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Original Research

Randomised phase II study of second-line olaratumab with mitoxantrone/prednisone versus mitoxantrone/prednisone alone in metastatic castration-resistant prostate cancer

Oliver W. Hakenberg [a,*,1], Jose Luis Perez-Gracia [b,1], Daniel Castellano [c], Tomasz Demkow [d], Tarek Ali [e], Orazio Caffo [f], Axel Heidenreich [g], Wolfgang Schultze-Seemann [h], Brieuc Sautois [i], Ivan Pavlik [j], Amy Qin [k,2], Ruslan D. Novosiadly [l], Ashwin Shahir [m], Robert Ilaria Jr [n,3], Johannes Nippgen [k,4]

[a] *Department of Urologie, Universitätsmedizin Rostock, Rostock, Germany*
[b] *Clinica Universidad De Navarra, Pamplona, Spain*
[c] *Medical Oncology Department (CiberOnc), Hospital 12 De Octubre, Madrid, Spain*
[d] *Centrum Onkologii - Instytut im. Marii Sklodowskiej-Curie, Warsaw, Poland*
[e] *Department of Urology, Josa Andras Teaching Hospital, Nyiregyhaza, Hungary*
[f] *Medical Oncology Department, Santa Chiara Hospital, Trento, Italy*
[g] *Department of Urology and Uro-Oncology, University Hospital Cologne, Cologne, Germany*
[h] *Department of Urology, University of Freiburg, Freiburg, Germany*
[i] *CHU Sart Tilman, University of Liège, Liège, Belgium*
[j] *Department of Urology, General University Hospital, And First Faculty of Medicine, Charles University, Prague, Czech Republic*
[k] *Eli Lilly and Company, Bridgewater, NJ, USA*
[l] *Eli Lilly and Company, NY, USA*
[m] *Eli Lilly and Company, Basingstoke, United Kingdom*
[n] *Eli Lilly and Company, Indianapolis, IN, USA*

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* *Corresponding author*: Universitätsmedizin Rostock Urologie, Ernst-Heydemann-Straße 6, Rostock, Mecklenburg-Vorpommern 18057, Germany. Fax: +49 381 494 7802.

E-mail addresses: oliver.hakenberg@med.uni-rostock.de (O.W. Hakenberg), jlgracia@unav.es (J.L. Perez-Gracia), cdanicas@hotmail.com (D. Castellano), demkow@coi.waw.pl (T. Demkow), tarekali@freemail.hu (T. Ali), orazio.caffo@apss.tn.it (O. Caffo), axel.heidenreich@uk-koeln.de (A. Heidenreich), wolfgang.schultze-seemann@uniklinik-freiburg.de (W. Schultze-Seemann), brieuc.sautois@chu.ulg.ac.be (B. Sautois), ivan.pavlik@vfn.cz (I. Pavlik), aqin@dsi.com (A. Qin), ruslan.novosiadly@lilly.com (R.D. Novosiadly), shahir_ashwin@lilly.com (A. Shahir), cancerdoc@mac.com (R. Ilaria), dr.nippgen@web.de (J. Nippgen).

[1] These authors contributed equally to this work. [2] Present address: Daiichi Sankyo, Inc., Basking Ridge, New Jersey, USA. [3] Present address: Celgene Corporation, Summit, New Jersey, USA. [4] Present address: Merck KGaA, Darmstadt, Germany.

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KEYWORDS
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Prostate cancer;
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Mitoxantrone;
Metastatic

Abstract ***Introduction:*** Platelet-derived growth factor receptor-α (PDGFRα) is expressed in primary prostate adenocarcinoma and in associated skeletal metastases. Olaratumab is a fully human monoclonal antibody that binds PDGFRα and blocks downstream signalling. This phase II study assessed the efficacy and safety of olaratumab in combination with mitoxantrone and prednisone (M/P) versus M/P alone in patients with metastatic castration-resistant prostate cancer (mCRPC) who progressed after docetaxel.
Methods: Patients were randomised to receive 21-d cycles of olaratumab (15 mg/kg, Days 1 and 8) plus mitoxantrone (12 mg/m^2, Day 1) and prednisone (5 mg, twice daily) or M/P alone. Progression-free survival (PFS) was the primary end-point. Secondary end-points included overall survival (OS), safety, and circulating tumour cell (CTC) counts.
Results: A total of 123 patients were randomised, 63 to olaratumab + M/P and 60 to M/P. Median PFS was 2.3 months for olaratumab + M/P and 2.4 months for M/P (hazard ratio [HR] = 1.29; 95% confidence interval [CI] = 0.87–1.90). Median OS was 14.2 months for olaratumab + M/P and 12.8 months for M/P (HR = 1.08; 95% CI = 0.72–1.61). Both treatment arms had similar toxicity profiles; neutropenia (24% versus 15%), anaemia (13% versus 14%) and fatigue (11% versus 9%) (olaratumab + M/P versus M/P, respectively) were the most common grade ≥3 events. High CTC count was associated with poorer OS in both arms. Patients with very high cell counts (>37 cells/7.5 ml) exhibited improved OS with olaratumab + M/P (interaction P = 0.043).
Conclusions: Olaratumab + M/P had an acceptable safety profile but did not improve the efficacy of M/P chemotherapy. Further study with selected patient populations and earlier in the disease course might be considered.

