Orteronel Switch Maintenance Therapy in Metastatic Castration Resistant Prostate Cancer After First-Line Docetaxel: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial (SAKK 08/11)

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BACKGROUND. We tested whether a switch maintenance treatment with orteronel, an oral inhibitor of androgen biosynthesis, prolongs disease control in men with metastatic castration-resistant prostate cancer (mCRPC) after documented disease stabilization with docetaxel.
METHODS. Men with mCRPC and non-progressive disease after a cumulative dose of $\geq$300 mg/m^2 docetaxel for first line treatment were randomized 1:1 to receive orteronel

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Trial Registration: This trial is registered with ClinicalTrials.gov with the identifier Trial ID: NCT01707966.

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Conflicts of interest: Richard Cathomas reports advisory role for Astellas, Janssen Cilag, Sanofi Aventis, Bayer, Pfizer, Novartis, and research grants from Janssen Cilag and Sanofi Aventis. Simon Crabb reports advisory role for Astellas, Bayer, Sanofi, Janssen, and grants from AstraZeneca. Christian Rothermundt reports advisory role for Pfizer, GSK, Novartis. Enrico Roggero reports advisor role for Bayer, Pfizer, Astellas. Silke Gillessen reports advisory role or speakers bureau for Astellas, Amgen, Bayer, CureVac, Dendreon, ESSA Pharmaceuticals, Janssen Cilag, Janssen Diagnostics, Millennium, Nektar Therapeutics, Novartis, Orion Pharma, Pfizer, ProteoMediX, Sanofi Aventis. In addition, Silke Gillessen has a patent WO 2009138392 A1 pending.

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300 mg twice daily or placebo. The primary endpoint was event-free survival (EFS) defined as the time from randomization to death or the combination of at least two of radiographic, clinical, or PSA progression. Ninety-six patients per arm were planned to demonstrate an improvement of median EFS from 4 months on placebo to 6.7 months on orteronel (hazard ratio (HR) 0.6; type I error 5% and power 90%).

RESULTS. Forty-seven patients (23 orteronel, 24 placebo) were randomized before premature closure of the trial because of discontinuation of clinical development of orteronel. Median EFS was 8.5 months with orteronel and 2.9 months with placebo ($P = 0.001$; HR 0.32; 95%CI 0.15–0.65). Median radiographic progression-free survival (rPFS) was 8.5 and 2.8 months ($P = 0.02$; HR 0.42; 95%CI 0.20–0.91) in the orteronel and placebo arm, respectively. PSA decline $\geq$50% was seen in 57% on orteronel and 4% on placebo. Toxicity was mainly mild, one patient on orteronel developed transient grade 3 adrenal insufficiency and one grade 4 pneumonitis.

CONCLUSIONS. Orteronel significantly prolongs EFS in men with mCRPC who achieve disease stabilization with docetaxel. The concept of switch maintenance therapy in mCRPC warrants further research. *Prostate*

KEY WORDS: **castration-resistant prostate cancer; orteronel; maintenance; docetaxel**

INTRODUCTION

Chemotherapy with docetaxel in combination with prednisone was the first systemic treatment demonstrating a significant survival benefit in patients with metastatic castration resistant prostate cancer (mCRPC) [1]. Novel androgen receptor pathway inhibitors (API) such as abiraterone acetate and enzalutamide were recently found to prolong overall survival (OS) in patients with progressive mCRPC after docetaxel chemotherapy and also in chemotherapy-naïve patients [2–5].

Orteronel is a novel API that blocks the synthesis of gonadal and adrenal androgens by blockade of CYP17. Orteronel has been tested in two phase III clinical trials demonstrating clinical efficacy with significant improvement of radiographic progression free survival, PSA response and good tolerance but did not significantly prolong overall survival [6,7].

Chemotherapy with docetaxel can only be administered for a limited time period due to cumulative toxicity. Patients achieving disease response or stabilization on docetaxel are currently observed until evidence of disease progression. In all reported mCRPC phase III trials enrolling patients after prior docetaxel chemotherapy, subsequent treatment was commenced in the setting of progressive disease. Trials in other malignancies, for example, lung cancer have shown that initiating an effective and well tolerated treatment immediately at the end of first-line chemotherapy (so called switch maintenance therapy) improves progression-free and overall survival [8,9]. This may also hold true for early administration of active and well tolerated novel hormonal agents in men with mCRPC, but has not yet been tested in a prospective randomized fashion.

