Cancer Therapy: Clinical

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Phase II Randomized Study of Figitumumab plus Docetaxel and Docetaxel Alone with Crossover for Metastatic Castration-Resistant Prostate Cancer

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Abstract

Purpose: Figitumumab is a human IgG_2 monoclonal antibody targeting insulin-like growth factor 1 receptor (IGF-1R), with antitumor activity in prostate cancer. This phase II trial randomized chemotherapy-naïve men with progressing castration-resistant prostate cancer to receive figitumumab every 3 weeks with docetaxel/prednisone (Arm A) or docetaxel/prednisone alone (Arm B1). At progression on Arm B1, patients could cross over to the combination (Arm B2).

Experimental Design: Prostate-specific antigen (PSA) response was the primary endpoint; response assessment on the two arms was noncomparative and tested separately; $H_0 = 0.45$ versus $H_A = 0.60$ ($\alpha = 0.05$; $\beta = 0.09$) for Arm A; $H_0 = 0.05$ versus $H_A = 0.20$ ($\alpha = 0.05$, $\beta = 0.10$) for Arm B2. A comparison of progression-free survival (PFS) on Arms A and B1 was planned.

Results: A total of 204 patients were randomized and 199 treated (Arm A: 97; Arm B1: 102); 37 patients crossed over to Arm B2 (median number of cycles started: Arm A = 8; B1 = 8; B2 = 4). PSA responses occurred in 52% and 60% of Arms A and B1, respectively; the primary PSA response objective in Arm A was not met. Median PFS was 4.9 and 7.9 months, respectively (HR = 1.44; 95% confidence interval, 1.06–1.96). PSA response rate was 28% in Arm B2. The figitumumab combination appeared more toxic, with more treatment-related grade 3/4 adverse events (75% vs. 56%), particularly hyperglycemia, diarrhea, and asthenia, as well as treatment-related serious adverse events (41% vs. 15%), and all-causality grade 5 adverse events (18% vs. 8%).

Conclusion: IGF-1R targeting may merit further evaluation in this disease in selected populations, but combination with docetaxel is not recommended. *Clin Cancer Res; 20(7); 1925–34. ©2014 AACR.*

Introduction

Prostate cancer is the second most common male cancer diagnosed globally, and the third leading cause of death among men in developed countries (1). Targeting androgen receptor signaling remains the standard of care in advanced prostate cancer (2, 3), reducing prostate-specific antigen (PSA) expression, inducing tumor regression, and relieving symptoms. However, PSA levels eventually increase in many patients, suggestive of re-activation of androgen receptor signaling and progression to castration-resistant prostate cancer (CRPC). Ligand-dependent and -independent resistance mechanisms have been described; postulated ligand-independent mechanisms include androgen receptor splice variants, androgen receptor modulation by kinase signaling, and epithelial–mesenchymal transition (3).

Until recently, the main treatment for CRPC was docetaxel once every 3 weeks in combination with prednisone, which is associated with a modest median overall survival of 19 months (4, 5). Recently, cabazitaxel (a cytotoxic chemotherapy; ref. 6), abiraterone (an inhibitor of androgen biosynthesis; ref. 7), enzalutamide (8), radium-223 (9), and sipuleucel-T (an active cellular immunotherapy; ref. 10) have proven efficacious for this disease. Despite these advances, treatment options for men with CRPC remain limited.

The insulin-like growth factor (IGF) pathway is required for normal growth and development, and is linked with carcinogenesis (11). In prostate cancer, the IGF pathway and androgen receptor signaling interact in multiple ways, with elevated IGF-1 receptor (IGF-1R) concentration being

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Translational Relevance

Insulin-like growth factor 1 receptor (IGF-1R) signaling is implicated in prostate carcinogenesis, and preclinical and clinical studies have shown that targeting IGF-1R has antitumor activity in prostate cancer models. Figitumumab is a human IgG_2 monoclonal antibody that binds and downregulates IGF-1R. In a pre-prostatectomy study in treatment-naïve patients, single-agent figitumumab markedly reduced prostate-specific antigen levels. These data led to a randomized phase II trial in patients with chemotherapy-naïve castration-resistant metastatic prostate cancer. Patients received either docetaxel/prednisone plus figitumumab, or docetaxel/prednisone alone, with crossover at progression. The addition of figitumumab to docetaxel/prednisone did not provide benefit, but antitumor activity was observed in patients who progressed on docetaxel/prednisone alone and crossed over to docetaxel/prednisone plus figitumumab. Further research on the blockade of IGF-1R/PI3K/AKT signaling is merited in advanced prostate cancer, perhaps particularly in speckle-type POZ protein (SPOP)-mutated disease where raised steroid receptor coactivator-3 levels generate high IGF ligand levels, in combination with next-generation androgen receptor targeting drugs.

associated with increased risk of prostate cancer (12–16). Aberrant IGF-1R signaling through the PI3K/AKT pathway is implicated in prostate carcinogenesis through loss of phosphatases, including phosphatase and tensin homolog. Circulating IGF-1 also promotes androgen-responsive growth in human prostate cancer cell xenografts (17). Elevated expression of IGF-1 mRNA, as well as increased IGF-1R mRNA expression levels, have been correlated with progression of human prostate cancer models to androgen independence (18, 19). Furthermore, not only has IGF-1 been shown to directly activate the androgen receptor in the absence of androgens in prostatic tumor cell lines (20), contributing to the failure of androgen deprivation therapy and the development of CRPC, but components of the IGF pathway may be required elements for androgen-induced gene expression. This is supported by the reduced PSA accumulation and tumor growth observed in IGF-1–deficient human prostate cancer cell xenografts (17).