1. Introduction

Prostate cancer is the second most frequently diagnosed cancer in men next to skin cancer. GLOBOCAN cancer incidence data indicate that 1.1 million men were diagnosed with prostate cancer worldwide in 2012 [1]. Patients with metastatic prostate cancer undergo hormone ablation, either surgical or medical castration, to slow the progression of the disease, but metastatic castration-resistant prostate cancer (mCRPC) develops within 18–24 months [2,3]. Docetaxel is the first-line chemotherapy treatment for mCRPC, but progression is likely to occur. Cabazitaxel is an established second-line chemotherapy; abiraterone and enzalutamide are additional available hormonal treatments [4]. However, even with these treatments, prognosis for patients with mCRPC remains poor; thus, the development of more specific targeted therapy with better tolerance and efficacy is needed.

Mitoxantrone was used to treat mCRPC before the introduction of docetaxel and cabazitaxel. In combination with corticosteroids, mitoxantrone is effective in decreasing bone pain associated with osseous metastases in mCRPC. It also increases the rate of prostate-specific antigen (PSA) decline and increases the time to PSA and clinical progression [5–7]. However, second-line mitoxantrone treatment of mCRPC has not been shown to impact overall survival (OS) [5,6].

The interaction of platelet-derived growth factor (PDGF) isoforms and their receptors (PDGFRs) mediate tissue homeostasis, especially mesenchymal cell growth, differentiation, and motility [8]. Activation of the PDGF signalling pathway is involved in the development and progression of multiple malignancies [8–10]. Elevated or aberrant PDGF receptor–ligand interactions have been implicated in affecting the tumour and stroma microenvironment and facilitating metastases [8–10].

Olaratumab (IMC-3G3) is a recombinant fully human immunoglobulin G class 1 (IgG1) monoclonal antibody that specifically targets PDGFRα, blocking PDGF-AA and –BB ligands from binding to the receptor [11]. The resultant inhibition of the ligand-induced receptor autophosphorylation and the phosphorylation of the downstream signalling molecules AKT and mitogen-activated protein kinase results in an inhibition of the proliferation and growth of a variety of human tumour types *in vitro* and *in vivo* [12]. Clinically, olaratumab has been shown to greatly improve OS when used for the treatment of soft tissue sarcoma in conjunction with doxorubicin [13].

Bone metastatic prostate cancer cells highly express PDGFRα [14]. Observations from a mouse model of experimental prostate cancer metastasis have shown that prostate cancer cells expressing PDGFRα survive and grow during early stages of bone marrow dissemination, while cells expressing lower levels or lacking this receptor do not [15]. The same mouse model also showed that functional blockade of human PDGFRα on prostate cancer cells with olaratumab inhibited the establishment

of early skeletal metastases and reduced the size of established skeletal metastases [14,15]. These results implicate PDGFRα in prostate cancer bone tropism.

A phase I study established the safety and tolerability of olaratumab in patients with advanced solid tumours without any dose-limiting toxicity observed [16]. In this study, 7 of 11 mCRPC patients (59%) enrolled demonstrated stable disease with one of these patients experiencing a PSA decline >50% and continuing on study for 39 weeks until disease progression.

These preclinical and phase I results led us to conduct a randomised phase II trial to assess the safety and efficacy of olaratumab in combination with mitoxantrone and prednisone (M/P) in patients with mCRPC.

2. Methods

2.1. Study design

This open-label, randomised, phase II study was conducted at 38 study centres in 7 countries. Patients were randomised 1:1 via an interactive voice or Web-response system to receive M/P plus olaratumab (olaratumab + M/P arm) or M/P arm during a 3-week (21-d) cycle. Randomisation was stratified according to best overall response to prior docetaxel-based chemotherapy (complete response [CR], partial response [PR], stable disease [SD] or progressive disease [PD], including clinical symptom progression and intolerance). The primary endpoint was progression-free survival (PFS). Secondary end-points included OS, objective response rate (ORR), duration of response, PSA doubling time, PSA response rate (≥50% and ≥30% decline in pre-treatment PSA) and the association of baseline circulating tumour cell (CTC) counts with efficacy end-points. This study (ClinicalTrials.gov:NCT01204710) was conducted according to the Declaration of Helsinki and with approval from institutional review boards of all participating study sites. All participants provided written informed consent prior to any study-related procedures. The trial was funded by the study sponsor and designed by the principal investigator (O.H.) and the sponsor.