The aim of this investigator-initiated trial was to test the hypothesis that starting orteronel directly after disease stabilization with docetaxel in men with mCRPC could prolong event-free survival (EFS) and consequently maintain quality of life (QoL).

PATIENTS AND METHODS

Trial Design and Conduct

The trial was planned as an international, multicenter, randomized, double-blind, placebo-controlled, phase III trial. The trial was performed in 17 hospitals in Switzerland and the United Kingdom.

Computer generated randomization was centralized at the SAKK Coordinating Center. Patients were stratified according to participating site, WHO performance status (0–1 vs. 2) and localization of metastases (bone only vs. presence of other metastases) using the minimization method in a 1:1 ratio.

Allocation of drug code numbers to the patient was performed by the pre-wholesaler and directly communicated to the sites. Patients, investigators, site staff, monitors, and a designated statistician were blinded to treatment allocation. For the case that emergency unblinding was necessary, a scratch off card was provided.

The trial was performed in accordance with the Declaration of Helsinki [10], the Guidelines of Good Clinical Practice issued by ICH [11] and the Swiss and European regulatory authorities' requirements [12–16]. It was approved by the local ethics review boards of all participating centers and Swissmedic.

The trial was registered at the National Institute of Health (www.clinicaltrial.gov; identifier number: Trial ID: NCT01707966).

Patients

Eligible patients were ≥18 years, castration resistant, had WHO performance status ≤2, and radiographically documented metastatic adenocarcinoma of the prostate. They were randomized within 3–6 weeks after the last dose of docetaxel chemotherapy having achieved at least disease stabilization defined as no evidence of disease progression according to PCWG2 [17]. Patients must have received a cumulative dose of docetaxel of ≥300 mg/m^2. Adequate laboratory values for blood count, liver, and renal function were required. Patients were excluded in the case of prior treatment with CYP17 inhibitors (including ketoconazole), prior chemotherapy other than docetaxel, uncontrolled arterial hypertension despite appropriate therapy, QTc interval >460 msec, or clinically relevant cardiac disease. Written informed consent was obtained from all patients.

Treatment and Assessments

Treatment consisted of orteronel 300 mg BID (three tablets of 100 mg BID) or placebo (three tablets BID) to be taken continuously with or without food each day 12 hr apart in a 28-day cycle. No regular prednisone was administered. All patients received best supportive care and continued treatment on LHRH analogues. Use of bone targeted agents such as bisphosphonates or denosumab (but not Radium-223) was permitted.

Patients had baseline imaging with computed tomography (chest, abdomen, pelvis) and a bone scan. The same imaging was repeated every 12 weeks. Clinical and laboratory investigations were performed every 2 weeks for the first two cycles and every 4 weeks thereafter. PSA was measured every 4 weeks. All patients had baseline evaluation of cardiac function and ECG was repeated every 12 weeks.

For the QoL assessment a questionnaire including FACT-P [18] including the FACT-P PCS pain subscale and a global indicator for treatment burden [19] was completed at baseline and on day 1 of each cycle for a maximum of seven cycles. Collection of spot urine was performed at baseline and on day 1 of cycle 4 (Swiss sites only). Urinary steroid metabolites were analyzed by gas chromatography-mass spectrometry [20].

Endpoints

The primary endpoint was EFS. An event was defined as one of the following: death from any cause; presence of radiographic progression AND symptomatic/clinical progression; presence of radiographic progression AND PSA progression; presence of symptomatic/clinical progression AND PSA progression. Radiographic progression included progression on bone scan or soft tissue disease progression according to PCWG2 criteria or modified RECIST 1.1. Radiographic assessments were performed at the local sites. Symptomatic/clinical progression was defined as occurrence of a skeletal related event due to bone metastases (defined as pathologic fracture, spinal cord compression, palliative radiation to bone or surgery to bone); physician decision for intervention due to new disease related complications (e.g., urinary obstruction, hydronephrosis); physician decision to initiate new systemic anticancer therapy or progressive disease related pain despite adequate analgesic treatment. PSA progression was defined as a ≥25% increase over baseline (if no PSA decline on trial treatment), ≥25% increase over the nadir (if PSA response to treatment <50%) or a ≥50% increase over the nadir (if PSA response to treatment was ≥50%). In any case an absolute PSA increase of ≥5 ng/ml was required and PSA progression had to be confirmed at the next assessment.