Figitumumab (CP-751,871) is a fully human IgG_2 monoclonal antibody that binds and downregulates IGF-1R, the main receptor in the IGF signaling pathway (21). In an androgen-independent model of prostate tumor growth, blockade of IGF-1R not only induced cell-cycle arrest, but also downregulated androgen-regulated gene expression and was associated with decreased androgen receptor nuclear localization (22, 23). IGF-1R blockade also increases sensitivity to chemotherapy tumor cell kill with cytotoxic chemotherapies in preclinical models (21, 24). In a phase Ib study that included 22 patients with advanced CRPC, figitumumab with docetaxel was well tolerated with promising antitumor activity (25). Moreover, figitumumab had antitumor activity as a single agent in newly diagnosed hormone-therapy naïve patients awaiting prostatectomy (26). Based on these findings, this randomized phase II study (NCT00313781) was undertaken to assess the efficacy of figitumumab in combination with docetaxel/prednisone in chemotherapy-naïve patients with metastatic CRPC.

Patients and Methods

Patients

Patients with histologically confirmed prostate cancer and evidence of metastatic disease either on bone scans or computed tomography who were chemotherapy-/radioisotope-naïve were included. For trial entry, CRPC was defined as disease progression after at least one hormonal treatment, with castrate levels of testosterone (<50 ng/dL or <1.7 nmol/L). Disease progression was defined as any of the following: an increase in PSA >50% over nadir on hormonal therapy according to the Prostate-Specific Antigen Working Group criteria published in 1999 (27); disease progression as defined by Response Evaluation Criteria in Solid Tumors (RECIST version 1.0; ref. 28); or $\geq$2 new bone lesions.

Additional eligibility criteria included: concurrent luteinizing hormone-releasing hormone (LHRH) agonist if the patient was not surgically castrated; Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$2; any adverse events from prior cancer therapy resolved to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE; version 3.0) grade $\leq$1 or not considered a safety risk by sponsor and investigator; stable pain level; and adequate hematologic and blood chemistry parameters.

Patients were excluded if they had received anti-androgen therapy within 4 to 6 weeks of study start (dependent on the therapy); radiation to >25% of bone marrow; local radiation within 2 weeks; chronic high-dose immunosuppressive steroids within 2 weeks; or products known to affect PSA level.

The study was conducted according to the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The study protocol was approved by the local regulatory authorities and institutional review boards at all participating institutions. Signed, informed consent was obtained from all patients before study entry.

Study design and treatment

This was a randomized, open-label, 2-arm, phase II study conducted at 16 sites. Patients were randomly assigned in a 1:1 ratio to receive either figitumumab 20 mg/kg (or 10 mg/kg before protocol amendment #3 in February 2007) by intravenous infusion plus docetaxel 75 mg/m^2 by infusion and prednisone 5 mg twice daily (Arm A), or docetaxel/prednisone (Arm B1) every 3 weeks. Patients randomized to docetaxel/prednisone alone were able to cross over to receive figitumumab and docetaxel/prednisone (combination treatment) following disease progression

(Arm B2). Inhibition of tubulin function by docetaxel has been shown to impact androgen receptor function and block cytoplasmic-to-nucleus shuttling of the androgen receptor (29). This in turn can upregulate signaling through the IGF-1R/PI3K/AKT axis. Therefore, there was a strong mechanistic rationale for pursuing this crossover. To be eligible to cross over, patients receiving docetaxel/prednisone must have satisfied one of the following criteria within 6 weeks from the last docetaxel administration after at least 3 courses of docetaxel: disease progression demonstrated by $\geq$2 new bone lesions, RECIST progression, PSA progression (defined in the next section), or increased pain at the metastatic site requiring >2 weeks of narcotics, radiation, or doubling the dose of corticosteroids.

All study drugs were started on day 1 of each 3-week cycle. Protocol-specified treatment interruptions and dose reductions were permitted to manage adverse events. No more than 2 dose reductions of docetaxel were permitted (to 60 and 45 mg/m^2). Figitumumab treatment could be delayed by up to one cycle (6 weeks from previous dose) for treatment-related toxicities. A maximum of 2 dose reductions of figitumumab were permitted (to 10 and 6 mg/kg).

