A Randomized Phase II Trial of Short-Course Androgen Deprivation Therapy With or Without Bevacizumab for Patients With Recurrent Prostate Cancer After Definitive Local Therapy

Rana R. McKay, Amado J. Zurita, Lillian Werner, Justine Y. Bruce, Michael A. Carducci, Mark N. Stein, Elisabeth I. Heath, Arif Hussain, Hai T. Tran, Christopher J. Sweeney, Robert W. Ross, Philip W. Kantoff, Susan F. Slovin, and Mary-Ellen Taplin

Rana R. McKay, Lillian Werner, Christopher J. Sweeney, Philip W. Kantoff, and Mary-Ellen Taplin, Dana-Farber Cancer Institute, Boston; Robert W. Ross, Bluebird Bio, Cambridge, MA; Amado J. Zurita and Hai T. Tran, MD Anderson Cancer Center, Houston, TX; Justine Y. Bruce, University of Wisconsin Carbone Cancer Center, Madison, WI; Michael A. Carducci, Johns Hopkins University; Arif Hussain, Greenebaum Cancer Center, Baltimore, MD; Mark N. Stein, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Elisabeth I. Heath, Karmanos Cancer Institute, Detroit, MI; and Philip W. Kantoff and Susan F. Slovin, Memorial Sloan Kettering Cancer Center, New York, NY.

Published online ahead of print at www.jco.org on April 4, 2016.

Supported by Genentech. Angiocrine analysis was funded by The Fairweather Family Fund and Uribe Family Fund at the Dana-Farber Cancer Institute (M.-E.T.).

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Mary-Ellen Taplin, MD, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02115; e-mail: mtaplin@partners.org.

© 2016 by American Society of Clinical Oncology

0732-183X/16/3416w-1913w/\$20.00

DOI: 10.1200/JCO.2015.65.3154

ABSTRACT

Purpose

Patients with recurrent prostate cancer after local treatment make up a heterogeneous population for whom androgen deprivation therapy (ADT) is the usual treatment. The purpose of this randomized phase II trial was to investigate the efficacy and toxicity of short-course ADT with or without bevacizumab in men with hormone-sensitive prostate cancer.

Patients and Methods

Eligible patients had an increasing prostate-specific antigen (PSA) of ≤ 50 ng/mL and PSA doubling time of less than 18 months. Patients had either no metastases or low burden, asymptomatic metastases (lymph nodes < 3 cm and five or fewer bone metastases). Patients were randomly assigned 2:1 to a luteinizing hormone-releasing hormone agonist, bicalutamide and bevacizumab or ADT alone, for 6 months. The primary end point was PSA relapse-free survival (RFS). Relapse was defined as a PSA of more than 0.2 ng/mL for prostatectomy patients or PSA of more than 2.0 ng/mL for primary radiation therapy patients.

Results

Sixty-six patients received ADT + bevacizumab and 36 received ADT alone. Patients receiving ADT + bevacizumab had a statistically significant improvement in RFS compared with patients treated with ADT alone (13.3 months for ADT + bevacizumab v 10.2 months for ADT alone; hazard ratio, 0.47; 95% CI, 0.29 to 0.77; log-rank $P = .002$). Hypertension was the most common adverse event in patients receiving ADT + bevacizumab (36%).

Conclusion

ADT combined with bevacizumab resulted in an improved RFS for patients with hormone-sensitive prostate cancer. Long-term follow-up is needed to determine whether some patients have a durable PSA response and are able to remain off ADT for prolonged periods. Our data provide rationale for combining vascular endothelial growth factor–targeting therapy with ADT in hormone-sensitive prostate cancer.

J Clin Oncol 34:1913-1920. © 2016 by American Society of Clinical Oncology

INTRODUCTION

The initial therapy for men with systemic prostate cancer is **androgen deprivation therapy (ADT)**. For nonmetastatic, prostate-specific antigen (PSA) only, or low-volume metastatic disease, ADT is commonly prescribed in an intermittent fashion.^{1,2} Investigational strategies are needed to explore regimens that can either prolong time to castration resistance or improve quality of life by prolonging the duration of the off phase of intermittent ADT.

Angiogenesis is known to play an important role in prostate cancer pathogenesis.³ **Vascular endothelial growth factor-A (VEGF-A)** is present in both localized and metastatic tumors, and increased plasma concentrations of VEGF have been associated with disease progression.⁴⁻⁶ Preclinical studies demonstrate that VEGF inhibition with ADT results in significant suppression of tumor growth in comparison with either VEGF inhibition or ADT alone.⁷ These data support a role for VEGF in prostate cancer

progression and also support the hypothesis that inhibition of VEGF in combination with ADT may prolong response to ADT.

Bevacizumab is a monoclonal antibody to VEGF with demonstrated efficacy in several solid tumors, including glioblastoma and colorectal, lung, ovarian, and renal cell cancer.⁸⁻¹³ Although the addition of bevacizumab to docetaxel improved progression-free survival and response rates in metastatic castration-resistant prostate cancer (mCRPC), it failed to improve overall survival (OS).¹⁴

The benefit of short-term ADT combined with bevacizumab in hormone-sensitive recurrent prostate cancer has not been explored. In this randomized phase II study, we compare the efficacy and toxicity of 6 months of ADT with or without bevacizumab in men with hormone-sensitive disease.

PATIENTS AND METHODS

Patient Population

Eligible patients had histologically documented prostatic adenocarcinoma treated with radical prostatectomy (RP), radiotherapy, or cryotherapy. PSA recurrence with PSA doubling time of less than 18 months and PSA ≤ 50 ng/mL was required. There was no minimum PSA requirement for RP patients. Patients treated with primary radiotherapy had to have a PSA ≥ 2.0 ng/mL. Asymptomatic metastatic disease was allowed (lymph nodes < 3 cm in greatest diameter and five or fewer bone metastases). Prior ADT was allowed if it was administered for ≤ 8 months and testosterone recovered to within 50 ng/dL of the institutional normal range. Prior chemotherapy was allowed if there were six or fewer cycles and they were given more than 6 months before enrollment. Additional eligibility criteria included Eastern Cooperative Oncology Group performance status of 0 to 1 and predefined hematologic criteria. Exclusions that were bevacizumab specific included inadequately controlled hypertension; congestive heart failure; myocardial infarction; unstable angina; stroke; transient ischemic attack; symptomatic peripheral vascular disease; bleeding diathesis; coagulopathy; abdominal fistula, perforation, or abscess; nonhealing wound, or significant proteinuria.