Secondary endpoints included OS, radiographic progression-free survival (rPFS), time to PSA progression, PSA response (30%, 50%, 90%, and best), QoL and pain response as well as evaluation of adverse events (according to Common Terminology Criteria for Adverse Events version 4.0; CTCAE v4.0).

The primary QoL endpoint was the change from baseline in FACT-P total score across the whole observation period.

To assess the apparent CYP17 blockade, precursor-to-product metabolite ratios [21] were derived from steroid measurements (Fig. 4).

Statistical Analysis

Sample size was calculated based on the primary endpoint of EFS. It was planned to randomize 192 patients (96 in each arm) to detect an improvement in EFS to 6.67 months in the experimental arm compared to 4 months in the placebo arm (hazard ratio (HR) = 0.6) with a type I error of 5% and a power of 90%. The number of events required for primary analysis was 163. An interim efficacy analysis was planned after 65 events. All analyses were based on the intention-to-treat (ITT) population. All time-to-event endpoints were calculated from randomization until event of interest. Patients not experiencing an event were censored at the last available assessment or at initiation of a different treatment or at the date of unblinding. The medians and corresponding confidence intervals (CI) were estimated using the Kaplan–Meier method and compared between treatment arms

using log-rank tests. The HRs were estimated using Cox models. Due to the small number of samples the QoL endpoints were only analyzed descriptively using median and quartiles as well as boxplots. To assess the apparent CYP17A1 activity, ratios 1 and 2 were log-transformed and compared descriptively between treatment arms using line plots and associated with PSA response using waterfall plots.

Two-tailed tests with a significance level of 0.05 were used for all analyses. As no adjustment for multiple testing was applied for analyses other than the primary endpoint analysis, they were exploratory and hypothesis generating. All analyses were performed using SAS 9.2 (SAS Institute) and R 3.0.3 (http://www.r-project.org).

RESULTS

Patient Characteristics

In June 2014, the manufacturer announced to stop further development of orteronel in prostate cancer due to negative results of two phase III trials [6,7,22]. Due to this decision the present trial was prematurely closed in July 2014. A total of 47 patients were randomized between November 9, 2012 and July 17, 2014. Twenty three patients were randomized to the orteronel arm and 24 to the placebo arm. All randomized patients are included in the ITT population and are reported here.

The two groups were generally well balanced for baseline demographic and clinical characteristics (Table I).

TABLE I. Demographical and Clinical Patient Characteristics at Baseline

	Arm A (Orteronel) N = 23	Arm B (Placebo) N = 24
Age, years, median (IQR)	70 (61–74)	70.5 (66–76.5)
WHO PS		
PS 0	13 (57%)	12 (50%)
PS 1	9 (39%)	11 (46%)
PS 2	1 (4%)	1 (4%)
Gleason score		
Score 5–7	5 (22%)	6 (25%)
Score 8–10	14 (61%)	15 (62%)
Missing	4 (17%)	3 (13%)
Site of metastases		
Bone	20 (87%)	17 (71%)
Lymph nodes	12 (52%)	15 (63%)
Lung	3 (13%)	2 (8%)
Liver	2 (9%)	1 (4%)
Other	4 (17%)	6 (25%)
Response to docetaxel		
Stable disease	11 (48%)	9 (37%)
Partial response	12 (52%)	15 (63%)
Cumulative dose of docetaxel, mg/m^2, median (IQR)	450 (400–673)	510 (443–600)
Time from last docetaxel to study treatment, days, median (IQR)	36 (29–41)	35.5 (30.5–40)

Efficacy

Median treatment duration with orteronel was 5.1 months (range 2.7–10.2) compared to 2.8 months (range 2.0–4.2) in the placebo arm. The main reasons for discontinuation of treatment were disease progression, patient refusal and toxicity for 14 (61%), 4 (17%), and 3 (13%) patients on orteronel compared to 20 (83%), 4 (17%), and 0 (0%) patients on placebo, respectively (Fig. 1).