2.2. Patient enrolment

Eligible patients were males aged ≥18 years with histologically confirmed prostate cancer and radiographic evidence of metastatic prostate cancer (stage M1 or D2) that was unresponsive or refractory to medical or surgical castration and with a serum testosterone level of <50 ng/dl (castration resistant). Patients using luteinizing hormone–releasing hormone agonists continued these while on study treatment. Patients had disease progression (clinical or radiographic) during docetaxel or within 120 d of receiving docetaxel chemotherapy. Patients had a serum PSA ≥10 ng/ml; an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2 and adequate hematologic, hepatic and renal function. Patients who had received more than one prior cytotoxic chemotherapy regimen for metastatic disease, prior therapy with mitoxantrone, or an inhibitor of PDGF or PDGFR were not eligible.

2.3. Study procedures

Patients in the olaratumab + M/P arm received olaratumab intravenously at 15 mg/kg over 1 h on Days 1 and 8 of each 21-d cycle. Patients in both arms received mitoxantrone (12 mg/m^2) intravenously on Day 1 of the 21-d cycle and prednisone (5 mg) orally, twice daily and every day. Patients continued to receive treatment with study therapy until evidence of disease progression, death, intolerable toxicity or other withdrawal criteria were met. Mitoxantrone was administered for a maximum of 12 cycles (total cumulative dose of ≤144 mg/m^2). Patients in the olaratumab + M/P arm who became intolerant of mitoxantrone could continue with olaratumab monotherapy. At the time of disease progression, patients in the M/P arm could elect to receive optional olaratumab monotherapy until unacceptable toxicity or disease progression.

Following a baseline radiographic assessment of disease within 21 d prior to randomisation, patients underwent radiographic assessment at 9 weeks (±3 d) following the first treatment and thereafter every 6 weeks (±3 d) until radiographic documentation of PD. Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) [17] for tumour measurements were used to determine PFS, ORR, and duration of response. Safety parameters were assessed throughout the study until 30 d after discontinuation of study treatment or death, whichever occurred first. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 4.02) [18]. A limited number of samples for pharmacokinetic analysis was obtained during the study; therefore, pharmacokinetic data analysis was not conducted.

2.4. Biomarkers

Patients had whole blood collected (10 ml, via venepuncture into a CellSave Preservative tube) prior to cycle 1 for the determination of CTC count. Counts were performed using CellSearch technology at Esoterix (LabCorp Company, Mechelen, Belgium). The CTC count groups were defined using a 5 cells/7.5 ml cutpoint [19] and a third quartile (75th percentile) cutpoint of 37 cells/7.5 ml.

2.5. Statistical methods

Efficacy analysis was based on the modified intent-to-treat (mITT) population that included all patients who

were randomised and treated. The safety population included all patients who received any amount of study therapy.

Tumour response was assessed according to RECIST v1.1. The PFS and OS were evaluated by the Kaplan–Meier method [20]. The PFS and OS comparison between treatment arms was accomplished using the log-rank test, stratified by prior response to docetaxel chemotherapy. Hazard ratios (HR), including 95% confidence interval (CI), were calculated using the Cox proportional hazards model.

All analyses were done using SAS Version 8.2 or later. Additional statistical methodology is available in the online supplement.

3. Results

3.1. Baseline patient and disease characteristics

Beginning October 2010, a total of 123 patients were randomised at 38 study centres in seven countries (63 olaratumab + M/P; 60 M/P), and 121 received at least one dose of study treatment (62 olaratumab + M/P; 59 M/P; mITT population; Fig. 1). Nineteen patients from the M/P arm elected to receive optional olaratumab monotherapy after PD. Demographic and baseline disease characteristics were well balanced between both treatment arms (Table 1) except for an imbalance in ECOG scores (greater PS 1 in olaratumab + M/P arm and greater PS 0 in M/P arm). Most study patients were White (99.2%). The mean patient age was 67.4 years (range: 40–81 years).

At the time of primary data cut-off (28 September 2012), 60 patients (96.8%) in the olaratumab + M/P arm and all 59 patients in the M/P arm were off treatment. The most common reasons for discontinuation of treatment in both arms were radiographic PD (41 patients, 33.9%) and clinical progression (32 patients, 26.4%) and AEs (17 patients, 14.0%). Of the nineteen patients from the M/P arm who crossed over to olaratumab (i.e. received follow-on treatment with olaratumab after an event of PD), at the time of data cut-off, 15 crossover patients (78.9%) were off treatment. For these patients, the most common reasons for treatment discontinuation were radiographic PD (six patients, 31.6%) and clinical progression (four patients, 21.1%).

3.2. Treatment

For patients in the olaratumab + M/P arm, the median (range) duration of olaratumab therapy was 20.6 weeks (3.0–116.9) and of mitoxantrone therapy was 19.6 weeks (0–42.3). Patients in the M/P arm had a median (range) duration of mitoxantrone therapy of 15.1 weeks (3.0–39.0). Patients who crossed over to optional

