

Randomized, Placebo-Controlled, Phase III Trial of Sunitinib Plus Prednisone Versus Prednisone Alone in Progressive, Metastatic, Castration-Resistant Prostate Cancer

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ABSTRACT

Purpose

We evaluated angiogenesis-targeted sunitinib therapy in a randomized, double-blind trial of metastatic castration-resistant prostate cancer (mCRPC).

Patients and Methods

Men with progressive mCRPC after docetaxel-based chemotherapy were randomly assigned 2:1 to receive sunitinib 37.5 mg/d continuously or placebo. Patients also received oral prednisone 5 mg twice daily. The primary end point was overall survival (OS); secondary end points included progression-free survival (PFS). Two interim analyses were planned.

Results

Overall, 873 patients were randomly assigned to receive sunitinib ($n = 584$) or placebo ($n = 289$). The independent data monitoring committee stopped the study for futility after the second interim analysis. After a median overall follow-up of 8.7 months, median OS was 13.1 months and 11.8 months for sunitinib and placebo, respectively (hazard ratio [HR], 0.914; 95% CI, 0.762 to 1.097; stratified log-rank test, $P = .168$). PFS was significantly improved in the sunitinib arm (median 5.6 v 4.1 months; HR, 0.725; 95% CI, 0.591 to 0.890; stratified log-rank test, $P < .001$). Toxicity and rates of discontinuations because of adverse events (AEs; 27% v 7%) were greater with sunitinib than placebo. The most common treatment-related grade 3/4 AEs were fatigue (9% v 1%), asthenia (8% v 2%), and hand-foot syndrome (7% v 0%). Frequent treatment-emergent grade 3/4 hematologic abnormalities were lymphopenia (20% v 11%), anemia (9% v 8%), and neutropenia (6% v < 1%).

Conclusion

The addition of sunitinib to prednisone did not improve OS compared with placebo in docetaxel-refractory mCRPC. The role of antiangiogenic therapy in mCRPC remains investigational.

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INTRODUCTION

Docetaxel-based chemotherapy is standard front-line treatment for metastatic castration-resistant prostate cancer (mCRPC), with demonstrated survival benefits compared with mitoxantrone plus prednisone.¹⁻³ Treatment options for men with mCRPC after progression on docetaxel-based chemotherapy are historically limited, although recent advances have led to the approvals of cabazitaxel, abiraterone acetate, and enzalutamide.⁴⁻⁶ The role of antiangiogenic therapies in mCRPC has also been investigated, based on cumulative evidence suggesting that prostate cancer growth is dependent on

angiogenesis. The proangiogenic factor vascular endothelial growth factor (VEGF) and its receptors (VEGFRs) are expressed in prostate tumors,⁷⁻⁹ and increasing VEGF plasma levels correlate with progressive disease.¹⁰⁻¹² Additionally, VEGF plasma and urine levels are independent predictors of overall survival (OS) in CRPC.^{13,14} Platelet-derived growth factor (PDGF) and its receptors (PDGFRs) have also been implicated in prostate cancer progression.¹⁵⁻¹⁷

Sunitinib malate (SUTENT; Pfizer Inc, New York, NY), a multitargeted inhibitor of VEGFRs, PDGFRs, and other receptor tyrosine kinases,¹⁸⁻²³ is approved for treatment of advanced renal

cell carcinoma (RCC), gastrointestinal stromal tumor (GIST), and pancreatic neuroendocrine tumors (NETs). Three phase II trials of single-agent sunitinib in progressive mCRPC suggested antitumor activity, as assessed by both $\geq 50\%$ decline in prostate-specific antigen (PSA) levels and tumor shrinkage, with an acceptable safety profile.²⁴⁻²⁶ In two of the studies, sunitinib was given at a starting dose of 50 mg/d on a 4-week-on-2-week-off schedule,^{24,25} and, in the third, sunitinib was given at 37.5 mg/d on a continuous dosing schedule.²⁶ Based on these promising results and an unmet therapy need in this patient population, we conducted a phase III trial of sunitinib plus prednisone in men with progressive mCRPC after docetaxel-based chemotherapy.