Median follow up was 17 months in the orteronel arm and 18.4 months in the placebo arm. The primary endpoint was reached with a median EFS of 8.5 months (95%CI 3.2–16.0) on orteronel compared to 2.9 months (95%CI 2.7–3.9) on placebo ($P = 0.001$, HR 0.32; 95%CI 0.15–0.65) (Fig. 2A). The secondary endpoint median rPFS was 8.5 months (95%CI 3.5–14.2) on orteronel and 2.8 months (95%CI 2.7–5.6) on placebo ($P = 0.02$, HR 0.42; 95%CI 0.20–0.91) (Fig. 2B). All efficacy results are summarized in Table II (see also Suppl. Fig. S1). The waterfall plot for PSA response on trial treatment is shown in Figure 3.

Nearly 80% of the patients in both arms received at least one further systemic treatment. Subsequent treatments after discontinuation of trial treatment are summarized in Table III. Since only a few deaths have occurred OS data is not mature.

Adverse Events

All related adverse events during or within 30 days of termination of trial treatment are summarized in Table IV. One patient receiving orteronel experienced adrenal insufficiency (grade 3) with uncertain causal relationship to trial drug as he had undergone prednisone tapering in the days before admission. He recovered quickly on reintroduction of prednisone. One further patient on orteronel suffered grade 4 pneumonitis that was classified as probably related to trial drug. He had a full recovery after drug discontinuation.

Quality of Life and Pain Assessment

Twenty-two patients in the orteronel arm and 23 in the placebo arm completed the baseline and at least

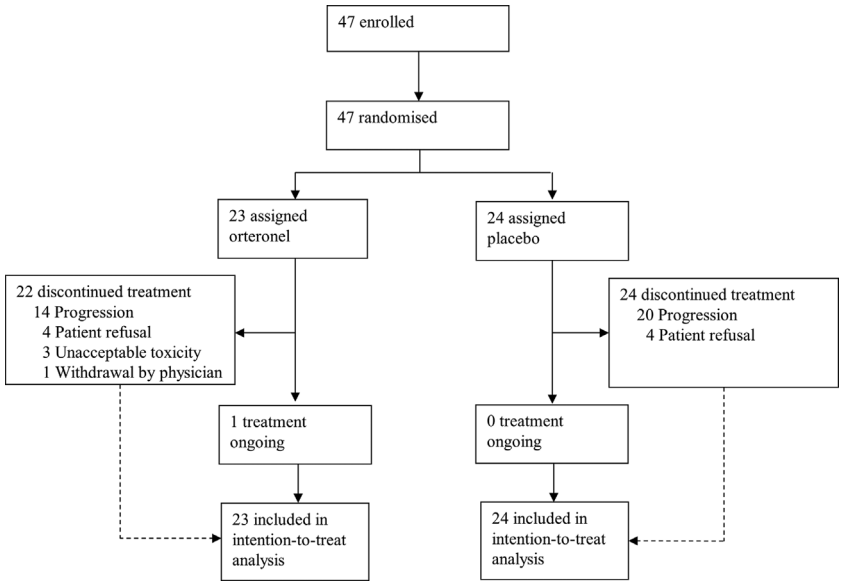

Fig. 1. Trial profile.

one subsequent questionnaire for QoL and pain. The two treatment arms indicated similar changes in FACT-P total scores (Suppl. Fig. S2). The secondary QoL endpoints showed consistent findings. However, the number of patients providing data was small and decreasing continuously. Thus, no meaningful analysis of pain over the course of treatment was possible.

