 2013. All model

Table 2. Sensitivity analysis inputs.

Variable	Base case	PSA distribution	Univariate SA range
Medical inputs			
Overall survival[a]	1	Uniform	±25%
Hazard of 1st SRE – denosumab[a]	1	Uniform	±25%
Hazard 1st SRE – zoledronic acid[b]	1	Normal	0.8659, 1.159
Hazard of 2+ SRE – denosumab[a]	1	Uniform	±25%
Hazard of 2+ SRE – zoledronic acid[b]	1	Normal	0.8659, 1.146
Costs			
Renal monitoring	$35.04	Normal	1.42, 68.66
Vertebral fracture	$7876	Normal	6908, 8843
Non-vertebral fracture	$7876	Normal	6908, 8843
Spinal cord compression	$13,761	Normal	10,325, 17,197
Bone surgery	$24,799	Normal	15,511, 34,087
Therapeutic radiation	$8471	Normal	7968, 8974
Utilities			
Baseline	0.70	Normal	0.67, 0.73
Vertebral fracture	−0.13	Uniform	−0.2, −0.07
Non-vertebral fracture	−0.13	Uniform	−0.2, −0.07
Spinal cord compression/bone surgery	−0.17	Uniform	−0.32, −0.2
Therapeutic radiation	−0.07	Uniform	−0.13, −0.02

[a]Time to overall survival, 1st SRE, and 2nd + SRE were modeled using a Weibull survival curve. A multiplier of the associated hazard function was used to vary event probabilities.
[b]The hazards for the zoledronic acid time to 1st SRE and 2nd+ SRE models were modeled using a Weibull survival curve. The sensitivity analysis parameter varies the relative hazard of denosumab compared with zoledronic acid according to the mean and confidence intervals given in the trial publication.

costs were, when necessary, inflated to 2010 prices using the Bureau of Labor Statistics' Consumer Price Index (all urban consumers, medical care). Costs and QALYs were discounted at 3% per annum.

Analysis

The primary outcome was the discounted incremental cost per QALY gained (i.e., incremental cost-utility ratio, ICUR). In addition to the base case analysis and the scenario analyses described above, univariate and probabilistic sensitivity analyses (PSA) were conducted to identify variables to which model outcomes were most sensitive. PSA parameters are reported in Table 2.

Results

Model parameters were estimated to reproduce outcomes from the clinical trial comparing denosumab vs zoledronic acid in bone-metastatic prostate cancer patients[5]. The base case model results (Table 3) were consistent with these findings: denosumab resulted in a reduced proportion of patients experiencing at least one SRE (−5.85%) and resulted in a lower total number of SREs per patient (−0.241). Because denosumab patients had fewer SREs, they also accrued more modeled QALYs (+0.0074) and incurred fewer modeled SRE-related costs (−$2340). However, these benefits were achieved at the expense of higher drug-related costs (+$10,181). Consequently, the net estimated costs were increased by $7841 in denosumab-treated vs zoledronic acid-treated patients, resulting in an ICUR of $1,058,741/QALY (Table 3).

Table 3. Base case model results.

	Denosumab	Zoledronic acid	Difference
Proportion with no SREs or death	42.63%	35.36%	7.27%
Proportion with SREs	39.95%	45.81%	−5.85%
SREs per patient	1.036	1.277	−0.241
Proportion alive	34.20%	34.20%	0.00%
Total life years	1.410	1.410	0.000
Discounted QALYs	0.9306	0.9232	0.0074
Discounted drug costs	$23,144	$12,963	$10,181
Discounted SRE costs	$8824	$11,164	−$2340
Total discounted overall costs	$31,968	$24,127	$7841
ICUR for denosumab			$1,058,741

In scenario analysis, denosumab's ICUR was $1,383,251 and $1,051,499 when average wholesale drug price was used and when patients continued therapy until death, respectively. When the duration of analysis was extended to 60 months, the QALYs gained and SREs avoided were +0.0107 and −0.370, respectively; resulting in an ICUR of $933,424. When the estimated generic price of zoledronic therapy was used (e.g., 50% of the base case cost), the ICUR was $1,780,275 (in the 27 month analysis) and $1,516,411 (in the 60 month analysis). In the base case, SRE-related disutility was assumed to be maintained permanently. When this assumption was changed to a duration of 12 months post-SRE (after which the patient returns to the background utility), denosumab's ICUR increased to $2,878,162/QALY.