Study Design and Treatment

This was a randomized, open-label phase II study conducted through the Prostate Cancer Clinical Trial Consortium at eight academic centers: Dana-Farber Cancer Institute (Boston, MA; $n = 22$), Memorial Sloan Kettering Cancer Institute (New York, NY; $n = 20$), University of Wisconsin (Madison, WI; $n = 19$), MD Anderson Cancer Center (Houston, TX; $n = 14$), Johns Hopkins University (Baltimore, MD; $n = 13$), Cancer Institute of New Jersey (New Brunswick, NJ; $n = 11$), Karmanos Cancer Institute (Detroit, MI; $n = 2$), and the University of Maryland (Baltimore, MD; $n = 1$). A total of 68 events were required to have 80% power to detect a 50% reduction in the hazard of relapse, which assumes that the median time to PSA relapse will be 6 months among patients treated with ADT alone and 12 months among patients treated with ADT + bevacizumab with one-sided $\alpha = .025$. The target sample size was 100 patients. Patients were randomly assigned (2:1) to leuprolide acetate 22.5 mg intramuscularly or goserelin acetate 10.8 mg subcutaneously once every 3 months and bicalutamide 50 mg orally once per day versus leuprolide acetate 22.5 mg intramuscularly or goserelin acetate 10.8 mg subcutaneously once every 3 months, bicalutamide 10 mg orally once per day, and bevacizumab 15 mg/kg intravenously once every 3 weeks for 6 months. Randomization stratification factors included age (≤ 60 v > 60 years), prior RP (yes v no), and metastatic disease status (yes v no). The stratified permuted block method was used for randomization allocation.

Participants were evaluated at baseline, every 3 months for those on the ADT alone arm or every 3 weeks for those on the ADT + bevacizumab

arm during the active treatment phase, and every 2 months during follow-up until PSA relapse. Institutional review boards of the participating institutions approved the study, which was conducted per the Declaration of Helsinki in accordance with the World Medicines Association and its amendments.

The primary end point was relapse-free survival (RFS). Relapse was defined as a PSA of more than 0.2 ng/mL for RP patients or PSA of more than 2.0 ng/mL for those who received primary radiation therapy. RFS was defined as the time from random assignment to relapse or death as a result of any cause. Among patients alive without relapse, RFS was censored at the date of the last PSA measurement. Participants remained on study during treatment unless progression defined by Prostate Cancer Clinical Trials Working Group-2 (PSA increase by $\geq 25\%$ and at ≥ 2 ng/mL above nadir confirmed at 3 weeks or later) or progression defined by Response Evaluation Criteria in Solid Tumors version 1.1.¹⁵ Secondary end points included the percentage of patients with a PSA of less than 0.2 ng/mL at therapy completion, toxicity as determined by Common Terminology Criteria for Adverse Events version 3.0, and assessment of cytokines and angiogenic factors (CAFs). Testosterone level was recorded during follow-up until PSA progression or recovery, defined as a testosterone level of more than 200 ng/dL.

Biomarker Measurements

Plasma for biomarker assessment was collected at baseline, on day 22, at 3 months, at 6 months, and at relapse and was stored at -80°C . Concentrations of 34 CAFs were measured in duplicate at the MD Anderson Cancer Center. These factors were selected on the basis of their link to established biology, the mechanism of action of bevacizumab, and commercial availability. Samples were thawed overnight at 4°C and then centrifuged at $1500 \times g$ to remove debris. CAFs were measured per manufacturers' instructions with multiplex bead suspension array kits using a Bio-Plex 200 system (Bio-Rad Laboratories, Hercules, CA), including customized high-sensitivity T-cell (HSTCMAG28SPMX13) and angiogenesis (HAGP1MAG-12K-09) panels, cytokine panel II (HCYP2MAG-62K-03), a bone panel (HBNMAG-51K-03), kidney injury panel I (HKI5MAG-99K-02), and a soluble cytokine receptor (HSCRMAG-32K-04) panel (all from EMD Millipore, Billerica, MA). Two of 34 CAFs (6%) were rejected because of the number of out-of-range samples.

Statistical Analysis

Baseline characteristics were summarized as numbers and percentages for categorical variables and as medians with interquartile ranges for continuous variables. The primary analysis used an intention-to-treat approach to compare RFS between patients assigned to ADT + bevacizumab versus ADT alone. The stratified log-rank test initially planned for the primary analysis included the following stratification factors and resulted in eight subgroups: age (≤ 60 v > 60 years), prior RP (yes v no), and metastatic disease status (yes v no). Because of the small sample sizes of these subgroups, a stratified log-rank test was not appropriate, so a log-rank test was used. We also performed a Cox regression model adjusting for the above covariates. RFS was summarized graphically by using Kaplan-Meier methodology. Hazard ratio (HR) and 95% CIs from a Cox regression model were calculated.

CAF levels at baseline and month 6, percentage change between month 6 and baseline, and relapse and percentage change between time of relapse and baseline were summarized as medians and interquartile ranges by arm. The Wilcoxon rank sum test was used to assess whether the percentage of change in biomarker levels between month 6 and baseline differed by treatment. The Cox regression model was used to assess the association of biomarker levels at baseline, interaction between markers and treatment, and percentage of change between month 6 and baseline biomarker levels with RFS. HRs and 95% CIs were determined for subgroups from the interaction between markers and treatment test. To assess the association, we dichotomized biomarker levels at the median. Because

of the limited sample size and the exploratory nature of these analyses, no correction for multiple testing was performed. Glucose, hemoglobin A1c (HbA1c), and lipids at baseline, during treatment, at end of treatment, and after treatment (for lipids only) were compared with baseline levels by using a Wilcoxon signed rank test.

RESULTS

Baseline Patient Characteristics

In total, 102 participants were enrolled from January 2009 to December 2012. The baseline characteristics between arms were well-balanced for known prognostic factors (Table 1). The majority of the patients were older than 60 years (75%) and had Gleason 7 disease (54%). The percentage of patients treated with RP (82% ADT + bevacizumab arm v 83% ADT alone arm) and those with metastatic disease (32% ADT + bevacizumab arm v 36% ADT alone arm) was similar between arms.

Treatment Exposure

Sixty-six patients were assigned to ADT + bevacizumab and 36 to ADT alone (Fig 1). In the ADT + bevacizumab arm, two patients never received treatment, one discontinued treatment before completion because of the development of proteinuria, and two discontinued treatment by choice. In the ADT-alone arm, one patient never received treatment and one discontinued treatment by choice. Of the seven patients who discontinued treatment, follow-up information was available for one patient.

Efficacy

At the time of final analysis, 77 patients had experienced a PSA relapse, and patients were observed until PSA relapse. After completing treatment, 80% of patients treated with ADT + bevacizumab ($n = 51$ of 64; 95% CI, 67% to 89%) and 77% of patients treated with ADT alone ($n = 27$ of 35; 95% CI, 60% to 90%) had a PSA of less than 0.2 ng/mL. The median RFS for the ADT + bevacizumab arm was 13.3 months (range, 0 to 49 months) compared with 10.2 months (range, 0 to 21 months) for the ADT-alone arm, and this difference was statistically significant (log-rank $P = .002$; HR, 0.47; 95% CI, 0.29 to 0.77; Fig 2). One-year RFS was 57% (95% CI, 43% to 68%) for patients receiving ADT + bevacizumab compared with 31% (95% CI, 16% to 48%) for patients receiving ADT alone. After adjusting for age, prior RP, and metastasis status, the HR for comparing ADT + bevacizumab versus ADT alone was 0.49 (95% CI, 0.30 to 0.82; $P = .01$). None of the patients experienced radiographic progression before PSA progression. In patients who remained free from PSA relapse, the median follow-up was 16 months ($n = 17$) in the ADT + bevacizumab arm and 5 months in the ADT-alone arm ($n = 8$).