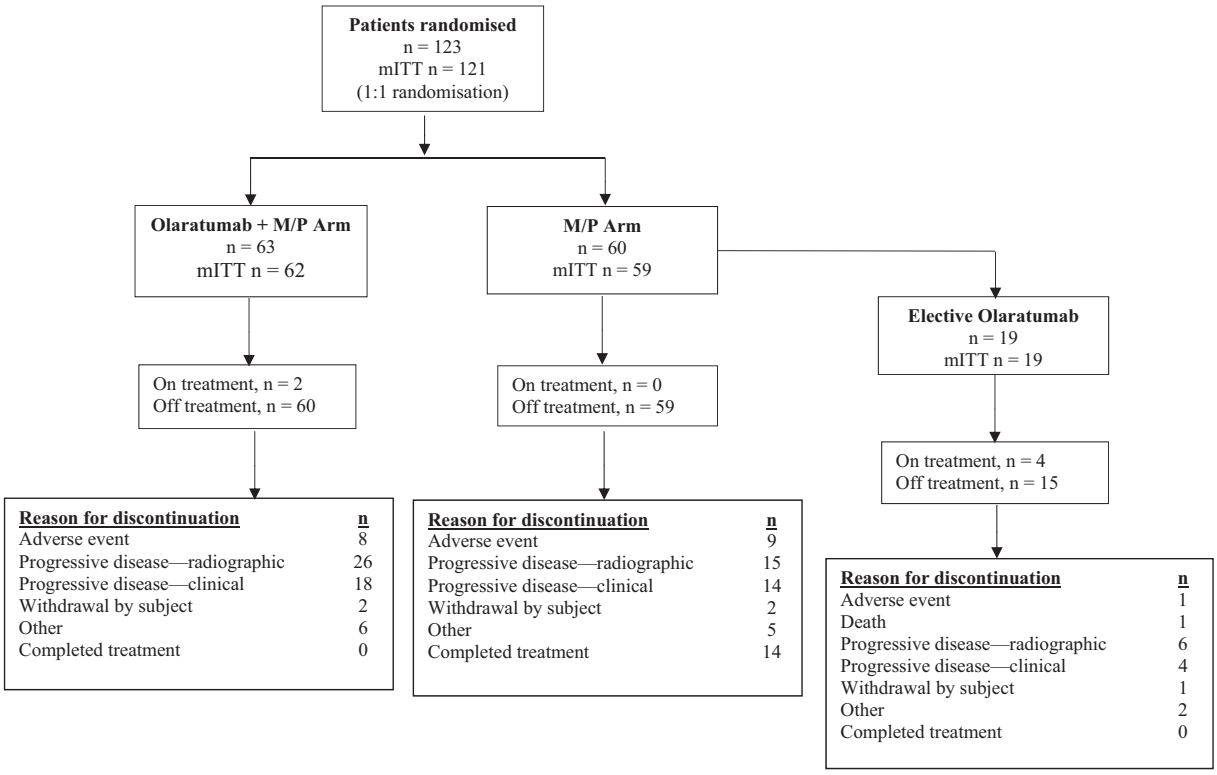

Fig. 1. Patient disposition. The diagram depicts the flow of patients in the study. The modified intent-to-treat (mITT) population included all patients who were randomised and received any quantity of a study drug, either olaratumab or mitoxantrone/prednisone (M/P).

Table 1
Patient and disease characteristics.

Characteristics	Olaratumab + M/P arm (N = 62)	M/P arm (N = 59)
Age (y)		
Mean (Std Dev)	67.4 (6.5)	67.4 (7.5)
Median	68.0	69.0
Range	51–81	40–79
Race, n (%)		
White	62 (100.0)	58 (98.3)
Multiple	0	1 (1.7)
Ethnicity, n (%)		
Hispanic or Latino	2 (3.2)	3 (5.1)
Non-Hispanic or Latino	60 (96.8)	56 (94.9)
ECOG PS, n (%)		
0	23 (37.1)	29 (49.2)
1	35 (56.5)	27 (45.8)
≥2	4 (6.5)	3 (5.1)
Best overall response to prior docetaxel-based chemotherapy, n (%)		
CR/PR/SD	33 (53.2)	36 (61.0)
PD/NE	29 (46.8)	23 (39.0)
Previous surgery, n (%)	39 (62.9)	39 (66.1)
Previous radiotherapy, n (%)	30 (38.4)	32 (54.2)
Duration of disease[a], (months)		
Mean (Std Dev)	69.8 (47.4)	57.1 (40.9)
Median	52.7	43.0
Range	14.2–202.1	13.4–181.4

CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; M/P = mitoxantrone/prednisone; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease; Std Dev = standard deviation.
[a] Duration of disease is the time from the histological confirmation of cancer to date of randomisation.

olaratumab monotherapy treatment (n = 19 patients) had a median duration of olaratumab therapy of 10.0 weeks (range: 3.0–38.0). Post-study anti-cancer treatments were similar for both treatment arms (Online Supplement, Table S1).

3.3. Efficacy outcomes

As of the primary data cut-off date, 52 patients (83.9%) in olaratumab + M/P arm and 54 patients (91.5%) in the M/P arm had PFS-relevant events (Table 2). The median PFS was similar in both treatment arms, 2.3 months with olaratumab + M/P and 2.4 months with M/P (HR = 1.29; 95% CI = 0.87–1.90; Fig. 2A).