Univariate sensitivity analysis (Figure 2) indicated that results were robust to the hazard of first SRE in the denosumab group, and health state utility values for spinal cord compression/surgery to the bone and bone radiation. With regard to the per-administration prices for drug

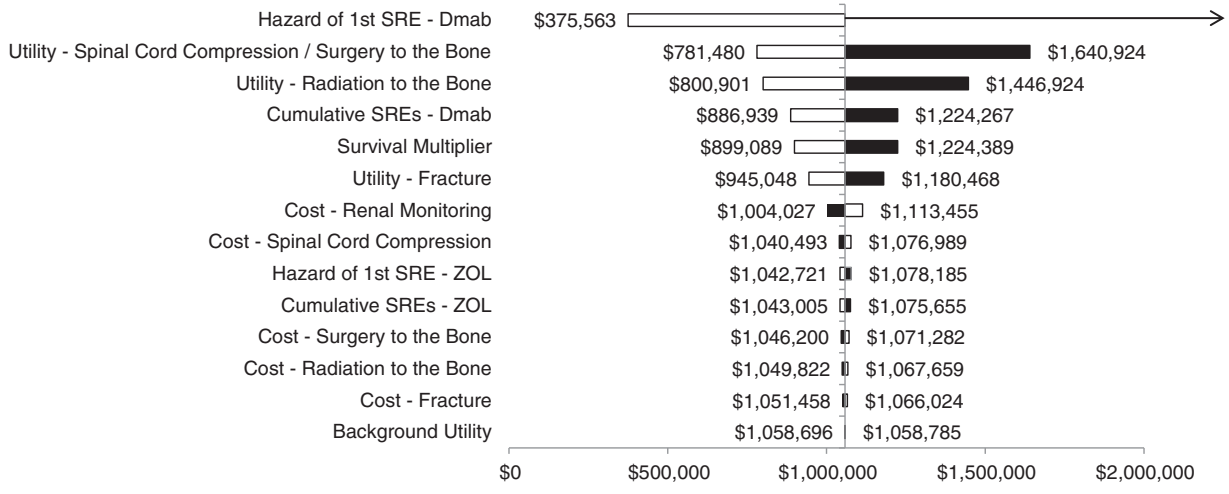

Figure 2. Univariate sensitivity analysis results. The pivot point in the tornado diagram represents the base case cost per QALY gained with denosumab ($1,058,741). The arrow indicates that denosumab was dominated (i.e., more expensive and produced fewer QALYs) in that scenario. Black and white bars indicate results generated with maximum and minimum values in the sensitivity analysis, respectively. Dmab, denosumab; SRE, skeletal-related event; ZOL, zoledronic acid.

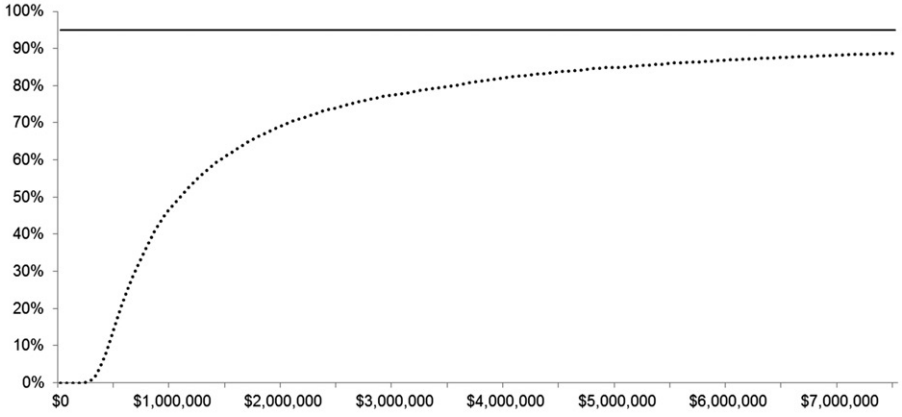

Figure 3. Cost-effectiveness acceptability curve. The horizontal line represents the 95% probability of denosumab being cost-effective to zoledronic acid.

acquisition, cost neutrality was achieved with a $570/administration reduction in denosumab's price (i.e., $1650 to $1080) or a $651/administration increase of zoledronic acid's price (i.e., $886 to $1537).