Treatment continued until disease progression (biochemical, clinical, or imaging), unacceptable toxicity, or completion of 12 months of treatment (unless there were compelling reasons to continue). Patients with disease progression determined by PSA levels alone could continue treatment if it was deemed to be providing a clinical benefit, as could those with worsening bone scans.

Study endpoints and assessments

The primary endpoint was PSA response (defined below) in both Arm A and Arm B2. Secondary endpoints included progression-free survival (PFS), safety, and biomarker evaluation, including the effect of study drug on the total number of circulating tumor cells (CTC).

To acquire these data, a PSA baseline reference value was obtained from blood samples taken before the first dose of study drug. Additional samples were taken on day 15 of each cycle, again at the end of treatment, and during the follow-up visit. The primary efficacy summary measure was PSA response rate, where PSA response was defined as best response of either PSA normalization or partial PSA response.

The categories of best response were: PSA normalization, partial PSA response, PSA progression, stable PSA response, RECIST progression, symptomatic deterioration, early death, and indeterminate. PSA normalization was defined as PSA $\leq$0.2 ng/mL on 2 successive evaluations at least 3 weeks apart and no imaging or clinical evidence of disease progression. Partial PSA response was defined as $\geq$50% decrease in PSA from baseline (defined as the last PSA value before crossover for patients entering Arm B2), on 2 successive evaluations at least 3 weeks apart and no imaging or clinical evidence of disease progression. PSA progression was defined at the timepoint when PSA increased on 2 successive evaluations taken 1 week apart after dosing in cycle 3, and was defined as follows: (i) an increase in PSA $\geq$50% and $\geq$5 ng/mL above the nadir of all on-study evaluations before the current evaluation, for subjects who achieved PSA response earlier during study; (ii) an increase in PSA $\geq$25% over baseline, for subjects whose PSA had not decreased on study; (iii) an increase in PSA $\geq$25% and $\geq$5 ng/mL over the nadir of all on-study evaluations before the current evaluation, for patients whose PSA had decreased on study but had not met criteria for PSA response. Stable PSA response was defined as PSA changes documented at least 6 weeks after enrollment that did not meet the criteria for PSA normalization, partial PSA response or confirmed PSA progression.

RECIST progression was defined as the best response when objective progression per RECIST was documented within 12 weeks from enrollment and the patient did not qualify for any of the best responses defined above. Symptomatic deterioration was defined as the best response when a patient discontinued treatment because of global deterioration in health status within 12 weeks from enrollment and did not qualify for any of the best responses defined above. Early death was defined as the best response when a patient died within 6 weeks from enrollment and did not qualify for any of the best responses defined above. Finally, indeterminate was defined as the best response when none of the best responses defined above were applicable.

PFS was defined as the time from randomization to first event of disease progression, which was defined as one or more of the following: confirmed PSA progression; $\geq$2 new bone lesions; progressive disease according to RECIST; increased pain requiring one or more of the following: narcotics for >2 weeks, radiation therapy, doubling the corticosteroid dose, radionuclide therapy, or palliative chemotherapy; intervention for any prostate cancer-related events (e.g., radiation, surgery); new symptoms related to tumor growth; or death because of any cause. Patients were followed until disease progression irrespective of whether they were receiving study drug before progression.

For enumeration of CTCs, blood samples were collected at screening, approximately 30 minutes before dosing in odd numbered cycles and at end of treatment. The CTCs were enumerated using the CellSearch system (Immunicon) as previously described (30). Patients enrolled in this study were not required to have measurable disease; however, disease assessment was undertaken to document imaging evidence of progression.

Statistical analysis

This study evaluated the PSA response rate of the combination of figitumumab with docetaxel/prednisone in chemotherapy-naïve patients (Arm A). The primary efficacy endpoint, PSA response, was evaluated in all patients who received at least one dose of study drug (except those who discontinued before cycle 3 because of PSA progression only) and had a baseline PSA reference value. In Arm A, the null hypothesis was H_0: $P \leq 0.45$ and the alternative was H_A: $P > 0.45$, where P is the probability of PSA response. Because the hypotheses were one-sided, testing was done at one-sided level $P = 0.05$. With a planned sample size of 100, the study

had power 91% for an alternative of $P = 0.6$. If the null hypothesis was rejected at the one-sided 0.05 significance level, figitumumab would be considered active in this setting.

This study also evaluated the PSA response rate of combination treatment after progression on docetaxel/prednisone alone (Arm B2). A 40-patient, 2-stage design (31) was used to test the null hypothesis H_0: $P \leq 0.05$ versus the alternative H_A: $P > 0.05$, ensuring 5% probability of type I error and 90% power for an alternative of 0.2. Twenty patients receiving combination treatment after progression on docetaxel/prednisone alone were to be enrolled in the first stage; if one or more PSA responses were observed among them, an additional 20 patients receiving combination treatment were to be recruited. If 5 or more responses were observed among the 40 patients in Arm B2, the null hypothesis would be rejected.

