Orteronel plus prednisone in patients with chemotherapy-naive metastatic castration-resistant prostate cancer (ELM-PC 4): a double-blind, multicentre, phase 3, randomised, placebo-controlled trial

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Summary

Background Orteronel is an investigational, partially selective inhibitor of CYP 17,20-lyase in the androgen signalling pathway, a validated therapeutic target for metastatic castration-resistant prostate cancer. We assessed orteronel in chemotherapy-naive patients with metastatic castration-resistant prostate cancer.

Methods In this phase 3, double-blind, placebo-controlled trial, we recruited patients with progressive metastatic castration-resistant prostate cancer and no previous chemotherapy from 324 study centres (ie, hospitals or large urologic or group outpatient offices) in 43 countries. Eligible patients were randomly assigned in a 1:1 ratio to receive either 400 mg orteronel plus 5 mg prednisone twice daily or placebo plus 5 mg prednisone twice daily. Randomisation was done centrally with an interactive voice response system and patients were stratified by region (Europe, North America, and not Europe or North America) and the presence or absence of radiographic disease progression at baseline. The two primary endpoints were radiographic progression-free survival and overall survival, determined in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT01193244.

Findings From Oct 31, 2010, to June 29, 2012, 2353 patients were assessed for eligibility. Of those, 1560 were randomly assigned to receive either orteronel plus prednisone (n=781) or placebo plus prednisone (n=779). The clinical cutoff date for the final analysis was Jan 15, 2014 (with 611 deaths). Median follow-up for radiographic progression-free survival was 8·4 months (IQR 3·7–16·6). Median radiographic progression-free survival was 13·8 months (95% CI 13·1–14·9) with orteronel plus prednisone and 8·7 months (8·3–10·9) with placebo plus prednisone (hazard ratio [HR] 0·71, 95% CI 0·63–0·80; p<0·0001). After a median follow-up of 20·7 months (IQR 14·2–25·4), median overall survival was 31·4 months (95% CI 28·6–not estimable) with orteronel plus prednisone and 29·5 months (27·0–not estimable) with placebo plus prednisone (HR 0·92, 95% CI 0·79–1·08; p=0·31). The most common grade 3 or worse adverse events were increased lipase (137 [17%] of 784 patients in the orteronel plus prednisone group *vs* 14 [2%] of 770 patients in the placebo plus prednisone group), increased amylase (77 [10%] *vs* nine [1%]), fatigue (50 [6%] *vs* 14 [2%]), and pulmonary embolism (40 [5%] *vs* 27 [4%]). Serious adverse events were reported in 358 [46%] patients receiving orteronel plus prednisone and in 292 [38%] patients receiving placebo plus prednisone.

Interpretation In chemotherapy-naive patients with metastatic castration-resistant prostate cancer, radiographic progression-free survival was prolonged with orteronel plus prednisone versus placebo plus prednisone. However, no improvement was noted in the other primary endpoint, overall survival. Orteronel plus prednisone was associated with increased toxic effects compared with placebo plus prednisone. On the basis of these and other data, orteronel is not undergoing further development in metastatic castration-resistant prostate cancer.

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Introduction

Androgens and the androgen receptor signalling pathway are crucial therapeutic targets in metastatic castration-resistant prostate cancer.[1] One of the molecular changes leading to metastatic disease is the upregulation of androgen biosynthesis enzymes, causing an increase in intratumoural androgen concentrations and androgen-receptor signalling.[2,3] These therapeutic targets have been validated in phase 3 trials with abiraterone acetate and enzalutamide in patients with progressive metastatic castration-resistant prostate cancer.[4–7]

Before the availability of these drugs, patients with castration-resistant prostate cancer were treated with several second-line hormone-directed strategies that yielded short-duration responses in some cases; however, effects on overall survival were not shown.[8] Docetaxel in combination with prednisone was shown to prolong life and was approved in 2004, but many patients with metastatic castration-resistant prostate cancer do not

receive it due to its toxic effects.[9–11] At the time of the commencement of the orteronel ELM-PC 4 trial, an unmet need remained for safe, non-cytotoxic, effective treatment for patients with metastatic castration-resistant prostate cancer. Following phase 3 trials in chemotherapy-naive patients, abiraterone and enzalutamide have both become available as first-line therapy for this disease.[4,6]

Orteronel (TAK-700) is an investigational, non-steroidal, selective inhibitor of CYP 17,20-lyase, a key enzyme in the androgen biosynthesis CYP17 pathway. Orteronel is partially selective for CYP 17,20-lyase, thus inhibiting androgen synthesis; by contrast abiraterone inhibits both androgen synthesis via CYP 17,20-lyase and cortisol synthesis via 17α-hydroxylase. Furthermore, by contrast with abiraterone, orteronel is a reversible inhibitor of CYP17A1, is a non-steroidal compound, and it can be taken without regard to food. Abiraterone is also given in combination with a low-dose glucocorticoid, such as prednisone, whereas orteronel offers the potential to be given without added steroids in some disease settings.[12] Results from a phase 2 trial[12] showed that orteronel (with or without prednisone) greatly decreased concentrations of testosterone, dehydroepiandrosterone-sulphate (DHEA-S), and prostate-specific antigen (PSA) in patients with metastatic castration-resistant prostate cancer.[12] The phase 2 evidence led to two large phase 3 trials in patients with this disease that had been treated with docetaxel or were chemotherapy-naive (ELM-PC 5[13] and ELM-PC 4). As previously reported in ELM-PC 5,[13] orteronel plus prednisone did not significantly improve the primary endpoint of overall survival compared with prednisone alone. However, patients given orteronel plus prednisone had a longer radiographic progression-free survival (median 8·3 months *vs* 5·7 months with prednisone alone) and more patients given orteronel plus prednisone had a PSA decline of 50% or more than did those given prednisone alone, confirming the activity of orteronel plus prednisone in metastatic castration-resistant prostate cancer noted in a phase 2 trial.[12,13]

