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Multitargeted tyrosine kinase inhibition produces discordant changes between 99mTc-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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Abstract

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

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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.

Keywords

prostate cancer; tyrosine kinase inhibitor; sunitinib; cabozantinib; bone scan; bone metastases

BACKGROUND

Skeletal scintigraphy has long been a cornerstone of disease assessment in prostate cancer. Technetium-99m methylene diphosphonate (^{99m}Tc MDP) bone scans are widely used and provide an indirect measure of tumor activity as they detect tracer deposition by osteoblasts along bone mineralization fronts.[1, 2] Prostate cancer bone metastases can be imaged this way as 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]

Multi-targeted tyrosine kinase inhibition is an emerging treatment strategy for advanced prostate cancer. In particular, tyrosine kinase inhibitor (TKI) therapy has produced exciting 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.

Several possible explanations exist. Treatment induced bone scan changes may be explained by the death of tumor cells, changes in tumor perfusion, changes in peri-tumoral 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 TKI therapy may provide new insights.

Sunitinib is an orally-administered TKI that inhibits several kinases including VEGFR2, PDGFR-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] Despite this, we previously observed instances of marked bone scan improvements among phase II study participants with metastatic CRPC treated with sunitinib at our institution.

In order to gain insight about the effects of multi-targeted 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 change in bone scan findings from baseline to the first repeat bone scan during treatment (12 weeks). 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 scan and PSA responses.

MATERIALS & 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 a total of 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 two consecutive measurements at least 1 week apart; PSA was required to be ≥ 2 ng/mL above the nadir value. Among those enrolled, 17 had received prior docetaxel chemotherapy. Concurrent bisphosphonate treatment was allowed. All participants gave written informed consent with Dana Farber/Harvard Cancer Center Institutional Review Board approval.

The primary endpoint of the trial was PSA response rate, defined as confirmed ≥ 50% decline in PSA from baseline. Secondary endpoints included objective response rate, safety and tolerability, and changes in serum biomarkers. Biomarkers included bone-specific alkaline phosphatase (BSAP), soluble vascular endothelial growth factor receptor-2 (sVEGFR2), leptin, placental growth factor (PLGF), N-telopeptide (NTx), and platelet derived growth factor aa (PDGFaa).

All men were treated with sunitinib in 6-week cycles consisting of 50 mg daily for 4 weeks followed by 2 weeks off. Dose reductions were allowed to 37.5 mg or 25 mg. Treatment continued until intolerance to therapy or disease progression, defined as presence of new metastasis or PSA increase of ≥ 25% above nadir.

Serum PSA was measured on day 1 of each 6-week cycle. Radiographic assessments were done at baseline, every 12 weeks, and at study end or subject withdrawal. These assessments took place during the scheduled 2-week off-treatment interval at the conclusion of the second cycle of study-directed therapy. Responses were assessed using RECIST. Landmark analysis was carried out 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 week bone scan images among study participants for whom those two imaging studies were completed. Two radiologists specialized in nuclear medicine and one nuclear medicine physician assessed each set of images in consensus. Bone scan changes were assessed according to the categories detailed in Table 1. Our objective was to define the incidence of at least a partial bone scan response during the interval between baseline and 12 week bone scan. We also examined concomitant changes in serum PSA.

RESULTS

A total of 34 eligible participants were enrolled in the study. Baseline characteristics are summarized in Table 2. The median duration of treatment was two cycles (range: 1 – 15 cycles). The most common reason for discontinuation of therapy was PSA progression.

As previously reported, response analysis at 12 weeks revealed one partial response by RECIST criteria. An additional 18 subjects had stable disease by RECIST at that time point.

One confirmed PSA response was observed in each group. An additional eight men in group A and seven men in group B had stable PSA at week 12.

For the present analysis, we included those 28 patients who were assessed by both PSA and bone scan at baseline and 12 weeks follow-up. We found 6 cases of at least partial bone scan response (partial response + complete response; see Table 3). Bone scan images and clinical data relevant to these cases are summarized in Figure 1.

In order to qualitatively assess concordance between bone scan and PSA assessment of response, we plotted interval percent change in PSA for subjects grouped by bone scan response category (see Figure 2). Bone scan response category correlated poorly with percent change in PSA.