As of the final data cut-off date for OS (01 October 2013), a total of 50 patients (80.6%) in the olaratumab + M/P arm and 46 patients (78.0%) in the M/P arm had reached the OS end-point (Table 2). Median OS was similar for both treatment arms with 14.2 months for olaratumab + M/P and 12.8 months for M/P (HR = 1.08; 95% CI = 0.72–1.61; Fig. 2B).

Tumour response (measurable or non-measurable) was assessed by investigators for all mITT patients (Table 2). The overall response rate (CR + PR) was 8.1% (n = 5) for patients treated with olaratumab + M/P and 1.7% (n = 1) for patients treated with M/P. The disease control rate (CR + PR + SD) was 56.5% in the olaratumab + M/P arm and 59.3% in the M/P arm.

The proportion of patients with a decrease in PSA ≥50% from baseline was 22.6% (n = 14) in the olaratumab + M/P arm and 18.6% (n = 11) in the M/P arm (P = 0.6571; Table 2).

3.4. CTC counts

The mITT population included 103 patients with evaluable baseline CTC counts. The CTC count groups were defined using a 5 cells/7.5 ml cutpoint [19] and a third quartile (75th percentile) cutpoint of 37 cells/7.5 ml. Patient subgroups defined by >5-cell and >37-cell cutpoints exhibited shorter median OS in both treatment arms than patients with <5-cell and <37-cell cutpoints (Interaction Model, Table 3). When the treatment arms were combined (Main Effects Model, Table 3), the >5-cell and >37-cell CTC count patient subgroups had statistically significant shorter OS compared to the rest of the study population (P < 0.001 at both cutpoints). The same pattern was also seen for PFS (both statistical models). When the CTC count was considered as a continuous variable, increasing CTC count was negatively associated with OS (Online Supplement, Table S2; see Table 4).

Treatment arms were also compared within the CTC count subgroups (Interaction Model). For patients with CTC counts exceeding the 37-cell cutpoint, there was evidence of better OS with olaratumab + M/P (12.2 months versus 5.8 months, HR = 0.43, p = 0.095; interaction P = 0.043; Table 3).

3.5. Safety

The treatment arms had similar numbers of patients with one or more grade ≥3 treatment-emergent adverse event (TEAE): 35 (56.5%) olaratumab + M/P versus 36 (61%) M + P arm. The most frequently reported grades ≥3 TEAEs in either arm were neutropenia (24% versus 15%), anaemia (13% versus 14%) and fatigue (11% versus 9%). The incidence of serious adverse events (SAEs) was higher in the olaratumab + M/P arm (n = 26, 42%) versus the M/P arm (19, 32%); the most common SAEs were haematological. The number of patients presenting AEs leading to discontinuation of any study drug was similar in both arms: 15 (24%) in the olaratumab + M/P arm (most commonly, haematological) and 12 (20%) in the M/P arm (most commonly, haematological and general disorders). Infusion-related reaction (cycle 1) was observed in the olaratumab + M/P arm in 5 (8%) patients, with 3 (5%) patients of grade ≥3.

The chief cause of death was disease progression (70% olaratumab + M/P; 66% M/P arm). The incidence of AEs leading to death was also similar in both arms: four patients in the olaratumab + M/P arm (stroke,

Table 2
Summary of efficacy measures.

Efficacy measure	Olaratumab + M/P arm (N = 62)		M/P arm (N = 59)	Elective olaratumab (N = 19[a])
Progression-free survival[b]				
Number of events, n (%)	52 (83.9)		54 (91.5)	
Number censored, n (%)	10 (16.1)		5 (8.5)	
Median (mo)	2.3		2.4	
(95% CI)	(2.2–2.8)		(2.2–3.8)	
Hazard ratio, stratified[c]		1.29		
(95% CI)		(0.87–1.90)		
Log rank P value, stratified[c]		0.2201		
Overall survival[d]				
Number of events, n (%)	50 (80.6)		46 (78.0)	
Number censored, n (%)	12 (19.4)		13 (22.0)	
Median (mo)	14.2		12.8	
(95% CI)	(12.2–16.0)		(8.1–16.4)	
Hazard ratio, stratified[c]		1.08		
(95% CI)		(0.72–1.61)		
Log rank P value, stratified[c]		0.7291		
Best overall response rate, n (%)[b]				
CR	1 (1.6)		0	0
PR	4 (6.5)		1 (1.7)	0
Objective response, CR + PR	5 (8.1)		1 (1.7)	0
(95% CI[e])	(3.5–17.5)		(0.3–9.0)	(0.0–16.8)
P value		0.2078		
SD	30 (48.4)		34 (57.6)	5 (26.3)
Disease control, CR + PR + SD	35 (56.5)		35 (59.3)	5 (26.3)
(95% CI[e])	(44.1–68.1)		(46.6–70.9)	(11.8–48.8)
PD	18 (29.0)		16 (27.1)	7 (36.8)
NE	1 (1.6)		0	0
NA	8 (12.9)		8 (13.6)	7 (36.8)
PSA				
Patients with PSA decrease ≥50%[f]	14 (22.6)		11 (18.6)	0
(95% CI[e])	(14.0–34.4)		(10.7–30.4)	(0.0–16.8)
Patients with PSA decrease ≥30%[g]	14 (22.6)		10 (16.9)	5 (26.3)
(95% CI[e])	(14.0–34.4)		(9.5–28.5)	(11.8–48.8)
Patients with PSA doubled	35 (56.5)		25 (42.4)	8 (42.1)
Median PSA doubling time (wk)	9.4		14.3	12.1
(95% CI)	(8.1–14.9)		(10.4–17.1)	(4.0–21.1)