We report the findings of the ELM-PC 4 trial, which investigated orteronel plus prednisone versus placebo plus prednisone in chemotherapy-naive men with progressive metastatic castration-resistant prostate cancer.

Methods

Study design and participants

In this randomised, double-blind, placebo-controlled phase 3 trial, patients with progressive, chemotherapy-naive metastatic castration-resistant prostate cancer were enrolled from 324 study centres (either hospitals or large urologic or group [multispecialty] outpatient offices; all study centres had access to local labs and affiliated hospitals) in 43 countries (appendix pp 4–11). Eligible male patients were aged 18 years or older with histologically or cytologically confirmed adenocarcinoma of the prostate; radiographically documented nodal, bone, or visceral metastatic disease; and biochemical or radiographic evidence of disease progression (per Response Evaluation Criteria In Solid Tumors [RECIST] 1.1[14] or Prostate Cancer Working Group criteria [PCWG2][15]). In addition, eligible patients had previous surgical or medical castration with testosterone concentrations less than 50 ng/dL at screening; an estimated survival of at least 12 months; an Eastern Cooperative Oncology Group performance status of 0–1; absence of pain or pain not requiring opioids or narcotics; screening PSA of 2 ng/mL or higher; adequate renal, hepatic, haematological, and cardiac function; use of effective barrier contraception or true abstinence; and an overall stable medical condition. Exclusion criteria were: previous therapy with orteronel, ketoconazole, aminoglutethimide, or abiraterone; known hypersensitivity to study drugs; anti-androgen therapy or exposure to radioisotope therapy or external beam radiation within 4 weeks of first dose of study drug; other treatments for prostate cancer (other than GnRH analogues) that were not discontinued 2 weeks before first dose of study drug; continuous oral prednisone, oral dexamethasone, or other systemic corticosteroids for more than 14 days within 3 months before screening; previous chemotherapy for prostate cancer; CNS metastases; treatment with any investigational compound within 30 days of first dose of study drug or actively ongoing in another clinical trial of prostate cancer; current spinal cord compression, current bilateral hydronephrosis, or current bladder neck outlet obstruction; diagnosis of or treatment for another systemic malignancy within 2 years of first dose of study drug or residual disease from a previous malignancy; known HIV infection, active chronic hepatitis B or C, life-threatening illness unrelated to cancer, or other disorder that might interfere with study participation; uncontrolled nausea, vomiting, or diarrhoea despite therapy; known gastrointestinal disease or gastrointestinal procedure that could interfere with absorption or tolerance of orteronel; likely inability to comply with the protocol or cooperate fully with the investigator and site personnel; or prostate cancer confined to just the prostate bed or immediate adjacent tissue (appendix pp 12–13). The study was approved by institutional review boards and done per the Declaration of Helsinki, the International Conference on Harmonisation, and Good Clinical Practice guidelines. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to receive either orteronel plus prednisone or placebo plus prednisone. Randomisation, stratified by region (Europe, North America, and not Europe or North America) and presence or absence of radiographic disease progression at baseline, was achieved in a blinded manner by kit assignments obtained through a centralised interactive voice response system generated by an external vendor.

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See **Online** for appendix

Through this process, every patient received a designated identification number. Both patients and investigators were masked to treatment assignment. An independent data monitoring committee had access to unmasked data for the interim analysis, met at regularly scheduled meetings to review emerging safety data, and provided recommendation regarding study continuation.

Procedures

Patients received continuous doses of either 400 mg orteronel (2×200 mg tablets; Takeda Pharmaceutical Company Ltd, Osaka, Japan) or matching placebo twice daily (total dose of 800 mg per day), at the same time every day, about 12 h apart, without regards to food in 28-day cycles. All patients received prednisone 5 mg twice daily. We chose the dose for this trial on the basis of the maximum effective reductions in testosterone and DHEA-S noted in the phase 2 trial.[12] Patients in Japan received orteronel 300 mg twice daily (3×100 mg tablets twice daily, for a total dose of 600 mg per day), following a protocol amendment based on preliminary safety and pharmacokinetic results from an ongoing phase 1 study[16] compared with findings from the US phase 2 study.[12] According to adverse events, the dose of orteronel could be reduced from two tablets twice daily to one tablet in the morning and two tablets in the afternoon, to one tablet twice daily, or dose could be held until the event was resolved or stabilised. In Japan, the dose of orteronel could be reduced from three 100-mg tablets twice daily to two tablets twice daily, to one tablet in the morning and two tablets in the afternoon, or dose could be held until the event was resolved or stabilised.

