VOL 1 · 2010

Defining the Role of Bone-Targeted Therapy in the Management of Breast and Prostate Cancer and Multiple Myeloma

Proceedings from a Clinical Roundtable Discussion

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This program is supported by educational grants from Amgen Inc, Millennium Pharmaceuticals Inc and Novartis Pharmaceuticals Corporation.

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Last review date: March 2010
Release date: March 2010
Expiration date: March 2011
Estimated time to complete: 3 hours

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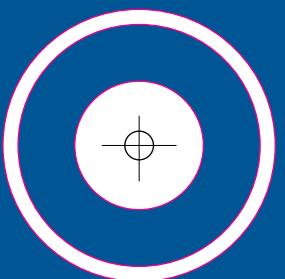
JOURNAL CLUB

2010



CD 1

CD 1 TRACKS

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JOURNAL CLUB

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A Continuing Medical Education Program

OVERVIEW OF ACTIVITY

Bone is the most common site for cancer metastases, and these metastases can result in systemic concerns, such as hypercalcemia, in addition to local problems, such as pain, fracture and spinal cord or nerve root compression. Thus, therapeutic and supportive management of bone health is a critical component of comprehensive care for the oncology patient. Cancer-related bone complications are not isolated in the metastatic setting but can result from therapeutic agents used in the treatment of breast and prostate cancer. In advanced multiple myeloma, bone-directed therapy is a routine component of initial systemic treatment, but research has failed to demonstrate an effect of treatment on the natural history of the disease. The search for alternatives with which to treat these conditions more effectively and with less toxicity drives ongoing research and the application of novel agents. Oncology clinicians must possess a clear understanding of the benefits and risks associated with bone-directed treatment approaches and remain up to date on how best to integrate emerging data and agents into the therapeutic algorithm. To that end, this activity is designed to expose oncology clinicians to the available peer-reviewed evidence and expert perspectives on this evidence that can be translated into strategies for addressing this challenging complication of cancer and its systemic management.

LEARNING OBJECTIVES

- Summarize the incidence of bone metastases among patients with various solid tumors and describe the effect of skeletal-related events (SREs) on quality of life and overall survival.
- Describe the bone remodeling process and the different mechanisms of action by which systemic bone-directed therapies affect the microenvironment, reduce SREs and promote bone health.
- Develop an evidence-based treatment algorithm for the management of documented skeletal metastases that incorporates bone-targeted systemic therapies.
- Recognize the prevalent bone complications of advanced multiple myeloma, and educate patients about the risks and benefits of treatment with intravenous bisphosphonates and other bone-directed agents.
- Inform patients with breast and prostate cancer about the risk of treatment-induced bone loss, and recommend strategies to minimize this side effect.
- Compare and contrast the adverse events induced by bone-directed therapies, their effect on the selection of therapy and the management of side effects.
- Discuss with patients the potential benefits of proper diet, exercise, vitamin D and calcium in reducing the risk of cancer recurrence.
- Counsel appropriately selected patients who are at risk for cancer-related bone complications about participation in ongoing clinical trials.

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This program is supported by educational grants from Amgen Inc, Millennium Pharmaceuticals Inc and Novartis Pharmaceuticals Corporation.

Last review date: March 2010; Release date: March 2010; Expiration date: March 2011

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BONE-DIRECTED THERAPY FOR EARLY BREAST AND PROSTATE CANCER

Key Papers/Presentations

Brufsky A et al. **The effect of zoledronic acid on aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: The Z-FAST study 5-year final follow-up.** San Antonio Breast Cancer Symposium 2009;**Abstract 4083**.

Coleman R et al. **Impact of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-FAST, ZO-FAST, and E-ZO-FAST.** San Antonio Breast Cancer Symposium 2009;**Abstract 4082**.

Eidtmann H et al. **The effect of zoledronic acid on aromatase inhibitor associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36 months follow-up of ZO-FAST.** San Antonio Breast Cancer Symposium 2008;**Abstract 44**.

Gnant M et al; ABCSG-12 Trial Investigators. **Endocrine therapy plus zoledronic acid in premenopausal breast cancer.** *N Engl J Med* 2009;360(7):679-91.

Smith MR et al, for the Denosumab HALT Prostate Cancer Study Group. **Denosumab in men receiving androgen-deprivation therapy for prostate cancer.** *N Engl J Med* 2009;361(8):745-55.

EFFECT OF ZOLEDRONIC ACID ON AROMATASE INHIBITOR-ASSOCIATED BONE LOSS IN BREAST CANCER

DR LOVE: Adam, would you summarize your paper on the effect of zoledronic acid on aromatase inhibitor-induced bone loss in postmenopausal women receiving adjuvant letrozole?

DR BRUFSKY: As background, a decade ago, we knew aromatase inhibitors were going to be used in the treatment of ER-positive breast cancer and that fracture and bone loss were potential side effects. A study was conducted with zoledronic acid in a population of volunteers without breast cancer who were postmenopausal and had low bone mineral density. The results were published in the *New England Journal* and showed that a single dose of zoledronic acid improved density in the spine and hip (Reid 2002).

In addition, the clodronate trials conducted for patients with primary operable breast cancer were initially reporting the possibility of a disease-free survival benefit. When we decided to investigate further, Michael Gnant had already begun a bisphosphonate trial with premenopausal women (Gnant 2009), so we evaluated therapy in postmenopausal patients. The trials required that women have a T-score higher than minus 2 to enroll, and all of the patients received letrozole.

There were three trials — Z-FAST, ZO-FAST and E-ZO-FAST — and combined, approximately 2,100 women enrolled. Bone mineral density was evaluated yearly in these women, and if it fell below a T-score of minus 2 in their hip or spine, then they received delayed zoledronic acid.

The Z-FAST trial has the most mature data, and we presented the five-year follow-up data at the recent

San Antonio meeting (Brufsky 2009; [1.1]). It is not surprising that, in patients receiving up-front treatment with zoledronic acid, bone mineral density was improved in the spine and the hip at three years compared to patients on the delayed-treatment arm. The question is whether these data are currently clinically relevant.

Clearly, bisphosphonates prevent bone loss in women receiving aromatase inhibitors.I believe that we will eventually be using more than five years of antihormonal therapy for breast cancer, so this will become more of a clinically relevant issue later.

