avoid this issue, it would be best if we could design trials to be large enough to have power to detect a survival advantage before or even with a crossover. However, this may not be feasible. As an alternative, in the case of a disease such as cancer, where DFS is not only a well-accepted surrogate for survival but also a correlate of quality of life, it will continue to be necessary to develop and use statistical methods that reliably and transparently explore the survival advantage of a new therapy. In the context of the protocol-defined primary outcome analyses of DFS, methods such as IPCW can provide important additional evidence to guide therapeutic choices.

In conclusion, for the BIG 1-98 trial, the results from the IPCW analysis of OS, in addition to the ITT analyses for DFS and OS, enlighten the interpretation of the results. Thus, we commend the author's decision to introduce these methods to readers of *Journal of Clinical Oncology*. Although in this particular case, the refined IPCW estimate of OS may not influence treatment decisions, one can envision situations where it might. Ideally, studies should not require estimation techniques such as this, but rather they should be designed to provide estimates that do not require assumptions or models. However, our responsibility to our clinical trial participants often means that we must forgo the optimal design. In these cases, we must sometimes sacrifice some of the information we had hoped to obtain. The use of methods such as these helps minimize this sacrifice.

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Denosumab for Prevention of Skeletal-Related Events in Patients With Bone Metastases From Solid Tumors: Incremental Benefit, Debatable Value

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See accompanying article 1125

Bone metastases are both frequent and morbid complications in many cancers. Most common in patients with advanced breast, prostate, and lung cancers, bone metastases are also seen in patients with other malignancies. Although the exact incidence of bone metastases in the broad population is not precisely known, it is estimated that skeletal involvement is present in more than half of those deaths resulting from advanced cancer.[1] Bone metastases may impact survival, and they also often compromise quality of life in the form of several complications that have emerged as a collection of defined skeletal-related events (SREs), including pathologic fractures, spinal cord compression, the need for surgery or radiation for a symptomatic bone lesion, and hypercalcemia of malignancy.[2] This collection of SREs represents a set of measurable clinical outcomes that can serve as an index of efficacy of potential interventions for patients with known skeletal metastases.

Bisphosphate therapy, most commonly the use of zoledronic acid, has been the cornerstone of secondary prevention of SREs in patients with solid tumors during approximately the last decade. Placebo-controlled randomized trials of populations with prostate cancer[3] and other solid tumors that do not include breast or prostate cancer[4] demonstrated significant reductions in frequency and number of SREs and median time to development of an SRE for patients who were given zoledronic acid versus a placebo. A noninferiority trial of patients with bone metastases from breast cancer or multiple myeloma[5] revealed comparability of zoledronic acid with pamidronate as an effective control arm. After the approval of zoledronic acid as a treatment for hypercalcemia of malignancy in 2001, zoledronic acid was approved in 2002 as an indication for treatment of patients with bone metastases from solid tumors and multiple myeloma.

Nevertheless, the use of zoledronic acid or other commercially available bisphosphonates for reducing SREs in patients with bone metastases remains limited by the requirement of adequate baseline renal function and a need to monitor the bisphosphonates with each subsequent administration of zoledronic acid, as well as by the potential for symptoms of an acute phase reaction, a small but worrisome risk of osteonecrosis of the jaw, hypocalcemia, and other adverse effects. At the same time, enthusiasm for use of zoledronic acid and other bisphosphonates in potentially eligible patients may remain muted by the recognition that the efficacy of these agents is still relatively modest.

Osteoclasts are the mediators of bone destruction and are largely regulated by the receptor activator of NF-κB ligand (RANKL). Denosumab, previously approved for osteoporosis, is a fully human monoclonal antibody that specifically inhibits RANKL, has been demonstrated to inhibit osteoclast-mediated

bone destruction,[6,7] and suppresses markers of bone turnover such as elevated urinary *N*-telopeptide (uNTx), which represents excessive bone resorption activity and correlates with SREs[8,9] in patients with bone metastases from breast cancer.[10]

In the current issue of *Journal of Clinical Oncology*, Henry et al[11] report the results of a phase III randomized trial that directly compared the development of skeletal-related events (SREs) on either denosumab or zoledronic acid in patients with multiple myeloma or bone metastases in the setting of a solid tumor (excluding breast or prostate cancer). Two similar randomized trials of denosumab versus zoledronic acid have been completed in patients with bone metastases from either breast cancer[12] or prostate cancer[13]; each demonstrated a statistically significant improvement in SRE reduction with denosumab compared with zoledronic acid that was not accompanied by an improvement in survival benefit.

The current study enrolled 1,776 bisphosphonate-naive patients with bone metastases from a wide range of cancer types, with the leading subpopulations comprised of patients with non–small-cell lung cancer (NSCLC; 40%), multiple myeloma (10%), small-cell lung cancer (9%), and renal cell carcinoma (6%). Patients were stratified according to the type of underlying cancer as well as according to whether they had experienced a prior SRE, as was the case for half of the enrolled patients. This well-conducted study was designed to test for noninferiority of denosumab compared with the current standard of zoledronic acid. Each agent was administered on day 1 of a 28-day schedule, with denosumab as a subcutaneous injection and zoledronic acid as an intravenous (IV) infusion along with placebo of the other agent.