DISCUSSION

We analyzed baseline and week 12 bone scan images of men who participated in a phase II study of sunitinib for metastatic CRPC. We found 6 of the 28 evaluable subjects exhibited partial or complete responses by bone scan. Further, these assessments may underestimate treatment-induced bone scan effects as they took place during the 2-week scheduled off-treatment interval at the conclusion of the second cycle of therapy (6 week cycle: 4 weeks on treatment, 2 weeks off treatment). The observed incidence of bone scan improvement is surprising given that the primary analysis of the study found only two PSA responses and one partial response by RECIST-criteria. These findings may be relevant to the assessment of prostate cancer therapeutic response to other multi-targeted TKIs.

This phase II study was intended to evaluate the anti-tumor activity of sunitinib for metastatic CRPC. Bone scan response in the absence of PSA or RECIST response was not a pre-specified endpoint. The primary endpoint of this phase II study was a confirmed 50% decline in PSA.

Objective response rate by RECIST criteria was a secondary endpoint. Neither of these endpoints is designed to systematically assess for or describe bone scan responses that are discordant from other measurements of drug activity. Further, the duration of bone scan improvements was not assessed as the majority of participants were taken off of study due to PSA progression when PSA rose to 25% above its nadir value.

Assessment of therapeutic response in clinical trials is a topic of much discussion. RECIST criteria are widely used but are particularly limited in the assessment of men with prostate cancer. Metastatic CRPC commonly features bone metastases (80 - 90% in two recent phase III trials[10, 11]), often as the only site of metastasis. RECIST criteria do not adequately address this component of disease. The Prostate Cancer Clinical Trials Working Group 2 (PCWG2) has been a central guide to clinical trial design in advanced prostate cancer. PCWG2 recommends independent reporting of PSA, imaging, and clinical measures rather than grouped categorizations such as complete or partial response. All the same, it recommends assessment of bone scans only for the presence or absence of progression criteria: 2 or more new lesions compared with a prior scan.[5]

Sunitinib did not improve overall survival for men with metastatic CRPC when it was later studied in a randomized, double-blind, placebo-controlled phase III study.[7] It produced significant but modest improvements in secondary endpoints PFS (5.6 vs. 3.7 months, p=0.008) and ORR (5.5% vs. 1.9%, p=0.050). It is therefore surprising that a relatively high incidence of substantial bone scan improvement was observed within this retrospective analysis. In addition, reversible improvements in bone scans may be underestimated in this study population due to the 2-week off-treatment interval immediately prior to restaging

scans. These findings should prompt further discussion and study of imaging-related endpoints in prostate cancer clinical trials. This is particularly important in light of the promising early-phase activity demonstrated by cabozantinib (XL184), a TKI with targets that overlap those of sunitinib.

Cabozantinib has demonstrated exciting activity as assessed by bone scan in the treatment of CRPC metastatic to bone. Available data from the early clinical experience with cabozantinib for metastatic prostate cancer reveal high incidence of bone scan improvements but low rates of PSA or RECIST criteria responses.[6] Despite a growing number of therapies that improve survival among men with CRPC (docetaxel[12, 13], sipuleucel-T[14], cabazitaxel[11], abiraterone[10], radium-223, and MDV3100), the high observed incidence of marked bone scan improvement with cabozantinib treatment is without precedent in published literature. Prominent in vitro targets of the multi-targeted cabozantinib are VEGFR2 and MET (see Table 4). There is overlap between the therapeutic targets of sunitinib and of cabozantinib, most notably VEGFR2 but also to a lesser extent KIT and RET. The target(s) most responsible for observed bone scan improvements are not known.

Clinical trial experience with targeted therapy for advanced prostate cancer is not limited to sunitinib and cabozantinib. Published literature on TKIs for the treatment of CRPC in prostate cancer specific studies also includes gefitinib (EGFR)[18-20], erlotinib (EGFR)[21, 22], dasatinib (SRC)[23, 24], AZD0530 (SRC)[25], SU5416 (VEGFR2)[26], AZD2171 (VEGF1&2)[27], and imatinib[28]. Monoclonal antibodies have also been studied with figitumumab (IGF-1R)[29], pertuzumab (HER2)[30] and notably with a negative phase III trial of bevacizumab (VEGF)[31]. To date, no TKI or monoclonal antibody has demonstrated a survival benefit in for metastatic CRPC.