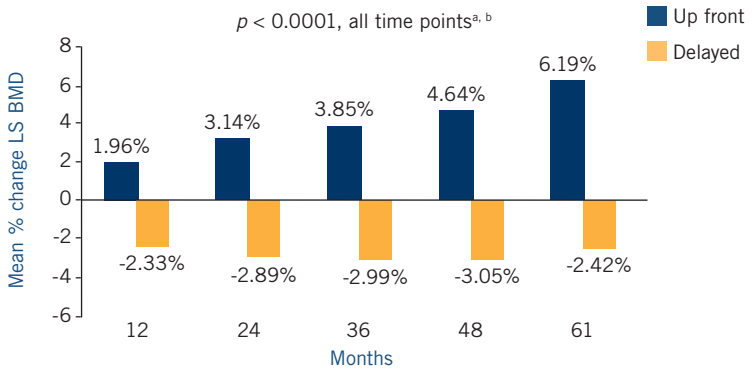
Of great interest, however, at the 2008 San Antonio meeting, the 36-month follow-up data from the ZO-FAST trial demonstrated a significant disease-free survival benefit for patients who received up-front therapy (Eidtmann 2008).

DR ANDERSON: Z-FAST was a well-done trial, and it teaches us that we can delay and decrease changes in bone mineral density. The clinically relevant question is, how will this affect the likelihood of developing fractures or not? I know the trial was not powered to demonstrate that, but over time I believe we will be able to discern that effect.

1.1

Z-FAST: Effect of Up-Front versus Delayed Zoledronic Acid on Aromatase Inhibitor-Associated Bone Loss in Postmenopausal Women with Early Breast Cancer

Mean percent change in lumbar spine bone mineral density (LS BMD) from baseline



[a] *p*-value corresponds to INTERGROUP comparisons. [b] Intragroup comparisons from baseline to all time points for both groups were significant ($p \leq 0.0003$).

Brufsky A et al. San Antonio Breast Cancer Symposium 2009;**Abstract 4083**.

POTENTIAL IMPACT OF BISPHOSPHONATES ON THE PREVENTION OF METASTASES

DR LOVE: Allan, could you present your case that addresses the issue of adjuvant bisphosphonates in premenopausal women?

DR LIPTON: This is a 34-year-old premenopausal woman with ER-positive, HER2-negative breast cancer with six positive nodes, who

absolutely refused chemotherapy. She had normal bone mineral density and her physician put her on tamoxifen and referred her to me with the question of whether or not she should also receive adjuvant zoledronic acid.

DR BRUFSKY: This patient fits the profile of women treated on the ABCSG-12 trial. I would probably treat her with an LHRH agonist and tamoxifen and it's likely that she will develop osteoporosis. Therefore, I believe it's reasonable to administer a bisphosphonate, and hopefully, she will also derive a benefit in terms of reduced risk of cancer relapse with the bisphosphonate.

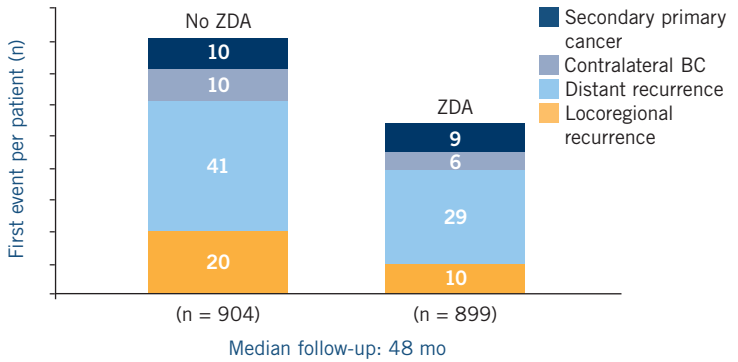
DR LOVE: Adam, would you summarize ABCSG-12, which evaluated endocrine therapy and zoledronic acid in premenopausal women?

DR BRUFSKY: This study consisted of 1,800 women with ER-positive, Stage I or Stage II breast cancer who received goserelin monthly for three years. The patients were randomly assigned to receive anastrozole, anastrozole with zoledronic acid, tamoxifen or tamoxifen with zoledronic acid. In a bone mineral density substudy of 400 patients, clear losses in bone were evident in the women who did not receive the bisphosphonates (Gnant 2009; [1.2]).

The relative risk reduction in the rate of recurrence was basically one third in the patients who received zoledronic acid. The number of locoregional recurrences was 10 versus 20 and the number of distant recurrences was 29 versus 41 in the patients who did versus did not

1.2

ABCSG-12: Zoledronic Acid (ZDA) Added to Adjuvant Endocrine Therapy Improves Disease-Free Survival (DFS) by 36 Percent in Premenopausal Patients with ER-Positive Early Breast Cancer (BC)



Hazard ratio (95% CI) for DFS versus no ZDA = 0.64 (0.46-0.91), $p = 0.01$

"The addition of zoledronic acid to adjuvant endocrine therapy increased the rate of disease-free survival, as compared with endocrine therapy alone... This difference is similar to the 5-year absolute difference in disease-free survival observed in trials comparing tamoxifen with aromatase inhibitors in postmenopausal women with early breast cancer."

Gnant M et al; ABCSG-12 Trial Investigators. *N Engl J Med* 2009;360(7):679-91.

receive the bisphosphonates, respectively. The question is whether the benefit is worth it. These women fared extraordinarily well. Their disease-free survival at five years was approximately 93 to 94 percent, so we're talking about increasing it to about 95 percent with zoledronic acid.

DR LOVE: After the ABCSG-12 data were initially presented at ASCO 2008, the discussant, Martine Piccart-Gebhart, commented on the "seed and soil" hypothesis as a biological explanation for how zoledronic acid might impact distant metastases (1.3, 1.4, 1.5). Do you have any thoughts on the biologic processes that might be involved?

DR SMITH: One potential explanation would be that the bone microenvironment is involved in trafficking tumor cells before they become productive metastases to other sites. So, in addition to having direct bone effects, the bisphosphonates may have indirect effects by preventing recurrence at other sites.