Scheduled visits were at the beginning of each of the first seven cycles and then every three cycles until treatment discontinuation. Patients who discontinued treatment before radiographic progression were followed every 12 weeks until progression. Tumour assessments by radiographic imaging, pain assessment via Brief Pain Inventory-Short Form worst pain scale (BPI-SF, 0–10),[17] and previous 24 h opioid-use recall questionnaire were completed at screening, every other cycle up to cycle 7, then every three cycles until disease progression, and thereafter as clinically indicated. Sample collection for laboratory assessments including PSA and testosterone occurred before dosing at least every three cycles. Circulating tumour cell (CTC) enumeration occurred at cycles 1, 3, 4, 5, 7, 10, and at the end-of-treatment visit. Patients could continue treatment until central review confirmation of radiographic progression or until receipt of subsequent antineoplastic therapy, unacceptable toxic effects, or death. Safety and dosing compliance were assessed during every study visit, at treatment discontinuation, and at the end-of-treatment visit. A central imaging centre independently reviewed films and made the determination of whether radiographic disease progression had occurred. Additional procedures are listed in the appendix. We assessed toxic effects according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.02.

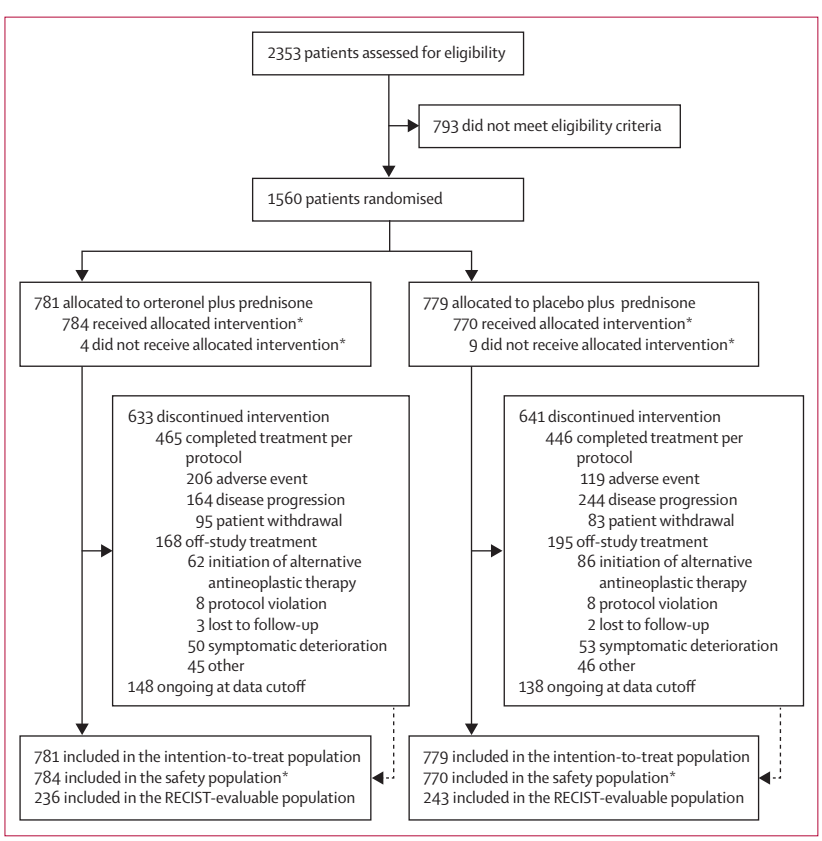


Figure 1: **Trial profile**

*Four patients randomised to the orteronel plus prednisone group and two patients in the placebo plus prednisone group did not receive the assigned treatment; seven patients randomised to receive placebo plus prednisone may have received at least one dose of orteronel in error and thus they are summarised in the orteronel plus prednisone group for analysis of safety population only.

Outcomes

This study had two primary outcomes: radiographic progression-free survival and overall survival. Key secondary endpoints were the proportion of patients with a 50% or greater decrease in PSA from baseline (PSA50) at 12 weeks, the proportion of patients with an unfavourable CTC count (≥5 cells per 7·5 mL of blood) at baseline and converted to a favourable count (<5 cells per 7·5 mL of blood) at 12 weeks, and time to pain progression per worst pain item in the BPI-SF and changes in opioid analgesic use. Other secondary endpoints were safety assessments, time to docetaxel-based chemotherapy and time to subsequent therapy, frequency of skeletal-related events, time to radiographic progression-free survival or skeletal-related event, duration of PSA response, time to PSA progression, overall objective response rate, proportion of patients with ≥90% PSA decline from baseline (PSA90) at 12 weeks and any time during the study, and proportion of patients with PSA50 at any time

during the study beginning 4 weeks following the start of the study drug. Further details about the endpoints are outlined in the appendix (pp 14, 15).