PATIENTS AND METHODS

Patients

The study population comprised patients with histologically or cytologically confirmed adenocarcinoma of the prostate that was metastatic and castration-resistant (refractory to androgen ablation), with surgical or ongoing chemical castration and baseline testosterone level ≤ 50 ng/dL. Other eligibility criteria included the following: failure of one previous docetaxel-based regimen, because of either disease progression (docetaxel resistant) or intolerance; documented evidence of progressive disease, defined by either PSA progression (minimum of two rising values obtained ≥ 1 week apart, with the last result being ≥ 2.0 ng/mL), new or increasing nonbone disease on the basis of RECIST,²⁷ or positive bone scan with ≥ 2 new lesions²⁸; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; and adequate organ function. Patients were excluded if they had received more than one prior chemotherapy regimen in the metastatic disease setting; impending complication from bone metastases; urinary obstruction requiring medical intervention; known brain metastases; clinically significant cardiovascular events or disease during the preceding 6 months, including ongoing cardiac dysrhythmias of National Cancer Institute Common Terminology Criteria for Adverse Events grade ≥ 2 ; uncontrolled hypertension; grade ≥ 3 hemorrhage within 4 weeks; or ongoing treatment with therapeutic doses of coumadin or heparin. All patients provided written, informed consent.

Study Design and Treatment

This was an international, double-blind, placebo-controlled, randomized phase III study. Stratification criteria were ECOG performance status (0 ν 1); docetaxel-resistant ν docetaxel-intolerant; nature of disease progression at entry (PSA progression only ν radiographic progression); and previous therapy with a VEGF pathway inhibitor (yes ν no ν unknown). Patients were randomly assigned 2:1 to either oral sunitinib at a starting dose of 37.5 mg/d or matched placebo on a continuous dosing schedule, in 28-day cycles. In both arms, patients also received oral prednisone (or prednisolone, where prednisone was not commercially available) 5 mg twice daily. If toxicity occurred, the sunitinib or placebo dose could be either interrupted or reduced to 25 mg/d and then to 12.5 mg/d. In the absence of grade > 1 nonhematologic or grade > 2 hematologic toxicity, the sunitinib or placebo dose could be escalated to 50 mg/d at the third cycle start. Patients remained on study as long as they derived clinical benefit and were followed until death. The study was run in accordance with the Declaration of Helsinki, in compliance with the International Conference on Harmonization Good Clinical Practice Guidelines and applicable local regulatory requirements and laws, and was approved by the institutional review board or independent ethics committee of each participating center.

Study End Points and Assessments

The primary end point was OS, defined as the time from random assignment to death. Secondary end points included progression-free survival (PFS), defined as the time from random assignment to first documentation of objective progressive disease (as determined by investigators using radiographic, but not PSA, progression) or death on study from any cause (whichever occurred first), objective response rate (ORR), and safety.

Disease was assessed by tumor imaging and bone scan at baseline and every 8 weeks thereafter, and to confirm a response or if progression was suspected. Bone scan progression was defined by the presence of two new lesions in order to account for bone scan flare. Tumor response was evaluated by using RECIST (version 1.0). Disease assessments were initially reviewed by a central independent third-party core imaging laboratory to determine disease response and progression. However, independent review was stopped after the second interim analysis when a decision was made to halt the study, and PFS and ORR analyses reported here used investigator-derived assessments.

Safety and tolerability were monitored throughout the study by physical examination, hematology and biochemistry tests, ECOG performance status, vital signs and cardiac function (12-lead ECG), and by recording all adverse events (AEs), graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Statistical Analysis

A 35% improvement in median OS from 12 months (placebo) to 16.2 months (sunitinib) was considered clinically relevant. A total of 501 OS events would be required to detect this improvement by using a stratified log-rank test with an overall one-sided significance level of 0.025 and approximately 85% power. With 2:1 randomization, a planned accrual period of 18.8 months, and a minimum follow-up period of 13.3 months, it was estimated that 819 patients would need to be enrolled. Two interim analyses were planned, the first (after 120 PFS events) for safety and futility on the basis of PFS, and the second (after approximately 225 OS events; 45% of the total needed) for safety, efficacy, and futility on the basis of OS. A Pocock-like stopping boundary was used for futility.²⁹ The nominal significance level for the interim and final efficacy analyses was determined by using the Lan-DeMets procedure³⁰ with an O'Brien-Fleming stopping rule.³¹ The O'Brien-Fleming stopping boundary was used for efficacy stopping criteria, and the futility stopping criteria were constructed by using rho stopping boundary. Interim analyses were reviewed by an independent third-party data monitoring committee (DMC).