In the PSA, where model parameters were randomly varied 1000-times around pre-specified distributions to generate new model outcomes, the median ICUR was $1,068,037/QALY (95% credible interval: $328,954/QALY-Dominated). None of the PSA simulations had an ICUR less than the $100,000/QALY threshold. That is, this analysis indicates a 0% likelihood that denosumab is cost-effective vs zoledronic acid at that threshold. The cost-effectiveness acceptability curve (Figure 3) indicates that at no point does the probability that denosumab is cost-effective reach 95%, and therefore the upper limit of the 95% up to a threshold of $7.5 million per QALY.

Discussion

This analysis estimated that, relative to zoledronic acid, the use of denosumab for the prevention of SREs in bone-metastatic prostate cancer resulted in more QALYs, fewer SREs and SRE-related costs, and greater overall costs. The resultant base case ICUR was $1,058,741, which exceeds what is traditionally considered good value for money in the US ($50,000–$100,000/QALY). This estimate also exceeds previous ICUR estimates of oncologic supportive care therapies that do not affect survival[22–24], the median ICUR range reported across all non-dominated oncologic therapies[25], and the acceptable threshold for a hypothetical *life-extending* therapy reported from a survey of oncologists ($300,000/QALY)[26]. Sensitivity analysis indicated that results were robust to the hazard of first SRE in the denosumab group and the health state utility values associated with spinal cord compression, surgery to the bone, and radiation to the bone.

Cost-effectiveness analyses can be a source of intense debate as they formally assign a value to a therapy. This is particularly true in cases such as the present one, which reports that the cost of a more effective, novel therapy may exceed its benefits. Therefore, great care was taken in the selection of inputs and assumptions for this model so as to provide a defensible estimate of denosumab's ICUR relative to zoledronic acid. For example, we adopted assumptions that favored denosumab, such as the assumption that all SREs would be sufficiently severe so as to result in substantial additional healthcare costs, even though Hillner *et al.*[27] and other reports[15] have suggested that some SREs may be asymptomatic or have limited or no impact on costs and QALYs. It should also be noted that the protocol of the Fizazi *et al.*[5] clinical trial upon which this analysis is based required that skeletal events be assessed by skeletal surveys every 12 weeks or by radiographic assessments during the course of care. It is possible that this approach resulted in systematic over-identification of asymptomatic or clinically minor events that would not normally be detected and/or treated in routine, non-experimental, clinical practice[15,19,28,29]. If true, this would mean that use of the Fizazi *et al.* data over-estimates the absolute number of clinically symptomatic and/or treatable events prevented by denosumab vs zoledronic acid, thereby over-estimating denosumab's savings and QALY gains and under-estimating its ICUR.

Four previous pharmacoeconomic evaluations of denosumab vs zoledronic acid in bone-metastatic prostate cancer have been published[15,30,31]. Ford *et al.*[15] reported two UK government payer-perspective cost-effectiveness analyses: an analysis by Amgen-maker of denosumab-submitted to the UKs NICE (subsequently referred to as Amgen Submission) and an analysis by NICE's independent assessment group (subsequently referred to as NICE AG). Stopeck *et al.*[30] and Lothgren *et al.*[31] reported