Statistical analysis

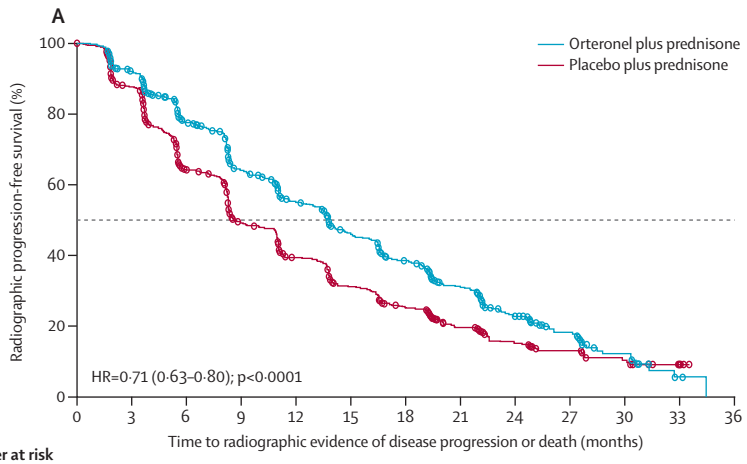
Assuming an exponential distribution for overall survival, 900 deaths were required for 90% power to detect a hazard ratio (HR) of 0·8 (median survival 27·5 months with orteronel plus prednisone *vs* 22 months with placebo plus prednisone) with a two-sided log-rank test at a 4·5% overall significance level (ie, pre-assigned α for overall survival of 0·045). A total of 1454 patients were required for randomisation. The protocol-specified final analysis for radiographic progression-free survival and the first interim analysis for overall survival were planned at 412 radiographic progressive disease events. With 412 radiographic progressive disease events and an exponential distribution assumption for time to radiographic disease progression or death, we calculated 90% power to detect an HR of 0·67 (median radiographic progression-free survival 9 months with orteronel plus prednisone *vs* 6 months with placebo plus prednisone) using a two-sided log-rank test at a 0·5% level (α=0·005). The study was not stopped after the interim analysis to allow subsequent analysis of overall survival. With the O'Brien-Fleming method and the fallback procedure proposed by Wiens,[18] if radiographic progression-free survival is significant at an α of 0·005 at the planned interim analysis (radiographic progression-free survival final analysis), the α spent for overall survival would be less than 0·00001 at the planned interim analysis analysis and 0·05 at the final analysis; otherwise, the α spent for overall survival would be less than 0·00001 at the planned interim analysis and 0·045 at the final analysis. The progressive availability of new alternative treatments invalidated the original study assumptions regarding median overall survival. Thus, the planned interim analysis for overall survival, at 600 deaths, was amended to become the final analysis for overall survival (ie, at 67% of the originally planned 900 deaths), with a consequent reduction of power from 90% to 76·6%. We did an updated analysis of radiographic progression-free survival at this final analysis for overall survival (1051 radiographic progression-free survival events).

We compared radiographic progression-free survival, overall survival, and time to pain progression in the intention-to-treat population using stratified log-rank testing with HRs and 95% CIs estimated using the unadjusted stratified Cox model. We used a stratified Cox regression model to assess the treatment effects on overall survival using baseline prognostic factors as covariates. We tested PSA and favourable CTC response rates using the Cochran-Mantel-Haenszel χ^2 test. We analysed the safety population by treatment received. We did the statistical analyses with SAS version 9.1 (Cary, NC, USA). This trial is registered with ClinicalTrials.gov, NCT01193244.

	Orteronel plus prednisone (n=781)	Placebo plus prednisone (n=779)
Age		
Median (years)	71·0 (65·0–77·0)	72·0 (66·0–77·0)
≥70 years	453 (58%)	470 (60%)
Region		
Europe	421 (54%)	420 (54%)
Non-Europe and non-North America	190 (24%)	190 (24%)
North America	170 (22%)	169 (22%)
Radiographic disease progression		
No	381 (49%)	379 (49%)
Yes	400 (51%)	400 (51%)
ECOG PS*		
0	530 (68%)	516 (66%)
1	250 (32%)	262 (34%)
2	1 (<1%)	1 (<1%)
BPI-SF worst pain score	2·0 (0–4·0)	2·0 (0–4·0)
PSA (ng/mL)	55·8 (19·8–150·0)	55·3 (18–150·0)
Haemoglobin ≤12 g/dL	206 (26%)	216 (28%)
Alkaline phosphatase >175 U/L	192 (25%)	186 (24%)
Lactate dehydrogenase >225 U/L	186 (24%)	187 (24%)
Estimated creatinine clearance		
≥90 mL/min	390 (50%)	353 (45%)
<90 mL/min	391 (50%)	425 (55%)
Missing	0	1 (<1%)
Time since initial diagnosis (years)	4·4 (2·3–8·2)	4·9 (2·4–8·6)
Measurable disease		
No	545 (70%)	536 (69%)
Yes	236 (30%)	243 (31%)
Gleason score*		
≤6	120 (15%)	132 (17%)
7	238 (30%)	229 (29%)
≥8	382 (49%)	371 (48%)
Missing	41 (5%)	47 (6%)
Visceral disease		
No	647 (83%)	636 (82%)
Yes	134 (17%)	143 (18%)
Metastases		
Bone	730 (93%)	705 (91%)
Liver	27 (3%)	45 (6%)
Lung	71 (9%)	70 (9%)
Lymph node	346 (44%)	329 (42%)
Other	97 (12%)	105 (14%)
Missing	2 (<1%)	2 (<1%)
Previous cancer therapy		
ADT	684 (88%)	699 (90%)
Denosumab	46 (6%)	36 (5%)
Hormonal	378 (48%)	367 (47%)
Non-hormonal	403 (52%)	412 (53%)

Data are n (%) or median (IQR). BPI-SF=Brief Pain Inventory-Short Form. ECOG-PS=Eastern Cooperative Oncology Group performance status. PSA=prostate-specific antigen. CTC=circulating tumour cells. ADT=Androgen deprivation therapy. *Percentages may not add to 100% due to rounding.