DR LIPTON: Larry Norton and Joan Massagué's self-seeding hypothesis is consistent with that explanation also. Under their hypothesis, breast cancer cells enter the bloodstream and go to the bone microenvironment, where they may reside for long periods of time prior to being reactivated back into the bloodstream and other tissue. If that's true, then bisphosphonates may well inhibit or kill those dormant tumor cells in the bone marrow microenvironment.

DR PEARSE: The serum half-life of the bisphosphonates is relatively short, so a direct antitumor effect of zoledronic acid is probably not the major mechanism of action. Once the drug is in the bone, it's available for transport across the osteoclast to deliver to adjacent cells. It's never been documented how much zoledronic acid would be found in tumor metastases and whether the concentrations would be enough to suppress neoangiogenesis or change the gamma delta T-cell milieu.

DR LOVE: We are still awaiting presentation of the full AZURE

1.3

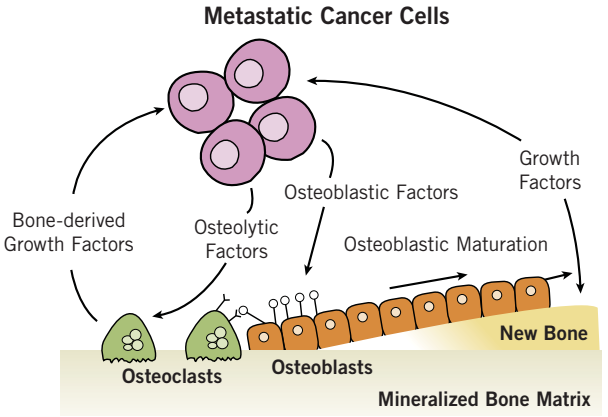
Seed and Soil Hypothesis and Bisphosphonate Mechanism of Action: Commentary by Dr Piccart-Gebhart

"The main target of bisphosphonates is the osteoclast and the remarkable vicious cycle that exists between osteoclasts and tumor cells present in bone (1.4). The latter promote osteoclast formation and activity, either directly through the production of parathyroid hormone-related peptide or indirectly through the production of the RANK ligand, which is a key survival factor for osteoclasts.

Osteoclasts, in turn, release growth factors, such as TGF beta, which further encourage tumor cell proliferation and survival. Bisphosphonates are able to interrupt this vicious cycle, thereby exerting a profound influence on 'the soil.' But an anti-tumor activity directed at 'the seed' is also possible. Indeed, a decade of in vitro and in vivo preclinical experiments suggest that bisphosphonates may have direct anti-tumor activity outside of the bone marrow microenvironment (1.5), including, for example, antiangiogenic effects and synergistic effects with chemotherapy, endocrine therapy and radiotherapy."

Piccart-Gebhart M. Discussion, ASCO 2008.

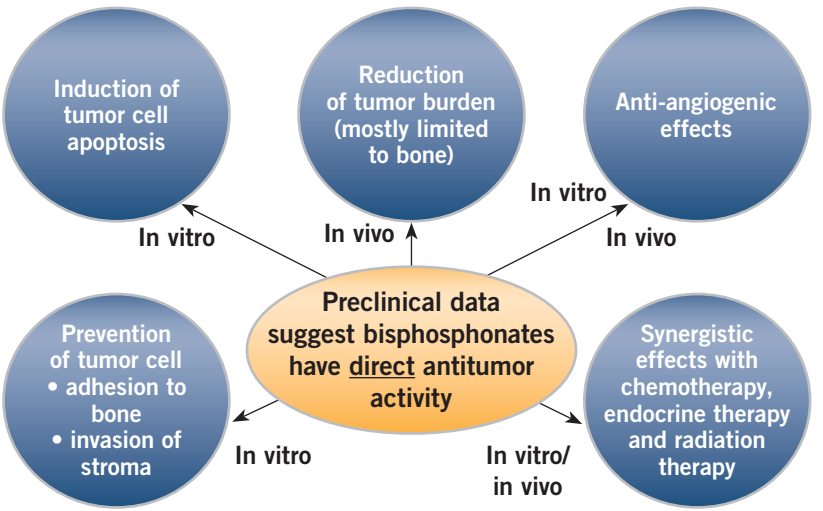
1.4 The "Vicious Cycle" of Osteolytic Metastases and Potential Effect of Bisphosphonates on the Process



Tumor-derived growth factors promote osteoclast activation and subsequent osteoclast-mediated bone resorption. Bone resorption releases growth factors and cytokines from the bone matrix that promote tumor growth. Bisphosphonates act to interrupt this "vicious cycle" by inhibiting osteoclast-mediated bone resorption, which results in decreased levels of growth factors and cytokines that promote tumor growth.

Reproduced and adapted with permission from the American Association for Cancer Research: Guise TA et al. **Basic mechanisms responsible for osteolytic and osteoblastic bone metastases.** *Clin Cancer Res* 2006;12:6213s–6216s.

1.5 Preclinical Evidence for Direct Antitumor Activity of Bisphosphonates



Modified from Piccart-Gebhart M. Discussion, ASCO 2008.

trial data set in terms of this issue, but there were some provocative data from an analysis of patients who received zoledronic acid and chemotherapy in the preoperative setting. Could you discuss what we know about that trial thus far?

DR BRUFSKY: The AZURE trial was conducted in Europe and consisted of 3,360 women with Stage II or Stage III breast cancer. The patients received neoadjuvant or adjuvant therapy with a fairly intensive regimen of bisphosphonates versus no bisphosphonates. All of the patients received standard therapies, such as chemotherapy or endocrine therapy or both, as indicated. Of these women, 205 received zoledronic acid and chemotherapy in the neoadjuvant setting. The pathologic complete response rate was doubled in the women who received the bisphosphonate compared to those who did not (Winter 2008).

I know of no trial in which the pathologic complete response rate did not predict disease-free survival, so I expect this trial will be positive. Until the large trials are complete, I'm not recommending this approach to every woman. However, if a patient comes in with a borderline T-score, I suspect that the data will push me toward bisphosphonate therapy.

1.6

Perspectives of Prof Ian Smith and Dr Eric Winer on the Use of Adjuvant Bisphosphonates for Early Breast Cancer

PROF SMITH: The reduction in distant metastases associated with zoledronic acid in ABCSG-12 is one of the most important observations of this past year, and I believe we're "pussy-footing" around with bisphosphonates. If I was a woman with early breast cancer, I would want to be on a bisphosphonate. First, it prevents bone loss and there is very little downside, particularly if it's administered once every six months. People have gotten hung up on the osteonecrosis of the jaw, but it's a very rare problem. Second, there appears to be an outcome benefit associated with the bisphosphonate.