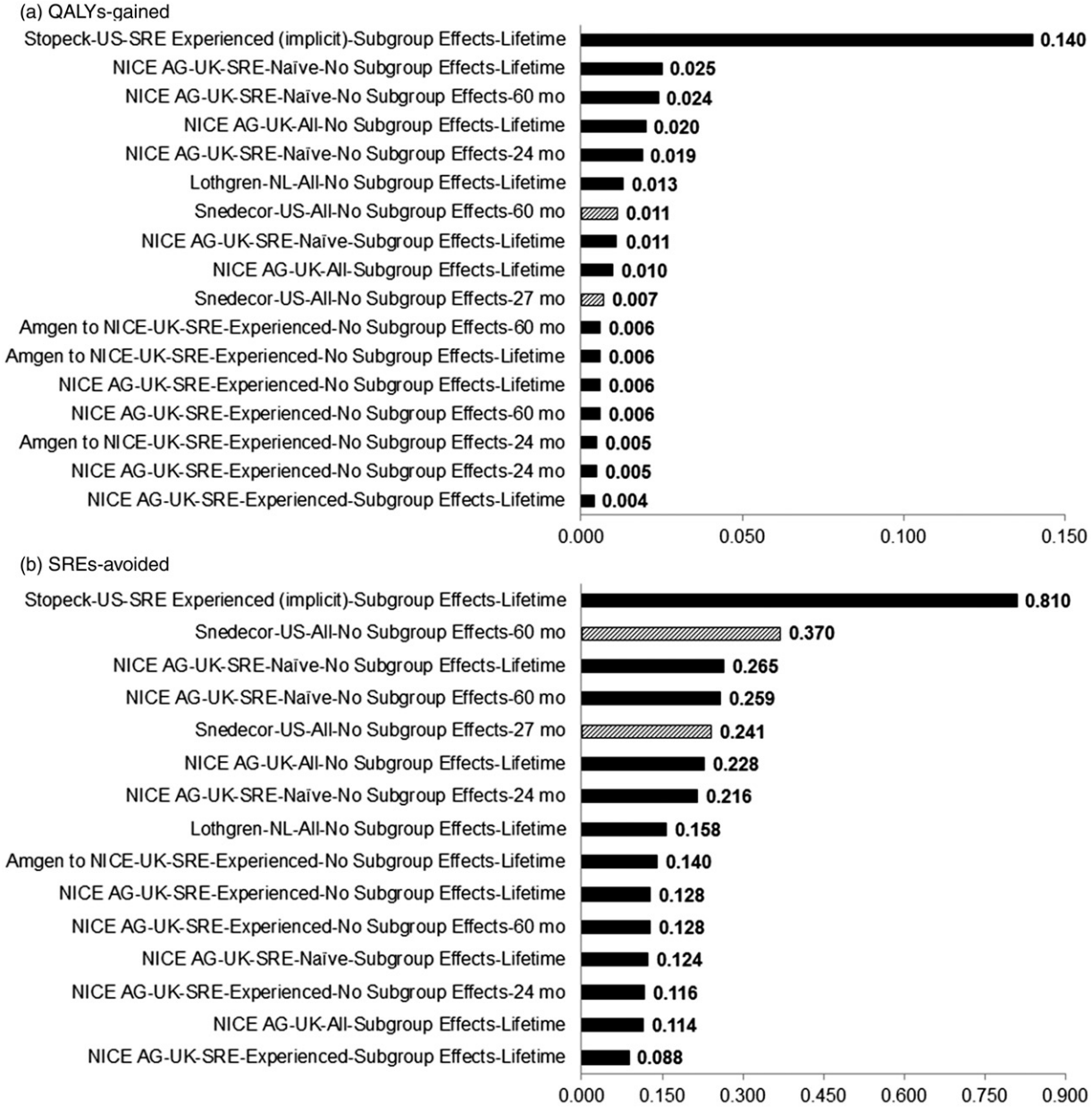

Figure 4. Outcomes of cost-effectiveness analyses of denosumab vs zoledronic acid in bone metastatic prostate cancer. The *x*-axis is organized by Author-Country-Patient Group-Source of SRE Risk-Time Horizon. SRE-experienced and naïve refer to patients who have and have not experienced an SRE at baseline, respectively. In scenarios with sub-group effects, SRE risk/hazard ratios specific to SRE-experienced and naïve groups were applied to those groups in the analysis; whereas otherwise rates were drawn from pooled estimates regardless of whether the analysis referred to a specific patient group.

cost-effectiveness analyses from US managed care and Dutch government payer perspectives, respectively.

