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

Johann S. de Bono¹, Josep M. Piulats², Hardev S. Pandha³, Daniel P. Petrylak⁴, Fred Saad⁵, Luis Miguel A. Aparicio⁶, Shahneen K. Sandhu¹, Peter Fong¹, Silke Gillissen⁷, Gary R. Hudes⁸, Tao Wang⁹, Judith Scranton⁹, and Michael N. Pollak¹⁰

¹Royal Marsden NHS Foundation Trust and The Institute of Cancer Research UK, Sutton, UK; ²Institut Català d'Oncologia, L'Hospitalet, Barcelona, Spain; ³University of Surrey, Surrey, UK; ⁴Yale University Cancer Center, New Haven, CT, USA; ⁵Centre Hospitalier de l'Université de Montreal, Montreal, Canada; ⁶A Coruña University Hospital, A Coruña, Spain; ⁷Kantonsspital St Gallen, St Gallen, Switzerland; ⁸Fox Chase Cancer Center, Philadelphia, PA, USA; ⁹Pfizer Inc, Groton, CT, USA; ¹⁰Lady Davis Institute for Medical Research, Jewish General Hospital and McGill University, Montreal, Quebec, Canada

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Corresponding Author: Johann S. de Bono, Drug Development Unit, Royal Marsden Hospital, Sutton, Surrey SM2 5PT, UK. Phone: +44-208-642-7979; Fax: +44-208-642-7979; E-mail: johann.de-Bono@icr.ac.uk

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Johann S. de Bono has served Pfizer as a consultant/advisor. Daniel P. Petrylak has served Sanofi-Aventis as a consultant/advisor and has received research funding from Pfizer. Silke Gillessen has served Pfizer and Sanofi-Aventis as a consultant/advisor. Tao Wang and Judith Scranton are Pfizer employees and own Pfizer stock. Michael N. Pollak has served Pfizer and Novo Nordisk as a consultant/advisor and has received research funding from Pfizer and Novo Nordisk. Josep M. Piulats, Hardev S. Pandha, Fred Saad, Luis Miguel A. Aparicio, Shahneen K. Sandhu, Peter Fong, and Gary R. Hudes have no potential conflicts of interest to declare.

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 IgG2 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 (PSA) levels. These data led to a randomized phase II trial in chemotherapy-naïve castration-resistant metastatic prostate cancer patients. 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 SPOP-mutated disease where raised SRC3 levels generate high IGF ligand levels, in combination with next-generation AR targeting drugs.

Abstract

Background: Figitumumab is a human IgG2 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).

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

Results: 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 (hazard ratio 1.44; 95% confidence interval [CI]: 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.

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 (AR) signaling and progression to castration-resistant prostate cancer (CRPC). Ligand-dependent and -independent resistance mechanisms have been described; postulated ligand-independent mechanisms include AR splice variants, AR modulation by kinase signaling, and epithelial–mesenchymal transition (3).

Until recently, the main treatment for CRPC was docetaxel once every 3 weeks (q3w) in combination with prednisone, which is associated with a modest median overall survival of 19 months (4, 5). Recently, cabazitaxel (a cytotoxic chemotherapy) (6), abiraterone (an inhibitor of androgen biosynthesis) (7), enzalutamide (8), radium-223 (9), and sipuleucel-T (an active cellular immunotherapy) (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 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 (PTEN). 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 IgG2 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 down-regulated androgen-regulated gene expression and was associated with decreased AR 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 (PSAWG) criteria published in 1999 (27); disease progression as defined by Response Evaluation Criteria in Solid Tumors (RECIST version 1.0) (28); or ≥ 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 ≤ 2 ; any adverse events (AEs) from prior cancer therapy resolved to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE; version 3.0) grade ≤ 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 4–6 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, two-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 (IV) infusion plus docetaxel 75 mg/m² by infusion and prednisone 5 mg twice daily (Arm A), or docetaxel/prednisone (Arm B1) q3w. 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 AR function and block cytoplasmic-to-nucleus shuttling of the AR (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. In order 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 ≥ 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 AEs. No more than two dose reductions of docetaxel were permitted (to 60 mg/m² and 45 mg/m²). Figitumumab treatment could be delayed by up to one cycle (6 weeks from previous dose) for treatment-related toxicities. A maximum of two dose reductions of figitumumab were permitted (to 10 mg/kg 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 (CTCs).