DR WINER: The important questions with regard to ABCSG-12 and the use of adjuvant bisphosphonates to prevent recurrence are, will these observations be confirmed in ongoing studies? Will the results be confirmed in a broader subset of women with breast cancer? And will these putative prevention benefits be bone specific or affect metastases in general? Aside from premenopausal women who were treated as they were on ABCSG-12, I don't rush to use adjuvant bisphosphonates to prevent recurrence.

Interview, *Breast Cancer Update* Audio Series. Ian E Smith, MD, December 11, 2009; Eric P Winer, MD, January 21, 2009.

MECHANISMS OF ACTION OF BISPHOSPHONATES AND THE RANK LIGAND INHIBITOR DENOSUMAB

DR LOVE: Matt, would you summarize the mechanisms of action of bisphosphonates and denosumab?

DR SMITH: Pathologic osteoclast activation is what underlies the clinical problems we see in metastatic bone disease. That's true in breast cancer, multiple myeloma and prostate cancer. Osteoblastic metastases have high levels of bone turnover, which includes excess activity of both osteoblasts and osteo-

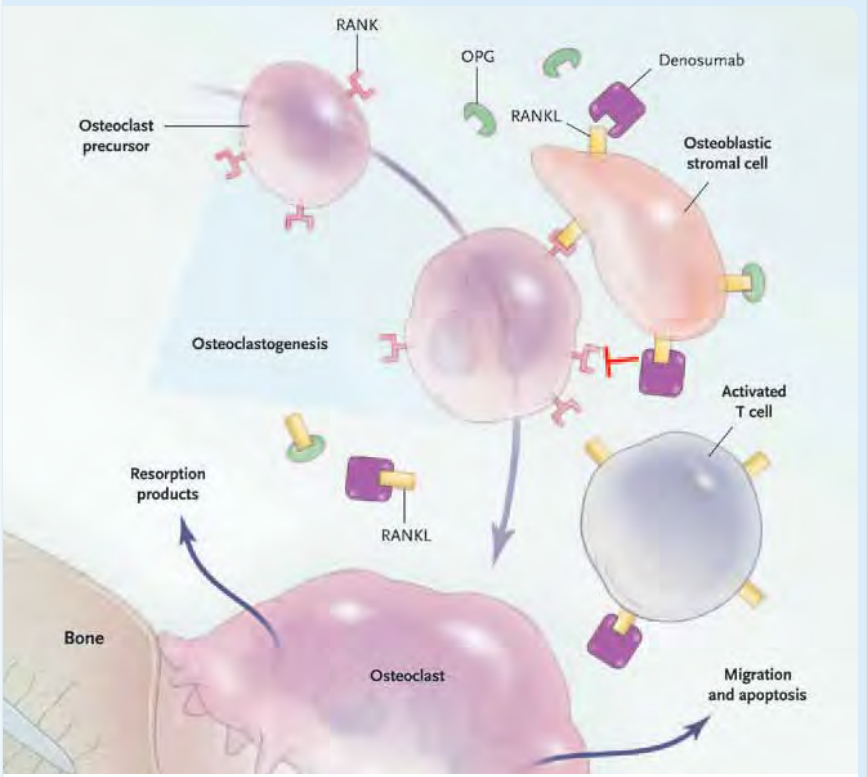
clasts, and a wealth of data supports the central role of pathologic osteoclast activation.

One of the most interesting and important advances in understanding basic bone biology is the recognition of the receptor activator of the NF-kappaB (RANK) ligand pathway. We have learned that the RANK ligand pathway is key to the communication between the building and resorbing bone cells — osteoblasts and osteoclasts — and plays a central role in osteoclast activation, differentiation and survival. Denosumab is a human monoclonal antibody that specifically binds and inactivates RANK ligand, inhibiting osteoclast activation (1.7).

Bisphosphonates act by a completely different mechanism of action, and the

1.7

The Skeletal Action of Denosumab



"RANKL, a member of the tumor necrosis factor superfamily of ligands and receptors, promotes the differentiation, activation, and survival of bone-resorbing osteoclasts. Osteoprotegerin (OPG) that is produced by osteoblasts, the key modulator of RANKL, acts as a natural soluble decoy receptor for RANKL and blocks its effects. Denosumab functions like OPG and has the effect of decreasing osteoclastogenesis, as revealed by diminished biochemical markers of bone resorption."

individual agents have slightly varied mechanisms, but fundamentally they are taken up by osteoclasts. The more potent agents, such as zoledronic acid, induce osteoclast apoptosis.

We knew from early testing that denosumab was highly potent. Then, most intriguingly, a clinical trial demonstrated that it was able to markedly inhibit osteoclast activity in patients with bisphosphonate-refractory metastatic disease.

Although these patients had extensive bone disease and high levels of osteoclast activity despite treatment with a potent IV bisphosphonate, denosumab resulted in marker normalization in the majority of patients (Fizazi 2009). This result is stunning because these are the most difficult patients to treat from a bone perspective.

DENOSUMAB IN MEN WITH EARLY PROSTATE CANCER RECEIVING ANDROGEN DEPRIVATION THERAPY

DR LOVE: Len, can you present your patient in whom the issue of bone arose with regard to androgen deprivation therapy?

DR GOMELLA: He was a 73-year-old man who was diagnosed with T1C, Gleason 3+4 prostate cancer with a PSA of 18 ng/mL. He elected to undergo external beam radiation therapy with approximately two years of androgen deprivation therapy (ADT). His wife actually raised the concern about the development of osteoporosis as a result of antiandrogen treatment. We discussed the standard interventions, such as vitamin D and calcium supplementation in addition to weight-bearing exercise. She asked about alendronate, which is what she was receiving and which isn't approved for this indication in prostate cancer. I told her that I was okay with his receiving treatment, which he did without complication.

DR LOVE: Matt, would you discuss your recent publication in the *New England Journal* on the effects of denosumab in men receiving ADT for nonmetastatic prostate cancer?