All of these analyses found denosumab to be cost-effective: Stopeck *et al.*[30] ($49,405/QALY); Lothgren *et al.*[31] (€42,933/QALY); Amgen submission and NICE models (range of £35,732–£249,575 without discounted denosumab depending on scenarios assumed, but dominant in all scenarios assuming a discounted cost for denosumab[15]). In contrast, the present analysis estimated denosumab's cost per QALY to be >$1,000,000.

To understand why our cost effectiveness results are radically different from these other analyses, one must consider differences across studies in three main factors that affect the cost effectiveness ratio: total incremental drug cost, total SREs avoided, and the QALYs gained per SRE avoided. Figure 4 compares the five economic analyses (including reported sub-group and scenario analyses) in terms of estimated QALYs gained and SREs avoided with denosumab relative to zoledronic acid. Despite small variations with regard to model structure,

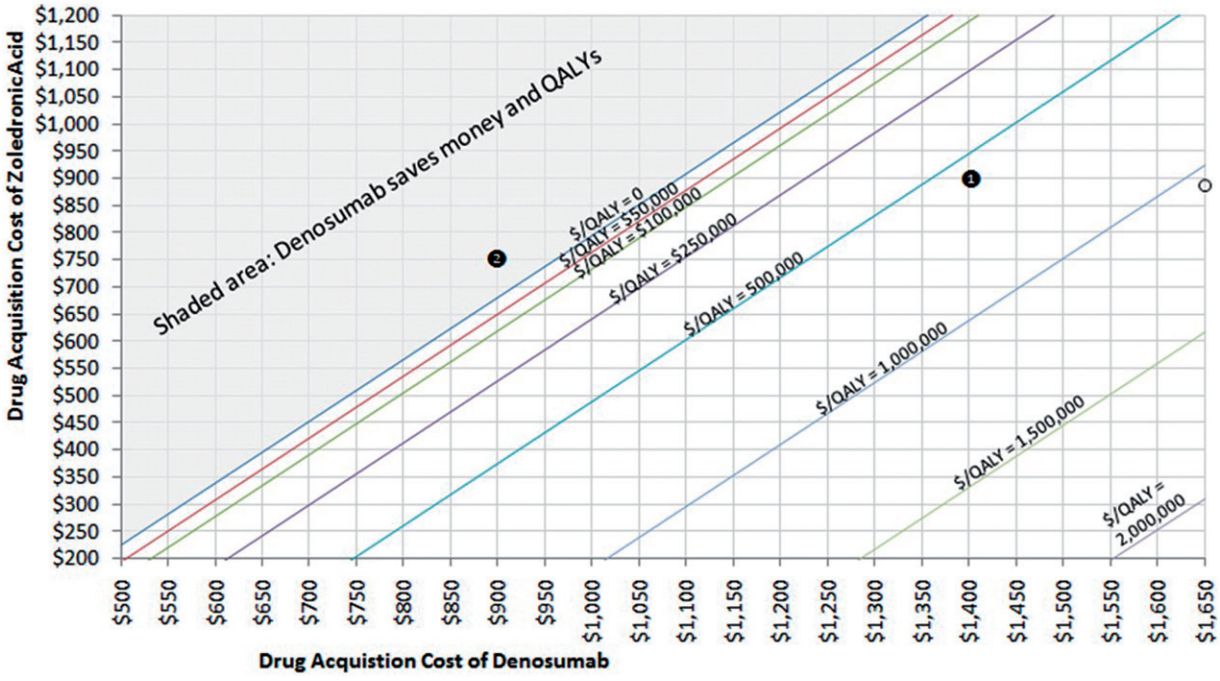

Figure 5. Costs per QALY for combination of denosumab and zoledronic acid acquisition costs. Start with a price for denosumab (on *x*-axis) and select a cost per QALY level (represented by a line on the graph) gives the associated price of zoledronic acid (on *y*-axis).