Finally, to further explore efficacy of the regimen, a comparison of PFS on Arm A with PFS on Arm B using a 1-sided 0.1 significance level log-rank test was planned. If the true A/B HR were 0.67, the sample size would be large enough for adequate (90%) power to conclude regimen A to be of interest. Kaplan–Meier methods were used for estimation. The HR and 95% confidence interval (CI) were generated using proportional hazards regression modeling.

Results

Between October 2006 and July 2009, 204 patients were randomized equally between Arm A and Arm B1, of whom 199 were treated (97 on Arm A and 102 on Arm B1). Five patients in Arm A received figitumumab 10 mg/kg as starting dose before protocol amendment #3 in February 2007, whereas the other 92 patients in Arm A received figitumumab 20 mg/kg as starting dose. Patient demographics and baseline disease characteristics are presented in Table 1. The most frequently involved metastatic site was bone. Eighty-seven of 102 patients in Arm A were PSA response evaluable. Among the 15 unevaluable patients, 5 did not have treatment, 8 were treated but discontinued treatment prematurely (before cycle 3 because of PSA progression only), and 2 were without adequate baseline assessment.

In Arm B1, 37 patients progressed on docetaxel/prednisone and were crossed over to figitumumab plus docetaxel/prednisone (Arm B2); disease progression in these patients was based on PSA progression only ($n = 1$ 2; 32%), RECIST-defined progression only ($n = 10$; 27%), both PSA and RECIST progression ($n = 5$; 14%), and other ($n = 10$; 27%). Baseline characteristics of crossover patients were similar to those of Arm A and the entire Arm B1 cohort (Table 1). Five crossover patients were not evaluable for the primary endpoint: 4 had an inadequate baseline assessment and 1 discontinued treatment prematurely (Fig. 1).

Study drug exposure

The study treatments were given in 21-day cycles. The median number of treatment cycles started was 8 (range, 1–35 cycles) for Arm A, and 8 (range, 1–32 cycles) for Arm B1. In Arm A, the figitumumab infusion was interrupted or cycle delayed in 35 patients (36%) because of adverse events, and 7 patients (7%) required a reduction in the figitumumab dose. More patients in Arm A had a docetaxel dosing regimen modification because of adverse events than in Arm B1; the docetaxel infusion was interrupted or cycle delayed in 38 patients (39%) and 14 patients (14%) in Arms A and B1, respectively, whereas the docetaxel dose was reduced in 28 patients (29%) and 20 patients (20%), respectively. Arm B2 patients had had a minimum of 3 courses and a median of 6 cycles of docetaxel (range, 3–24 cycles) before crossover following disease progression on docetaxel/prednisone alone and went on to start a median of 4 treatment cycles of figitumumab (range, 2–26 cycles) and a median of 4 treatment cycles of docetaxel (range, 2–13 cycles). Adverse events led to a figitumumab infusion interruption or cycle delay in 9 patients (24%) and dose reduction in 3 patients (8%) from Arm B2, and to a docetaxel dosing delay in 10 patients (27%) and dose reduction in 8 patients (22%).

PSA response rate

In Arm A, none of the patients achieved PSA normalization; 45 (52%) patients had a partial PSA response and 27 (31%) patients had a stable PSA response. In Arms B1 and B2, PSA normalization was reported in 3 (3%) and 1 (3%) patients, respectively; 56 (57%) and 8 (25%) patients had a partial PSA response; and 21 (21%) and 9 (28%) patients had a stable PSA response.

The PSA response rate (PSA normalization plus partial PSA response; primary endpoint) was 52% (90% CI, 42.4–61.0) and 60% (90% CI, 51.4–68.5) in patients in Arm A and Arm B1, respectively (Table 2). Given that 87 patients in Arm A were PSA response evaluable, 48 or more observed PSA responses in Arm A were required to reject the null hypothesis at 1-sided significance level 0.05. Because 45 PSA responses were observed in Arm A, corresponding to a 1-sided P value of 0.125, the primary PSA response objective in Arm A was not met (i.e., there was no statistically significant evidence to conclude that Arm A had a PSA response rate greater than 45%).

For patients in Arm B2, a true PSA response probability of 0.20 or greater would be of interest, while a true PSA response probability of 0.05 or lower would not. Nine of 32 PSA evaluable patients were responders. The PSA response rate was 28% (90% CI, 15.5–43.9; Table 2), corresponding to a 1-sided P value of < 0.001; hence, the addition of figitumumab yielded a PSA response rate significantly greater than the null value of 5% in patients who had progressed on docetaxel/prednisone. Maximal PSA percent reductions from baseline are shown in Fig. 2.