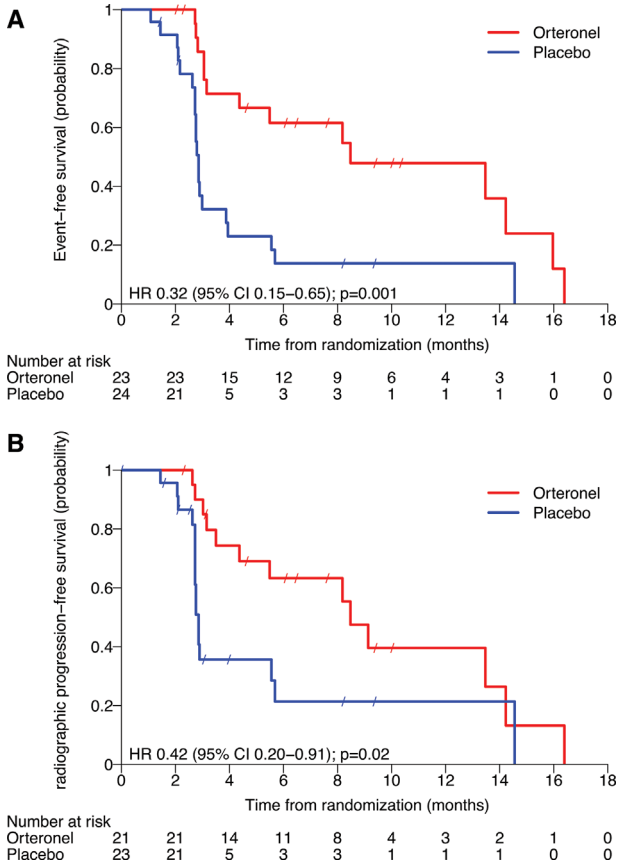

Fig. 2. Kaplan–Meier plots for event-free survival (EFS) (**A**) and radiographic progression-free survival (rPFS) (**B**).

Urinary Metabolites in Relation to Trial Treatment

The log-transformed ratios of urinary steroid hormones showed a definite blockade of CYP17 for all patients on orteronel (Fig. 4).

No clear association between the level of CYP17 inhibition and PSA response was found (Suppl. Fig. S3). The same applies to the association between the level of CYP17 inhibition and EFS or rPFS. The sample size however is very small and does not allow to answer this question.

DISCUSSION

In standard practice, men with mCRPC completing chemotherapy with docetaxel are followed clinically until disease progression, since all reported positive phase III trials post docetaxel included only patients with documented disease progression. Maintenance treatment, either as continuation of a drug already given concomitantly from the start of first line chemotherapy or a drug introduced after disease stabilization by first line chemotherapy (switch maintenance therapy), has been shown to improve outcome in several other malignancies.

Maintenance therapy with one of the novel endocrine agents following docetaxel is attractive as they are generally well tolerated but this concept has not

TABLE II. Overview of Efficacy Results

Endpoint	Orteronel (N = 23)	Placebo (N = 24)	*P*-value, HR (95%CI)
Event-free survival (EFS), median (95%CI)	8.5 months (3.2–16)	2.9 months (2.7–3.9)	$P = 0.001$[a], 0.32 (0.15–0.65)
Radiographic progression-free survival (rPFS), median (95%CI)	8.5 months (3.5–14.2)	2.8 months (2.7–5.6)	$P = 0.02$[a], 0.42 (0.20–0.91)
Time to PSA progression, median (95%CI)	6.5 months (2.7–10.3)	1.8 months (1.1–2.9)	$P = 0.004$[a], 0.37 (0.18–0.75)
Time to radiographic progression from last docetaxel dose, median (95%CI)	9.6 months (5.3–15.0)	4.0 months (3.7–6.4)	–
Time to symptomatic/clinical progression, median (95%CI)	14.4 months (4.4–NR[b])	3.0 months (2.8–5.7)	–
PSA decline ≥30%, n (%) (95%CI)	17 (74%) (52–90%)	2 (8%) (1–27%)	<0.001[c]
PSA decline ≥50%, n (%) (95%CI)	13 (57%) (35–77%)	1 (4%) (0–21%)	<0.001[c]
PSA decline ≥90%, n (%) (95%CI)	2 (9%) (1–28%)	0 (0%)	–

[a]Log-rank test.
[b]NR, not reached.
[c]Fisher's exact test.

so far been investigated for mCRPC. Despite the fact that this trial had to be prematurely closed after the inclusion of 47 of 192 planned patients due to the manufacturer's decision to abrogate further development of the CYP17 inhibitor orteronel for prostate cancer, there was a significant improvement in EFS and rPFS. The rPFS of 8.5 months found in our trial is comparable to other novel agents used in second line after prior docetaxel: rPFS on abiraterone/prednisone was 5.6 months [2], on enzalutamide 8.3 months [3] and on orteronel (400 mg bd)/prednisone 8.3 months [6], respectively. In view of the fact that the patients in our trial were selected in the sense that they all had derived clinical benefit from docetaxel (PR or SD) and due to the small number of patients included the results have to be interpreted with caution.