CI = confidence interval; CR = complete response; PSA = prostate-specific antigen; M/P = mitoxantrone/prednisone; NA = not applicable; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease; Std Dev = standard deviation.

[a] For patients in M/P arm electing to receive olaratumab therapy after progressing on M/P, the best overall response assessment under M/P arm was based on all tumour assessments prior to the start of the olaratumab therapy. The best overall response while receiving optional olaratumab therapy was evaluated relative to the last tumour assessment before starting olaratumab treatment.

[b] Based on data cut-off of 28 September 2012.

[c] Stratified by the randomisation stratification factor: best overall response to prior docetaxel-based chemotherapy.

[d] Based on data cut-off of 01 October 2013.

[e] Estimated using binomial distribution (Wilson's method).

[f] The proportion of patients with a decrease in PSA ≥50% from the pre-treatment PSA to any time point, requiring confirmation no less than 3 weeks after the initial suggestion of response and occurring prior to documentation of PD.

[g] The proportion of patients with a decrease in PSA ≥30% from the pre-treatment PSA to Week 12 (or earlier for those who discontinue therapy without any confirmation).

weakness, bilateral chronic heart failure and multiorgan failure) and four patients in the M/P arm (cardiac arrest, cerebral bleeding and two patients with pneumonia). All deaths were considered unrelated to any study drug except one death (pneumonia) in the M/P arm, which was considered related to mitoxantrone.

Evaluable patients treated with olaratumab + M/P (n = 52) were tested for the formation of anti-drug antibodies (ADA) against olaratumab. Two (3.8%) patients had treatment-emergent ADA with neutralising antibodies detected. One patient showed transient treatment-emergent ADA (highest titre 1:160), and one patient exhibited persistent treatment-emergent ADA (1:40 titre), experienced an infusion-related reaction to olaratumab, and was discontinued from the study drug.

4. Discussion

Aberrant expression or activity of the PDGF family of receptors and ligands has been associated with tumour

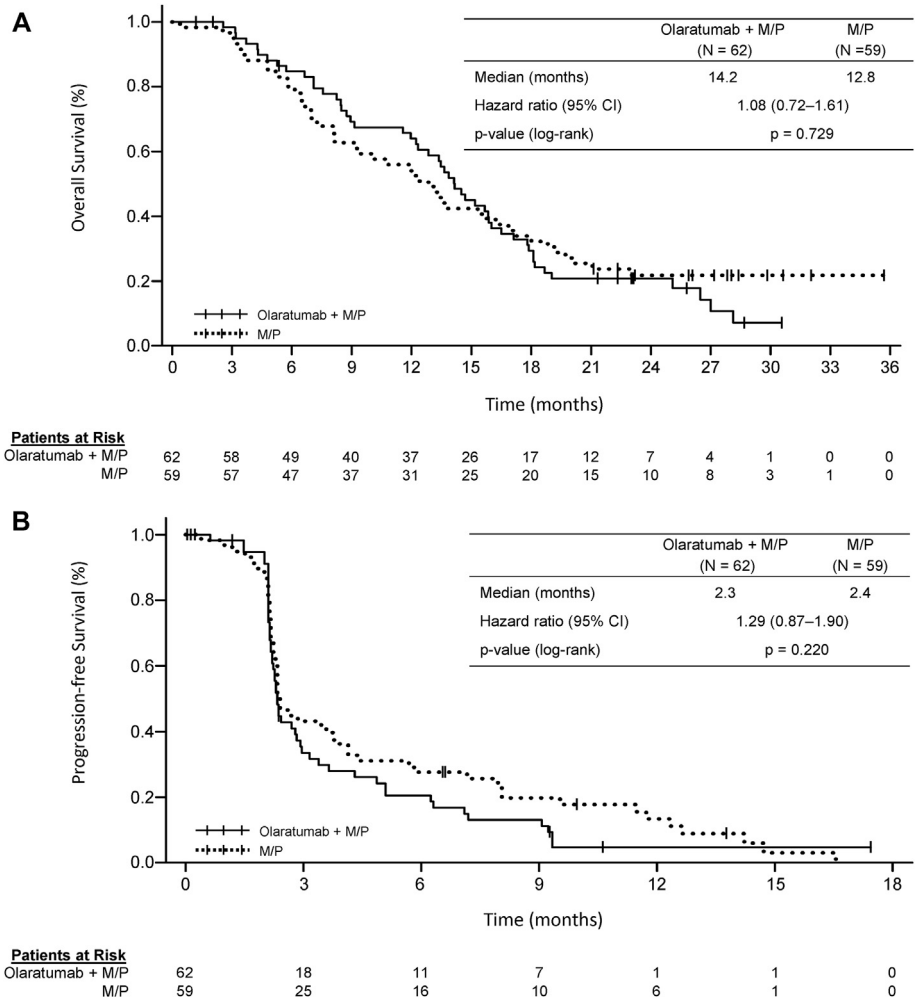

Fig. 2. Graphs of Kaplan–Meier estimates of (A) progression-free survival and (B) overall survival. Abbreviations: M/P = mitoxantrone/prednisone.