Of the 65 patients with available data, 71% of those who were treated with ADT + bevacizumab and 71% of those who were treated with ADT alone experienced a testosterone recovery (testosterone > 200 ng/dL). The median time to testosterone recovery was 9.9 months (range, 9.7 to 11.8 months) in the ADT + bevacizumab arm and 10.1 months (range, 9.6 to 11.4 months) in the ADT-alone arm. Of the 65 patients with data on testosterone

Table 1. Baseline Clinical Characteristics

Characteristic	ADT + Bevacizumab (n = 66)				ADT Alone (n = 36)				Entire Cohort (n = 102)			
	No.	%	Median	q1, q3	No.	%	Median	q1, q3	No.	%	Median	q1, q3
At diagnosis												
PSA, ng/mL	62		6.7	4.9, 11.3	33		6.5	4.7, 11.0	95		6.7	4.7, 11.2
Gleason score												
6	10	15			5	14			15	15		
7	34	53			21	58			55	54		
8-10	20	30			10	28			30	29		
Unknown	2	3			0	0			2	2		
Prior RP	54	82			30	83			84	82		
Prior RT	52	79			33	92			85	83		
At baseline												
Age, years	66		66	60, 69	36		63	60, 68	102		65	60, 69
> 60	15	23			11	31			26	25		
≤ 60	51	77			25	69			76	75		
ECOG performance status												
0	57	86			34	94			91	89		
1	8	12			1	3			9	9		
Unknown	1	2			1	3			2	2		
Presence of metastatic disease	21	32			13	36			34	33		
Bone metastases	8	12			3	8			11	11		
Lymph node metastases	13	20			11	31			24	24		
PSA, ng/mL	63		6.0	3.1, 10.8	34		7.3	4.3, 16.0	97		6.5	3.6, 12.8
PSADT, months	65		4.1	2.6, 8.6	36		4.8	2.8, 0.0	101		4.6	2.6, 8.9
Testosterone, ng/dL	65		362	267, 430	35		352	296, 475	100		362	272, 463
Alkaline phosphatase, U/L	63		64	52, 79	35		67	60, 85	98		66	53, 81
Hemoglobin, g/dL	65		14.4	13.9, 15.2	36		14.6	14.0, 15.2	101		14.5	13.9, 15.2

Abbreviations: ADT, androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; RP, radical prostatectomy; RT, radiotherapy.

Fig 1. CONSORT flow diagram. ADT, androgen deprivation therapy.

levels, 57 developed a relapse, 43 of whom relapsed before testosterone recovery. The median RFS since time of testosterone recovery was 4 months. Of patients who developed a relapse, 44% ($n = 34$ of 77) experienced testosterone recovery; 28% of patients ($n = 7$ of 25) remained in remission. Eight patients did not experience a PSA recurrence at 24 months, of whom four had testosterone recovery (range, 12.0 to 15.9 months).

Safety and Toxicity

The safety analysis includes the 99 patients who received at least one dose of the treatment drug. Table 2 summarizes all grade 2 or higher adverse events by arm. In the ADT + bevacizumab arm,

44 (69%; 95% CI, 56% to 80%) of 64 patients experienced grade 2 or 3 toxicities, of which hypertension was the most frequent ($n = 23$ [36%] of 64), followed by musculoskeletal pain, infection, and headache. In the ADT-alone arm, nine (26%; 95% CI, 12% to 43%) of 35 patients experienced grade 2 or 3 toxicities, of which hypertension and hot flashes were the most common. There were no grade 4 or 5 toxicities in either arm.

For patients in the ADT + bevacizumab arm, total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein significantly increased at 3 months and at the end of treatment compared with baseline (Appendix Table A1, online only). At

Table 2. Grade 2 or Higher Adverse Events by Treatment Arm

Adverse Event	ADT + Bevacizumab (n = 64)		ADT Alone (n = 35)	
	Grade 2	Grade 3	Grade 2	Grade 3
Hypertension	10	13	0	2
Musculoskeletal pain	5	3	0	1
Infection	7	1	0	0
Headache	6	1	1	0
Hot flashes	5	0	2	0
Fatigue	6	0	0	0
Proteinuria	5	0	0	0
Weakness	3	0	0	0
Allergic rhinitis	2	0	0	0
Arthritis	2	0	0	0
Urinary frequency/urgency	2	0	0	0
Hyponatremia	1	1	0	0
Dyspnea	1	0	0	1
Hypertriglyceridemia	1	0	1	0
Syncope	0	1	0	1

NOTE. Toxicities experienced by more than one patient are included. Abbreviation: ADT, androgen deprivation therapy.

Fig 3. Kaplan-Meier plot for relapse-free survival (RFS) by baseline (A) leptin, (B) interleukin-2, and (C) tumor necrosis factor α levels.

6 months after treatment, levels were not significantly different from baseline. A similar but less pronounced trend was observed in the ADT-alone arm.

Biomarkers

A total of 64 patients had CAF levels at baseline, of whom 35 (55%) had paired measurements at completion of therapy. Baseline characteristics and CAF levels were similar between arms for patients with available data (Appendix Tables A2 and A3, online only). By treatment arm, the only marker showing a change between baseline and completion of therapy that reached statistical significance was interleukin-1 β (IL-1 β ; -5% for ADT + bevacizumab ν 24% for ADT alone; $P = .04$; Appendix Table A4, online only).

We analyzed the association of pretreatment CAF levels with RFS (Appendix Table A5, online only). Lower leptin, IL-2, and tumor necrosis factor alpha levels were associated with significantly shorter RFS (Fig 3), and the same trends were observed in both arms separately (not shown). We next evaluated the interaction of these three CAFs with metastatic disease

status and found significance only for leptin (interaction $P = .006$). Lower leptin levels were associated with an increased risk of relapse only in patients without metastases (15 months for greater than median ν 10 months for less than or equal to median leptin; HR, 5.06; 95% CI, 2.26 to 11.32). However, leptin levels did not have an impact on outcomes in patients with metastasis (11 ν 11 months; HR, 0.96; 95% CI, 0.42 to 2.23). Higher leptin was significantly associated with lower baseline testosterone (399 ng/dL for median or less ν 303 ng/dL for greater than median leptin; $P = .014$).

We also analyzed whether baseline CAFs were differentially associated with RFS by treatment arm and identified a significant association for IL-6 and osteopontin (interaction $P = .03$ for each CAF). In patients with higher osteopontin or IL-6, type of treatment affected RFS (Fig 4): those receiving ADT + bevacizumab had a longer RFS than those who received ADT alone (osteopontin: 15 ν 10 months; HR, 0.44; 95% CI, 0.23 to 0.86; IL-6: 13 ν 10 months; HR, 0.45; 95% CI, 0.23 to 0.83). However, in patients with lower baseline osteopontin or IL-6, treatment did not have an impact on RFS.