All efficacy analyses used an intent-to-treat approach, whereas safety analyses included all patients who received ≥ 1 dose of study medication. OS and PFS were summarized by using Kaplan-Meier methods, and for each the median event time with corresponding two-sided 95% CI was provided, with the hazard ratio (HR) and its 95% CI. A log-rank test (one-sided, ≤ 0.025) was used to compare OS and PFS between arms, stratifying for ECOG performance status (0 ν 1) and type of disease progression (PSA progression only ν radiographic progression). ORR was summarized for each arm with the corresponding two-sided 95% CI by using an exact method based on binomial distribution. A point estimate of the ORR difference between arms and its corresponding 95% CI were calculated by using the normal approximation.

RESULTS

Patients

Between July 2008 and August 2010, 873 patients were randomly assigned from 152 sites in 22 countries, with 584 patients allocated to sunitinib and 289 to placebo (Fig 1). Baseline characteristics were well balanced between arms (Table 1). Median age was 68 years (range, 39 to 90 years) and approximately 49% had tumors with Gleason score ≥ 8 .

The study was stopped early on the recommendation of the DMC after a second interim analysis determined that an OS difference between arms was statistically improbable.

Treatment Exposure

Median treatment duration with sunitinib and placebo was 98 days (range, 1 to 783 days) and 97 days (range, 6 to 661 days), respectively. Median duration of study follow-up was 8.7 months. Median

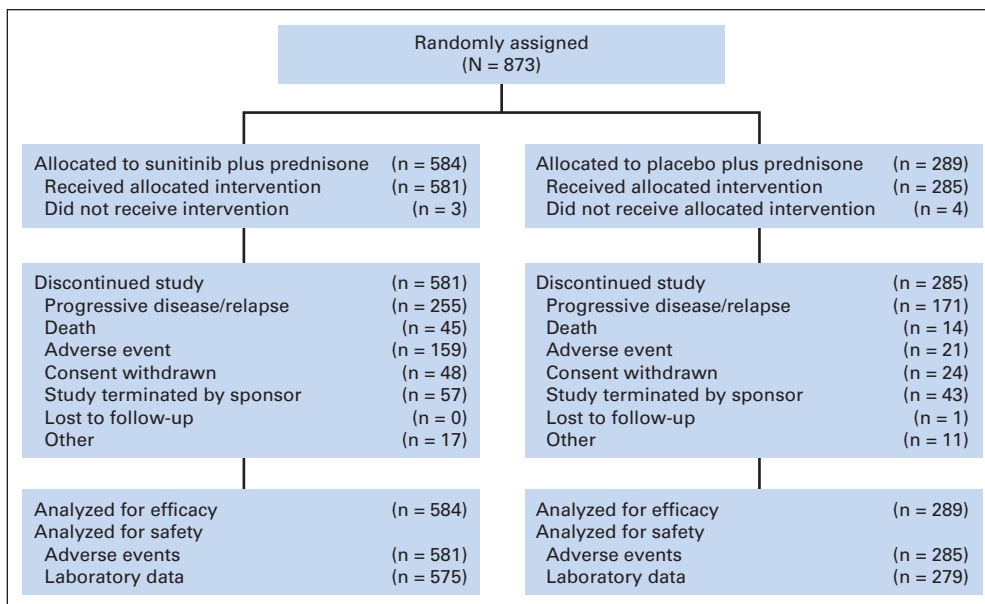


Fig 1. CONSORT diagram.

relative dose intensity for sunitinib was 82% overall, and > 95% for the first four cycles and > 65% for most other cycles. Relative dose intensity was not determined for placebo. A total of 32% of patients in the sunitinib arm required \geq one sunitinib dose reduction, to 25 mg and 12.5 mg in approximately 29% and 4% of patients, respectively. Of 581 patients who received the allocated intervention in the sunitinib arm (Fig 1), 44 (8%) had their dose increased to 50 mg/d, with no apparent effect on clinical outcome. The most common treatment-emergent AEs leading to sunitinib dose reduction or delay were hand-foot syndrome (11%) and diarrhea, fatigue, and asthenia (each 9%). The placebo dose was reduced to a nominal 25 mg in only 12 patients (4%) and to 12.5 mg in one patient (< 1%). At analysis, 581 patients (99%) and 285 patients (99%) in the sunitinib and placebo arms, respectively, had discontinued the study (including one patient lost to follow-up in the placebo arm; Fig 1). Fewer withdrawals occurred due to progressive disease in the sunitinib than the placebo arm (44% v 60%). Overall, 27% discontinued primarily because of an AE (most commonly fatigue or asthenia), compared with 7% on placebo.