DR SMITH: It's clear that ADT has a variety of side effects, including osteoporosis and a greater risk for fractures. ADT significantly decreases bone mineral density (BMD) of the hip, spine and other skeletal sites. The loss of bone is sufficient to explain that greater fracture risk.

Although it's recognized that this is a significant clinical problem, to be candid, we didn't know how to address it. A number of studies have been published, some of which I've been involved in, reporting that bisphosphonates and other agents increase BMD, but our goal with this study was to prevent the clinical outcome of fractures.

In this double-blind, multicenter study, we randomly assigned men receiving ADT for prostate cancer to receive denosumab or placebo. The absolute difference in the rate of vertebral fractures at three years was relatively low (Smith 2009; [1.8]). This speaks to the fact that we need to identify patients who require such therapy because not every patient receiving ADT requires medical therapy to prevent fractures.

In addition, although this was a three-year trial, our patients who are receiving salvage ADT are often

receiving it for much longer than three years. We conservatively designed the trial to study the first fracture event, because when you have one fracture, you're at risk for more.

I believe that because of the trial design, we're probably seeing the absolute minimal estimate of benefit that might be conferred by this approach in patients who are receiving longer-term therapy and are at risk for fractures at multiple sites. The intriguing aspect of this study was the striking magnitude of the fracture benefit — at two years we reported a 68 percent reduction in vertebral fractures and at three years a 62 percent reduction (1.8). The extent of this benefit corresponds to the best of any existing therapeutic agents for the treatment of osteoporosis in postmenopausal women. The other intriguing factor is that the magnitude of fracture benefit is superimposable on the data reported from the FREEDOM study, a trial of approximately 8,000 postmenopausal patients with osteoporosis (Cummings 2009). This trial used the same dose and schedule of denosumab, which proved to be effective for these women. The benefit in vertebral fracture reduction was similar to what we reported in our patient population of men receiving ADT (1.8).

DR LOVE: What do we know about the efficacy of bisphosphonates in reducing the fracture rate in men?

DR SMITH: Few data exist on fracture prevention in men in any setting. To the best of my knowledge, this is the first large fracture prevention study completed with men. Although some bisphosphonates are approved to treat osteoporosis in men, that approval is not based on a demonstration of a fracture benefit. It's based primarily on the bone mineral density effect.

I believe that the effects are likely to translate into a fracture reduction, but that has not been formally demon-

1.8

Effects of Denosumab on Bone Mineral Density (BMD) and Fractures in Men Receiving Androgen Deprivation Therapy for Nonmetastatic Prostate Cancer

	Denosumab (n = 734)	Placebo (n = 734)	Relative risk	*p*-value
Lumbar spine BMD* (% increase at 24 months)	5.6	-1.0	—	<0.001
Incidence of new vertebral fractures (% increase at 36 months)	1.5	3.9	0.38	0.006

* Denosumab therapy was also associated with significant increases in BMD at the total hip, femoral neck and distal third of the radius at all time points.

"In this study of men receiving androgen-deprivation therapy for prostate cancer, a significant increase in bone mineral density was seen with denosumab at all measured skeletal sites, including the lumbar spine, hip, and radius. Denosumab was associated with significant decreases, as compared with placebo, in the cumulative incidence of new vertebral fractures at 12, 24, and 36 months."

Smith MR et al. *N Engl J Med* 2009;361(8):745-55.

strated, and this is why I believe that our study is of particular importance. Hopefully the results will lead to greater adoption of this approach. ■

SELECT PUBLICATIONS

Cummings SR et al; FREEDOM Trial. **Denosumab for prevention of fractures in postmenopausal women with osteoporosis.** *N Engl J Med* 2009;361(8):756-65.

Fizazi K et al. **Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates.** *J Clin Oncol* 2009;27(10):1564-71.

Reid IR et al. **Intravenous zoledronic acid in postmenopausal women with low bone mineral density.** *N Engl J Med* 2002;346(9):653-61.

Winter MC et al. **The addition of zoledronic acid to neoadjuvant chemotherapy may influence pathological response — Exploratory evidence for direct anti-tumor activity in breast cancer.** San Antonio Breast Cancer Symposium 2008;**Abstract 5101**.

Whyte MP. **The long and the short of bone therapy.** *N Engl J Med* 2006;354(8):860-3.

BONE-DIRECTED THERAPY FOR ADVANCED BREAST AND PROSTATE CANCER AND MULTIPLE MYELOMA

Key Papers/Presentations

Fizazi K et al. **Denosumab treatment of prostate cancer with bone metastases and increased urine N-telopeptide levels after therapy with intravenous bisphosphonates: Results of a randomized phase II trial.** *J Urol* 2009;182(2):509-15.

Fizazi K et al. **Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates.** *J Clin Oncol* 2009;27(10):1564-71.

Henry D et al. **A double-blind, randomized study of denosumab versus zoledronic acid for the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma.** *Proc ESMO/ECCO* 2009;**Abstract 20LBA**.

Kumar S et al. **Novel three- and four-drug combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide, for newly diagnosed multiple myeloma: Encouraging results from the multi-center, randomized, phase 2 EVOLUTION study.** *Proc ASH* 2009;**Abstract 127**.

Palumbo AP et al. **A phase III study of VMPT versus VMP in newly diagnosed elderly myeloma patients.** *Proc ASCO* 2009;**Abstract 8515**.

Richardson PG et al. **High response rates and encouraging time-to-event data with lenalidomide, bortezomib, and dexamethasone in newly diagnosed multiple myeloma: Final results of a phase I/II study.** *Proc ASH* 2009;**Abstract 1218**.

Stopeck A et al. **Comparison of denosumab versus zoledronic acid for the prevention of skeletal-related events in breast cancer patients with bone metastases.** San Antonio Breast Cancer Symposium 2009;**Abstract 22**.

DENOSUMAB VERSUS ZOLEDRONIC ACID FOR THE PREVENTION OF SKELETAL-RELATED EVENTS IN PATIENTS WITH BREAST CANCER AND BONE METASTASES

DR LOVE: Adam, if a patient with metastatic breast cancer involving multiple bone lesions experiences worsening bone pain and perhaps a fracture and disease progression nine months into therapy on an

aromatase inhibitor and zoledronic acid, what systemic therapy would you administer next?

DR BRUFSKY: I would change the antihormonal therapy and continue zoledronic acid. Clinical trials show that after a first skeletal-related event (SRE), the rate of a second event is still reduced if you continue the bisphosphonate, at least up to 24 months.