The present analysis features several notable limitations. First, it is a retrospective review of an endpoint (12-week response by bone scan) that was not specified prior to the clinical trial and has not been validated in larger studies. Interpretation of such an analysis 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 unblinded experimental arm of the completed phase III study of sunitinib in this disease state would be a logical next step. Third, it is not prudent to conclusively ascribe mechanistic significance to these observations. It is provocative to observe a relatively high incidence of bone scan improvements with a drug that produces less than 10% objective response rate by currently-accepted criteria. Further work is needed to better define radiographic disease burden and response to treatment in prostate cancer metastatic to bone.

CONCLUSIONS

We found 6 of the 28 subjects with advanced prostate cancer exhibited partial or complete responses to sunitinib as assessed by ^{99m}Tc MDP bone scan. Rational development of multi-targeted 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. This can likely only be accomplished with dedicated basic, translational, and clinical study.

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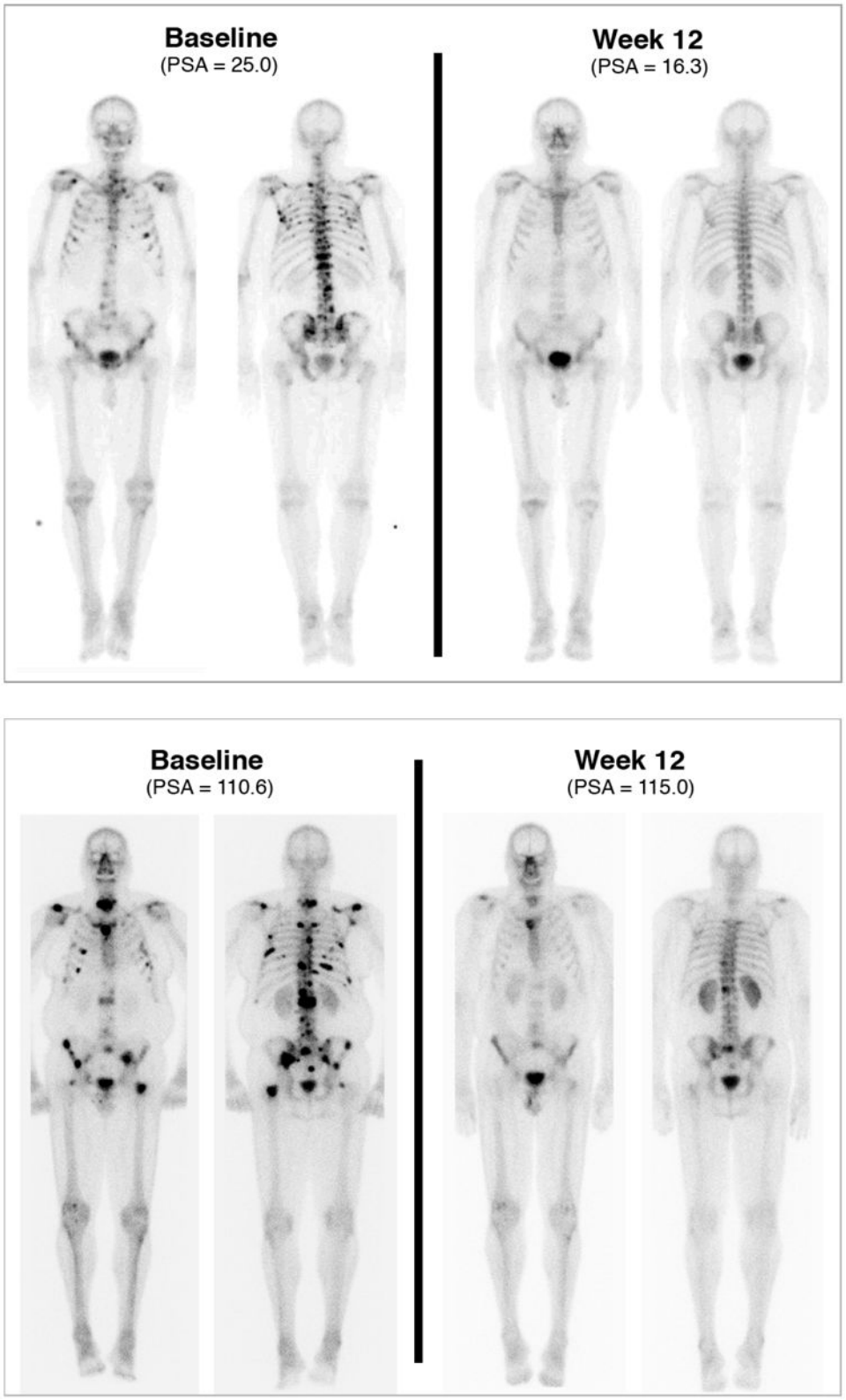