proliferation, invasion and angiogenesis [8–10]. Bone metastatic prostate cancer cells express PDGFRα, and preclinical research suggests that PDGFRα may play a role in prostate cancer bone tropism [14,15]. These observations provided the rationale to study the potential therapeutic effect of olaratumab in mCRPC after failed docetaxel chemotherapy in a randomised phase II study. M/P, which was a common second-line treatment at the time of study design, was chosen as the comparator. Study results showed that olaratumab added to M/P did not extend the median PFS or OS in docetaxel-refractory mCRPC patients compared to M/P alone nor did olaratumab improve tumour response or disease control rate. Analyses of pre-treatment and concomitant factors revealed no obvious imbalances that could have affected the study results. Likewise, clinical safety considerations likely did not impact results. Olaratumab with M/P showed an acceptable, monitorable and tolerable safety profile, consistent with previously published literature [13].

In a preclinical animal model, olaratumab, with or without the bisphosphonate zoledronic acid, had been effective in decreasing the number of further skeletal metastases in prostate models [14]. Imatinib, a small molecule PDGFR inhibitor, also showed preclinical efficacy but was ineffective in clinical trials of prostate cancer [21]. A potential explanation for the lack of clinical benefit in our study might be that PDGFRα, while being expressed in prostate cancer, is not causally related to tumour progression in CRPC patients. Instead, other signalling pathways known to induce tumour proliferation may drive CRPC progression, such as disruption to the PI3K antagonist, PTEN; copy number gain of oncogenic transcription factor *MYC*; and re-initiation of mitogenesis by reactivation of the AR pathway through accruing genomic aberrations [22]. Activation of these overlapping cellular signalling pathways also provides a compensatory mechanism in response to upstream receptor blockade by antibodies, such as olaratumab, allowing tumour cells to escape from targeted pathway inhibition and develop resistance to such drugs [23]. Multi-kinase inhibitors such as sunitinib have also been unsuccessful in providing survival benefit to CRPC patients [24]. Sunitinib is a

Table 3
Cox regression on OS and PFS, baseline dichotomised CTC counts.

Cutpoint (number of cells/ 7.5 ml)	Efficacy endpoint	Interaction model					Main effects model	
		High CTC[a]		Low CTC[b]		Interaction P value	High CTC	Low CTC
		Olaratumab + M/P	M/P	Olaratumab + M/P	M/P		Combined arms (n = 64)	Combined arms (n = 39)
5 cells[c]	Median OS (mo)	12.9	8.1	16.5	23.0	0.237[f]	11.6	19.0
	HR[d] (95% CI)	0.92 (0.55–1.55); P = 0.750[e]		1.65 (0.72–3.77); P = 0.461			3.05 (1.86–4.99)[g]; P < 0.001[f]	
37 cells[h]	Median OS (mo)	12.2	5.8	15.7	15.3	0.043	6.7	15.7
	HR (95% CI)	0.43 (0.19–0.97); P = 0.095		1.19 (0.71–2.02); P = 0.510			2.98 (1.79–4.97); P < 0.001	
5 cells	Median PFS (mo)	2.3	2.3	2.4	4.9	0.189	2.3	3.6
	HR (95% CI)	1.14 (0.67–1.93); P = 0.632		2.06 (0.99–4.25); P = 0.150			2.26 (1.44–3.55)[i]; P = 0.0003	
37 cells	Median PFS (mo)	2.1	2.2	2.4	3.2	0.493	2.2	2.4
	HR (95% CI)	1.04 (0.47–2.26); P = 0.930		1.44 (0.86–2.41); P = 0.333			1.89 (1.18–3.02); P = 0.0112	