Table 1: **Patient demographics and baseline characteristics**

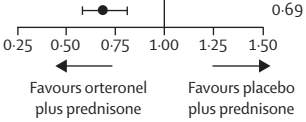


Number at risk

Orteronel plus prednisone	781	656	525	416	336	267	207	113	65	34	14	2	0
Placebo plus prednisone	779	640	445	322	247	188	142	73	44	22	15	5	0

	Orteronel plus prednisone	Placebo plus prednisone
Median progression-free survival, months (95% CI)	13·8 (13·1–14·9)	8·7 (8·3–10·9)
Progression-free survival events, n	489	562
Patients without radiographic evidence of disease progression	434	351

B



	Median radiographic progression-free survival (months)		HR (95% CI)
	Orteronel plus prednisone	Placebo plus prednisone	
All patients			
ALL (N=1560)	13·81	8·68	0·71 (0·63–0·80)
Age			
<70 years (n=637)	13·84	8·55	0·70 (0·58–0·84)
≥70 years (n=923)	13·81	8·74	0·73 (0·62–0·85)
Region			
Europe (n=841)	13·84	8·74	0·71 (0·60–0·83)
Non-Europe and non-North America (n=380)	12·95	8·32	0·64 (0·50–0·82)
North America (n=339)	13·81	10·91	0·79 (0·61–1·03)
Radiographic disease progression at baseline			
No (n=760)	16·50	11·05	0·68 (0·57–0·82)
Yes (n=800)	11·31	8·32	0·73 (0·62–0·86)
Baseline PSA			
<20 ng/ml (n=404)	18·18	11·34	0·77 (0·59–1·00)
20–50 ng/ml (n=338)	13·87	9·96	0·77 (0·59–1·01)
>50 ng/ml (n=818)	11·60	8·25	0·66 (0·56–0·78)
Baseline LDH			
≤225 (n=1187)	15·22	10·98	0·72 (0·62–0·83)
>225 (n=373)	9·34	5·56	0·63 (0·50–0·80)
Gleason score			
Low <8 (n=719)	15·35	10·85	0·67 (0·56–0·81)
High ≥8 (n=753)	11·87	8·35	0·74 (0·62–0·87)
Disease measurability			
No (n=1081)	16·54	11·05	0·70 (0·60–0·82)
Yes (n=479)	8·55	6·97	0·71 (0·58–0·87)
Previous primary therapy			
Hormonal (n=745)	13·87	11·01	0·72 (0·60–0·87)
Non-hormonal (n=815)	13·74	8·32	0·69 (0·58–0·81)

Role of funding source

The authors designed the study in collaboration with employees of the funder, Millennium Pharmaceuticals, who also assisted with study design, data collection and analysis, and writing of the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

Between Oct 31, 2010, and June 29, 2012, we screened 2353 patients for eligibility, of whom 1560 were randomly assigned to receive either orteronel plus prednisone (n=781) or placebo plus prednisone (n=779; figure 1). Baseline demographics and disease characteristics were balanced across groups (table 1). Patients had advanced disease: about half the patients in each group had radiographic progression at baseline and visceral disease was present in about a fifth of patients in both groups (table 1). The clinical cutoff date for the final analysis and the data presented here was Jan 15, 2014 (with 611 deaths).

The median duration of treatment was longer for the orteronel plus prednisone group than for the placebo plus prednisone group (10·1 months [range 0·03–35·6] *vs* 8·9 months [0·03–35·4]). 345 (44%) of the 781 patients in the orteronel plus prednisone group and 132 (17%) of the 779 patients in the placebo plus prednisone group had dose reductions during the study. The most common reasons for discontinuation were adverse events and disease progression (figure 1). Discontinuation to pursue alternative therapy before radiographic progression, whatever the underlying reason, was similar between the two groups (174 [22%] with orteronel plus prednisone *vs* 150 [19%] with placebo plus prednisone; figure 2).

At the first interim analysis (the planned final analysis for radiographic progression-free survival), 501 radiographic progression-free survival events (ie, events of radiographic disease progression or death) had occurred. Treatment with orteronel plus prednisone significantly reduced the risk of radiographic progression or death compared with placebo plus prednisone (median radiographic progression-free survival 11·0 months [95% CI 9·1–13·6] in the orteronel

Figure 2: **Radiographic progression-free survival at the time of final analysis of overall survival**

(A) Kaplan-Meier curves. 489 PFS events occurred in the orteronel plus prednisone group (347 radiographic progressive disease, 142 deaths), as did 562 in the placebo plus prednisone group (428 radiographic progressive disease, 134 deaths). In the orteronel plus prednisone group, three patients received alternative therapy before radiographic progression was documented, and 191 received it after radiographic progression. In the placebo plus prednisone group, four patients received alternative treatment before radiographic progression was documented, and 253 received it after radiographic progression. Of the 434 patients without radiographic progression in the orteronel plus prednisone group, 171 received alternative therapy; of the 351 patients without radiographic progression in the placebo plus prednisone group, 146 received alternative therapy. (B) Prespecified subgroup analyses. PFS=radiographic progression-free survival. HR=hazard ratio. PSA=prostate-specific antigen. LDH=lactate dehydrogenase.

plus prednisone group *vs* 8·3 months [8·2–8·6] in the placebo plus prednisone group; HR 0·70 [95% CI 0·50–0·80]; p<0·0001).

