Multitargeted Tyrosine Kinase Inhibition Produces Discordant Changes Between ^{99m}Tc-MDP Bone Scans and Other Disease Biomarkers: Analysis of a Phase II Study of Sunitinib for Metastatic Castration-Resistant Prostate Cancer

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One of the central unanswered questions in prostate cancer research is the significance of tyrosine kinase inhibitor (TKI)–induced improvements in ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) bone scans. Multitargeted tyrosine kinase inhibition has recently shown promise in the management of castration-resistant prostate cancer. In some cases, TKI inhibition has produced unprecedented improvements in bone metastases as detected by ^{99m}Tc-MDP bone scans. The significance of these improvements is not known. In order to gain insight about the effects of TKIs on bone scans in prostate cancer, we systematically evaluated images from a phase II study of sunitinib, a multitargeted TKI. **Methods:** We analyzed images and data from a previously reported open-label phase II study that enrolled 34 men with advanced castration-resistant prostate cancer. Participants received sunitinib in 6-wk cycles (50 mg daily; 4 wk on, 2 wk off). We examined baseline and 12-wk bone scan images. Partial response was defined as an improvement of at least 50% in previous metastatic lesions subjectively or a change from prior diffuse skeletal metastases (superscan) to recognizable individual metastatic lesions. Our primary objective was to define the incidence of at least partial bone scan response. We also examined concomitant changes in CT and prostate-specific antigen (PSA) evidence of disease. **Results:** Analysis at 12 wk revealed 1 partial response by the response evaluation criteria in solid tumors (RECIST) and 2 confirmed PSA responses. There were 25 subjects who underwent bone scans at both time points (baseline and week 12) and who had bone metastases detectable at baseline. Within that group of 25, we found 5 bone scan partial responses and 1 complete response. None of those 6 subjects exhibited a PSA response (≥50% decline from baseline) or RECIST response. **Conclusion:** We found a relatively high rate of ^{99m}Tc-MDP bone scan response to sunitinib among men with metastatic prostate cancer. Further, we found that none of the subjects exhibiting bone scan responses experienced concordant improvements in PSA or CT evidence of disease by accepted criteria. This discordance argues that osteoblastic assessment provides an incomplete assessment of treatment-induced changes. Rational development of multitargeted TKIs for prostate cancer requires improved understanding of treatment-induced bone scan changes. Optimal imaging strategies may include evaluation of perfusion or direct tumor activity.

Key Words: bone scan; prostate cancer; tyrosine kinase inhibitor; sunitinib; bone metastases

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Skeletal scintigraphy has long been a cornerstone of disease assessment in prostate cancer. ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) bone scans are widely used and provide an indirect measure of tumor activity because they detect tracer deposition by osteoblasts along bone mineralization fronts (*1,2*). Prostate cancer bone metastases can be imaged this way because they are associated with elevated activity by both osteoblasts and osteoclasts (*3,4*). Further, ^{99m}Tc-MDP bone scans are an established component of disease assessment in prostate cancer clinical trials (*5*).

Multitargeted tyrosine kinase inhibition with orally administered small-molecule tyrosine kinase inhibitors (TKIs) is an established strategy for the management of numerous malignancies including chronic myeloid leukemia, breast cancer, renal cell carcinoma, non–small cell lung cancer, melanoma, and others. It has only recently emerged as a potential treatment strategy for advanced prostate cancer. In particular, TKI therapy has preliminarily been shown to produce unprecedented improvements in the ^{99m}Tc-MDP bone scans of men with castration-resistant prostate cancer (CRPC) metastatic to bone (*6*). The clinical significance and mechanism responsible for these bone scan improvements have not yet been well defined.

There are several possible explanations for the dramatic bone scan changes. Treatment-induced bone scan changes may be caused by the death of tumor cells, changes in tumor

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perfusion, changes in peritumoral osteoblast activity, or other factors. Although no TKI has been approved for the management of prostate cancer, several agents have been examined in clinical trials. Formal evaluation of bone scan responses to each of these TKIs may provide additional insights.