Circulating tumor cells

In total, 46 patients in Arm A and 39 patients in Arm B1 had $\geq$5 CTCs per 7.5 mL blood at baseline (Table 1). The number of CTCs seemed to drop in both arms through

Table 1. Patient characteristics at baseline

Patient characteristic	Figitumumab + docetaxel/ prednisone (Arm A; $n = 102$)	Docetaxel/ prednisone alone[a] (Arm B1; $n = 102$)	Figitumumab + docetaxel/prednisone (crossover from B1; Arm B2; $n = 37$)[b]
Mean age, y (SD)	68.9 (7.4)	67.9 (7.5)	66.2 (6.4)
Ethnic background			
White	94 (92)	97 (95)	35 (95)
Black	4 (4)	2 (2)	1 (3)
Other	4 (4)	3 (3)	1 (3)
ECOG performance status, *n* (%)			
0	52 (51)	56 (55)	21 (57)
1	43 (42)	43 (42)	15 (41)
2	1 (<1)	2 (2)	1 (3)
Missing	6 (6)	1 (<1)	0
Measurable disease present, *n* (%)[c]	66 (65)	66 (65)	25 (68)
Lesion site, *n* (%)			
Bone	85 (83)	81 (80)	28 (76)
Pelvis	16 (16)	20 (20)	9 (24)
Lung	12 (12)	15 (15)	4 (11)
Liver	13 (13)	12 (12)	1 (3)
Mediastinum	5 (5)	10 (10)	2 (5)
Peritoneum	8 (8)	7 (7)	4 (11)
Other[d]	64 (63)	61 (60)	22 (59)
Number of lesion sites, *n* (%)			
1	27 (27)	24 (24)	9 (24)
2	25 (25)	23 (23)	9 (24)
3	19 (19)	13 (13)	6 (16)
4	7 (7)	11 (11)	4 (11)
>4	23 (22)	28 (28)	8 (22)
Missing	1 (<1)	3 (3)	1 (3)
Prior surgery, *n* (%)[e]	58 (57)	71 (70)	24 (65)
Prior radiation therapy, *n* (%)[e]	59 (58)	65 (64)	24 (65)
Prior hormonal therapy, *n* (%)[e]	93 (91)	96 (94)	34 (92)
Baseline PSA level, ng/mL[f]			
Mean (SD)	288.0 (500.9)	189.0 (314.4)	169.5 (234.1)
Median (range)	105.0 (6.1–3,683)	96.4 (6.3–2,124)	82.5 (0.4–1,095)
Patients with ≥5 CTCs per 7.5 mL, *n* (%)	46 (45)	39 (38)	17 (46)
Median number of CTCs per 7.5 mL blood (ULQ)	16.5 (10, 73)	52.0 (20, 192)	65.0 (18, 214)

Abbreviation: ULQ, upper and lower quartile.

[a]Figitumumab was added to treatment for patients progressed on docetaxel/prednisone alone.

[b]Patient characteristics for Arm B2 are as at the start of the study, not the status at crossover, with the exception of baseline PSA which was at time of crossover.

[c]At least 1 target lesion ≥2 cm (>1 cm by spiral computed tomography).

[d]Includes ascites, brain, breast, subcutaneous, and not reported.

[e]Not reported in Arms A and B1, respectively, for: prior surgery, $n = 1$ and $n = 3$; prior radiation therapy, $n = 1$ and $n = 3$ ($n = 1$ for Arm B2); prior hormonal therapy, $n = 3$ and $n = 2$ ($n = 1$ for Arm B2).

[f]Baseline PSA data not available for $n = 1$ each in Arms A and B1, and for $n = 2$ in Arm B2.

cycles 1 to 5, although this was most marked in patients receiving docetaxel/prednisone alone: the mean percentage decrease in CTCs from baseline at cycle 5 was 23% in the figitumumab plus docetaxel/prednisone arm and 41% in patients receiving docetaxel/prednisone alone. Analyses of CTCs were not pursued at crossover.

Progression-free survival

In Arms A, B1, and B2, respectively, 88 (91%), 77 (75%), and 31 patients (84%) had experienced a progression event at the time of analysis. In the majority of cases, these events were related to objective (PSA or RECIST-defined) progression; 87 patients (90%) in Arm A, 77 patients (75%) in

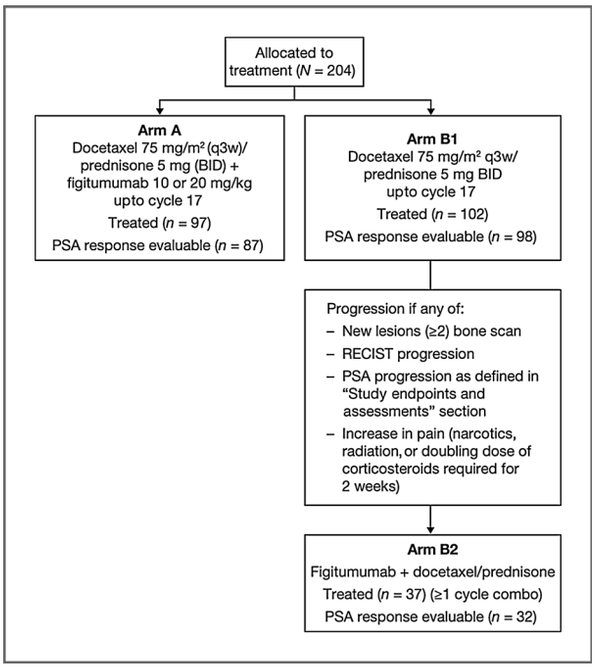

Figure 1. Study schema (CONSORT diagram).