The remaining findings for radiographic progression-free survival reported here are from the updated analysis done at the final analysis for overall survival. At this time point, median follow-up for radiographic progression-free survival was 8·4 months (IQR 3·7–16·6): 10·8 months (4·9–19·0) in the orteronel plus prednisone group and 8·3 months (3·7–14·1) in the placebo plus prednisone group. At this analysis, 347 (44%) of 781 patients in the orteronel plus prednisone group and 428 (55%) of 779 patients in the prednisone group had radiographic progression. 142 (18%) patients in the orteronel plus prednisone group and 134 (17%) patients in the prednisone group died without documented radiographic progression. Radiographic progression-free survival was improved with orteronel plus prednisone versus placebo plus prednisone at this updated analysis (median radiographic progression-free survival 13·8 months [95% CI 13·1–14·9] for the orteronel plus prednisone group *vs* 8·7 months [8·3–10·9] for the placebo plus prednisone group; HR 0·71 [95% CI 0·63–0·80]; p<0·0001; figure 2A). The effect of orteronel plus prednisone on radiographic progression-free survival was much the same across all prespecified subgroups (figure 2B).

At data cutoff, median follow-up was 20·7 months (IQR 14·2–25·4): 20·8 months (IQR 14·8–25·2) in the orteronel plus prednisone group and 20·6 months (13·7–25·5) in the placebo plus prednisone group. We recorded 294 (38%) deaths in the orteronel plus prednisone group versus 317 (41%) deaths in the placebo plus prednisone group. Orteronel plus prednisone did not significantly improve overall survival compared with placebo plus prednisone (median overall survival 31·4 months [95% CI 28·6–not estimable] for the orteronel plus prednisone group *vs* 29·5 months [27·0–not estimable] for the placebo plus prednisone group; HR 0·92 [95% CI 0·79–1·08]; p=0·31; figure 3A). Findings were consistent across subgroups except for patients with PSA concentration higher than 50 ng/mL at baseline (figure 3B). The appendix includes adjusted analyses for overall survival (p 16).

Overall, 353 (45%) patients treated with orteronel plus prednisone and 395 (51%) patients treated with placebo plus prednisone received subsequent therapy for prostate cancer (appendix p 19). In a pre-specified sensitivity analysis, censoring patient data at the start of any alternative therapy, orteronel plus prednisone was not