Fig 4. Kaplan-Meier plot for relapse-free survival (RFS) by baseline (A) osteopontin less than or equal to median, (B) osteopontin greater than median, (C) interleukin-6 (IL-6) less than or equal to median, and (D) interleukin-6 greater than median. Interaction $P = .03$ for (A,B) osteopontin and (C,D) interleukin-6. ADT, androgen deprivation therapy; B, bevacizumab.

DISCUSSION

In this study, we demonstrate that treatment with short-term ADT + bevacizumab was feasible, although it was associated with more toxicity than ADT alone in hormone-sensitive prostate cancer. When compared with ADT, the addition of bevacizumab resulted in a statistically significant improvement of RFS and improved 1-year RFS.

Although the use of antiangiogenic therapy in prostate cancer remains investigational, these results indicate that further evaluation of anti-VEGF-targeting therapy combined with ADT is warranted and may be a rational approach to prolong response to ADT even after ADT is discontinued.

A number of phase III studies have investigated antiangiogenic therapies in mCRPC, including bevacizumab, cabozantinib, sunitinib, and aflibercept (Appendix Table A6, online only).^{14,16-19} Although none of these agents have demonstrated improvements in OS, bevacizumab, cabozantinib, and sunitinib have demonstrated improvements in progression-free survival suggesting activity. Furthermore, docetaxel has demonstrated antiangiogenic properties, and early use in patients with hormone-sensitive disease shows improved OS.^{20,21} Taken together, these results suggest that with improved VEGF targeting or biomarkers of response, there may be a role for antiangiogenic therapies in prostate cancer. Further studies are warranted to identify the target population most likely to benefit.

There have been limited studies investigating the efficacy of antiangiogenic therapies in patients with hormone-sensitive prostate cancer. We previously investigated multimodality therapy with docetaxel, bevacizumab, and ADT in men for whom PSA treatment failed after local therapy and demonstrated that a subset of patients experienced a durable PSA remission.²² At a median follow-up of 27.5 months, 46% of patients were free from further therapy and 92% had testosterone ≥ 100 ng/dL.²² Furthermore, we evaluated neoadjuvant docetaxel with bevacizumab in localized high-risk prostate cancer.²³ In that phase II study of 41 men undergoing RP, 29% achieved a greater than 50% reduction in tumor volume as measured by magnetic resonance imaging. The impact of chemotherapy and antiangiogenic therapy in the context of RP and radiotherapy is also an area of ongoing investigation.

In this study, the most common grade 3 toxicity was hypertension; approximately 20% of patients treated with ADT + bevacizumab experienced grade 3 events. This is higher than the rate (7%) observed in Cancer and Leukemia Group B 90401 (CALGB 90401 [Alliance] A Randomized Double-Blinded Placebo Controlled Phase III Trial Comparing Docetaxel and Prednisone With and Without Bevacizumab [IND #7921, NSC #704865] in Men With Hormone Refractory Prostate Cancer), a phase III trial of docetaxel with or without bevacizumab in mCRPC. Furthermore, we demonstrate that therapy was associated with increased lipids, which returned to baseline after discontinuation of treatment. This finding is consistent with multiple prospective studies that demonstrated lipid alterations with ADT.^{24,25} The effect on lipid levels was more pronounced in the ADT + bevacizumab arm. Although the study was not powered to detect differences in the two cohorts, it was reassuring that levels returned to baseline after therapy was discontinued. Bevacizumab is not being further developed for any stage of prostate cancer; however, newer anti-VEGF agents are worthy of investigation in combination with other active therapies. The balance of benefit compared with toxicities will remain important.

Given the limited efficacy of VEGF-targeted therapies in unselected patients, we measured a broad set of relevant CAFs and evaluated their association with clinical outcomes, screening for candidate markers that predicted benefit from bevacizumab. We found that lower pretreatment levels of leptin, IL-2, and tumor necrosis factor alpha were associated with shorter RFS. Of these, perhaps the most intriguing is leptin. Patients with low leptin had a higher risk for relapse, but this relationship was confined to those without metastasis. Higher leptin is linked to obesity and metabolic syndrome in humans, but studies that examined the association between leptin and the risk of prostate cancer have been contradictory.²⁶ We hypothesized that leptin may have an impact on baseline testosterone levels and testosterone recovery after treatment. Patients with higher leptin had lower baseline testosterone and, in patients who achieved testosterone recovery, there was a trend for longer time to testosterone recovery in those with higher leptin (10.2 months for patients with less than or equal to median leptin *v* 9.7 months for patients with greater than median leptin).

Also of interest was our finding of a relationship between pretreatment IL-6 and osteopontin and relative benefit from bevacizumab. In patients with higher levels, those treated with bevacizumab were less likely to experience relapse. However, we found no difference in RFS by treatment in patients with lower levels. Like leptin, IL-6 is an adipokine, but its biologic significance is likely greater in castration-resistant than in castration-sensitive disease. The role of osteopontin, which is involved in bone remodeling, immune response, and inflammation, is less clear in prostate cancer.^{27,28} Our data are consistent with renal cell carcinoma, in which higher levels of both osteopontin and IL-6 have been linked to increased benefit from VEGF-targeted therapy.^{29,30} These biomarkers warrant further investigation in the context of anti-VEGF therapies.

Although this was a randomized, phase II study, there were several limitations. We did not use the stratified log-rank test intended for the primary analysis, given imbalances in the number of patients per strata. Furthermore, the biomarker analysis was exploratory in nature without adjustment for multiple comparisons.

In conclusion, we demonstrated that short-term ADT + bevacizumab was feasible and resulted in improvements in RFS compared with ADT alone. We identified biomarkers with potential prognostic and predictive potential. Given the expanding treatment armamentarium for hormone-sensitive prostate cancer, predictive biomarkers are necessary to identify patients likely to benefit from any approach incorporating anti-VEGF therapy.²⁰ Our data suggest that ADT + bevacizumab may benefit a subset of patients with hormone-sensitive disease. We provide a rationale for combining VEGF therapy with ADT to prolong the off-ADT cycle during intermittent ADT. Long-term follow-up is needed to determine whether some patients will have durable PSA responses with testosterone recovery and be able to remain off further prostate cancer therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Robert W. Ross, Philip W. Kantoff, Mary-Ellen Taplin

Financial support: Amado J. Zurita, Mary-Ellen Taplin

Administrative support: Philip W. Kantoff, Mary-Ellen Taplin

Provision of study materials or patients: Amado J. Zurita, Michael A. Carducci

Collection and assembly of data: Rana R. McKay, Amado J. Zurita, Lillian Werner, Justine Y. Bruce, Michael A. Carducci, Mark N. Stein, Elisabeth I. Heath, Arif Hussain, Christopher J. Sweeney, Susan F. Slovin, Mary-Ellen Taplin