To acquire these data, a PSA baseline reference value was obtained from blood samples taken prior to 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 ≤ 0.2 ng/mL on two 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 two 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: 1) an increase in PSA $\geq 50\%$ and ≥ 5 ng/mL above the nadir of all on-study evaluations prior to the current evaluation, for subjects who achieved PSA response earlier during study; 2) an increase in PSA $\geq 25\%$ over baseline, for subjects whose PSA had not decreased on study; 3) an increase in PSA $\geq 25\%$ and ≥ 5 ng/mL over the nadir of all on-study evaluations prior to 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 due to 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; ≥ 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 due to any cause. Patients were followed until disease progression irrespective of whether they were receiving study drug prior to 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 prior to cycle 3 due to 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. Since 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, two-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 five 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 hazard ratio (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, while 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, five did not have treatment, eight were treated but discontinued treatment prematurely (prior to cycle 3 due to PSA progression only), and two 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 ($n = 12$; 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: four had an inadequate baseline assessment and one 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 AEs, and seven patients (7%) required a reduction in the figitumumab dose. More patients in Arm A had a docetaxel dosing regimen modification due to AEs 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, while the docetaxel dose was reduced in 28 patients (29%) and 20 patients (20%), respectively. Arm B2 patients had had a minimum of three 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 nine patients (24%) and dose reduction in three patients (8%) from Arm B2, and to a docetaxel dosing delay in ten patients (27%) and dose reduction in eight 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. Since 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.

CTCs

In total, 46 patients in Arm A and 39 patients in Arm B1 had ≥ 5 CTCs per 7.5 mL blood at baseline (Table 1). The number of CTCs appeared to drop in both arms through cycles 1–5, 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 cross-over.

PFS

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 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 three 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 AEs 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 AE (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 AEs: 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 AEs were reported in the figitumumab plus docetaxel/prednisone Arm A, compared with 8 (8%) in the docetaxel/prednisone alone Arm B1. Only one grade 5 all-causality AE 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 AEs 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.

Discussion

In this phase II study, combining the anti-IGF-1R monoclonal antibody, figitumumab (20 mg/kg, IV), 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 appeared to have a detrimental impact on PFS compared with docetaxel/prednisone alone: median PFS was 4.9 months (95% CI: 4.1–5.9) versus 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 AR signaling and could potentially upregulate the IGF-1R/PI3K/AKT axis, thus making the combination with figitumumab more active post-docetaxel at cross-over 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 castrate-resistant prostate cancer. Docetaxel has been combined with many biological 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 AEs 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 AEs 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 AEs was under-estimated in Arm B1, since all AEs 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 under-treatment with docetaxel; AE-related 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 AEs (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 AEs, 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 co-activator-3 (SRC3) 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 AR 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).

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Authors' Contributions

Conception and design: J. S. de Bono, D. P. Petrylak, G. R. Hudes, J. Scranton

Development of methodology: J. Scranton

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. S. de Bono, J. M. Piulats, H. S. Pandha, D. P. Petrylak, F. Saad, L.

M. A. Aparicio, S. K. Sandhu, P. Fong, S. Gillessen, G. R. Hudes, J. Scranton

Writing, review, and/or revision of the manuscript: J. S. de Bono, J. M. Piulats, H. S. Pandha, D. P. Petrylak, F. Saad, L.M.A. Aparicio, S. K. Sandhu, P. Fong, S. Gillessen, G. R. Hudes, T. Wang, J. Scranton, M. N. Pollak

Administrative, technical, or material support (i.e. reporting or organizing data, constructing databases): J. S. de Bono, H. S. Pandha, S. K. Sandhu, P. Fong, S. Gillessen, G. R. Hudes, T. Wang, J. Scranton, M. N. Pollak

Study supervision: P. Fong

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TABLES AND FIGURES

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)^f
Mean age, years (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 (%) ^b	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 ^c	64 (63)	61 (60)	22 (59)
Number of lesion sites, <i>n</i> (%)			
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, <i>n</i> (%) ^d	58 (57)	71 (70)	24 (65)
Prior radiation therapy, <i>n</i> (%) ^d	59 (58)	65 (64)	24 (65)
Prior hormonal therapy, <i>n</i> (%) ^d	93 (91)	96 (94)	34 (92)
Baseline PSA level, ng/mL ^e			