DR LOVE: How does denosumab compare to continued zoledronic acid in this setting?

DR LIPTON: Two studies presented at recent European meetings have evaluated these agents. One study compared them in Stage IV breast cancer, specifically in patients with bone metastases. In terms of the primary event, which was time to the first SRE, it demonstrated that denosumab was noninferior (Stopeck 2009).

The secondary endpoint was superiority, and the hazard ratio was approximately 0.8, so events were decreased by approximately 20 percent with denosumab compared to zoledronic acid. In the multiple event analysis, a significant benefit was evident with denosumab, but no difference was observed in time to disease progression or overall survival.

The other study was a double-blind, randomized trial comparing these two agents as treatment for bone metastases in advanced cancer, excluding breast and prostate, or multiple myeloma. The primary endpoint was SREs and, again, denosumab was noninferior (Henry 2009). In terms of superiority, the *p*-value was not significant, although it was close. Again, multiple events seem to favor denosumab, but no significant difference was observed in disease progression or survival. It appears from these two studies that denosumab may be beneficial in delaying or preventing SREs.

DR LOVE: Allan, if denosumab were available today, putting aside reimbursement or cost issues, would you use it, and if so, how?

DR LIPTON: In metastatic breast cancer it decreased events by 20 percent, which is probably as good as what we observed with zoledronic acid compared to pamidronate, so it would be difficult, considering evidence-based medicine, not to offer it to our patients. One can argue this with the other tumors in which the *p*-values were not significant at this point, although close.

DR LOVE: Matt, what is your opinion of the breast cancer data with denosumab?

DR SMITH: Zoledronic acid is a good agent, and the trial was conducted with patients with severe disease, so it was far from certain that denosumab could prove superiority. However, denosumab was superior in every way that you could possibly analyze the SRE endpoint, and it reduced the incidence of disease-related skeletal complications by a convincing and clinically important margin (Stopeck 2009; [2.1]). I believe that this speaks volumes about the efficacy of denosumab.

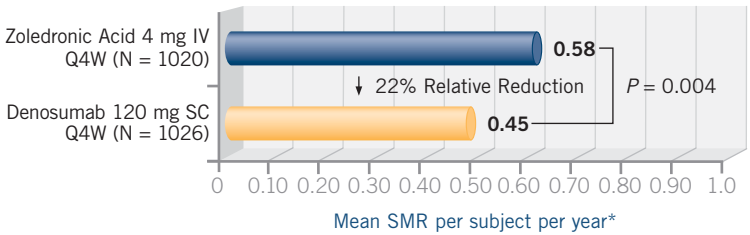
DR LOVE: If denosumab were available for breast cancer, would you switch patients to it or even consider using it before zoledronic acid?

DR SMITH: I believe the totality of data support using denosumab

up front but not so much to switch patients who are currently receiving bisphosphonate treatment. That issue was not addressed by the study. If it was available and I was initiating therapy for breast cancer, I would choose denosumab rather than zoledronic acid.

2.1

Denosumab versus Zoledronic Acid for the Prevention of Skeletal-Related Events (SREs) in Patients with Stage IV Breast Cancer and Bone Metastases



* Skeletal morbidity rate (SMR) = number of SREs for each subject (allowing 1 per 3-week assessment), divided by the subject's time at risk.

With permission from Stopeck A et al. Presentation. San Antonio Breast Cancer Symposium 2009;**Abstract 22**.

IMPACT OF PROTEASOME INHIBITORS AND IMMUNOMODULATORY AGENTS ON THE TUMOR AND BONE MICROENVIRONMENT IN MULTIPLE MYELOMA

DR LOVE: Ken, would you discuss some of the recent advances in the treatment of newly diagnosed MM?

DR ANDERSON: With the advent of novel therapies since 1998, particularly in the past five years, we now have bortezomib, lenalidomide, thalidomide and liposomal doxorubicin, and the median survival in multiple myeloma has increased significantly.

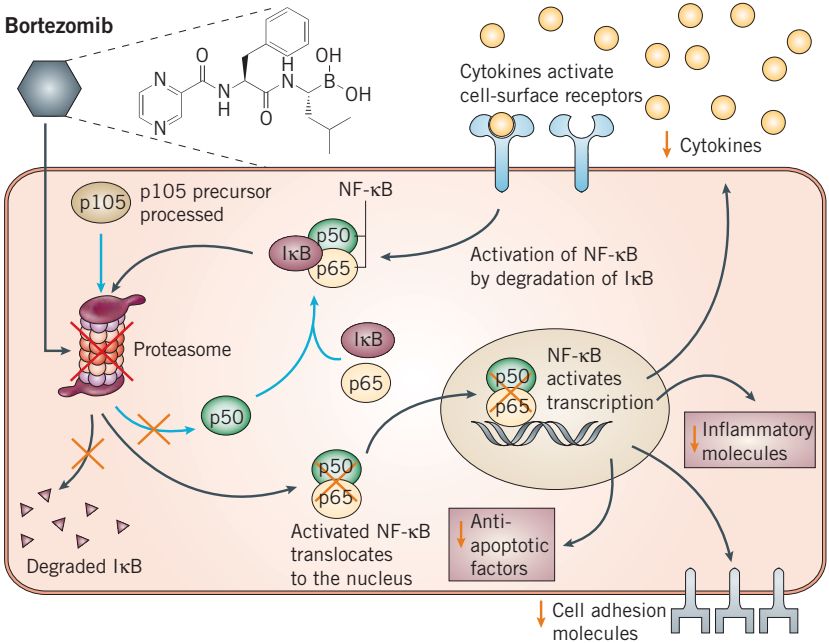
Bortezomib and lenalidomide, via different mechanisms, have a beneficial effect on bone. They both inhibit osteoclastogenesis and foster new bone formation, osteoblast function and maturation.

DR BRUFSKY: Which do you believe is responsible for the anticancer effect of these agents — the direct effect on the tumor or the effect on the microenvironment?