Data analysis and interpretation: Rana R. McKay, Amado J. Zurita, Lillian Werner, Michael A. Carducci, Hai T. Tran, Mary-Ellen Taplin

Manuscript writing: All authors

Final approval of manuscript: All authors

REFERENCES

1. Agarwal PK, Sadetsky N, Konety BR, et al: Treatment failure after primary and salvage therapy for prostate cancer: Likelihood, patterns of care, and outcomes. *Cancer* 112:307-314, 2008
2. Hussain M, Tangen CM, Berry DL, et al: Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med* 368:1314-1325, 2013
3. Lin J, Kelly WK: Targeting angiogenesis as a promising modality for the treatment of prostate cancer. *Urol Clin North Am* 39:547-560, 2012
4. Bok RA, Halabi S, Fei DT, et al: Vascular endothelial growth factor and basic fibroblast growth factor urine levels as predictors of outcome in hormone-refractory prostate cancer patients: A Cancer and Leukemia Group B study. *Cancer Res* 61:2533-2536, 2001
5. Duque JL, Loughlin KR, Adam RM, et al: Measurement of plasma levels of vascular endothelial growth factor in prostate cancer patients: Relationship with clinical stage, Gleason score, prostate volume, and serum prostate-specific antigen. *Clinics (Sao Paulo)* 61:401-408, 2006
6. George DJ, Halabi S, Shepard TF, et al: The prognostic significance of plasma interleukin-6 levels in patients with metastatic hormone-refractory prostate cancer: Results from Cancer and Leukemia Group B 9480. *Clin Cancer Res* 11:1815-1820, 2005
7. Nicholson B, Gulding K, Conaway M, et al: Combination antiangiogenic and androgen deprivation therapy for prostate cancer: A promising therapeutic approach. *Clin Cancer Res* 10:8728-8734, 2004
8. Escudier B, Pluzanska A, Koralewski P, et al: Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: A randomised, double-blind phase III trial. *Lancet* 370:2103-2111, 2007
9. Kreisl TN, Kim L, Moore K, et al: Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol* 27:740-745, 2009
10. Pujade-Lauraine E, Hilpert F, Weber B, et al: Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *J Clin Oncol* 32:1302-1308, 2014
11. Reck M, von Pawel J, Zatloukal P, et al: Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for non-squamous non-small-cell lung cancer: AVAIL. *J Clin Oncol* 27:1227-1234, 2009
12. Saltz LB, Clarke S, Díaz-Rubio E, et al: Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. *J Clin Oncol* 26:2013-2019, 2008
13. Sandler A, Gray R, Perry MC, et al: Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 355:2542-2550, 2006
14. 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* 30:1534-1540, 2012
15. 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* 26:1148-1159, 2008
16. Michaelson MD, Oudard S, Ou YC, et al: Randomized, placebo-controlled, phase III trial of sunitinib plus prednisone versus prednisone alone in progressive, metastatic, castration-resistant prostate cancer. *J Clin Oncol* 32:76-82, 2014
17. Petrylak DP, Vogelzang NJ, Budnik N, et al: Docetaxel and prednisone with or without lenalidomide in chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (MAINSAIL): A randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol* 16:417-425, 2015
18. Smith MR, De Bono JS, Sternberg CN, et al: Final analysis of COMET-1: Cabozantinib (Cabo) versus prednisone (Pred) in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) previously treated with docetaxel (D) and abiraterone (A) and/or enzalutamide (E). *J Clin Oncol* 33, 2015 (suppl 7; abstr 139)
19. Tannock IF, Fizazi K, Ivanov S, et al: Aflibercept versus placebo in combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): A phase 3, double-blind randomised trial. *Lancet Oncol* 14:760-768, 2013
20. Sweeney CJ, Chen YH, Carducci M, et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 373:737-746, 2015
21. Sweeney CJ, Miller KD, Sissons SE, et al: The antiangiogenic property of docetaxel is synergistic with a recombinant humanized monoclonal antibody against vascular endothelial growth factor or 2-methoxyestradiol but antagonized by endothelial growth factors. *Cancer Res* 61:3369-3372, 2001
22. McKay RR, Gray KP, Hayes JH, et al: Docetaxel, bevacizumab, and androgen deprivation therapy for biochemical disease recurrence after definitive local therapy for prostate cancer. *Cancer* 121:2603-2611, 2015
23. Ross RW, Galsky MD, Febbo P, et al: Phase 2 study of neoadjuvant docetaxel plus bevacizumab in patients with high-risk localized prostate cancer: A Prostate Cancer Clinical Trials Consortium trial. *Cancer* 118:4777-4784, 2012
24. Saylor PJ, Smith MR: Metabolic complications of androgen deprivation therapy for prostate cancer. *J Urol* 189:S34-S42, 2013 (suppl 1); discussion S43-S44
25. Smith MR, Finkelstein JS, McGovern FJ, et al: Changes in body composition during androgen deprivation therapy for prostate cancer. *J Clin Endocrinol Metab* 87:599-603, 2002
26. Mistry T, Digby JE, Desai KM, et al: Obesity and prostate cancer: A role for adipokines. *Eur Urol* 52:46-53, 2007
27. Anborgh PH, Mutrie JC, Tuck AB, et al: Pre- and post-translational regulation of osteopontin in cancer. *J Cell Commun Signal* 5:111-122, 2011
28. Castellano G, Malaponte G, Mazzarino MC, et al: Activation of the osteopontin/matrix metalloproteinase-9 pathway correlates with prostate cancer progression. *Clin Cancer Res* 14:7470-7480, 2008
29. Nixon AB, Halabi S, Shterev I, et al: Identification of predictive biomarkers of overall survival (OS) in patients (pts) with advanced renal cell carcinoma (RCC) treated with interferon alpha (I) with or without bevacizumab (B): Results from CALGB 90206 (Alliance). *J Clin Oncol* 31, 2013 (suppl; abstr 4520)
30. Tran HT, Liu Y, Zurita AJ, et al: Prognostic or predictive plasma cytokines and angiogenic factors for patients treated with pazopanib for metastatic renal-cell cancer: a retrospective analysis of phase 2 and phase 3 trials. *Lancet Oncol* 13:827-837, 2012

GLOSSARY TERMS

androgen deprivation therapy (ADT): therapy which results in a reduction of circulating testosterone levels, which may be achieved by surgical castration, by LHRH agonists or antagonists, by androgen receptor blockers, or by androgen synthesis blockers.

angiogenesis: the process involved in the generation of new blood vessels. Although this is a normal process that naturally occurs and is controlled by so-called on and off switches, blocking tumor angiogenesis (antiangiogenesis) disrupts the blood supply to tumors, thereby preventing tumor growth.

bevacizumab: also called Avastin (Genentech, South San Francisco, CA). Bevacizumab is a recombinant, humanized, monoclonal antibody

that binds and neutralizes the vascular endothelial growth factor, thus acting as an antiangiogenic agent.