CI = confidence interval; CTC = circulating tumour cell; HR = hazard ratio; N = total number of patients; n = number of patients in the specified category; M/P = mitoxantrone/prednisone; OS = overall survival; PFS = progression-free survival.
[a] Patients with high relative CTC counts, as identified by CTC counts of greater than or equal to the threshold.
[b] Patients with low relative CTC counts, as identified by CTC counts less than the threshold.
[c] The 5 cells/7.5 ml cutpoint corresponds to approximately quartile 2 (8 cells). The 5-cell cutpoint resulted in these numbers of patients in the subgroups: n = 32 for both treatment arms in the high CTC subgroup; n = 21 and n = 18 for the Olaratumab + M/P and M/P arms, respectively, for the low CTC subgroup.
[d] Hazard ratio for death from any cause (or progressive disease for PFS) comparing Olaratumab + M/P subgroup versus M/P subgroup within CTC counts subgroups. Hazard ratio >1 indicates increasing hazards with Olaratumab + M/P subgroup compared to M/P subgroup.
[e] P values presented for tests of contrasts within interaction model have been adjusted using the Hochberg method assuming four post hoc tests.
[f] P value is not adjusted.
[g] Hazard ratio for death from any cause comparing high versus low CTC counts subgroups.
[h] The 37 cells/7.5 ml cutpoint corresponds to quartile 3 (75%). The 37-cell cutpoint resulted in these numbers of patients in the subgroups: n = 17 and n = 11 for the Olaratumab + M/P and M/P arms, respectively, for the high CTC subgroup, and n = 36 and n = 39 for the Olaratumab + M/P and M/P arms, respectively, for the low CTC subgroup.
[i] Hazard ratio for progression of disease comparing high versus low CTC counts subgroups.

multitarget inhibitor of VEGFRs, PDGFRs and other receptor tyrosine kinases. In a randomised phase III trial, the addition of sunitinib to prednisone did not improve OS compared with placebo in docetaxel-refractory mCRPC [24]. Similarly, cabozantinib, another multi-kinase inhibitor, failed to show statistically significant OS improvement in a phase III trial in patients with mCRPC and progressive disease after docetaxel [25]. The apparent clinical lack of effect of PDGFRα blockade in our study might also be due to

Table 4
Treatment-emergent adverse events.

	Olaratumab + M/P arm (N = 62), n (%)		M/P (N = 59), n (%)	
	All grades	Grade ≥3	All grades	Grade ≥3
TEAEs with frequency ≥10%				
Fatigue[a]	29 (47)	7 (11)	21 (36)	5 (9)
Neutropenia[a]	24 (39)	15 (24)	17 (29)	9 (15)
Anaemia[a]	20 (32)	8 (13)	15 (25)	8 (14)
Nausea	15 (24)	0	14 (24)	1 (2)
Diarrhoea	12 (19)	0	7 (12)	0
Decreased appetite	11 (18)	0	6 (10)	0
Thrombocytopaenia[a]	8 (13)	4 (6)	6 (10)	4 (7)
Pain in extremity	8 (13)	0	3 (5)	0
Arthralgia	7 (11)	1 (2)	3 (5)	0
Back pain	6 (10)	0	7 (12)	1 (2)
Bone pain	6 (10)	0	4 (7)	1 (2)
Peripheral oedema	6 (10)	0	5 (8.5)	1 (2)
Special interest AEs with frequency ≥5%				
Infusion-related reactions[a,b]	5 (8)	3 (5)	2 (3)	1 (2)
Any SAE	26 (42)	21 (34)	19 (32)	19 (32)

M/P = mitoxantrone/prednisone; TEAE = treatment-emergent adverse event; SAE = serious adverse event.
[a] Pooled term.
[b] All infusion-related reactions occurred with cycle 1.

the clinical characteristics of the patient population enrolled representing mCRPC with very advanced stages of bone disease. Relative to the TAX327 study in docetaxel-naïve patients with a 16.5 months median survival for mitoxantrone [26], the median OS for mitoxantrone in our study for previously docetaxel-treated patients was 3.7 months shorter, even though about 30% of patients in both arms received abiraterone as post-study treatment. This result supports the notion of an advanced, poor prognosis patient population enrolled in this study. In contrast, the mouse model of experimental metastasis where olaratumab was effective in decreasing the number of metastases, modelled the early stages of PDGFRα-dependent prostate cancer cell bone marrow dissemination [14].

High CTC counts usually prognosticate poor PFS and OS in metastatic prostate cancer [19]. In our study, a high CTC count was also associated with poor OS in both treatment arms. The prespecified analysis indicated that patients with a very high CTC count (>37/7.5 ml) might benefit from olaratumab treatment. Interestingly, the 5 cells/7.5 ml CTC count cutpoint that is commonly used in prostate cancer provided a directional, but not a significant, prediction of an effect of olaratumab on OS. Both the CTC 37-cell and 5-cell cutpoint results require prospective validation.

Although the use of the CTC 5 cells/7.5 ml cutpoint is increasingly accepted as a biomarker to guide patient treatment for mCRPC [27], our results suggest the need for scrutiny of other CTC cutpoints, especially when investigating new treatments. Certainly, investigating CTC androgen receptor mutations (e.g. AR-V7) is proving to be another possible means by which CTC cells could be useful as prognostic and predictive markers for tailoring mCRPC treatment [28].

In conclusion, the anti-PDGFRα monoclonal antibody olaratumab added to M/P treatment in advanced docetaxel-refractory mCRPC with bone metastases did not improve PFS or OS, while relative safety of olaratumab could be demonstrated. However, in view of preclinical work implicating PDGFα in the pathogenesis of prostate cancer metastases, further study with different patient populations and notably earlier in the disease course might be considered.

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Conflict of interest statement

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Appendix A. Supplementary data

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