Mean (SD)	288.0 (500.9)	189.0 (314.4)	169.5 (234.1)
Median (range)	105.0 (6.1–3683)	96.4 (6.3–2124)	82.5 (0.4–1095)
Patients with ≥ 5 CTCs per 7.5 mL, <i>n</i> (%)	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)

^aFigitumumab was added to treatment for patients progressed on docetaxel/prednisone alone; ^bat least one target lesion ≥ 2 cm (>1 cm by spiral computed tomography); ^cincludes ascites, brain, breast, subcutaneous, and not reported; ^dnot 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); ^ebaseline PSA data not available for *n* = 1 each in Arms A and B1, and for *n* = 2 in Arm B2; ^fpatient 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.

Abbreviations: CTCs, circulating tumor cells; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; ULQ, upper and lower quartile.

Table 2. Best response^a in evaluable patients

	Figitumumab + docetaxel/ prednisone (Arm A) (n = 87)	Docetaxel/ prednisone alone (Arm B1) (n = 98)	Figitumumab + docetaxel/ prednisone (crossover from B1) (Arm B2) (n = 32)
n (%)			
PSA response; primary endpoint) [90% CI]	45 (52) [42.4–61.0]	59 (60) [51.4–68.5]	9 (28) [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)

^aBest responses are defined in the section “Study Endpoints and Assessments”.

Abbreviations: CI, confidence interval; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.

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)	
	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)

Figure 1. Study schema (CONSORT diagram).

Abbreviations: BID, twice daily; PSA, prostate-specific antigen; q3w, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

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 (Arm A, Arm B1), no (crossover) baseline record (Arm B2). Abbreviation: PSA, prostate-specific antigen.

Figure 3. Kaplan–Meier plot of progression-free survival (PFS).

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: <http://globocan.iarc.fr> (accessed on November 7, 2013).
2. Attard G, Cooper CS, de Bono JS. Steroid hormone receptors in prostate cancer: a hard habit to break? *Cancer Cell* 2009;16:458–62.
3. Attard G, de Bono JS. Translating scientific advancement into clinical benefit for castration-resistant prostate cancer patients. *Clin Cancer Res* 2011;17:3867–75.
4. Petrylak DP, Tangen CM, Hussain MH, Lara PN Jr, Jones JA, Taplin ME, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004;351:1513–20.
5. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al, on behalf of the TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502–12.
6. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al, on behalf of the TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010;376:1147–54.
7. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al, on behalf of the COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;364:1995–2005.

8. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al, on behalf of the AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;367:1187–97.
9. Parker C, Nilsson S, Heinrich D, O’Sullivan JM, Fossa SD, Chodacki A, et al. Updated analysis of the phase III, double-blind, randomized, multinational study of radium-223 chloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (ALSYMPCA). *J Clin Oncol* 2012;30(Suppl.) (abstr. LBA4512).
10. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al, on behalf of the IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363:411–22.
11. Massoner P, Ladurner-Rennau M, Eder IE, Klocker H. Insulin-like growth factors and insulin control a multifunctional signalling network of significant importance in cancer. *Br J Cancer* 2010;103:1479–84.
12. Renehan AG, Zwahlen M, Minder C, O’Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet* 2004;363:1346–53.
13. Roddam AW, Allen NE, Appleby P, Key TJ, Ferrucci L, Carter HB, et al. Insulin-like growth factors, their binding proteins, and prostate cancer risk: analysis of individual patient data from 12 prospective studies. *Ann Intern Med* 2008;149:461–71, W83–W88.
14. Ozkan EE. Plasma and tissue insulin-like growth factor-I receptor (IGF-IR) as a prognostic marker for prostate cancer and anti-IGF-IR agents as novel therapeutic strategy for refractory cases: a review. *Mol Cell Endocrinol* 2011;344:1–24.