Efficacy

OS, the primary end point, did not differ significantly between treatment arms (Fig 2), with a median of 13.1 months (95% CI, 12.0 to 14.1 months) and 11.8 months (95% CI, 10.8 to 14.2 months) with sunitinib and placebo, respectively, and HR of 0.914 (95% CI, 0.762 to 1.097; $P = .168$; stratified log-rank test). A high proportion of patients in each arm (42% and 38% in the sunitinib and placebo arms, respectively) was censored in the OS analysis. The most frequent reason for censoring was that the patient was alive at the time of data analysis.

Based on investigator-derived assessment of disease response and progression, PFS was significantly longer with sunitinib compared with placebo (median PFS, 5.6 months [95% CI, 5.4 to 6.5 months] v 4.1 months [95% CI, 3.6 to 5.6 months]; HR = 0.725 [95% CI, 0.591 to 0.890]; $P < .001$; stratified log-rank test; Fig 3). In this analysis, 56% and 48% of patients were censored in the sunitinib and placebo arms,

respectively. The most common reason for censoring was study termination before disease progression.

A total of 327 and 167 patients in the sunitinib and placebo arms, respectively, had measurable disease with baseline target assessments. ORR was marginally higher with sunitinib (6%; 95% CI, 4% to 9%) than with placebo (2%; 95% CI, < 1% to 5%). The odds ratio for sunitinib v placebo was 3.56 (95% CI, 1.0 to 19.0; $P = .040$). No complete responses were observed. The proportion of patients with a best response of stable disease \geq 3 months was similar in each arm (26% and 30% for sunitinib and placebo, respectively).

Safety

A higher proportion of patients on sunitinib than on placebo reported treatment-related AEs (94% v 62%). The most frequent sunitinib- or placebo-related, nonhematologic any-grade toxicities were diarrhea (41% v 9%), decreased appetite (35% v 12%), nausea (35% v 12%), fatigue (30% v 15%), hand-foot syndrome (29% v 3%), dysgeusia (28% v 8%), and vomiting (25% v 7%), in the sunitinib versus placebo arms, respectively. The most commonly reported grade 3 or 4 AEs were fatigue (9% v 1%), asthenia (8% v 2%), and hand-foot syndrome (7% v 0%; Table 2). Bone and back pain of any cause were reported less frequently in the sunitinib than in the placebo arm (bone pain: 12% v 16%; back pain: 15% v 21%). With the exception of anemia, the incidence of treatment-emergent hematologic abnormalities (mostly grade 1 or 2) was substantially higher in patients receiving sunitinib. In particular, grade 3 lymphopenia was more common with sunitinib than placebo (Table 2). However, opportunistic infections were not observed. The incidence of grade 4 hematologic toxicity was low in both arms (\leq 2%; Table 2).

A total of 57 patients (10%) in the sunitinib arm and 30 patients (11%) in the placebo arm died during the study. The large majority of deaths were due to prostate cancer (72% in the sunitinib arm and 80% in the placebo arm). Other causes of death reported in \geq two patients overall included pneumonia ($n = 1$ in each arm), sepsis ($n = 2$, both in the sunitinib arm), and cardiopulmonary arrest ($n = 1$ in each arm).