The patient population included in our trial was different from all other trials with novel endocrine agents: in this trial patients had to have non-progressive disease after docetaxel treatment and trial treatment was planned to start 3–6 weeks after last application of docetaxel. Median docetaxel dose was 450 mg/m^2 corresponding to six cycles of 3-weekly docetaxel. None of the patients had received either

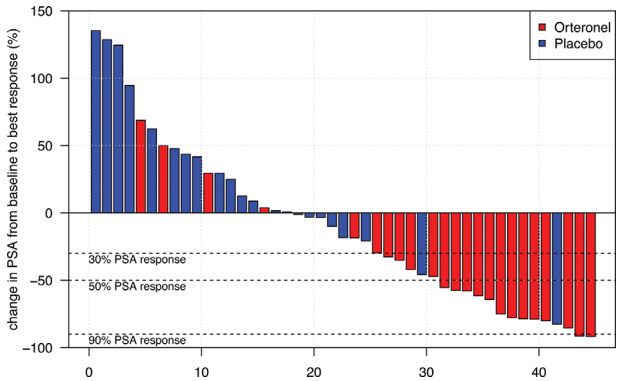

Fig. 3. Waterfall plot for best PSA response on treatment.

TABLE III. Subsequent Therapies After Discontinuation of Trial Treatment

Variable	Orteronel (N = 23) n (%)	Placebo (N = 24) n (%)
Subsequent treatment		
Yes	18 (78)	19 (80)
No	3 (13)	2 (8)
Orteronel ongoing	1 (4)	0 (0)
Unknown	1 (4)	3 (13)
Abiraterone or Enzalutamide	16 (70)	15 (63)
Specify subsequent treatment (more than one applicable)		
Abiraterone	10 (44)	11 (46)
Cabazitaxel	10 (44)	8 (33)
Carboplatin	4 (17)	0 (0)
Dexamethasone	0 (0)	2 (8)
Docetaxel	4 (17)	3 (13)
Enzalutamide	9 (39)	9 (38)
Epirubicin	1 (4)	0 (0)
Etoposide	1 (4)	0 (0)
Paclitaxel	3 (13)	0 (0)
Prednisone	0 (0)	1 (4)
Radium-223	4 (17)	3 (13)
Stilboestrol	1 (4)	0 (0)

TABLE IV. Adverse Events Under Treatment and Until 30 Days After Treatment Stop or Start of New Treatment That Are Possibly, Probably, or Definitely Related to Trial Treatment

	Orteronel (N = 23)				Placebo (N = 24)		
AE category	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)
Adrenal insufficiency			1 (4)				
Anemia		1 (4)					
Cardiac disorders						1 (4)	
Creatinine increased	1 (4)						
Elevated liver enzymes		1 (4)					1 (4)
Fatigue	2 (9)	4 (17)	2 (9)		2 (8)		
GGT increased		1 (4)					
Gastrointestinal disorders	8 (35)	3 (13)	1 (4)		2 (8)	1 (4)	1 (4)
Genital edema							1 (4)
Hot flashes	3 (13)					1 (4)	
Hypertension		3 (13)					2 (8)
Hypokalemia	1 (4)		1 (4)				
Infection	1 (4)					2 (8)	
Lipase/amylase increased			1 (4)				
Muscle weakness	1 (4)						
Nausea/vomiting	4 (17)	6 (26)			2 (8)		1 (4)
Neurological disorders	3 (13)	3 (13)					1 (4)
Pain	4 (17)					1 (4)	
Peripheral edema	2 (9)				2 (8)	1 (4)	
Psychiatric disorders	1 (4)		1 (4)				
Pulmonary disorders		1 (4)		1 (4)		1 (4)	
QTc prolongation			1 (4)				

abiraterone or enzalutamide prior to chemotherapy. This limits the applicability of our results in the current treatment landscape but our trial provides evidence for a proof of concept that needs to be tested for patients with prior exposure to API's in forthcoming trials.

We used a different orteronel dose than in the phase 3 trials [6,7]: instead of 400 mg BID plus low dose prednisone only 300 mg BID without prednisone were administered. This approach was based on results from two trials demonstrating that orteronel doses of 300 mg BID without prednisone appeared equally effective not only in terms of suppression of measurable androgen synthesis but also in terms of clinical response [23,24].

The patients in the control arm of our trial received placebo without prednisone. Most patients included had received low-dose prednisone with prior docetaxel and investigators were encouraged to taper prednisone before trial inclusion. However, some misbalance in the use of low-dose prednisone cannot be excluded since it was not used as a stratification criterion. From a clinical point of view, it appears unlikely that a possible misbalance might have significantly changed the results. Likewise, a misbalance in the use of bone targeting agents (e.g., denosumab or zoledronic acid) cannot be excluded. However, none of these agents has demonstrated any impact on efficacy endpoints in several large trials and hence an impact on the results presented appears unlikely.