The trial met its primary end point of demonstrating statistically significant noninferiority for time to development of first on-study SRE, with a hazard ratio (HR) of 0.84 (95% CI, 0.71 to 0.98). When adjusted for multiple comparisons to test for superiority, the *P* value for superiority for time to development of first on-study SRE was .06. The median time to development of the first on-study SRE was 20.6 versus 16.3 months in favor of denosumab.

Recipients of denosumab also experienced a greater decrease in serum markers of bone turnover; after 12 weeks of therapy, uNTx corrected for urine creatinine decreased by a median of 76% for denosumab versus 65% for zoledronic acid ($P < .0001$), whereas bone-specific alkaline phosphatase decreased a median of 37% with denosumab versus 29% with zoledronic acid.

There was no difference in progression-free survival or overall survival (OS) for the entire study population, although an ad hoc analysis revealed a trend toward more favorable survival in patients with NSCLC who received denosumab (HR, 0.79; 95% CI, 0.65 to 0.95), whereas those with multiple myeloma demonstrated more favorable survival (HR, 2.26; 95% CI, 1.13 to 4.50) in recipients of zoledronic acid.

The analysis of adverse effects (AEs) revealed somewhat mixed results, with the overall total rate of AEs similar between the two arms but with significant differences in the frequencies of several particular toxicities. There was a strong trend ($P = .07$) toward a higher rate of renal AEs with zoledronic acid (10.9% *v* 8.3%), despite the fact that renal function was monitored and dose adjustments were adhered to for zoledronic acid in keeping with current recommendations, including an initial dose adjustment for 17.3% of patients who had a baseline creatinine clearance below 60 mL/min. Symptoms of an acute phase reaction in the first three days were significantly more common in recipients of zoledronic acid than in recipients of denosumab (14.5% *v* 6.9% of patients). In contrast, hypocalcemia was approximately twice as common in patients enrolled onto the denosumab arm as in patients enrolled onto the zoledronic acid arm (10.8% *v* 5.8%; $P =$ not reported), although in the clear majority of cases, this was not associated with significant clinical sequelae. Confirmed cases of ONJ were experienced in just over 1% of patients at or before 2 or 3 years from the start of treatment with either agent.

How should we interpret the significance of these results? Denosumab clearly emerges as a compelling option and an arguably superior choice in many respects. First, this treatment is clearly at least as effective as zoledronic acid in preventing subsequent SREs in the diverse clinical trial population that was the subject of this study, and in many respects, it emerges as the superior treatment. Placing these results of the Henry et al[11] trial in the larger context of randomized phase III trials comparing denosumab with zoledronic acid in patients with breast[12] or prostate cancer,[13] the consistency of the results is remarkable, as highlighted in Table 1.

The lack of restriction on the ability to administer denosumab to the significant subset of patients with decreased creatinine clearance offers a clear advantage of denosumab versus zoledronic acid; it also obviates the requirement of monitoring renal function before each infusion of zoledronic acid. In addition, the significant decrease in the risk of acute phase reactions in the days after treatment with denosumab compared with zoledronic acid also represents a modest benefit that is nevertheless meaningful for many patients who are particularly bothered by these symptoms. Denosumab also offers the convenience to patients and treating centers of a subcutaneous injection rather than a monthly infusion, which is particularly beneficial for those patients not concurrently receiving IV anticancer therapies. Nevertheless, denosumab does not offer a survival benefit in the predefined study population in any of these randomized trials, and it presents its own toxicity concerns, including hypocalcemia and ONJ, among others.

The results of this trial, in combination with favorable results from similar trials that enrolled patients with bone metastases from breast cancer[12] and prostate cancer,[13] led to the US Food and Drug Administration approval of denosumab in November 2010 to reduce the development of SREs in patients with bone metastases in the setting of a solid tumor. This indication for denosumab does not include patients with multiple myeloma, presumably in light of the more favorable survival seen in the ad hoc analysis of patients with multiple myeloma in the Henry et al[11] trial. This new indication for denosumab concretely defines it as an appropriate treatment option for patients with solid tumors and bone metastases. But is it the new standard of care in this setting?

Alongside the numerator of the incremental gains provided by a new therapy, it is highly relevant to consider the denominator of the added costs. Here, unfortunately, denosumab presents a counterbalance to its modest but real advantages. Given that denosumab is nearly twice the cost of zoledronic acid, it is appropriate to question whether the modest reduction in the rate of SREs, even with the conveniences and cost savings of subcutaneous administration and the lack of a need to closely monitor creatinine levels, justifies an estimated increase in costs of hundreds of millions of dollars per year to the US health care system. Moreover, the availability of a generic version of zoledronic acid in early 2013 will offer a far less expensive but still comparable alternative to reduce the

Table 1. Results of Phase III Randomized Trials Comparing Zoledronic Acid With Denosumab