Table 1. Baseline Patient Characteristics by Treatment Arm

Characteristic	Sunitinib + Prednisone (n = 584)		Placebo + Prednisone (n = 289)	
	No.	%	No.	%
Age, years				
Median	69		68	
Range	39-90		47-86	
ECOG performance status				
0	292	50	145	50
1	292	50	144	50
Gleason score				
≤ 6	76	13	43	15
7	177	30	88	30
8-10	296	51	129	45
Not done/missing	35	6	29	10
Disease progression at entry				
PSA progression only	316	54	144	50
Radiographic progression	267	46	145	50
Prior therapy with VEGF inhibitor	14	2	6	2
Number of prior systemic treatment regimens*				
1	503	86	249	86
2	59	10	31	11
> 2	21	4	9	3
Not reported	1	< 1	0	0
Prior cycles of docetaxel†				
Median	8		8	
Range	< 1-160		< 1-70	
Reasons for stopping docetaxel				
Disease progression	534	91	265	92
Intolerance	50	9	24	8

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; VEGF, vascular endothelial growth factor.

*Includes hormone therapy and chemotherapy (ie, docetaxel), and excludes ketoconazole, estrogens, and antiandrogens.

†One docetaxel cycle is 3 weeks.

The percentage of deaths due to unknown causes was higher in the sunitinib arm (11% v 0%).

DISCUSSION

Compared with placebo, the addition of sunitinib to prednisone did not significantly prolong OS in men with mCRPC after failure of a docetaxel-based regimen. PFS was significantly improved with sunitinib compared with placebo (median PFS 5.6 months v 4.1 months; $P < .001$) and ORR was also higher with sunitinib than placebo (6% v 2%; $P = .040$). Based on these results, use of antiangiogenic therapy in unselected patients with advanced prostate cancer remains investigational.

In addition to improvement in PFS and response rate, there was less back and bone pain reported among patients randomly assigned to receive sunitinib compared with placebo. Taken together, these results suggest that there may be a role for sunitinib or other antiangiogenic therapy in prostate cancer, but that further investigation is required to identify the most appropriate patient population. Although in a different setting, our results are similar to a recently reported Cancer and Leukemia Group B (CALGB) 90401 study that

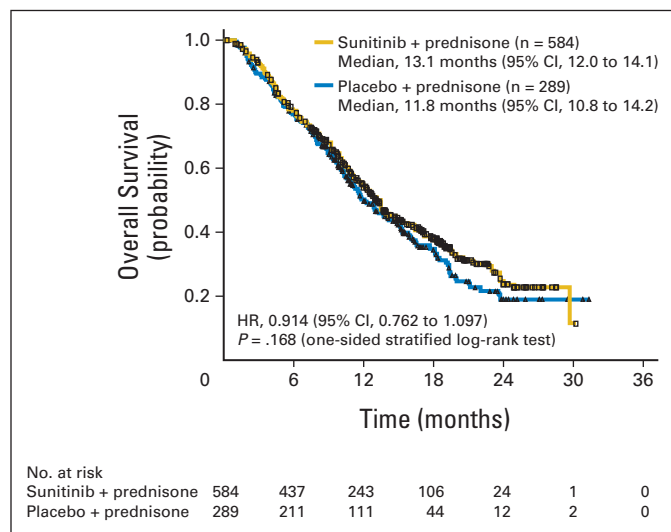


Fig 2. Kaplan-Meier estimates of overall survival by treatment arm. HR, hazard ratio.

compared docetaxel and prednisone with and without bevacizumab in mCRPC³² and also failed to reveal an OS advantage despite significantly improved PFS and other efficacy end points.

The reason that improved PFS does not appear to translate to OS benefit with antiangiogenic agents is not clear. The magnitude of PFS may be too small to affect OS, or other factors may be involved. A phase III trial in mCRPC with lenalidomide was also discontinued early because of futility³³ and, in the first-line mCRPC setting, the VENICE (VEGF Trap Administered With Docetaxel in Metastatic Androgen-Independent Prostate Cancer) phase III aflibercept study failed to meet its primary end point of extending OS compared with placebo.³⁴ The multikinase inhibitor sorafenib has revealed some antitumor activity in phase II studies in mCRPC.³⁵⁻³⁷ However, no sorafenib phase III studies have been pursued in this indication. In a