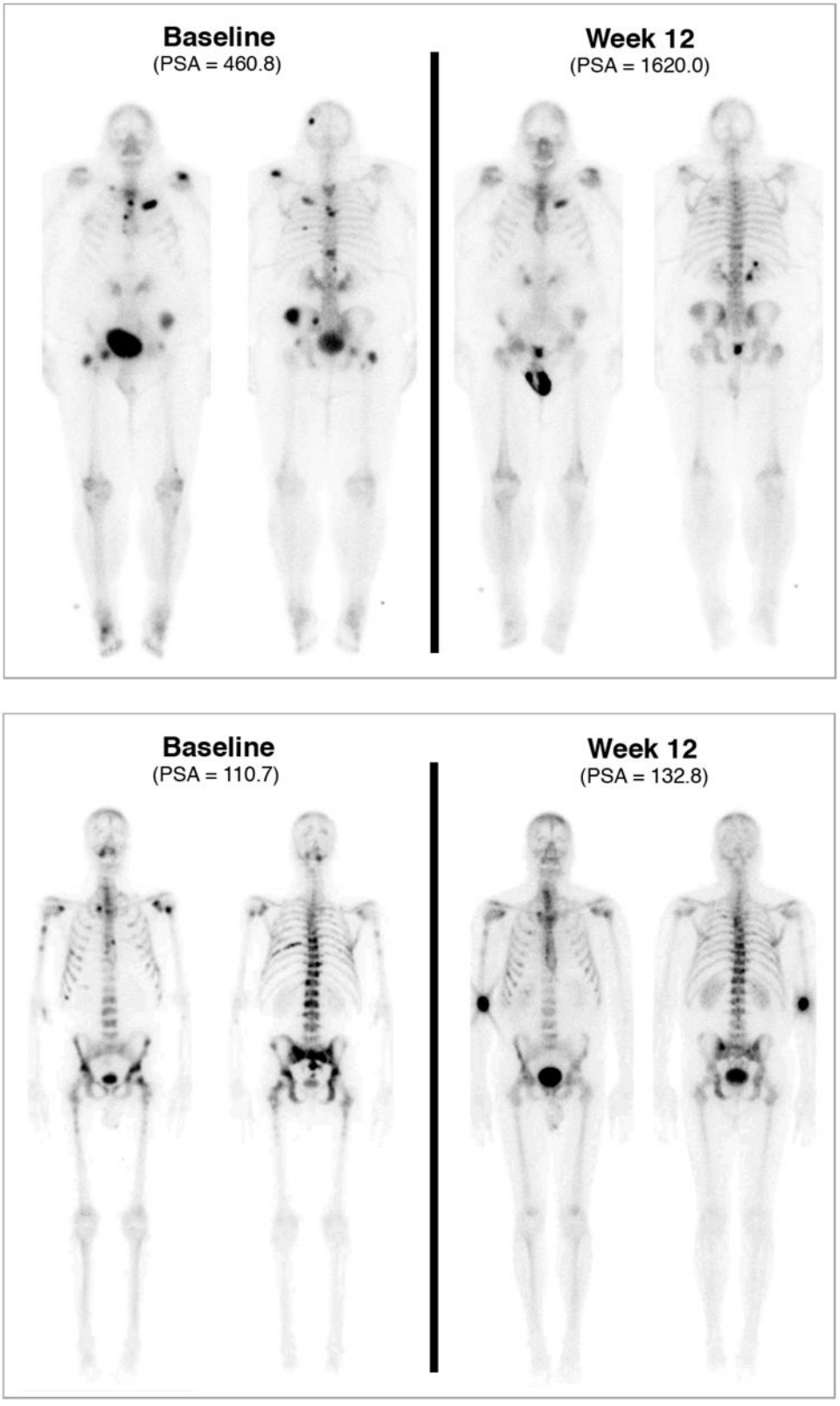

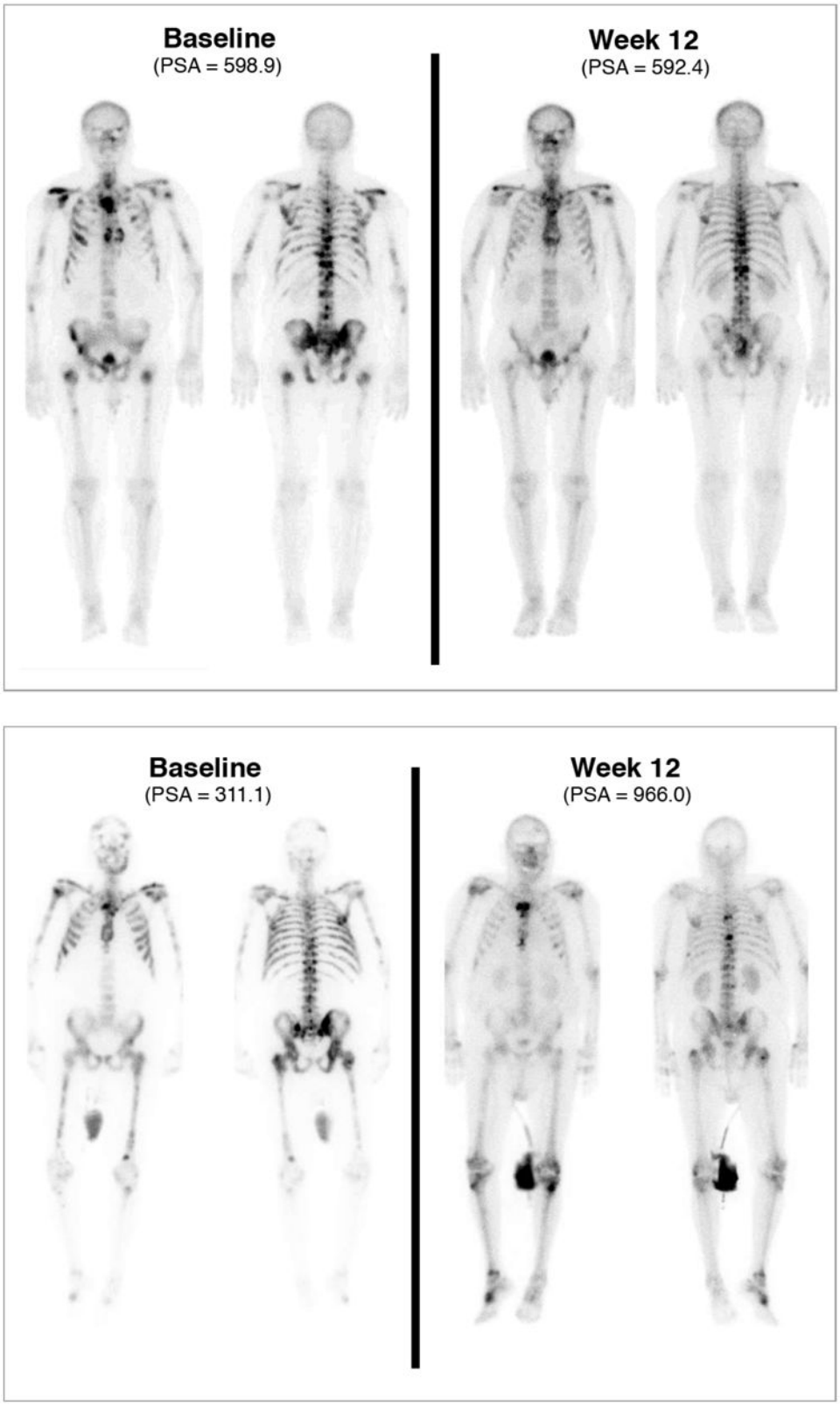

Figure 1. Clinical data for subjects with partial or complete response by bone scan

a. Complete bone scan response, with no lesion to indicate metastatic disease on the follow-up scan. Partial response of the retroperitoneal nodal metastasis was also observed on CT. PSA declined by 35%.

b. 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%.

c. 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%.

d. Significant improvement of bone metastases in bilateral humeri, ribs, vertebrae, pelvic bones, and femora, caetgorized as partial response. PSA increased by 20%.

e. Marked improvement of bone metastases throughout axial and appendicular skeleton, categorized as partial response. CT scan of the chest/abdomen/pelvis revealed treatment response at a pelvic side wall mass and at metastatic nodes. PSA declined by 1%.

f. Prior superscan improved to recognizable individual metastatic lesions of sternum, rib, thoracic spine, pelvic bones, and proximal femora, categorized as partial response. New liver metastasis was found on CT. PSA increased by 211%.