Arm B1, and 30 patients (81%) in Arm B2 had objective progression. The remaining type of progression event was patient started a new treatment, with progression unknown (Arm A, $n = 1$; Arm B2, $n = 1$). Two patients withdrew their consent for additional follow-up before progression (Arms A and B1, $n = 1$ each), and 3 patients in Arm B1 started a new treatment without progression.

Median PFS after 171 events was 4.9 months (95% CI, 4.1–5.9) for patients in Arm A and 7.9 months (95% CI, 6.0–8.9) for patients in Arm B1 [HR = 1.442; 95% CI, 1.060–1.961; 2-sided log-rank test $P = 0.019$ (1-sided log-rank test $P = 0.991$); Fig. 3]. These data demonstrate that the results favor Arm B1. For patients in Arm B2, median PFS was 4.0 months (95% CI, 3.3–4.8).

Safety

Overall, there were more treatment-related grade 3/4 adverse events in Arm A than in Arm B1 (75% vs. 56%). In patients receiving figitumumab plus docetaxel/prednisone, neutropenia (not counting febrile neutropenia) was the most frequent grade 3/4 treatment-related adverse event (32%; Table 3). The incidence of grade 3/4 treatment-related neutropenia observed in Arms A and B1 was similar (32% and 33%, respectively). A clinically meaningful difference between Arms A and B1 was observed in the number of subjects with the following treatment-related adverse events: diarrhea (57.7%, 33.3%), decreased appetite (49.5%, 25.5%), fatigue (42.3%, 34.3%), asthenia (36.1%, 27.5%), hyperglycemia (33.0%, 13.7%), stomatitis (18.6%, 7.8%), muscle spasm (15.5%, 4.9%), and febrile neutropenia (12.4%, 6.9%).

More treatment-related serious adverse events (SAEs) were reported in patients receiving figitumumab plus docetaxel/prednisone compared with docetaxel/prednisone alone (41% vs. 15%). Febrile neutropenia was the most common SAE in both treatment arms (12% vs. 7%). In addition, 10 (27%) of 37 patients who progressed on docetaxel/prednisone had treatment-related SAEs while subsequently receiving figitumumab plus docetaxel/prednisone. In total, 17 (18%) grade 5 all-causality adverse events were reported in the figitumumab plus docetaxel/prednisone Arm A, compared with 8 (8%) in the docetaxel/prednisone alone Arm B1. Only 1 grade 5 all-causality adverse event was considered to be treatment-related: hypovolemic shock related to nausea, vomiting, and diarrhea occurring in a patient receiving figitumumab plus docetaxel/prednisone.

Treatment-related adverse events were the primary reason for treatment discontinuation in 15 (15%) and 12 (12%) patients in Arms A and B1, respectively, and in 4 (11%) patients in Arm B2.

Table 2. Best response[a] in evaluable patients

n (%)	Figitumumab + docetaxel/ prednisone (Arm A; $n = 87$)	Docetaxel/prednisone alone (Arm B1; $n = 98$)	Figitumumab + docetaxel/ prednisone (crossover from B1; Arm B2; $n = 32$)
PSA response; primary endpoint	45 (52)	59 (60)	9 (28)
90% CI	(42.4–61.0)	(51.4–68.5)	(15.5–43.9)
PSA normalization	0	3 (3)	1 (3)
Partial PSA response	45 (52)	56 (57)	8 (25)
Stable PSA	27 (31)	21 (21)	9 (28)
PSA progression	5 (6)	8 (8)	8 (25)
RECIST progression	1 (1)	1 (1)	1 (3)
Symptomatic deterioration	6 (7)	0 (0)	0 (0)
Early death	2 (2)	1 (1)	0 (0)
Indeterminate	1 (1)	8 (8)	5 (16)

[a]Best responses are defined in the section "Study Endpoints and Assessments."