background/baseline utility, trial data availability, and handing of adverse events, the results of the present analysis are broadly comparable (and in some cases more favorable towards denosumab) to those of the three European analyses. Thus, the large difference in ICURs may be largely due, in large part, to differences in incremental drug-associated costs. Specifically, in Europe, denosumab's incremental acquisition cost is substantially lower than in the US. For example, in Lothgren *et al.*'s[31] Dutch analysis the per-administration drug-associated costs for denosumab and zoledronic acid were €486 and €451, respectively (difference = €35). In our US-based analysis, per-administration drug-associated costs are $1682 for denosumab and $1075 for zoledronic acid (difference = $607). In light of this, Figure 5 presents combinations of inputs that result in various ICUR values using the 27-month base case scenario. Using this figure, one can determine the price of denosumab that may be justifiable given a price for zoledronic acid and a given willingness to pay per QALY. For instance (Example 1 on Figure 5), in a plan currently paying $900 per infusion for zoledronic acid and $1400 per injection for denosumab, the ICUR for denosumab would be slightly above $500,000. Alternatively, a plan paying only $750 per infusion for zoledronic acid and $900 for denosumab would be saving both money and QALYs and would therefore lie in the shaded area.

Nowhere is the importance of a lower incremental drug cost more apparent than in Amgen's own analysis submitted to NICE. Before discounting denosumab's cost with a confidential patient access scheme required by NICE for reimbursement approval, denosumab's ICUR for bone-metastatic prostate cancer patients was £157,276[15]. With the discounted price, zoledronic acid was dominated; i.e., denosumab cost less and saved more QALYs. In fact NICE AG[15] specifically noted that even a slight price reduction for zoledronic acid would render a discounted denosumab cost-ineffective[15], highlighting the importance of denosumab's price relative to zoledronic acid in this setting.

However, differences in incremental drug acquisition cost alone cannot explain the difference in results between this analysis and the other US-based analysis conducted by Stopeck *et al.*[30] given that denosumab was associated with an incremental per-administration drug-associated cost of $607 in both analyses. To some degree, the difference may be driven by Stopeck *et al.*'s application of utilities to modes of administration, with denosumab's administration being associated with a smaller utility loss than zoledronic acid's. The present analysis did not incorporate these values because it is unclear how such gains in utilities can be derived with a reasonable degree of certainty and validity. (Of note, such effects were not collected directly in the clinical trial upon which the present analysis was based, and Stopeck *et al.* do not provide sufficient details of their estimation methods in the analysis). The difference in cost effectiveness between the this analysis and that by Stopeck *et al.* appears to be driven largely by differences in

estimated SREs avoided and QALYs gained. Stopeck *et al.* reported 5–35-times more QALYs gained and 2–9-times more SREs avoided than the other analyses (Figure 4). These large differences appear to stem from Stopeck *et al.*'s adjustment of the SRE rates in their analysis to reflect a US 'real-world', managed-care perspective as opposed to a within trial analysis. Specifically, zoledronic acid SRE rates were derived by comparing published rates from an insurance claims database analysis by Hatoum *et al.*[32] (among metastatic breast, prostate, and lung cancer patients) to SRE rates reported in the denosumab clinical trials. On the basis of this calculation, the authors report "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 III clinical trials. The adjusted annual SRE rates in clinical practice for denosumab and zoledronic acid were 1.500 and 1.903, respectively".

The higher SRE-rate assumption made by Stopeck *et al.*[30] is not problematic in and of itself, as it is arguably possible that patients in the US routine clinical setting who initiate SRE-limiting therapy do so after experiencing an SRE. However, while Stopeck *et al.* upwardly adjusted the SRE rate to implicitly reflect a SRE-experienced cohort, they appear not to have downwardly adjusted survival and utility assumptions to correspond to this patient population[15]. Instead survival and baseline utility assumptions from the phase III clinical trial (where only 24% of patients were SRE-experienced) were applied. Therefore, the net effect of Stopeck *et al.*'s selective adjustment is the creation of a 'hybrid' population which simultaneously had high SRE rates reflecting a 75% SRE-experienced cohort as in Hatoum *et al.*[32] coupled with survival rates and baseline/background utilities reflecting a 24% SRE-experienced cohort as in Fizazi *et al.*[5]. This is problematic because the occurrence of an SRE is associated with lower survival and quality-of-life[15].