vascular endothelial growth factor (VEGF): 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 with poor prognosis. VEGF-A, -B, -C, -D, and -E are members of the larger family of VEGF-related proteins.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

A Randomized Phase II Trial of Short-Course Androgen Deprivation Therapy With or Without Bevacizumab for Patients With Recurrent Prostate Cancer After Definitive Local Therapy

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Rana R. McKay

Research Funding: Pfizer (Inst), Bayer Healthcare Pharmaceuticals (Inst)

Amado J. Zurita

Consulting or Advisory Role: Incyte

Research Funding: Pfizer

Lillian Werner

No relationship to disclose

Justine Y. Bruce

No relationship to disclose

Michael A. Carducci

Consulting or Advisory Role: Medivation, Astellas Pharma, Blue Earth Diagnostics, AstraZeneca

Mark N. Stein

Research Funding: Janssen Pharmaceuticals (Inst), Medivation (Inst), Oncocetivics (Inst), Merck Sharp & Dohme (Inst), Bavarian Nordic (Inst), AbbVie (Inst)

Elisabeth I. Heath

Honoraria: Bayer Diagnostics, Dendreon, Sanofi

Speakers' Bureau: Sanofi Pasteur MSD, Genentech

Research Funding: Tokai Pharmaceuticals (Inst), Seattle Genetics (Inst), Agensys (Inst), Dendreon (Inst), Genentech (Inst), Millennium Pharmaceuticals (Inst), Celldex (Inst), Inovio Pharmaceuticals (Inst), Celgene (Inst)

Arif Hussain

No relationship to disclose

Hai T. Tran

Honoraria: Teva Pharmaceuticals Industries

Consulting or Advisory Role: Teva Pharmaceuticals Industries

Research Funding: Amgen

Christopher J. Sweeney

Stock or Other Ownership: Leuchemix, BIND Biosciences

Consulting or Advisory Role: Sanofi, Janssen Biotech, Astellas Pharma, Bayer Healthcare Pharmaceuticals, BIND Biosciences, Genentech, AstraZeneca

Research Funding: Janssen Biotech (Inst), Exelixis (Inst), Astellas Pharma (Inst)

Patents, Royalties, Other Intellectual Property: Leuchemix: parthenolide, dimethylaminoparthenolide; Exelixis: abiraterone plus cabozantinib combination

Robert W. Ross

Employment: Bluebird Bio

Stock or Other Ownership: Bluebird Bio

Philip W. Kantoff

Stock or Other Ownership: Bellicum Pharmaceuticals, Blend Therapeutics, Metamark Genetics

Consulting or Advisory Role: Bavarian Nordic, Janssen Pharmaceuticals, Millennium Pharmaceuticals, MorphoSys, Pfizer, Astellas Pharma, Bellicum Pharmaceuticals, BIND Biosciences, Blend Therapeutics, Endocyte, Metamark Genetics, Medivation, Merck, MTG Biotherapeutics, OncoCellMDX, OncoGenex, SOTIO, Sanofi, Tokai Pharmaceuticals, Bayer Healthcare Pharmaceuticals, Genentech, Cristal Therapeutics, Ipsen Pharmaceuticals, Omnitura, MorphoSys

Research Funding: Medivation (Inst), Sanofi (Inst), OncoGenex (Inst), Aragon Pharmaceuticals (Inst), Amgen (Inst), Astellas Pharma (Inst), Bayer (Inst), Bavarian Nordic (Inst), Dendreon (Inst), Exelixis (Inst), Janssen (Inst)

Expert Testimony: Sanofi, Janssen Pharmaceuticals

Travel, Accommodations, Expenses: Sanofi, Janssen Pharmaceuticals, BIND Biosciences, Bavarian Nordic, Millennium Pharmaceuticals

Susan F. Slovin

Consulting or Advisory Role: Bayer Pharmaceuticals

Mary-Ellen Taplin

Honoraria: Medivation/Astellas Pharma, Janssen Oncology, Bayer Healthcare Pharmaceuticals, Tokai Pharmaceuticals

Consulting or Advisory Role: Medivation/Astellas Pharma, Janssen Oncology, Bayer Pharmaceuticals, Tokai Pharmaceuticals

Research Funding: Genentech (Inst), Medivation/Astellas Pharma (Inst), Janssen Oncology (Inst), Bayer Healthcare Pharmaceuticals (Inst), Tokai Pharmaceuticals (Inst)

Travel, Accommodations, Expenses: Medivation/Astellas Pharma, Janssen Oncology, Bayer Healthcare Pharmaceuticals

Acknowledgment

We thank the Prostate Cancer Clinical Trials Consortium for their support of this clinical trial.

Appendix

Table A1. Glucose, HgBA1c, and Lipid Trends at Baseline, During Treatment, and at the End of Treatment

Glucose, HgBA1c, or Lipid (mg/dL)*	ADT + Bevacizumab					ADT Alone				
	No.	%	Median	q1, q3	<i>P</i>	No.	%	Median	q1, q3	<i>P</i>
Glucose										
Baseline	65		99	92, 110	Reference	36		98	90, 103	Reference
> 110	15	23				6	17			
3 months on treatment	57		96	92, 109	.71	33		104	95, 114	.05
> 110	13	23				9	27			
End of treatment	57		99	92, 110	.86	32		98	90, 112	.90
> 110	13	23				7	22			
HgBA1c										
Baseline	65		5.6	5.4, 5.9	Reference	35		5.6	5.4, 5.8	Reference
> 6.5	6	9				2	6			
3 months on treatment	55		5.7	5.5, 6.0	.24	32		5.7	5.5, 6.3	.19
> 6.5	4	7				5	16			
End of treatment	53		5.6	5.3, 5.9	.78	29		5.6	5.4, 5.9	.96
> 6.5	4	8				3	10			
Total cholesterol										
Baseline	65		177	156, 196	Reference	35		162	144, 204	Reference
> 200	16	25				9	25			
3 months on treatment	61		213	181, 232	< .001	34		181	157, 207	.18
> 200	37	61				12	35			
End of treatment	56		203	186, 241	< .001	32		189	162, 203	.15
> 200	30	54				8	25			
6 months after treatment	35		180	160, 210	.21	10		167	134, 193	.88
> 150	10	29				2	25			
Triglycerides										
Baseline	65		114	82, 152	Reference	36		107	91, 153	Reference
> 150	17	26				10	27			
3 months on treatment	61		136	102, 189	.04	34		121	93, 152	.67
> 150	26	43				10	29			
End of treatment	56		146	98, 233	.02	30		118	84, 170	.96
> 150	25	45				8	27			
6 months after treatment	35		109	69, 177	.66	10		109	83, 145	.44
> 150	12	34				2	25			
High-density lipoprotein										
Baseline	65		48	32, 54	Reference	36		46	42, 56	Reference
< 40	13	20				4	11			
3 months on treatment	61		51	45, 63	.01	34		52	47, 60	.04
< 40	4	7				3	9			
End of treatment	56		51	45, 63	.04	31		53	45, 57	.13
< 40	7	13				4	13			
6 months after treatment	35		109	69, 177	.75	10		109	83, 145	.39
< 40	12	34				2	25			
Low-density lipoprotein										
Baseline	65		108	82, 124	Reference	35		92	75, 116	Reference
> 129	14	22				4	11			
3 months on treatment	61		123	108, 149	< .001	34		103	84, 115	.38
> 129	28	46				5	15			
End of treatment	55		122	102, 147	.02	31		207	85, 127	.16
> 129	23	42				5	15			
6 months after treatment	34		106	87, 133	.29	10		98	74, 114	.61
> 129	10	29				2	25			

NOTE. Glucose and lipid values were collected during fasting state. *P* values in bold are statistically significant.