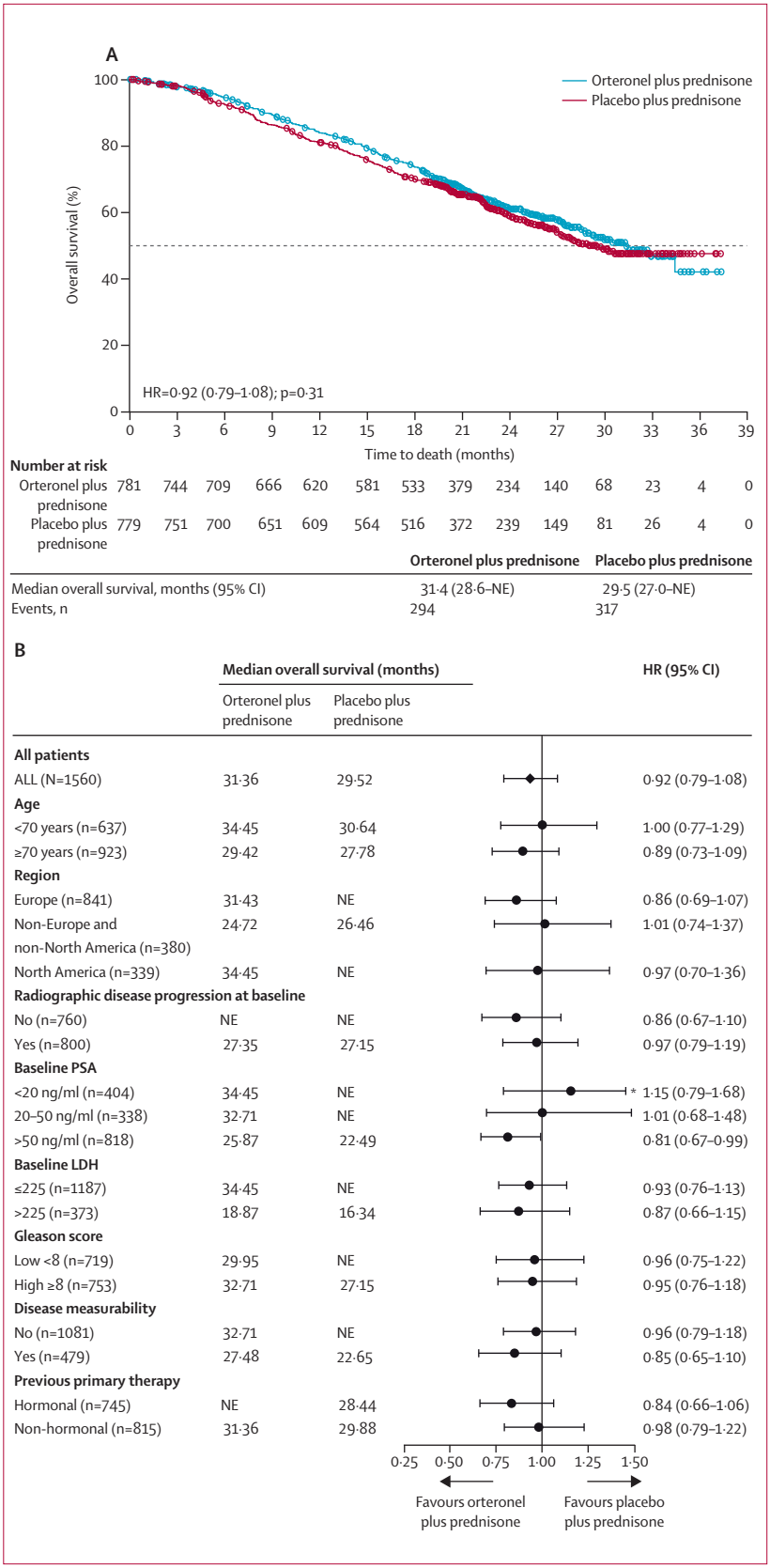


Figure 3: **Final analysis of overall survival**

(A) Kaplan-Meier curves. 294 deaths occurred in the orteronel plus prednisone group as did 317 in the placebo plus prednisone group. (B) Prespecified subgroup analyses. NE=not estimable. HR=hazard ratio. PSA=prostate-specific antigen. LDH=lactate dehydrogenase. *HRs and confidence bounds greater than 1·5 are omitted from the plot.

	Orteronel plus prednisone		Placebo plus prednisone		Effect size (95% CI)†	p value†
	n/N	% (95% CI) or median (95% CI)	n/N	% (95% CI) or median (95% CI)		
PSA50 response‡ at 12 weeks	333/781	43% (39–46)	192/779	25% (22–28)	RR 1·73 (1·49–2·00)	<0·0001
Proportion of patients with a favourable CTC count at 12 weeks following an unfavourable count at baseline	120/781	15% (13–18)	71/779	9% (7–11)	RR 1·69 (1·28–2·22)	0·0002
CTC conversion rate§ at 12 weeks in patients with unfavourable counts at baseline	120/300	40% (34–46)	71/288	25% (20–30)	RR 1·62 (1·27–2·07)	<0·0001
Median time to pain progression, months (95% CI)¶	121/781	NE (28·6–NE)	124/779	NE (NE–NE)	HR 0·89 (0·69–1·14)	0·34

HR=hazard ratio. PSA=prostate-specific antigen. RR=relative risk. CTC=circulating tumour cells. NE=not estimable. *All key secondary efficacy endpoints were assessed in the intention-to-treat population. †For descriptive purposes only. We calculated HRs by stratified log-rank testing with 95% CIs via the unadjusted stratified Cox model. We calculated the RR and p values per Cochran-Mantel-Haenszel χ^2 test, stratified by region and radiographic disease progression at baseline. ‡PSA50 response was defined as the proportion of patients with ≥50% decrease in PSA from baseline. §We defined CTC conversion rate as the proportion of patients who converted from unfavourable (≥5 cells per 7·5 mL of blood) at baseline to favourable (<5 cells per 7·5 mL of blood) post-baseline; CTC counts at baseline and 12 weeks are summarised in the appendix. ¶We defined pain progression as the occurrence of one of the following and confirmed by an additional assessment, at least 3 weeks but not more than 5 weeks later: (1) the BPI-SF worst pain score is ≥4 with a ≥2 point increase over baseline in BPI-SF worst pain score with stable (<25% change in baseline oral morphine equivalent [OME] dose) or increased (≥25% change in baseline OME) analgesic use; (2) the BPI-SF worst pain score is ≥4 but not less than baseline with new or increased (relative to baseline) step II or step III analgesic use; or (3) the BPI-SF worst pain score is ≤3 but not less than baseline with new or increased (relative to baseline) step III analgesic use [WHO Steps of Analgesics: http://www.who.int/cancer/palliative/painladder/en/].

Table 2: **Prespecified key secondary efficacy endpoints***

associated with improved overall survival (HR 0·80, 95% CI 0·64–0·99; p=0·043, appendix p 16).

Since no significant difference in overall survival was noted between groups, we report statistical comparisons of the secondary efficacy endpoints only for descriptive purposes. The proportion of patients with a PSA50 response and CTC conversion at 12 weeks (table 2), median time to PSA progression, objective response by RECIST, median time to docetaxel-based chemotherapy, and median time to subsequent therapy (appendix pp 17–18) were improved with orteronel plus prednisone versus placebo plus prednisone, but we noted no difference in time to pain progression (table 2).

Compared with baseline, testosterone concentrations in the orteronel plus prednisone group fell below 0·2 ng/mL (the lowest detectable concentration) at 12 weeks and remained low at 24 weeks; the concentrations in the placebo prednisone group were 1·9 ng/dL at 12 weeks and 1·8 ng/dL at 24 weeks (appendix p 32).

The safety analyses included 784 patients in the orteronel plus prednisone group and 770 patients in the placebo plus prednisone group (figure 1, table 3). In both groups, more than 95% of patients had at least one on-study adverse event. 465 (59%) patients in the orteronel plus prednisone group and 313 (41%) patients in the placebo plus prednisone group had grade 3–4 adverse events. 326 (42%) patients in the orteronel plus prednisone group and 111 (14%) patients in the placebo plus prednisone group had investigator-ascribed drug-related adverse events of grade 3 or higher (appendix pp 20–30). On-study deaths (within 30 days of last dose) were similar in both treatment groups (60 [8%] in the orteronel plus prednisone group and 67 [9%] in the placebo plus prednisone group. There were no treatment-related deaths in this study.