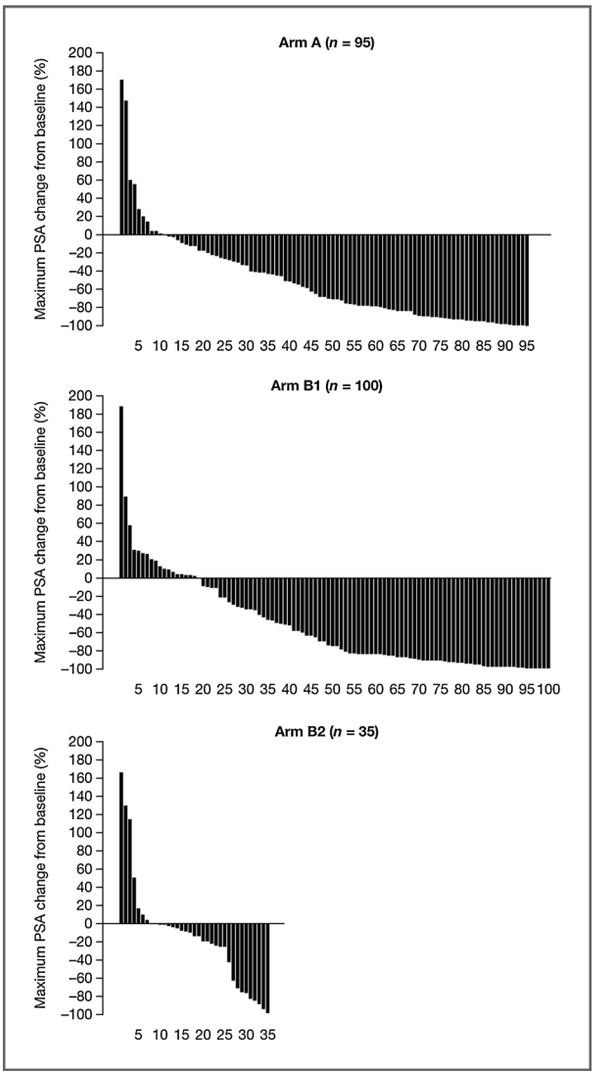

Figure 2. Waterfall plot showing the maximum PSA change from baseline. Reasons for missing patients include: no baseline record and/or no on-study records (Arms A and B1), no (crossover) baseline record (Arm B2).

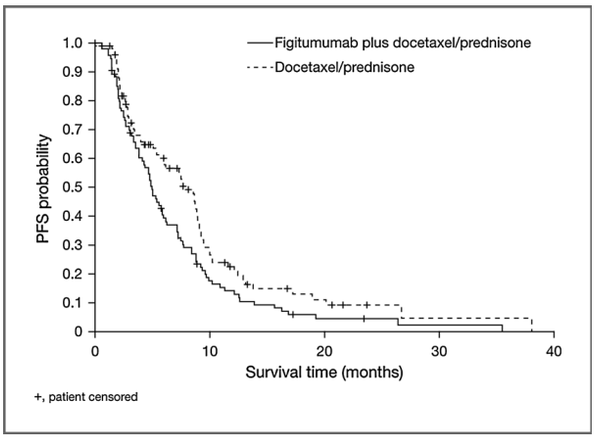

Figure 3. Kaplan–Meier plot of PFS.

Discussion

In this phase II study, combining the anti-IGF-1R monoclonal antibody, figitumumab (20 mg/kg, i.v.), with the standard regimen of docetaxel/prednisone did not improve the PSA response rate significantly above the null value of 45% in chemotherapy-naïve patients. Similarly, the addition of figitumumab seemed to have a detrimental impact on PFS compared with docetaxel/prednisone alone: median PFS was 4.9 months (95% CI, 4.1–5.9) vs. 7.9 months (95% CI, 6.0–8.9). The calculated HR was 1.442 (95% CI, 1.060–1.961), favoring docetaxel/prednisone alone. Overall survival data were not collected. These findings are disappointing given the encouraging declines in PSA expression following treatment with single-agent figitumumab in a single-center, phase II study of 14 patients with localized prostate cancer (26). Nevertheless, a PSA response of 28% (90% CI, 15.5–43.9) was observed in patients treated with the combination after disease progression with docetaxel/prednisone alone, suggesting that IGF-1R blockade may have some activity in this disease. The implications of these PSA falls are unclear; docetaxel has been implicated in impacting androgen receptor signaling and could potentially upregulate the IGF-1R/PI3K/AKT axis, thus making the combination with figitumumab more active post-docetaxel at crossover than in the docetaxel-naïve patients (19, 32).

Our data highlight the challenges of improving the activity of docetaxel monotherapy in the first-line setting of CRPC. Docetaxel has been combined with many biologic agents with distinct mechanisms of action including tyrosine kinase inhibitors, angiogenic inhibitors, BCL-2 inhibitors, and immunologic agents. To date, no drug has demonstrated improved overall survival when added to docetaxel in a phase III trial, and in some cases the addition proved detrimental to outcomes (33–37). Phase II trials such as ours are an important step in adequately evaluating the activity of novel agents; several recent phase III trials were started on the basis of phase I/II trial expansion cohorts (38).