Abbreviations: ADT, androgen deprivation therapy; HgBA1c, hemoglobin A1c.

*The unit of measure for glucose, HgBA1c, and lipids is mg/dL.

Table A2. Baseline Clinical Characteristics for Patients With Available Biomarker Data

Characteristic	ADT + Bevacizumab (n = 43)				ADT Alone (n = 21)				Entire Cohort (n = 64)			
	No.	%	Median	q1, q3	No.	%	Median	q1, q3	No.	%	Median	q1, q3
At diagnosis												
Gleason score												
6	4	9			2	10			6	9		
7	23	53			13	62			36	56		
8-10	15	35			6	28			21	33		
Unknown	1	3			0	0			1	2		
Prior RP	36	84			16	76			52	81		
Prior RT	51	72			21	100			52	81		
At baseline												
Age, years	43		66	60, 68	21		65	59, 71	64		66	60, 69
> 60	10	23			7	33			17	27		
≤ 60	33	77			14	67			47	73		
ECOG performance status												
0	39	91			20	95			59	92		
1	3	7			1	5			4	6		
Unknown	1	2			0	0			1	2		
Presence of metastatic disease	21	32			13	36			34	33		
Bone metastases	8	12			3	8			11	11		
Lymph node metastases	13	20			11	31			24	24		
PSA, ng/mL	41		6.0	3.3, 11.7	21		9.2	6.1, 18.9	62		7.0	3.8, 14.6*
PSADT, months	42		4.1	2.6, 7.6	21		4.4	3.0, 9.2	63		4.3	2.6, 8.1
Testosterone, ng/dL	42		358	267, 428	21		393	302, 491	62		358	277, 466
Alkaline phosphatase, U/L	41		61	52, 78	21		66	60, 70	62		65	53, 78
Hemoglobin, g/dL	42		14.4	13.8, 15.3	21		14.6	14.0, 15.2	63		14.4	13.9, 15.2

Abbreviations: ADT, androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; RP, radical prostatectomy; RT, radiotherapy.

*Minimum PSA was 0.3 ng/mL for the total cohort.

ADT With or Without Bevacizumab in Prostate Cancer

Table A3. Summary of Baseline Biomarker Levels

Biomarker	ADT + Bevacizumab (pg/mL) (n = 43)		ADT Alone (pg/mL) (n = 21)	
	Median	q1, q3	Median	q1, q3
Angiopoietin-2	2,142	1,557, 2,967	1,813	1,602, 3,284
BMP-9	119	82, 149	71	54, 138
Collagen	515	468, 593	511	451, 619
EGF	42	22, 68	52	19.2, 131
Endoglin	907	496, 1149	771	491, 944
Endothelin-1	74	51, 102	62	49, 93
GM-CSF	45.3	17.8, 105.8	74.9	22.7, 97.7
HGF	1,564	1,195, 2,073	1,599	1,006, 1,787
IFN- γ	4.3	1.9, 7.8	3.68	1.82, 8.9
IL-1 β	0.8	0.4, 1.4	0.50	0.3, 1.2
IL-2	1.2	0.7, 2.0	0.68	0.4, 1.8
IL-5	0.5	0.3, 1.0	0.57	0.4, 1.0
IL-6	0.7	0.4, 1.0	0.52	0.3, 1.5
IL-7	1.9	0.7, 3.1	2.16	1.1, 3.4
IL-8	1.6	1.2, 2.5	1.66	0.6, 2.0
IL-10	2.4	1.1, 3.3	1.77	0.7, 4.4
IL-12	0.4	0.1, 1.3	0.68	0.2, 1.3
IL-13	1.5	0.4, 2.8	1.45	0.4, 2.9
Leptin	13,755	6,570, 25,762	10,179	6,924, 15,333
Osteocalcin	10,063	7,975, 13,166	7,895	6,226, 18,118
Osteopontin	17,105	10,804, 21,462	19,302	13,709, 29,273
Osteoprotegerin	186	147, 254	169	124, 232
PLGF	45	33, 68	48	28, 66
SDF-1 α/β	4,294	3,173, 5,463	4,226	3,745, 5,383
sgp130	119,963	93,763, 139,225	111,333	92,805, 129,868
sIL-6R	17,518	14,537, 23,884	14,652	10,924, 19,589
sVEGFR-2	6,166	4,727, 8,256	6,410	3,773, 7,562
sVEGFR-3	2,148	1,528, 2,974	2,238	1,879, 2,789
TIMP-1	193	164, 218	187	168, 240
TNF- α	1.5	1.1, 2.8	0.97	0.6, 2.9
TRAIL*	24	18, 36	22	18, 30
VEGF- α	381	256, 683	403	234, 560

Abbreviations: ADT, androgen deprivation therapy; BMP, bone morphogenetic protein; EGF, epidermal growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HGF, hepatocyte growth factor; IFN, interferon; IL, interleukin; PLGF, placental growth factor; SDF, stromal cell-derived factor; sgp130, soluble gp130; sIL-6R, soluble interleukin 6 receptor; sVEGFR, soluble vascular endothelial growth factor receptor; TIMP, tissue inhibitor of metalloproteinases; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand; VEGF, vascular endothelial growth factor.

*At baseline, n = 28 for the ADT + bevacizumab arm and n = 14 for the ADT-alone arm.