Sunitinib is an orally administered TKI that inhibits several kinases including vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor-β, and KIT. Sunitinib treatment of metastatic CRPC was examined in a randomized placebo-controlled phase III study. In that study, sunitinib improved overall response rate and progression-free survival but failed to demonstrate improvement in its primary endpoint, overall survival (*7*). Therefore, it is no longer in development for the treatment of prostate cancer. However, we previously observed instances of marked bone scan improvements among phase II study participants with metastatic CRPC treated with sunitinib at our institution.

To gain insight about the effects of multitargeted TKI therapy on bone scans in advanced prostate cancer, we analyzed data from that open-label phase II study of sunitinib for metastatic CRPC. Specifically, we examined changes in bone scan findings from baseline to the first repeated bone scan during treatment (12 wk). Our goals were to assess the frequency of improvement in bone scan assessment of disease and to demonstrate the presence or absence of concordance between bone scans and other accepted measures of disease activity (PSA and CT scans).

MATERIALS AND METHODS

We analyzed data from a previously described (*8*) open-label phase II study of sunitinib treatment of men with advanced CRPC. That study enrolled 34 eligible men with histologically confirmed adenocarcinoma of the prostate and evidence of progression despite castrate testosterone (serum testosterone $<$ 50 ng/dL). Progression was defined as a rising PSA in 2 consecutive measurements at least 1 wk apart; PSA was required to be at least 2 ng/mL above the nadir value. Among those enrolled, 17 had received prior docetaxel chemotherapy. Concurrent bisphosphonate treatment was allowed. All participants provided written informed consent, and the study was approved by the Dana Farber/Harvard Cancer Center Institutional Review Board.

The primary endpoint of the trial was PSA response rate, defined as a confirmed PSA decline of at least 50% from baseline. A secondary endpoint was an objective response rate according to the response evaluation criteria in solid tumors (RECIST). All men were treated with sunitinib in 6-wk cycles consisting of 50 mg daily for 4 wk, followed by 2 wk off. Dose reductions to 37.5 or 25 mg were allowed. Treatment continued until intolerance to therapy or disease progression, defined as the presence of a new metastasis or a PSA increase of 25% or more above the nadir.

Serum PSA was measured on day 1 of each 6-wk cycle. Radiographic assessments were done at baseline, every 12 wk, and at study end or subject withdrawal. Bone scans were performed per institutional standard clinical practice using 740 MBq (20 mCi) of ^{99m}Tc-MDP, with anterior and posterior planar whole-body imaging performed at least 2.5 h after tracer injection; additional planar spot views were obtained as needed for clarification of ambiguous findings. Assessments took place during the scheduled 2-wk-off-treatment interval at the conclusion of the second cycle of study-directed therapy. Responses were assessed using RECIST. Landmark analysis was performed at week 12 to conform to initial reassessment guidelines as recommended by Prostate Cancer Clinical Trials Working Group II (*5*).

For the present analysis, we examined baseline and 12-wk bone scan images among study participants who had bone metastases at baseline and for whom those 2 imaging studies were completed. Two radiologists who were specialized in nuclear medicine, and 1 nuclear medicine physician, assessed each set of images in consensus. Bone scan changes were assessed according to the categories detailed in Table 1. Our primary objective was to define the incidence of at least a partial bone scan response during the interval between baseline and the 12-wk bone scan. We also examined concomitant changes in CT and PSA evidence of disease.

RESULTS

Thirty-four eligible participants were enrolled in the study. A total of 17 had received docetaxel chemotherapy (median number of cycles, 8; range, 3–14 cycles). At baseline, 27 had detectable bone metastases. Bisphosphonates had been used

TABLE 1
Bone Interpretation Criteria, Modified from Recommendations of Prostate Cancer Clinical Trials Working Group 2 (*5*)