Toxicity was substantially higher with figitumumab combination treatment than with docetaxel and prednisone, with an increased incidence of grade 3/4 treatment-related adverse events and SAEs reported with the combination treatment compared with docetaxel/prednisone alone. Although only one death in the figitumumab combination arm was considered treatment-related, it is notable that the rate of grade 5 adverse events from any cause was higher in both Arms A and B2 (18% and 22%) than in Arm B1 (8%), giving concern that the toxicity of combination treatment may have played a contributory factor in some cases. However, it is also possible that the rate of grade 5 adverse events was underestimated in Arm B1, because all adverse events were attributed to Arm B2 immediately after starting figitumumab at crossover. The relatively poor tolerability of the figitumumab combination may also account, at least in part, for the inferior efficacy observed in Arm A because of undertreatment with docetaxel; adverse event–related

Table 3. Treatment-related adverse events occurring in ≥15% of patients in any treatment group

	Figitumumab + docetaxel/prednisone (Arm A; $n = 97$)		Docetaxel/prednisone alone (Arm B1; $n = 102$)		Figitumumab + docetaxel/prednisone (crossover from B1; Arm B2; $n = 37$)	
Incidence, *n* (%)	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Diarrhea	56 (58)	13 (13)	34 (33)	0	10 (27)	0
Decreased appetite	48 (50)	4 (4)	26 (26)	1 (1)	17 (46)	3 (8)
Alopecia	46 (47)	5 (5)	51 (50)	3 (3)	17 (46)	2 (5)
Fatigue	41 (42)	9 (9)	35 (34)	8 (8)	13 (35)	5 (14)
Neutropenia	39 (40)	31 (32)	39 (38)	34 (33)	10 (27)	9 (24)
Dysguesia	36 (37)	1 (1)	37 (36)	0	12 (32)	0
Asthenia	35 (36)	10 (10)	28 (28)	4 (4)	13 (35)	3 (8)
Hyperglycemia	32 (33)	23 (24)	14 (14)	4 (4)	14 (38)	8 (22)
Nausea	28 (29)	3 (3)	26 (26)	0	8 (22)	0
Leukopenia	22 (23)	12 (12)	25 (24)	14 (14)	3 (8)	1 (3)
Stomatitis	18 (19)	1 (1)	8 (8)	2 (2)	0	2 (5)
Mucosal inflammation	15 (16)	2 (2)	12 (12)	0	1 (3)	0
Muscle spasm	15 (16)	0	5 (5)	0	5 (14)	0
Neuropathy peripheral	14 (14)	1 (1)	21 (21)	2 (2)	12 (32)	1 (3)
Lethargy	12 (12)	3 (3)	15 (15)	0	5 (14)	0
Vomiting	12 (12)	1 (1)	9 (9)	1 (1)	7 (19)	0
Edema peripheral	6 (6)	0	17 (17)	0	3 (8)	0
Anemia	6 (6)	0	16 (16)	0	6 (16)	1 (3)
Dyspnea	6 (6)	0	16 (16)	0	3 (8)	1 (3)
Nail disorder	7 (7)	0	15 (15)	0	7 (19)	1 (3)

treatment interruptions or delays with this agent were more than twice as common in Arm A than in Arm B1, and more patients needed a docetaxel dose reduction in Arm A compared with Arm B1. In other respects, safety findings in the current study were similar to those known to be class effects for IGF-1R inhibitors and previously reported figitumumab-associated adverse events (25, 39). Hyperglycemia, a known class effect of IGF-1R inhibitors, was reported in approximately one third of the patients in this study, and is likely related to impaired homeostatic control of insulin and blood glucose levels following abrogation of IGF-1R signaling (40). Other adverse events, including neutropenia, were expected toxicities associated with taxane treatment.

In conclusion, the primary objective of this study with respect to PSA response in Arm A patients with chemotherapy-naïve CRPC receiving figitumumab plus docetaxel/prednisone was not met, as there was no statistically significant evidence that PSA response in Arm A was greater than 0.45. The primary objective of the study with respect to PSA response in Arm B2 patients, however, was met and it was concluded that PSA response with the addition of figitumumab after progression on docetaxel/prednisone was significantly greater than 0.05. Despite discontinuation of figitumumab clinical development, IGF-1R may still be considered to be a valid investigational target for the treatment of prostate cancer. Additional data on the effect of targeting IGF-1R have been reported in clinical studies (14, 41), both in patients with localized prostate cancer (26) and particularly in patients with advanced CRPC (42, 43). Moreover, studies indicate that SPOP mutated CRPC have high steroid receptor coactivator-3 levels which result in high IGF ligand levels. These data, along with recent evidence indicating that the combination of an AKT inhibitor with an antiandrogen prolongs disease stabilization in a model of CRPC, provide further evidence for the strategy of targeting the androgen receptor and the IGF-1R/PI3K/AKT signaling axis (44), and the combination of IGF-1R inhibitors with novel endocrine anticancer agents such as enzalutamide may therefore prove fruitful in selected CRPC populations (45).

Disclosure of Potential Conflicts of Interest

D.P. Petrylak has received honoraria from the speakers bureau from Pfizer Inc. F. Saad is a consultant/advisory board member for Sanofi. S. Gillessen is a consultant/advisory board member for Bayer, Pfizer, Sanofi Aventis, Cellsearch, Curevac, Janssen Cilag, Astellas, Millennium, Novartis, and ProteoMedix. T. Wang is an Associate Director from Pfizer. T. Wang also has ownership interest (including patents) for PFE. M.N. Pollak is a consultant for Pfizer. M.N. Pollak also has a commercial research grant from Pfizer. No potential conflicts of interest were disclosed by the other authors.

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