In the placebo arm, we demonstrated that patients who benefitted from docetaxel have only a 4 months median time to radiographic progression from last docetaxel administration. This suggests that interrupting all treatment (apart from baseline castration) in mCRPC patients allows tumor cells to regrow quickly. Also, the median time to clinical/symptomatic progression of 3 months in the placebo arm is short. Introducing a generally well tolerated, efficacious therapy with another mechanism of action at this earlier time point may therefore lead to clinical benefit. The QoL data were not conclusive due to high interpatient variability and the small number of patients. Of note, the frequency of symptomatic/clinical progression was lower in the orteronel arm and the events occurred much later indicating a possible QoL benefit if treatment with an API is initiated early after the end of chemotherapy instead

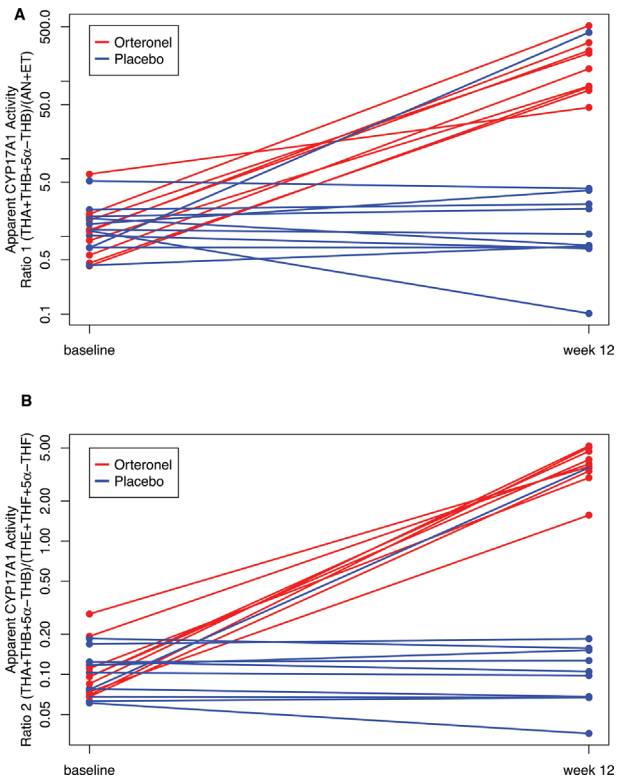

Fig. 4. Apparent CYP17A1 blockade before treatment and 12 weeks after treatment start assessed by log-transformed ratio 1 (**A**) and 2 (**B**). The following precursor-to-product metabolite ratios were derived: ratio 1 [tetrahydro-11-dehydrocorticosterone (THA) + tetrahydrocorticosterone (THB) + 5α-tetrahydrocorticosterone (5α-THB)]/[androsterone (An) + etiocholanolone (Et)] and ratio 2 [THA + THB + 5α-THB]/[tetrahydrocortisone (THE) + tetrahydrocortisol (THF) + 5α-tetrahydrocortisol (5α-THF)].

of deferred. Our trial however cannot answer the question whether early initiation of novel API's after chemotherapy compared to starting treatment at time of progression is beneficial for patients in terms of overall survival. The results of the two trials testing the API's abiraterone and enzalutamide before the use of docetaxel demonstrate that using novel API's early in asymptomatic patients can improve OS [4,5]. Trials are ongoing where API's are tested early in hormone-sensitive metastatic prostate cancer.

The downstream urine metabolites in all patients on orteronel were consistent with blockage of the target enzyme CYP17, a correlation of the degree of inhibition with response could not be seen, but the number of samples was small. This non-invasive approach could potentially be developed for testing adherence to therapy for this class of oral drugs.

Of note, high PSA response rates were seen on orteronel in our trial with patients who were stable or responding to docetaxel. This suggests an ongoing dependency on the androgen receptor pathway contradicting a postulated cross-resistance between docetaxel and novel APIs as was also demonstrated in the post-docetaxel trials using abiraterone or enzalutamide [2,3].

To conclude, our trial showed that early use of an API like orteronel in men achieving disease stabilization on docetaxel significantly prolongs EFS. However, if this translates into improved QoL or a benefit in OS remains to be proven. Our trial despite all its limitations clearly establishes a rationale to further develop the approach of immediate switch maintenance after successful completion of chemotherapy.

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