DR ANDERSON: It's both. We have demonstrated that they have distinct activities directed at the tumor induction of apoptosis and a variety of other actions (2.2). However, the characteristic that distinguishes bortezomib and lenalidomide from conventional chemotherapy is their ability to act in the microenvironment. By anti-angiogenic effects, inhibiting transcription and secretion of cytokines, they inhibit the ability of the cell to bind into the bone marrow microenvironment. These agents also activate the patient's cytotoxic T-cells, K-cells and NKT-cells.

2.2

Bortezomib Blockade of the NF-κB Pathway*



* A key factor in the ability of the proteasome inhibitor bortezomib to kill myeloma cells is that it blocks the activation of nuclear factor-κB (NF-κB). The activated NF-κB can enter the nucleus, which allows it to carry out many functions in the tumor cell that help the cell to survive and proliferate. By inhibiting the proteasome (red cross) and therefore the activation of NF-κB (orange crosses), bortezomib helps to reduce antiapoptotic factors; inflammatory molecules; cell adhesion molecules, which allow attachment cells to adhere to bone marrow cells; and cytokines, which promote the growth of myeloma cells.

Myeloma cells produce or induce osteoclast-activating factors (OAFs), which increase osteoclast formation in addition to produce osteoblast-inhibiting factors, which block bone formation. Bortezomib can induce bone formation by increasing BMP-2 production by osteoblasts, which in turn increases RunX-2 levels, which induces mesenchymal stem cells to differentiate into osteoblasts and enhance bone regeneration.†

* Reprinted by permission from Macmillan Publishers Ltd: Paramore A, Frantz S. *Nat Rev Drug Discov* 2003;2(8):611-2. Copyright 2003. † Roodman GD. *J Clin Invest* 2008;118(2):462-4.

NOVEL TRIPLE- AND QUADRUPLE-DRUG REGIMENS IN MULTIPLE MYELOMA

DR LOVE: Roger, when you really think about it, the major step forward in terms of bone issues in myeloma — maybe in contrast to the breast/prostate cancer model — is now our greater ability to control the neoplasia. However, treatment effects are also relevant. What do we know about the effects of corticosteroids on bone?

DR PEARSE: In myeloma, the disease itself is the most important issue to address in terms of bone health. Certainly, corticosteroid use

in induction therapy, maintenance therapy and autologous transplants has been shown to result in some degree of osteoporosis or reduction in bone mineral density.

DR LIPTON: Patients who receive chronic steroids have significant osteoporosis and risk of fracture. The more corticosteroids administered, the more one needs to worry about bone health. Additionally, studies have demonstrated that steroids are another potential risk factor contributing to the incidence of ONJ.

DR LOVE: Ken, encouraging data are emerging from your center and others on "triple therapy" with bortezomib and lenalidomide with dexamethasone. Would you describe what has been seen with the RVD regimen?

DR ANDERSON: In the laboratory and in animal models, bortezomib and lenalidomide have been used to overcome resistance to conventional drugs during Phase I/II clinical trials. If you combine bortezomib and lenalidomide, they trigger different apoptotic or death cascades when used along with dexamethasone. In the Phase II trial of patients with newly diagnosed myeloma, the overall response rate was 100 percent and the very good partial, near complete or complete response rate was 74 percent (Richardson 2009; [2.3]).

These data are extraordinary. We're about to begin an international trial with 1,000 patients with newly diagnosed myeloma who will receive RVD. Stem cells will be collected from every patient. Then half of the patients will be randomly assigned to receive high-dose melphalan followed by lenalidomide maintenance, and patients on the other arm will receive continued RVD therapy.

DR LOVE: How do the recent RVD data compare to findings with either one of these agents combined with dexamethasone?

DR ANDERSON: The RVD data are remarkably better. Although the up-front use of bortezomib/dexamethasone or lenalidomide/dexamethasone is associated with significant advances, the three-drug RVD combination shows unprecedented results (Richardson 2009).

2.3

Efficacy of Bortezomib/Lenalidomide/Dexamethasone (RVD) During a Phase II Trial of Patients with Newly Diagnosed Multiple Myeloma (N = 35)

Efficacy	Patients (%)
Overall response	35 (100)
Complete response	13 (37)
Near-complete response	7 (20)
Very good partial response	6 (17)
Partial response	9 (26)

RVD dose = 1.3 mg/m^2 bortezomib + 25 mg lenalidomide + 20 mg dexamethasone q3wk x 8 (dexamethasone was tapered to 10 mg during last four cycles)

After eight cycles, patients were eligible for maintenance treatment q3wk with lenalidomide d1-14, bortezomib d1, 8 and dexamethasone (10 mg) d1, 2, 8, 9.

Richardson PG et al. *Proc ASH* 2009;**Abstract 1218**.

In the upcoming international study, we will learn about the durability of these frequent and extended responses in patients who receive RVD with transplant later.

DR LOVE: The issue of drug delivery is key to the success of these novel agents, and in terms of bortezomib, a central factor is the neuropathy that can be seen. Ken, how much of an issue is this?

DR ANDERSON: Neuropathy is associated with proteasome inhibitors. That was particularly a problem when using bortezomib in patients with advanced multiple myeloma because the majority of patients are already experiencing neuropathy. However, we have since moved this agent to the up-front setting and have learned how to use it more effectively. Algorithms have been developed to dose reduce, extend the interval and/or briefly discontinue the agent for different grades of neuropathy. When we use bortezomib up front, even at the twice-weekly for two weeks schedule — days one, four, eight and 11 — less than five percent of patients experience Grade III neuropathy.

At ASCO 2009, Dr Palumbo presented data demonstrating that switching the administration of bortezomib from twice weekly to once a week can markedly reduce the incidence of neuropathy without a large cost in terms of efficacy (Palumbo 2009; [2.4]). In addition, a number of drugs are being combined with bortezomib that are promising in terms of the efficacy but that also markedly reduce the neuropathy associated with bortezomib. ■

2.4

Twice-Weekly versus Once-Weekly Bortezomib in a Phase III Trial Evaluating Bortezomib/Melphalan/Prednisone with or without Thalidomide as Initial Treatment for Elderly Patients with Multiple Myeloma

	Bortezomib twice weekly (n = 63)	Bortezomib once weekly (n = 190)
Complete response	25%	23%
Two-year progression-free survival	56%	58%
Sensory peripheral neuropathy (PN) Any grade Grade III-IV	 43% 14%	 21% 2%
PN discontinuation	16%	4%
Total planned dose	67.6 mg/m^2	46.8 mg/m^2
Total delivered dose	41 mg/m^2	40 mg/m^2

Palumbo AP et al. *Proc ASH* 2009;**Abstract 8515**.