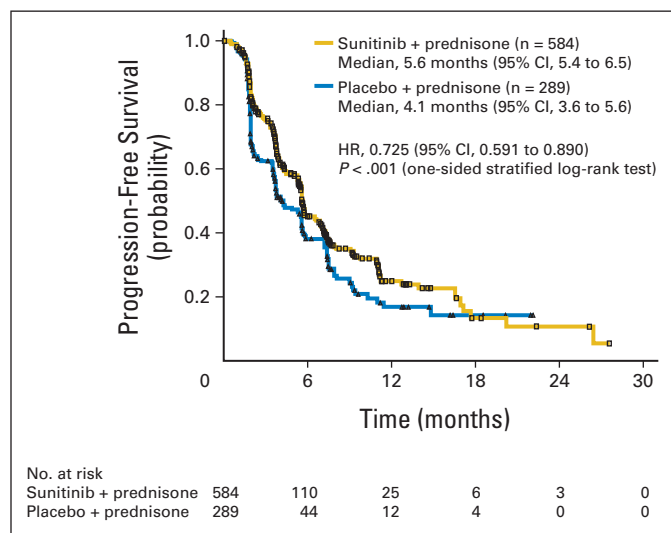


Fig 3. Kaplan-Meier estimates of progression-free survival by treatment arm. HR, hazard ratio.

Table 2. Grade ≥ 3 Treatment-Related Adverse Events and Treatment-Emergent Hematologic Abnormalities

Adverse Event	Sunitinib + Prednisone (n = 581)				Placebo + Prednisone (n = 285)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
Fatigue	49	8	2	< 1	4	1	0	0
Asthenia	44	8	3	< 1	6	2	1	< 1
Hand-foot syndrome	38	7	0	0	0	0	0	0
Diarrhea	28	5	0	0	0	0	0	0
Decreased appetite	25	4	1	< 1	2	< 1	0	0
Hypertension	24	4	0	0	1	< 1	0	0
Nausea	20	3	0	0	1	< 1	0	0
Mucosal inflammation	17	3	1	< 1	0	0	0	0
Pulmonary embolism	1	< 1	12	2	0	0	3	1
Vomiting	10	2	0	0	2	< 1	0	0
Stomatitis	9	2	0	0	0	0	0	0
Hematologic abnormalities*								
Anemia	39	7	11	2	17	6	5	2
Leukopenia	19	3	0	0	1	< 1	1	< 1
Neutropenia	31	5	1	< 1	0	0	2	< 1
Lymphopenia	110	19	7	1	29	10	3	1
Thrombocytopenia	19	3	8	1	3	1	0	0

NOTE. Occurring in $\geq 1\%$ of patients in at least one treatment arm. All adverse events and laboratory abnormalities graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Grade 5 treatment-related adverse events were reported in 12 (2%) of patients in the sunitinib arm and one patient (< 1%) in the placebo arm.

*For hematologic abnormalities, n = 574 in the sunitinib arm (apart from platelets, for which n = 573) and n = 279 in the placebo arm.

OS benefit),³² this study did not allow maintenance of VEGF inhibition beyond disease progression, despite OS benefit observed with postprogression continuation of bevacizumab in other tumor types (eg, colon cancer).⁴³ It is conceivable that prolonged VEGF inhibition may be required to achieve clinical benefit.

The safety profile of sunitinib did not point to any new or unexpected AEs compared with those previously reported in mCRPC^{24,25} or other tumor types, including GIST, RCC, and pancreatic NET.⁴⁴⁻⁴⁶ The 37.5 mg/d dose was chosen for its perceived flexibility in managing potential AEs, via dose titration or brief interruption. Nevertheless, tolerance to sunitinib was worse in the present trial. This poor tolerability may have been because of the older median age in this trial compared with trials in other cancer types (68 years v 56 to 62 years),⁴⁴⁻⁴⁶ to previous chemotherapy with docetaxel, and/or to combination treatment with prednisone. In the present study, 27% of patients halted sunitinib treatment before disease progression because of toxicity compared with 9%, 8%, and 17% of patients in the phase III GIST, RCC, and pancreatic NET trials, respectively.⁴⁴⁻⁴⁶ The relatively poor tolerance to sunitinib may have limited treatment and affected OS, and is a plausible explanation for the discrepancy between PFS and OS. To that point, the short treatment duration (median, 98 days) may have been sufficient to improve PFS but not OS.