Score	Criteria
Progressive disease	Appearance of ≥2 new lesions unequivocally diagnosed as bone metastasis, Confirmation of ambiguous results by other imaging modalities (CT or MRI), or A confirmatory scan performed 6 or more weeks later shows a minimum of 2 or more additional new lesions
Stable disease	Failure to attain partial response/complete response or progressive disease
Partial response	Subjectively ≥50% overall improvement in total abnormal tracer uptake (intensity × volume) of previous metastatic bone lesions, or Prior extensively diffuse skeletal metastases (superscan) turns into recognizable individual metastatic lesions
Complete response	No lesion to indicate metastatic disease
Nonevaluable	Extensively diffuse skeletal metastases (superscan) that does not allow meaningful interpretation of the differences between studies, or Technical or physiologic aspects resulting in nonevaluable images

in 17 subjects. The median duration of sunitinib treatment was 2 cycles (range, 1–15 cycles). The most common reason for discontinuation of therapy was PSA progression.

As previously reported (*8*), analysis at 12 wk revealed 1 partial response by RECIST. An additional 18 subjects had stable disease by RECIST at that time point. One confirmed PSA response was observed in each of the 2 groups (i.e., no prior docetaxel [group A] and docetaxel-resistant [group B]). An additional 8 men in group A and 7 men in group B had stable PSA at week 12.

For the present analysis, 28 of the 34 enrolled subjects were assessed by bone scanning at baseline and the 12-wk follow-up (i.e., 6 subjects discontinued trial participation before the start of therapy or during the first 12 wk of therapy). None of those subjects had started bisphosphonate therapy between the baseline and follow-up bone scans. Within that group of 28, 3 did not have bone metastases at baseline and were therefore not evaluable for bone scan response. Among those 25 subjects who had bone scans at both time points and bone metastases detectable at baseline, we found 6 cases of at least partial bone scan response (partial response plus complete response; Table 2). Bone scan images and clinical data relevant to 3 of these 6 cases are summarized in Figures 1–3 (the other 3 cases are described in Supplemental Figs. 1–3; supplemental materials are available online only at http://jnm.snmjournals.org). None of those 6 subjects exhibited a response by accepted PSA criteria (≥50% decline from baseline) or RECIST.

To qualitatively assess concordance between bone scan and PSA assessment of response, we plotted the interval percentage change in PSA for subjects grouped by bone scan response category (Fig. 4). Qualitatively, bone scan response category correlated poorly with percentage change in PSA.

DISCUSSION

We analyzed baseline and week-12 bone scan images of men in a phase II study of sunitinib for metastatic CRPC. Among the 25 subjects who could have exhibited a response, we found 6 cases of responses by bone scan. None of those 6 subjects exhibited a response at that time point by PSA criteria or by RECIST. The observed incidence of bone scan improvement is surprising given that CT and PSA responses were uncommon. These findings may be relevant to the assessment of therapeutic response to other multitargeted TKIs.

TABLE 2
PSA and Radiologic Response of All Patients as Grouped by Bone Scan Response

Patient no.	PSA baseline (ng/mL)	PSA follow-up evaluated at 12 wk* (ng/mL)	PSA change (%)	Bone scan*	CT scan notes†
1	25	16.3	−35	CR	Stable disease (retroperitoneal nodes)
2	110.6	115	4	PR	
3	460.8	1,620	252	PR	PD (new liver metastasis)
4	110.7	132.8	20	PR	
5	598.9	592.4	−1	PR	Stable disease (pelvic mass and nodes)
6	311.1	966	211	PR	PD (new liver metastasis)
7	41.9	117.6	180	Stable disease	Stable disease (pulmonary metastasis)
8	33.5	90.9	171	Stable disease	PD (paraaortic nodes)
9	212.3	555.2	162	Stable disease	
10	21.2	32.9	55	Stable disease	
11	7.6	11	45	Stable disease	
12	21	23	10	Stable disease	
13	26	17.5	−33	Stable disease	Stable disease (pelvic nodes)
14	6.3	2.9	−54	Stable disease	
15	17.6	6.3	−64	Stable disease	PR (retroperitoneal nodes)
16	29.8	135	353	PD	Stable disease (retroperitoneal nodes)
17	40.8	162.8	299	PD	
18	388.1	1,412	264	PD	Stable disease (retroperitoneal nodes)
19	47	66.9	42	PD	Stable disease (retroperitoneal nodes)
20	135	162	20	PD	Stable disease (paraaortic nodes)
21	34.1	27.5	−20	PD	
22	14.6	8.8	−40	PD	
23	157	557.9	255	NE	Stable disease (retroperitoneal nodes)
24	28.4	77.1	172	NE	Stable disease (pelvic nodes)
25	283.9	251.4	−11	NE	

*Evaluated at baseline and after 12 wk on study.