Consequently, the modeled population in Stopeck *et al.*[30] experienced an artificially high number of SREs over a longer survival time than would otherwise be expected for an SRE-experienced population, leading to higher estimated SRE-related utility loss and costs due to excess SREs. Because Stopeck *et al.* applied the treatment effects from Fizazi *et al.*[5] to the population at artifically high risk for SREs, the magnitude of SRE burden avoided by denosumab was proportionally over-estimated.

It is unclear why Stopeck *et al.*[30] did not derive SRE rates from Hatoum *et al.*'s[33] 2011 analysis in which the authors provided real-world SRE rates specific to bone-metastatic prostate cancer as well as rates specific to SRE-naïve (low-risk) and SRE-experienced (high-risk) patients. In their analysis, Hatoum *et al.*[33] reported SRE rates in SRE-naive and SRE-experienced patients receiving zoledronic acid annualized to be 0.36/year and 1.00/year, respectively. The authors also reported that 243 SRE-naïve and 218 SRE-experienced patients received zoledronic acid. Therefore, the true annualized SRE rate for bone metastatic prostate cancer patients treated with zoledronic acid can roughly be calculated as follows: $(243*0.36 + 218*1)/(243 + 218) = 0.66$. Based on Stopeck *et al.*'s 2.01 adjustment, their estimated annualized SRE rate of 1.903 for zoledronic acid-treated patients appears to be ~3-times higher than should reasonably be expected.

Stopeck *et al.*'s[30] SRE and QALY outcomes are patently discordant with similar analyses of SRE-experienced patients conducted by Amgen and NICE's independent assessment group, whereas the results of the present analysis are consistent with all but Stopeck *et al.* (Figure 4). Thus, taken as a whole, it appears that the US cost-effectiveness ratio reported in Stopeck *et al.* is too optimistic due to its excessively large estimated number of QALYs gains and SREs avoided relative to all other analyses.

The present study was limited by the restricted availability of clinical data and the need to use projection methods to model beyond the trial time frame. Survival and SRE data were derived from figures of the Fizazi *et al.*[5] trial report, where exact values were unavailable. Although our estimated curves closely approximated the reported Kaplan-Meier curves (data available upon request), the potential for inaccuracy remains. In addition, treatment discontinuation data were not reported in a manner allowing for exact calculation of the proportion of patients still on treatment after a specified amount of time, and therefore the reported median number of doses was a surrogate for the median time on-study. It is also important that the present analysis did not incorporate an effect of treatment administration on utility.

Current published drug prices were used in this analysis, although it is likely the incremental cost of denosumab will soon become much greater, as zoledronic acid is expected to lose patent protection in 2013. An influx of less-expensive, generic forms of zoledronic acid will widen the cost differential between the two drugs, thereby increasing denosumab's ICUR.

This analysis should not be interpreted as evidence that denosumab is ineffective in the prevention or delay of SREs in patients with bone-metastatic prostate cancer, as clinical trials have shown that denosumab is superior to zoledronic acid across a number of solid tumor types[5,34,35]. This analysis sought to determine the value of denosumab vs zoledronic acid from a pharmacoeconomic perspective, and therefore is not intended to determine individual patient treatment decisions, but rather to inform formulary and reimbursement decisions. In that regard, we found that the use of denosumab may disproportionally increase treatment costs without commensurate clinical benefits.

Conclusion

While denosumab may provide benefits relative to zoledronic acid in terms of preventing SREs, increased convenience of administration, and a possibly lower toxicity profile, the present analysis indicates that it results in an ICUR of $1,058,741, which is above what is typically considered good value for medical interventions in the US. This suggests that the choice of denosumab over zoledronic acid for the prevention of SREs in metastatic prostate cancer patients should be carefully considered.

Transparency

Declaration of funding
SJS, JAC, and MFB received a consulting fee from Novartis Pharmaceuticals (maker of zoledronic acid) related to the development of this analysis.

Declaration of financial/other relationships
SK was an employee of and stock owner in Novartis Pharmaceuticals at the time that the analysis was first drafted. SK is now an employee of Celgene Corporation and no longer owns stock in Novartis Pharmaceuticals. The peer reviewers on this manuscript have disclosed that they have no other relevant financial relationships.

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