15. Pollak M. Insulin-like growth factor-related signaling and cancer development. *Recent Results Cancer Res* 2007;174:49–53.
16. Pollak M. The insulin and insulin-like growth factor receptor family in neoplasia: an update. *Nat Rev Cancer* 2012;12:159–69.
17. Takahara K, Tearle H, Ghaffari M, Gleave ME, Pollak M, Cox ME. Human prostate cancer xenografts in lit/lit mice exhibit reduced growth and androgen-independent progression. *Prostate* 2011;71:525–37.
18. Nickerson T, Chang F, Lorimer D, Smeekens SP, Sawyers CL, Pollak M. In vivo progression of LAPC-9 and LNCaP prostate cancer models to androgen independence is associated with increased expression of insulin-like growth factor I (IGF-I) and IGF-I receptor (IGF-IR). *Cancer Res* 2001;61:6276–80.
19. Krueckl SL, Sikes RA, Edlund NM, Bell RH, Hurtado-Coll A, Fazli L, et al. Increased insulin-like growth factor I receptor expression and signaling are components of androgen-independent progression in a lineage-derived prostate cancer progression model. *Cancer Res* 2004;64:8620–9.
20. Culig Z, Hobisch A, Cronauer MV, Radmayr C, Trapman J, Hittmair A, et al. Androgen receptor activation in prostatic tumor cell lines by insulin-like growth factor-I, keratinocyte growth factor, and epidermal growth factor. *Cancer Res* 1994;54:5474–8.
21. Cohen BD, Baker DA, Soderstrom C, Tkalcevic G, Rossi AM, Miller PE, et al. Combination therapy enhances the inhibition of tumor growth with the fully human anti-type 1 insulin-like growth factor receptor monoclonal antibody CP-751,871. *Clin Cancer Res* 2005;11:2063–73.

22. Wu JD, Odman A, Higgins LM, Haugk K, Vessella R, Ludwig DL, et al. In vivo effects of the human type I insulin-like growth factor receptor antibody A12 on androgen-dependent and androgen-independent xenograft human prostate tumors. *Clin Cancer Res* 2005;11:3065–74.
23. Plymate SR, Haugk K, Coleman I, Woodke L, Vessella R, Nelson P, et al. An antibody targeting the type I insulin-like growth factor receptor enhances the castration-induced response in androgen-dependent prostate cancer. *Clin Cancer Res* 2007;13:6429–39.
24. Hellawell GO, Ferguson DJ, Brewster SF, Macaulay VM. Chemosensitization of human prostate cancer using antisense agents targeting the type 1 insulin-like growth factor receptor. *BJU Int* 2003;91:271–7.
25. Molife LR, Fong PC, Paccagnella L, Reid AH, Shaw HM, Vidal L, et al. The insulin-like growth factor-I receptor inhibitor figitumumab (CP-751,871) in combination with docetaxel in patients with advanced solid tumours: results of a phase Ib dose-escalation, open-label study. *Br J Cancer* 2010;103:332–9.
26. Chi KN, Gleave ME, Fazli L, Goldenberg SL, So A, Kollmannsberger C, et al. A phase II pharmacodynamic study of preoperative figitumumab in patients with localized prostate cancer. *Clin Cancer Res* 2012;18:3407–13.
27. Bublely GJ, Carducci M, Dahut W, Dawson N, Daliani D, Eisenberger M, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol* 1999;17:3461–7. [Errata in *J Clin Oncol* 2000;18:2644 and *J Clin Oncol* 2007;25:1154.]

28. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16.
29. Zhu ML, Horbinski CM, Garzotto M, Qian DZ, Beer TM, Kyprianou N. Tubulin-targeting chemotherapy impairs androgen receptor activity in prostate cancer. *Cancer Res* 2010;70:7992–8002.
30. de Bono JS, Scher HI, Montgomery RB, Parker C, Miller MC, Tissing H, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin Cancer Res* 2008;14:6302–9. [Erratum in *Clin Cancer Res* 2009;15:1506.]
31. Green SJ, Dahlberg S. Planned versus attained design in phase II clinical trials. *Stat Med* 1992;11:853–62.
32. Pandini C, Mineo R, Frasca F, Roberts CT Jr, Marcelli M, Vigneri R, et al. Androgens up-regulate the insulin-like growth factor-1 receptor in prostate cancer cells. *Cancer Res* 2005;65:1849–57.
33. Small E, Demkow T, Gerritsen WR, Rolland F, Hoskin P, Smith DC, et al. A phase III trial of GVAX immunotherapy for prostate cancer in combination with docetaxel versus docetaxel plus prednisone in symptomatic, castration-resistant prostate cancer (CRPC). 2009 Genitourinary Cancers Symposium, Orlando, FL, USA, February 26–28, 2009 (abstr. 7).