†CT scan was evaluated using RECIST; only soft-tissue lesions were considered. In subjects without definite evidence of soft-tissue disease, "CT scan notes" is left blank.

CR = complete response; PR = partial response; PD = progressive disease; NE = not evaluable.

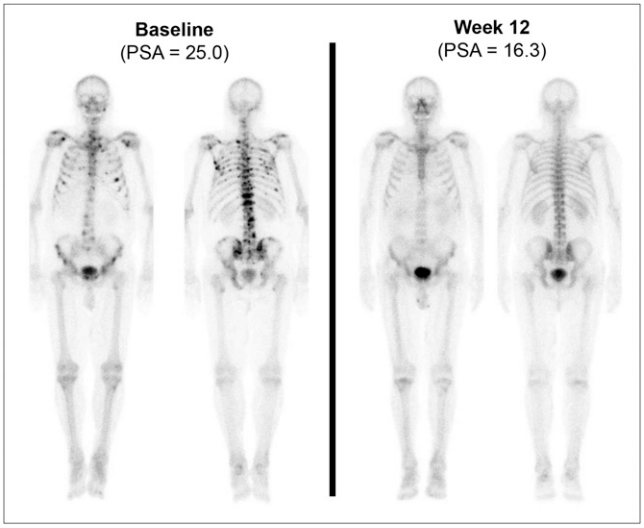

FIGURE 1. Complete bone scan response, with no lesion to indicate metastatic disease on follow-up scan. CT revealed stability of retroperitoneal nodal metastasis. PSA declined by 35%.

The reported assessments may underestimate sunitinib-induced bone scan effects. Follow-up imaging and PSA assessments took place during the 2-wk scheduled off-treatment interval at the conclusion of the second cycle of therapy (6-wk cycle: 4 wk on, 2 wk off). This treatment schedule may have led to prescan regression of improvements that occurred during the 4-wk on treatment. As most participants were removed from the study because of PSA progression that rose to 25% above its nadir, the duration of bone scan improvements is not known.

The assessment of therapeutic response in clinical trials is a topic of much discussion. Metastatic CRPC commonly features bone metastases (80%–90% in recent phase III trials (*9,10*)), often as the only site of metastasis. RECIST does not adequately address this. The Prostate Cancer Clinical Trials Working Group 2 recommends independent reporting of PSA, imaging, and clinical measures. It recommends assessment of bone scans only for the presence or absence of 2 or more new lesions, compared with a prior scan (*5*). Prostate cancer treatment trials have not historically been designed to systematically assess for bone scan responses that are discordant from other measurements of activity.

The relatively high incidence of bone scan improvement observed within this analysis is important in light of the promising early-phase activity demonstrated by cabozantinib (XL184), a TKI with targets that overlap those of sunitinib. Available data from the early clinical experience with cabozantinib reveal a high incidence of bone scan improvements but low rates of response by PSA criteria or RECIST (*6*). Despite a growing number of therapies that improve survival among men with CRPC (docetaxel (*11,12*), sipuleucel-T (*13*), cabazitaxel (*10*), abiraterone (*9*), ^{223}Ra (*14*), and MDV3100 (*15*)), the high observed incidence of marked bone scan improvement with cabozantinib treatment is without precedent. Prominent in vitro targets of cabozantinib are VEGFR2 (in vitro inhibitory concentration of 50%, 0.035 nM) and MET (in vitro inhibitory concentration of 50%, 1.8 nM). There is overlap between the targets of sunitinib and cabozantinib, most notably VEGFR2 (in vitro inhibitory concentration of 50%, 4 nM for sunitinib) but also KIT and RET. The targets responsible for the observed bone scan improvements are not known.