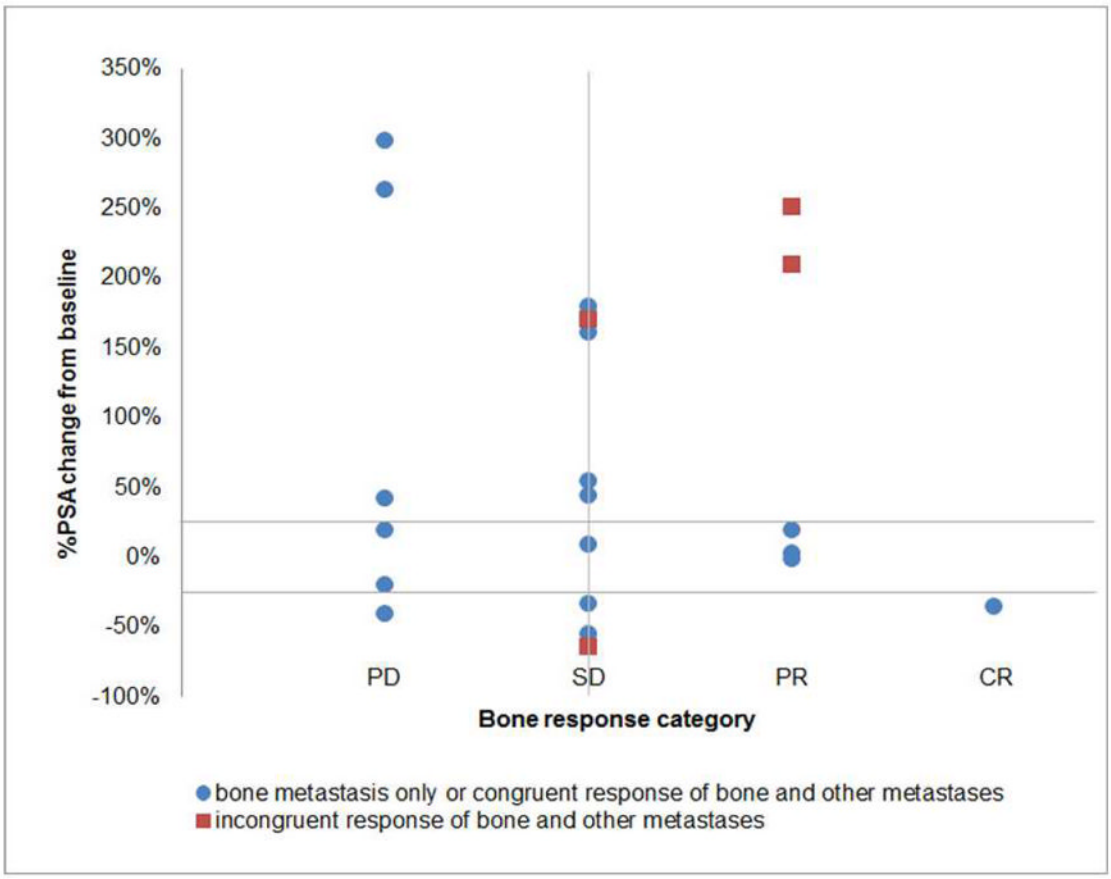

Figure 2. PSA changes among subjects grouped by bone scan response

Discordant correlation between PSA and bone scan responses (n = 22). Six patients were excluded. Three were excluded due to non-evaluable bone scan responses because diffuse skeletal metastases did not allow meaningful interpretation of the differences between studies. Two were excluded due to negative bone scans at baseline. One was excluded due to indeterminate lesions that may have reflected trauma.