- 34.** Kelly WK, Halabi S, Carducci M, George D, Mahoney JF, Stadler WM, et al. Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. *J Clin Oncol* 2012;30:1534–40.
- 35.** Petrylak DP, Fizazi K, Sternberg CN, Budnik N, De Wit R, Wiechno J, et al. A phase 3 study to evaluate the efficacy and safety of docetaxel and prednisone with or without lenalidomide in patients with castrate-resistant prostate cancer (CRPC): the MAINSAIL trial. Presented at the 37th ESMO Congress 2012;23:ixe15 (abstr. LBA24).
- 36.** Araujo JC, Trudel GC, Saad F, Armstrong AJ, Yu EY, Bellmunt J, et al. Overall survival (OS) and safety of dasatinib/docetaxel versus docetaxel in patients with metastatic castration-resistant prostate cancer (mCRPC): results from the randomized phase III READY trial. *J Clin Oncol* 2013;31(Suppl. 6) (abstr. LBA8).
- 37.** Tannock IF, Fizazi K, Ivanov S, Karlsson CT, Fléchon A, Skoneczna I, et al, on behalf of the VENICE investigators. 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* 2013;14:760–8.
- 38.** Antonarakis ES, Eisenberger MA. Phase III trials with docetaxel-based combinations for metastatic castration-resistant prostate cancer: time to learn from past experiences. *J Clin Oncol* 2013;31:1709–12.

39. Goto Y, Sekine I, Tanioka M, Shibata T, Tanai C, Asahina H, et al. Figitumumab combined with carboplatin and paclitaxel in treatment-naïve Japanese patients with advanced non-small cell lung cancer. *Invest New Drugs* 2012;30:1548–56.
40. Fernández AM, Kim JK, Yakar S, Dupont J, Hernandez-Sanchez C, Castle AL, et al. Functional inactivation of the IGF-I and insulin receptors in skeletal muscle causes type 2 diabetes. *Genes Dev* 2001;15:1926–34.
41. Friedlander TW, Weinberg VK, Huang Y, Mi JT, Formaker CG, Small EJ, et al. A phase II study of insulin-like growth factor receptor inhibition with nordihydroguaiaretic acid in men with non-metastatic hormone-sensitive prostate cancer. *Oncol Rep* 2012;27:3–9.
42. Higano CS, Alumkal JJ, Ryan CJ, Yu EY, Beer TM, Fox FE, et al. A phase II study of cixutumumab (IMC-A12), a monoclonal antibody (MAb) against the insulin-like growth factor 1 receptor (IGF-IR), monotherapy in metastatic castration-resistant prostate cancer (mCRPC): Feasibility of every 3-week dosing and updated results. Presented at the 2010 ASCO Genitourinary Congress (abstr. 189).
43. Rathkopf DE, Danila DC, Morris MJ, Slovin SF, Borwick LS, Momen L, et al. Anti-insulin-like growth factor-1 receptor (IGF-1R) monoclonal antibody cixutumumab (cix) plus mTOR inhibitor temsirolimus (tem) in metastatic castration-resistant prostate cancer (mCRPC): Results of a phase I pilot study. *J Clin Oncol* 2011;29(Suppl.) (abstr. e15081).
44. Thomas C, Lamoureux F, Crafter C, Davies BR, Beraldi E, Fazli L, et al. Synergistic targeting of PI3K/AKT pathway and androgen receptor axis significantly

delays castration-resistant prostate cancer progression in vivo. *Mol Cancer Ther* 2013;12:2342–55.

45. Li C, Ao J, Fu J, Lee D-F, Xu J, Lonard D, et al. Tumor-suppressor role for the SPOP ubiquitin ligase in signal-dependent proteolysis of the oncogenic co-activator SRC-3/AIB1. *Oncogene* 2011;30:4350–64.