Sunitinib did not improve overall survival for men with metastatic CRPC when it was later studied in a placebo-controlled phase III study (*7*). Clinical trial experience with targeted therapy for advanced prostate cancer has included targets such as endothelial growth factor receptor (*16–19*), SRC (*20–22*), vascular endothelial growth factor (*23–26*),

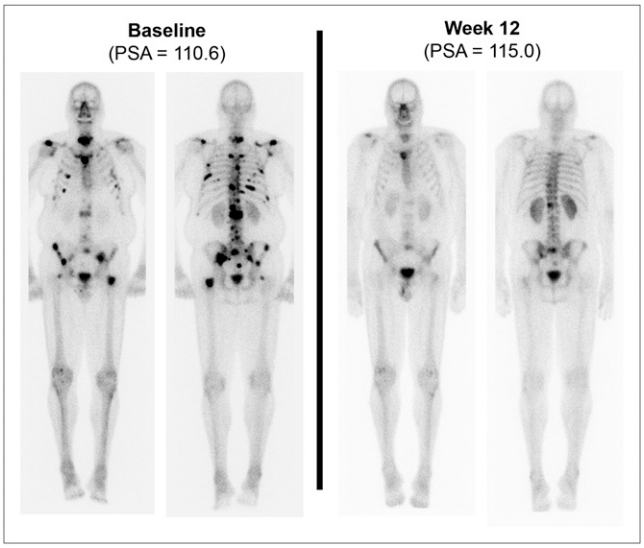

FIGURE 2. Interval resolution or markedly decreased intensity of multiple bone metastases involving spine, sternum, multiple bilateral ribs, scapulae, pelvic bones, and both femora, categorized as partial response. PSA increased by 4%.

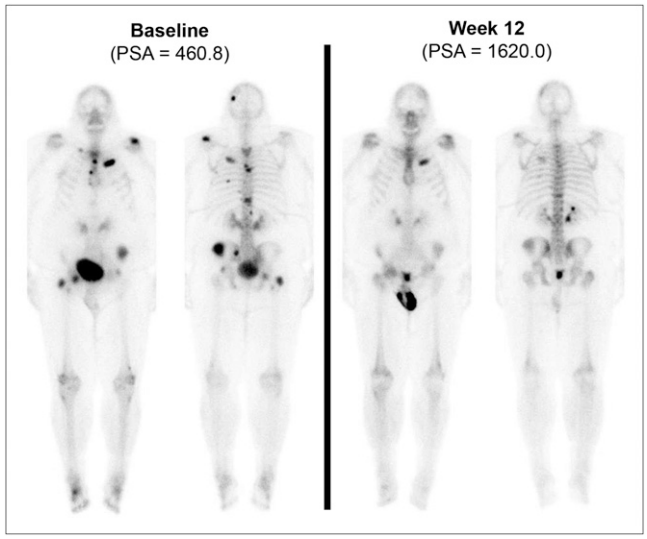

FIGURE 3. Interval resolution or marked improvement of all previously seen bone lesions, categorized as partial response. New liver metastasis was found on CT. PSA increased by 252%.