Table 1

Bone interpretation criteria, modified from Recommendations of the Prostate Cancer Clinical Trials Working Group 2 (PCWG2)[5] and MD Anderson criteria[9]

Score	Criteria
Progressive disease (PD)	Appearance of ≥ 2 new lesions unequivocally diagnosed as bone metastasis
	Confirm 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 (SD)	Failure to attain PR/CR or PD
Partial response (PR)	≥ 50% overall improvement of previous metastatic bone lesions, subjectively
	OR prior extensively diffuse skeletal metastases (“superscan”) turns into recognizable individual metastatic lesion(s)
Complete response (CR)	No lesion to indicate metastatic disease
Non-evaluable (NE)	Extensively diffuse skeletal metastases (“superscan”) that does not allow meaningful interpretation of the differences between studies
	OR technical or physiological aspects resulting in non-evaluable images

Table 2

Patient characteristics on sunitinib phase II

	Group A (no prior chemotherapy)	Group B (docetaxel resistant)
Number of subjects	17	17
Age (years)		
Median	71	65
Range	52-80	45-84
ECOG performance status		
0	12	7
1	5	9
2	0	1
Sites of disease		
Bone metastasis	12	15
PSA-only disease	1	0
PSA (ng/mL)		
Median	51	44
Range	7 – 602	8 – 752
Alkaline phosphatase (U/L)		
Median	99	126
Range	46 – 991	69 – 495
Hemoglobin (g/dL)		
Median	13.2	12.5
Range	10.7 – 14.9	8.3 – 14.1
Prior hormone therapies		
1-3	11	12
4-6	6	4
Prior cycles of chemotherapy		
Median	-	8
Range	-	3 – 14
Prior radiation therapy	8	10
Bisphosphonate use	6	11

Table 3

PSA and radiological response of all patients as grouped by bone scan response

Pt.	PSA baseline (ng/ml)	PSA F/U* (ng/ml)	PSA change (%)	Bone scan*	CT scan*
1	25	16.3	-35%	CR	PR (retroperitoneal nodes)
2	460.8	1620	252%	PR	PD (New liver metastasis)
3	311.1	966	211%	PR	PD (New liver metastasis)
4	110.7	132.8	20%	PR	
5	110.6	115	4%	PR	
6	598.9	592.4	-1%	PR	PR (pelvic side wall mass and nodes)
7	41.9	117.6	180%	SD	SD (pulmonary metastasis)
8	33.5	90.9	171%	SD	PD (New nodal metastasis)
9	212.3	555.2	162%	SD	
10	21.2	32.9	55%	SD	
11	7.6	11	45%	SD	
12	21	23	10%	SD	
13	26	17.5	-33%	SD	
14	6.3	2.9	-54%	SD	
15	17.6	6.31	-64%	SD	PR (retroperitoneal nodes)
16	29.8	135	353%	PD	PD (retroperitoneal nodes)
17	40.8	162.8	299%	PD	
18	388.1	1412	264%	PD	
19	47	66.9	42%	PD	
20	135	162	20%	PD	
21	34.1	27.5	-20%	PD	
22	14.6	8.8	-40%	PD	
23	157	557.9	255%	NE	
24	28.4	77.1	172%	NE	
25	283.9	251.4	-11%	NE	
26	28.2	75.6	168%	No progressionϕ	

Pt.	PSA baseline (ng/ml)	PSA F/U* (ng/ml)	PSA change (%)	Bone scan*	CT scan*
27	7	7.22	3%	No progressionϕ	
28	31.6	26.7	-16%	No progressionϕ	SD (pelvic nodes)

Abbreviations: Pt, patient; PSA, prostate-specific antigen; F/U, follow up

*Evaluate 12 weeks after treatment

ϕBone scan did not show metastasis at baseline and during follow up

Table 4

In vitro kinase inhibitor activities expressed as IC_{50} (nmol/L) values

	Sunitinib [nM]	Cabozantinib [nM]
VEGFR1/FLT		12.2
VEGFR2/KDR	4	0.035
VEGFR3/FLT-4		6.0
MET		1.8
PDGFR-beta	4, 10	
RET	50	9.8
KIT	1-10, 13	4.6
FLT3	250, 50 (ITD)	14.4
TIE2		14.3
AXL		7
CSF-1R	50-100	

Key: IC_{50} is the concentration required for 50% target inhibition. KIT is stem cell factor receptor. RET is glial cell-line-derived neurotrophic factor receptor. FLT3 is Fms-like tyrosine kinase-3. All values are as reported in the respective investigator's brochures. Please note that published literature has also reported in vitro inhibitory activity for sunitinib at VEGFR1 and VEGFR3.[15-17]