Figure 1

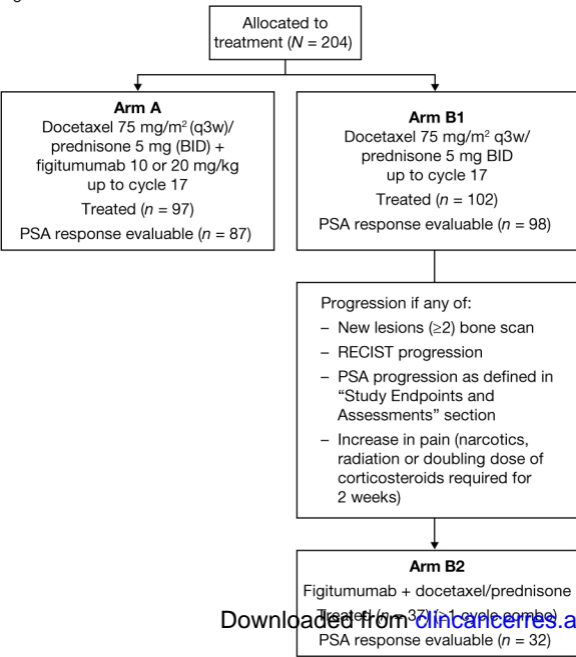


Figure 2

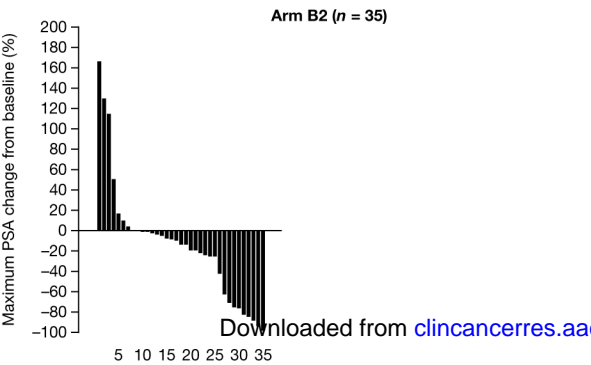
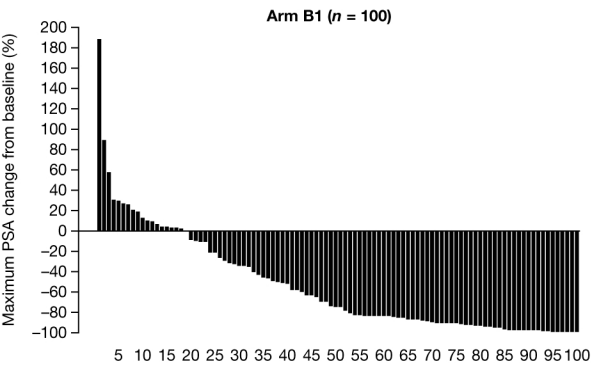
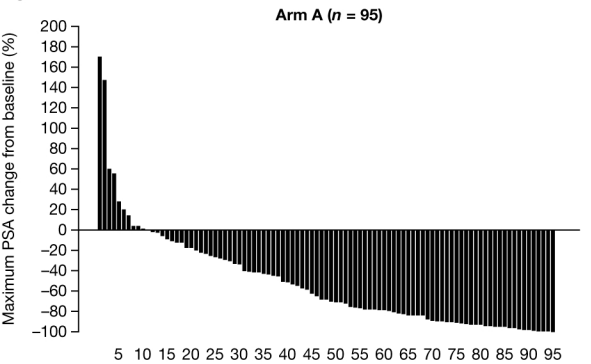
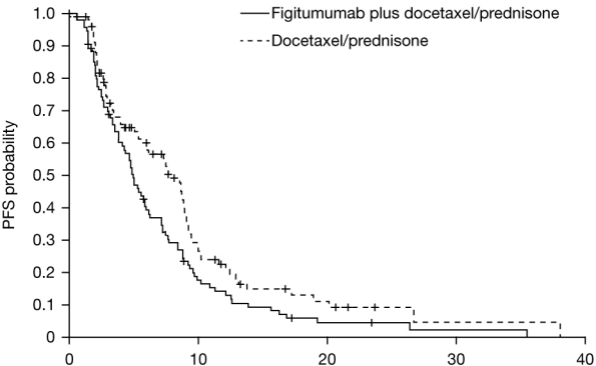


Figure 3



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

Johann S. de Bono, Josep Maria Piulats, Hardev S. Pandha, et al.

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