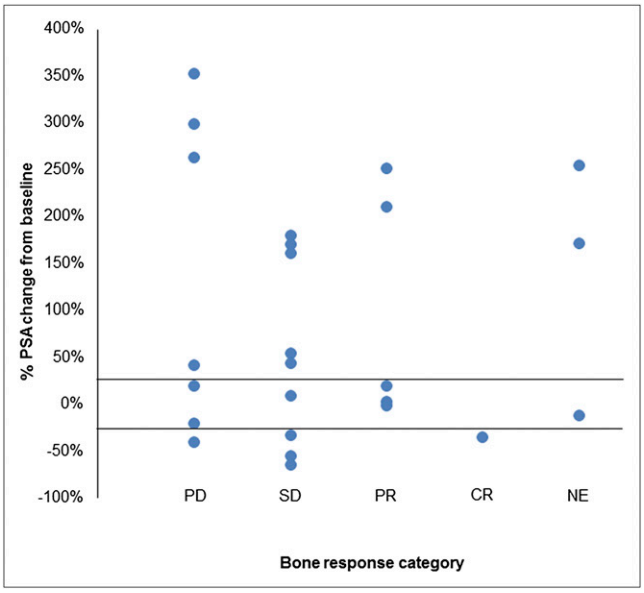

FIGURE 4. PSA changes among subjects grouped by bone scan response. Subjects grouped by bone scan response category (n = 25) display variable PSA changes during same study treatment period. CR = complete response; NE = not evaluable; PD = partial disease; PR = partial response; SD = stable disease.

insulinlike growth factor 1 receptor (*27*), and human epidermal growth factor receptor 2 (*28*). To date, no TKI or monoclonal antibody has demonstrated a survival benefit.

The present analysis features several limitations. First, it is a retrospective review of an endpoint (12-wk response by bone scan) that was not specified before the clinical trial and has not been validated in larger studies. Interpretation must therefore be done with caution. Second, the retrospective analysis of an unconventional endpoint in this phase II study is subject to chance observations in a relatively small cohort. Examination of the data from the experimental arm of the completed phase III study of sunitinib in this disease state would be a logical next step. Third, further work is needed to best assess radiographic disease burden and response to treatment in prostate cancer metastatic to bone.

Discordance between bone scan and other disease assessments indicates that osteoblast-based imaging provides an incomplete assessment of treatment-induced changes. Multitargeted TKIs may reduce ^{99m}Tc-MDP uptake through tumoristatic or tumoricidal effects, through direct osteoblast inhibition, or through their effects on lesion perfusion. Rational development of TKIs for the management of advanced prostate cancer requires an improved understanding of the mechanistic and clinical significance of treatment-induced bone scan improvements. Key potential future directions include direct tumor imaging with novel PET or SPECT agents and serial imaging of perfusion with either dynamic contrast-enhanced MRI or kinetic modeling of novel tracer uptake.

CONCLUSION

Systematic analysis of images from this phase II trial revealed a relatively high rate of bone scan response without concordant improvements in PSA or CT evidence of disease by accepted criteria. Rational development of multitargeted TKIs for the management of advanced prostate cancer will require an improved understanding of the mechanistic and clinical significance of TKI-induced bone scan improvements.

DISCLOSURE STATEMENT

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REFERENCES

1. Einhorn TA, Vigorita VJ, Aaron A. Localization of technetium-99m methylene diphosphonate in bone using microautoradiography. *J Orthop Res.* 1986;4:180–187.
2. Tilden RL, Jackson J Jr, Enneking WF, DeLand FH, McVey JT. 99m Tc-polyphosphate: histological localization in human femurs by autoradiography. *J Nucl Med.* 1973;14:576–578.
3. Cook RJ, Coleman R, Brown J, et al. Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. *Clin Cancer Res.* 2006;12:3361–3367.
4. Demers LM, Costa L, Lipton A. Biochemical markers and skeletal metastases. *Cancer.* 2000;88:2919–2926.
5. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol.* 2008;26:1148–1159.
6. Hussain M, Smith MR, Sweeney C, et al. Cabozantinib (XL184) in metastatic castration-resistant prostate cancer (mCRPC): results from a phase II randomized discontinuation trial [abstract]. *J Clin Oncol.* 2011;29(suppl). Available at: http://meeting.ascopubs.org/.
7. Michaelson MD, Oudard S, Ou Y, et al. Randomized, placebo-controlled, phase III trial of sunitinib in combination with prednisone (SU+P) versus prednisone (P) alone in men with progressive castration-resistant prostate cancer (mCRPC) [abstract]. *J Clin Oncol.* 2011;29(suppl). Available at: http://meeting.ascopubs.org/.
8. Dror Michaelson M, Regan MM, Oh WK, et al. Phase II study of sunitinib in men with advanced prostate cancer. *Ann Oncol.* 2009;20:913–920.
9. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med.* 2011;364:1995–2005.
10. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet.* 2010;376:1147–1154.
11. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med.* 2004;351:1513–1520.
12. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med.* 2004;351:1502–1512.
13. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med.* 2010;363:411–422.
14. Parker C, Heinrich D, O'Sullivan JM, et al. Overall survival benefit and safety profile of radium-223 chloride, a first-in-class alpha-pharmaceutical: Results from a phase III randomized trial (ALSYMPCA) in patients with castration-resistant prostate cancer (CRPC) with bone metastases [abstract]. *J Clin Oncol.* 2012;30. Available at: http://meeting.ascopubs.org/.