Since this trial was launched in 2008, a number of positive phase III mCRPC studies have been reported. Abiraterone acetate, in combination with prednisone, improved PFS and OS in docetaxel-pretreated patients and was recently reported to extend PFS in chemotherapy-naïve patients as well.^{5,47} Three other compounds, enzalutamide, cabazitaxel, and radium-223 dichloride, have also demonstrated survival benefit in mCRPC patients,^{4,6,48} and together these agents constitute a new and improved armamentarium for advanced prostate cancer treatment. However, since each therapy improves OS by only a few months compared with placebo, it is clear that further advances are needed. Antiangiogenic agents may yet have a role to play in treating patients with mCRPC, but their future development in this area will require enhanced patient selection by using predictive biomarkers of response to guide therapy in a rational manner.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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randomized phase II study, tasquinimod (an oral quinoline-3 carboxamide derivative targeting S100A9) improved PFS and OS compared with placebo in chemotherapy-naïve men with mCRPC and minimal symptoms.^{38,39} The results of a phase III trial investigating the role of tasquinimod are awaited.⁴⁰

A number of other VEGF tyrosine kinase inhibitors in development, such as axitinib, tivozanib, or the dual VEGFR-2/c-Met inhibitor cabozantinib, may still be of substantial interest in this indication. In particular, cabozantinib has demonstrated intriguing activity in advanced prostate cancer, particularly with regard to bone scan response,⁴¹ and will be studied in phase III trials. Whether c-Met inhibition contributes to this activity remains unknown. Interestingly, sunitinib may also produce bone scan responses in men who do not appear to be responding based on other outcome measures⁴²; the potential discrepancy between bone scan results and true clinical outcomes is an area of active investigation.

An important limitation to the overall interpretation of this study was the fact that the DMC recommended early termination after the second interim analysis. This confounded the analysis of PFS as well as response rates, and precluded central review of all imaging studies. In addition, the high censoring rate, which to a great extent reflected patient discontinuation from therapy before disease progression, could limit interpretation of PFS results. Furthermore, although progression was not defined in terms of PSA levels in this study, changes in PSA levels may potentially have influenced treatment decisions. Finally, like the CALGB 90401 study, which had similar results (ie, improvement in PFS, minus

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GLOSSARY TERMS

Antiangiogenic: A process involved blocking the generation of new blood vessels in a tumor, which disrupts the blood supply thereby preventing tumor growth.

mCRPC: Metastatic castration-resistant prostate cancer, progressive disease despite surgical castration or ongoing use of gonadotropin-releasing hormone agonists with confirmed castrate levels of testosterone.

PDGF (platelet-derived growth factor): A family of proteins that exists in the A, B, C, or D forms. PDGF is involved in proliferation pathways, especially of mesenchymal cell types. PDGF forms homodimers (eg, AA, BB, CC, DD) or heterodimers (eg, AB), which interact with appropriate cellular receptors.

PDGFR (platelet-derived growth factor receptor): The receptor for PDGF exists distinctly as the dimeric $\alpha\alpha$ or $\beta\beta$ form. All dimer combinations of PDGF A and B signal through PDGFR- $\alpha\alpha$; PDGF BB signals through PDGFR- $\beta\beta$; PDGF CC signals through the $\alpha\alpha$ and $\alpha\beta$ receptors; PDGF DD signals through the $\beta\beta$ and $\alpha\beta$ receptors.

Sunitinib (SU011248, Sutent): An oral small molecular tyrosine kinase inhibitor that exhibits potent anti-angiogenic and anti-tumor activity.

VEGF (vascular endothelial growth factor): VEGF is a cytokine that mediates numerous functions of endothelial cells including proliferation, migration, invasion, survival, and permeability. VEGF is also known as vascular permeability factor. VEGF naturally occurs as a glycoprotein and is critical for angiogenesis. Many tumors overexpress VEGF, which correlates to poor prognosis. VEGF-A, -B, -C, -D, and -E are members of the larger family of VEGF-related proteins.

VEGFR (vascular endothelial growth factor receptor): VEGFRs are transmembrane tyrosine kinase receptors to which the VEGF ligand binds. VEGFR-1 (also called Flt-1) and VEGFR-2 (also called KDR/Flk-1 [murine homologue]) are expressed on endothelial cells, while VEGFR-3 (also called Flt-4) is expressed on cells of the lymphatic and vascular endothelium. VEGFR-2 is thought to be principally responsible for angiogenesis and for the proliferation of endothelial cells. Typically, most VEGFRs have seven extracellular immunoglobulin-like domains, responsible for VEGF binding, and an intracellular tyrosine kinase domain.

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