Primary Cancer Site Evaluated by Trial	Time to First SRE				OS	Summary of AEs of Interest (trends and statistically significant; unadjusted)
	Median (months)	HR	95% CI	*P*		
Solid tumors (not breast or prostate) and myeloma[11]	20.6 *v* 16.3	0.84	0.71 to 0.98	< .001 (noninferiority) .06 adjusted (superiority)	No difference in overall population NSCLC: HR, 0.79; 95% CI, 0.66 to 0.95 Myeloma: HR, 2.26; 95% CI, 1.13 to 4.50	Zoledronic acid: more acute phase reaction symptoms, renal AEs Denosumab: more hypocalcemia
Breast cancer[12]	NR *v* 26.4	0.82	0.71 to 0.95	< .001 (noninferiority) .01 (superiority)	No difference	Zoledronic acid: more acute phase reaction symptoms, renal AEs Denosumab: more hypocalcemia, ONJ
Prostate cancer[13]	20.7 *v* 17.1	0.82	0.71 to 0.95	< .001 (noninferiority) .008 adjusted (superiority)	No difference	Zoledronic acid: more acute phase reaction symptoms, renal AEs Denosumab: more hypocalcemia, ONJ

Abbreviations: SREs, skeletal-related events; HR, hazard ratio; OS, overall survival; AEs, adverse effects; NSCLC, non–small-cell lung cancer; NR, not reached; ONJ, osteonecrosis of the jaw.

burden, both in terms of cost and morbidity, that emerge from SREs in patients with cancer each year. Some patients, physicians, practices, and health care systems may appropriately question whether the modest incremental gains provided by the newest therapy justify a disproportionate increase in cost.

Oncologists now increasingly find themselves in the unenviable position of being forced to choose whether to recommend therapies that confer rather modest benefits in absolute terms, yet which are priced aggressively and not well associated with a concept of value. It is unfortunate that there is still no serious effort in the United States to address difficult questions about whether the US health care system can and should pay for any US Food and Drug Administration-approved treatment that achieves statistical significance in an end point increasingly removed from what patients and physicians offer as a primary goal of treatment. Instead, efforts aimed toward fiscal responsibility are met with a shrill cry that raises an alarm about draconian health care rationing. Oncologists are left with the professional goal of maximizing outcomes for their patients; that goal may well challenge any hope we might have of serving as responsible stewards of what are ultimately limited societal resources.

This is not meant to say that a decrease in SREs is not a laudable goal and clinically significant end point; rather, it is no longer tenable to make treatment recommendations predicated on a comparison of efficacy and toxicity of alternative interventions in the absence of any consideration of the cost differential of these approaches. It is only fair that oncologists step back and ask whether the heady costs of the newest agents that offer relatively subtle supportive care advantages in bone health, pain control, reduction of nausea/vomiting, or need for blood product support provide such a clear advantage over far less expensive options that they compel the rapid escalation of health care costs in the United States—in fact, it would be socially irresponsible for oncologists to not feel somewhat conflicted. These costs are so great that it is appropriate to ask whether limited financial resources could arguably be spent with a greater impact within the limits of our current health care budget.

Both physicians and patients consistently identify improvement in survival as a critical goal in treating cancer, so identifying subsets for whom the choice of denosumab or zoledronic acid may confer a survival benefit would heighten the value of a more expensive therapy. It is therefore notable that, in a post hoc analysis of OS in the Henry et al[11] trial, the HR for NSCLC was statistically superior with denosumab for patients with advanced NSCLC. This result of improved OS with denosumab in patients with NSCLC is particularly impressive for denosumab in light of the fact that prior clinical research on zoledronic acid has demonstrated a survival benefit for patients with NSCLC who received zoledronic acid compared with placebo.[14]

A novel, selective approach to denosumab administration is illustrated by a phase II clinical trial[15] that enrolled 111 patients with significantly elevated uNTx levels despite at least 8 weeks of IV bisphonsphonate therapy who were then randomly assigned to continue bisphosphonate therapy or switch to denosumab. This approach was associated with a significantly higher probability of normalizing uNTx levels at week 13 in recipients of denosumab compared with those who continued IV bisphosphonate therapy (71% *v* 29%; $P < .001$) as well as decrease by roughly half of the incidence of SREs with a switch to denosumab over the 25-week treatment period (8% *v* 17%; $P =$ nonsignificant). This work suggests that an optimal and cost-effective strategy may be to initiate zoledronic acid for many patients with advanced solid tumors and skeletal metastases, after which bone turnover markers might be used to select patients who are most likely to benefit from a switch to denosumab.

The rising costs of cancer care test the limits of what the market can possibly bear. The economic reality is that American oncologists simply cannot reflexively recommend the latest and almost invariably most expensive new option for managing clinical end points that are, at best, secondary to the primary goals of cancer treatment if the costs escalate at a rate disproportionate with the benefits that these agents confer. In this setting, I believe it is most appropriate to consider denosumab a strong option to displace zoledronic acid for the large

target clinical population, though the need to balance costs and benefits should lead us to conclude that such a substitution falls short of a mandate for a new standard of care.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author indicated no potential conflicts of interest.

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