15. Scher H, Fizazi K, Saad F, et al. Effect of MDV3100, an androgen receptor signaling inhibitor (ARSI), on overall survival in patients with prostate cancer postdocetaxel: Results from the phase III AFFIRM study [abstract]. *J Clin Oncol.* 2012;30. Available at: http://meeting.ascopubs.org/.
16. Pezaro C, Rosenthal MA, Gurney H, et al. An open-label, single-arm phase two trial of gefitinib in patients with advanced or metastatic castration-resistant prostate cancer. *Am J Clin Oncol.* 2009;32:338–341.
17. Boccardo F, Rubagotti A, Conti G, et al. Prednisone plus gefitinib versus prednisone plus placebo in the treatment of hormone-refractory prostate cancer: a randomized phase II trial. *Oncology.* 2008;74:223–228.
18. Small EJ, Fontana J, Tannir N, et al. A phase II trial of gefitinib in patients with non-metastatic hormone-refractory prostate cancer. *BJU Int.* 2007;100:765–769.
19. Gravis G, Bladou F, Salem N, et al. Results from a monocentric phase II trial of erlotinib in patients with metastatic prostate cancer. *Ann Oncol.* 2008;19:1624–1628.
20. Yu EY, Massard C, Gross ME, et al. Once-daily dasatinib: expansion of phase II study evaluating safety and efficacy of dasatinib in patients with metastatic castration-resistant prostate cancer. *Urology.* 2011;77:1166–1171.
21. Yu EY, Wilding G, Posadas E, et al. Phase II study of dasatinib in patients with metastatic castration-resistant prostate cancer. *Clin Cancer Res.* 2009;15:7421–7428.
22. Lara PN Jr, Longmate J, Evans CP, et al. A phase II trial of the Src-kinase inhibitor AZD0530 in patients with advanced castration-resistant prostate cancer: a California Cancer Consortium study. *Anticancer Drugs.* 2009;20:179–184.
23. Stadler WM, Cao D, Vogelzang NJ, et al. A randomized phase II trial of the antiangiogenic agent SU5416 in hormone-refractory prostate cancer. *Clin Cancer Res.* 2004;10:3365–3370.
24. Ryan CJ, Stadler WM, Roth B, et al. Phase I dose escalation and pharmacokinetic study of AZD2171, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinase, in patients with hormone refractory prostate cancer (HRPC). *Invest New Drugs.* 2007;25:445–451.
25. Bajaj GK, Zhang Z, Garrett-Mayer E, et al. Phase II study of imatinib mesylate in patients with prostate cancer with evidence of biochemical relapse after definitive radical retropubic prostatectomy or radiotherapy. *Urology.* 2007;69:526–531.
26. Kelly WK, Halabi S, Carducci M, et al. Randomized, double-blind, placebo-controlled phase iii trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. *J Clin Oncol.* 2012;30:1534–1540.
27. Molife LR, Fong PC, Paccagnella L, et al. The insulin-like growth factor-I receptor inhibitor figitumumab (CP-751,871) in combination with docetaxel in patients with advanced solid tumours: results of a phase Ib dose-escalation, open-label study. *Br J Cancer.* 2010;103:332–339.
28. Agus DB, Sweeney CJ, Morris MJ, et al. Efficacy and safety of single-agent pertuzumab (rhuMAb 2C4), a human epidermal growth factor receptor dimerization inhibitor, in castration-resistant prostate cancer after progression from taxane-based therapy. *J Clin Oncol.* 2007;25:675–681.