SELECT PUBLICATIONS

Henry D et al. **A double-blind, randomized study of denosumab versus zoledronic acid for the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma.** *Proc ESMO/ECCO* 2009;**Abstract 20LBA**.

Palumbo AP et al. **A phase III study of VMPT versus VMP in newly diagnosed elderly myeloma patients.** *Proc ASCO* 2009;**Abstract 8515**.

POST-TEST

Defining the Role of Bone-Targeted Therapy in the Management of Breast and Prostate Cancer and Multiple Myeloma — 2010

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Which of the following bone-directed agents specifically binds and inactivates RANK ligand, thereby inhibiting osteoclast activation?**
   a. Bortezomib
   b. Clodronate
   c. Denosumab
   d. Zoledronic acid

2. **In the clinical trial comparing denosumab to zoledronic acid for the prevention of skeletal-related events in patients with Stage IV breast cancer and bone metastases, no statistically significant difference was evident in the incidence of osteonecrosis of the jaw between the two therapies.**
   a. True
   b. False

3. **In the Phase III trial comparing zoledronic acid to denosumab in patients with Stage IV breast cancer and bone metastases, the skeletal morbidity rate was significantly reduced with _____.**
   a. Denosumab
   b. Zoledronic acid
   c. Neither — there was no significant difference

4. **The five-year data from the Z-FAST study presented by Brufsky and colleagues at the 2009 San Antonio Breast Cancer Symposium showed that up-front zoledronic acid had a significant positive effect on bone density compared to delayed therapy in postmenopausal women receiving adjuvant letrozole.**
   a. True
   b. False

5. **In the AZURE trial, which evaluated neoadjuvant chemotherapy with or without zoledronic acid in patients with Stage II or Stage III breast cancer, the pathologic complete response rate was _____ in the women who received zoledronic acid compared to those who did not.**
   a. Lower
   b. Slightly higher
   c. Nearly doubled

6. **Fizazi and colleagues reported that, in patients with prostate cancer-related bone metastases and increased urine N-telopeptide levels despite intravenous bisphosphonate treatment, denosumab normalized urine N-telopeptide levels more frequently than did ongoing bisphosphonate therapy.**
   a. True
   b. False

7. **A multicenter Phase III study is evaluating the effects of denosumab on prolonging _____ in men with hormone-refractory prostate cancer.**
   a. Bone metastasis-free survival
   b. Progression-free survival
   c. Overall survival
   d. All of the above

8. **A Phase III trial evaluating the effects of denosumab on bone mineral density (BMD) and fractures in men receiving androgen deprivation therapy for nonmetastatic prostate cancer reported an improvement in BMD of the lumbar spine at 24 months of _____ in patients receiving denosumab.**
   a. One percent
   b. 5.6 percent
   c. 15.8 percent

9. **A recent Phase II trial of bortezomib/lenalidomide/dexamethasone (RVD) found that the overall response rate was _____ in patients with newly diagnosed multiple myeloma.**
   a. 34 percent
   b. 76 percent
   c. 100 percent
   d. None of the above

10. **The immunomodulating drug lenalidomide imparts both antitumor effects and beneficial effects on the bone.**
    a. True
    b. False

Post-test answer key: 1c, 2a, 3a, 4a, 5c, 6a, 7a, 8b, 9c, 10a

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Defining the Role of Bone-Targeted Therapy in the Management of Breast and Prostate Cancer and Multiple Myeloma — 2010

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Anticancer and bone-protective effects of zoledronic acid combined with endocrine therapy in breast cancer	4 3 2 1	4 3 2 1
Efficacy of denosumab in patients with bisphosphonate-refractory bone metastases from breast or prostate cancer	4 3 2 1	4 3 2 1
Clinical strategies using bortezomib and lenalidomide in addition to bone-directed therapy in the treatment of multiple myeloma	4 3 2 1	4 3 2 1
Risk of osteonecrosis of the jaw secondary to bone-directed therapies	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain: .....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain: .....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain: .....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Summarize the incidence of bone metastases among patients with various solid tumors and describe the effect of skeletal-related events (SREs) on quality of life and overall survival. . . . . 4 3 2 1 N/M N/A
- Describe the bone remodeling process and the different mechanisms of action by which systemic bone-directed therapies affect the microenvironment, reduce SREs and promote bone health. . . . . 4 3 2 1 N/M N/A
- Develop an evidence-based treatment algorithm for the management of documented skeletal metastases that incorporates bone-targeted systemic therapies. . . . . 4 3 2 1 N/M N/A
- Recognize the prevalent bone complications of advanced multiple myeloma, and educate patients about the risks and benefits of treatment with intravenous bisphosphonates and other bone-directed agents. . . . . 4 3 2 1 N/M N/A
- Inform patients with breast and prostate cancer about the risk of treatment-induced bone loss, and recommend strategies to minimize this side effect. . . . . 4 3 2 1 N/M N/A
- Compare and contrast the adverse events induced by bone-directed therapies, their effect on the selection of therapy and the management of side effects. . . . . 4 3 2 1 N/M N/A
- Discuss with patients the potential benefits of proper diet, exercise, vitamin D and calcium in reducing the risk of cancer recurrence . . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients who are at risk for cancer-related bone complications about participation in ongoing clinical trials . . . . . 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

- ☐ Yes, I am willing to participate in a follow-up survey.
- ☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty and editor for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Kenneth C Anderson, MD	4 3 2 1	4 3 2 1
Adam M Brufsky, MD, PhD	4 3 2 1	4 3 2 1
Leonard G Gomella, MD	4 3 2 1	4 3 2 1
Allan Lipton, MD	4 3 2 1	4 3 2 1
Roger N Pearse, MD, PhD	4 3 2 1	4 3 2 1
Matthew R Smith, MD, PhD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

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Professional Designation:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ RN ☐ PA ☐ Other .....

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This program is supported by educational grants from Amgen Inc,
Millennium Pharmaceuticals Inc and Novartis Pharmaceuticals Corporation.

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Last review date: March 2010
Release date: March 2010
Expiration date: March 2011
Estimated time to complete: 3 hours