Table A4. Association of Treatment and Percentage Change of Markers From Baseline to Therapy Completion (6 months)

Marker	ADT + Bevacizumab (pg/mL) (n = 22)		ADT Alone (pg/mL) (n = 13)		P
	Median (%)	q1, q3 (%)	Median (%)	q1, q3 (%)	
Angiopoietin-2	-6	-26, 1	-1	-15, 4	.37
BMP-9	19	-2, 54	37	10, 55	.39
Collagen	4	-9, 23	0.3	-11, 16	.62
EGF	28	-29, 77	-1	-24, 91	.71
Endoglin	-5	-26, 45	1	-25, 24	.76
Endothelin-1	-12	-35, 26	0.5	-6, 18	.63
GM-CSF	-16	-36, 3	5	-35, 31	.26
HGF	-9	-36, 7	-6	-12, 19	.17
IFN- γ	-19	-45, 37	4	-28, 73	.24
IL-1 β	-5	-41, 4	24	-13, 73	.04
IL-2	-8	-32, 26	31	-18, 105	.08
IL-5	-30	-46, 9	0	-39, 66	.29
IL-6	-10	-36, 26	12	-41, 38	.55
IL-7	-8	-23, 14	-16	-33, 0	.31
IL-8	-11	-29, 10	-6	-25, 36	.52
IL-10	-22	-41, 0	0	-18, 107	.11
IL-12	0	-12, 22	4	-4, 24	.57
IL-13	0	-18, 39	0	-175, 175	.71
Leptin	60	20, 111	22	-2, 83	.09
Osteocalcin	-0.3	-27, 26	-25	-40, 12	.25
Osteopontin	45	2, 56	12	-3, 34	.14
Osteoprotegerin	3	-16, 40	6	-10, 21	.78
PLGF	-7	-27, 44	7	-2, 44	.47
SDF-1 α/β	6	-9, 18	-2	-4, 12	.84
sgp130	3	-8, 17	12	-12, 36	.21
sIL-6R	8	-19, 17	4	-5, 40	.34
sVEGFR-2	5	-19, 35	4	-10, 36	.76
sVEGFR-3	3	-20, 30	-10	-21, 10	.34
TIMP-1	6	-10, 22	-0.2	-9, 3	.37
TNF- α	-2	-28, 27	42	-15, 79	.22
TRAIL*	3	-11, 28	3	-29, 34	> .99
VEGF- α	-22	-44, 7	2	-9, 20	.06

Abbreviations: BMP, bone morphogenetic protein; EGF, epidermal growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HGF, hepatocyte growth factor; IFN, interferon; IL, interleukin; PLGF, placental growth factor; SDF, stromal cell-derived factor; sgp130, soluble gp130; sIL-6R, soluble interleukin 6 receptor; sVEGFR, soluble vascular endothelial growth factor receptor; TIMP, tissue inhibitor of metalloproteinases; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand; VEGF, vascular endothelial growth factor.

*For the ADT + bevacizumab arm, n = 28 at baseline, and n = 18 at 6 months; for the ADT-alone arm, n = 14 at baseline, and n = 9 at 6 months.

ADT With or Without Bevacizumab in Prostate Cancer

Table A5. Univariate Analysis of the Association of Markers at Baseline and RFS

Marker	No. of Patients	No. of Events	Median RFS	<i>P</i>
Angiopoietin-2				.68
≤ median	32	28	11	
> median	32	28	12	
BMP-9				.11
≤ median	32	27	12	
> median	32	29	10	
Collagen				.71
≤ median	32	28	12	
> median	32	28	11	
EGF				.33
≤ median	32	27	12	
> median	32	27	11	
Endoglin				.31
≤ median	33	29	12	
> median	31	27	10	
Endothelin-1				.77
≤ median	32	28	11	
> median	32	28	12	
GM-CSF				.80
≤ median	32	28	10	
> median	32	28	12	
HGF				.64
≤ median	32	29	12	
> median	32	27	11	
IFN-γ				.42
≤ median	32	27	11	
> median	32	29	12	
IL-1β				.15
≤ median	32	28	11	
> median	32	28	12	
IL-2				.006
≤ median	32	29	10	
> median	32	27	12	
IL-5				.33
≤ median	32	27	11	
> median	32	29	12	
IL-6				.07
≤ median	32	28	10	
> median	32	28	12	
IL-7				.28
≤ median	32	27	11	
> median	32	29	12	
IL-8				.18
≤ median	32	28	11	
> median	32	28	12	
IL-10				.37
≤ median	32	28	10	
> median	32	28	12	
IL-12				.36
≤ median	32	29	11	
> median	32	27	12	
IL-13				.88
≤ median	32	28	12	
> median	32	28	11	
Leptin				.005
≤ median	32	29	10	
> median	32	27	13	
Osteocalcin				.69
≤ median	32	28	11	
> median	32	28	12	
Osteopontin				.11
≤ median	32	29	10	
> median	32	27	12	
Osteoprotegerin				.31
≤ median	32	29	11	
> median	32	27	12	

(continued on following page)

Table A5. Univariate Analysis of the Association of Markers at Baseline and RFS (continued)

Marker	No. of Patients	No. of Events	Median RFS	<i>P</i>
PLGF				.73
≤ median	32	28	12	
> median	32	28	11	
SDF-1 α/β				.59
≤ median	32	27	10	
> median	32	29	12	
sgp130				.60
≤ median	32	27	12	
> median	32	29	11	
sIL-6R				.56
≤ median	32	27	12	
> median	32	29	12	
sVEGFR-2				.44
≤ median	32	28	11	
> median	32	28	12	
sVEGFR-3				.19
≤ median	36	30	12	
> median	28	26	11	
TIMP-1				.30
≤ median	32	27	10	
> median	32	29	12	
TNF- α				.048
≤ median	32	28	10	
> median	32	28	12	
TRAIL				.44
≤ median	21	19	10	
> median	21	18	10	
VEGF- α				.52
≤ median	32	29	11	
> median	32	27	12	

NOTE. *P* values in bold are statistically significant.

Abbreviations: BMP, bone morphogenetic protein; EGF, epidermal growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HGF, hepatocyte growth factor; IFN, interferon; IL, interleukin; PLGF, placental growth factor; RFS, relapse-free survival; SDF, stromal cell-derived factor; sgp130, soluble gp130; sIL-6R, soluble interleukin-6 receptor; sVEGFR, soluble vascular endothelial growth factor receptor; TIMP, tissue inhibitor of metalloproteinases; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand; VEGF, vascular endothelial growth factor.

ADT With or Without Bevacizumab in Prostate Cancer

Table A6. Phase III Studies of Antiangiogenic Agents in mCRPC

Agent	Mechanism of Action	No.	Population	Treatment Arms	Primary End Point	OS (months)	<i>P</i>	PFS (months)	<i>P</i>
Bevacizumab ¹⁴	Monoclonal antibody to VEGF	1,050	mCRPC, chemotherapy naïve	Docetaxel + prednisone + bevacizumab	OS	22.6	.181	9.9	< .001
				Docetaxel + prednisone + placebo		21.5		7.5	
Cabozantinib ¹⁸	VEGFR-MET inhibitor	1,028	mCRPC, docetaxel and abiraterone and/or enzalutamide pretreated	Cabozantinib	OS	11	.212	5.5	< .001
				Placebo		9.8		2.8	
Sunitinib ¹⁶	VEGFR inhibitor	873	mCRPC, docetaxel pretreated	Sunitinib	OS	13.1	.168	5.6	< .001
				Placebo		11.8		4.1	
Aflibercept ¹⁹	Recombinant fusion protein, which acts as a decoy receptor for VEGF	1,224	mCRPC, chemotherapy naïve	Docetaxel + prednisone + aflibercept	OS	22.1	.38	6.9	.31
				Docetaxel + prednisone + placebo		21.2		6.2	

Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PFS, progression-free survival; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.