The most common all-cause, all-grade adverse events were nausea, fatigue, constipation, and diarrhoea; all were more common with orteronel plus prednisone than with placebo plus prednisone (table 3; appendix). The most common adverse events of grade 3 or higher were increased lipase, increased amylase, fatigue, and pulmonary embolism (table 3). Most events of lipase or amylase increases were apparently asymptomatic and subsided by cycle 7. Laboratory adverse events of interest were more common with orteronel plus prednisone than with placebo plus prednisone, including increased lipase and amylase (table 3). Serious adverse events were more common with orteronel plus prednisone than with placebo plus prednisone (358 [46%] vs 292 [38%]; appendix p 31). 232 (30%) patients in the orteronel plus prednisone group and 136 (18%) patients in the placebo plus prednisone group had adverse events leading to discontinuation; no individual adverse events resulted in discontinuation of greater than 3% of patients overall. 232 patients in the orteronel plus prednisone group and 136 in the placebo plus prednisone group discontinued because of drug-related toxic effects.

Discussion

Our findings show that radiographic progression-free survival, one of the co-primary endpoints, was significantly longer with orteronel plus prednisone than with placebo plus prednisone at both the first interim analysis and at the updated analysis. However, no difference was noted in the co-primary endpoint of overall survival.

At the conception of the ELM-PC 4 trial, the only regimen available that was proven to prolong life for patients with metastatic castration-resistant prostate cancer was docetaxel-based chemotherapy, which offered survival benefits but was associated with side-effects and was frequently not used, especially for elderly patients (panel).[9–11,19] During the ELM-PC 4 trial, several new and life-prolonging treatments became available, including abiraterone, enzalutamide, sipuleucel-T, and cabazitaxel.[4,7,20–23] In particular, abiraterone and enzalutamide became progressively

	Orteronel plus prednisone (n=784)*				Placebo plus prednisone (n=770)*			
	All grades	Grade 3	Grade 4	Grade 5	All grades	Grade 3	Grade 4	Grade 5
Total								
Any adverse event	769 (98%)	328 (42%)	137 (17%)	58 (7%)	732 (95%)	265 (34%)	48 (6%)	64 (8%)
Most common adverse events								
Nausea	281 (36%)	19 (2%)	0	0	115 (15%)	8 (1%)	0	0
Fatigue	267 (34%)	49 (6%)	1 (<1%)	0	157 (20%)	14 (2%)	0	0
Constipation	260 (33%)	7 (<1%)	1 (<1%)	0	118 (15%)	5 (<1%)	0	0
Diarrhoea	222 (28%)	33 (4%)	0	0	106 (14%)	8 (1%)	0	0
Increased lipase†	185 (24%)	56 (7%)	81 (10%)	0	29 (4%)	6 (<1%)	8 (1%)	0
Vomiting	177 (23%)	15 (2%)	0	0	107 (14%)	7 (<1%)	0	0
Muscle spasms	172 (22%)	8 (1%)	0	0	117 (15%)	2 (<1%)	0	0
Decreased appetite	165 (21%)	11 (1%)	0	0	72 (9%)	3 (<1%)	0	0
Back pain	156 (20%)	20 (3%)	1 (<1%)	0	190 (25%)	30 (4%)	0	0
Increased amylase‡	147 (19%)	52 (7%)	25 (3%)	0	24 (3%)	8 (1%)	1 (<1%)	0
Weight decreased	119 (15%)	6 (<1%)	0	0	47 (6%)	2 (<1%)	0	0
Arthralgia	114 (15%)	15 (2%)	0	0	118 (15%)	7 (<1%)	0	0
Asthenia	107 (14%)	17 (2%)	0	0	68 (9%)	14 (2%)	0	0
Dizziness	104 (13%)	4 (<1%)	0	0	46 (6%)	1 (<1%)	0	0
Hypertension	98 (13%)	29 (4%)	1 (<1%)	0	76 (10%)	30 (4%)	0	0
Anaemia	84 (11%)	23 (3%)	5 (<1%)	1 (<1%)	95 (12%)	34 (4%)	4 (<1%)	0
Peripheral oedema	84 (11%)	5 (<1%)	0	0	88 (11%)	3 (<1%)	0	0
Dyspnoea	84 (11%)	10 (1%)	1 (<1%)	0	42 (5%)	3 (<1%)	0	0
Insomnia	82 (10%)	2 (<1%)	0	0	62 (8%)	0	0	0
Blood creatinine increased	81 (10%)	4 (<1%)	0	0	20 (3%)	2 (<1%)	0	0
Hot flush	80 (10%)	0	0	0	76 (10%)	0	0	0
Abdominal pain	77 (10%)	6 (<1%)	1 (<1%)	0	41 (5%)	3 (<1%)	0	0
Pain in extremity	75 (10%)	7 (<1%)	0	0	91 (12%)	5 (<1%)	0	0
Additional adverse events of interest								
ALT increased	50 (6%)	15 (2%)	2 (<1%)	0	11 (1%)	1 (<1%)	0	0
AST increased	39 (5%)	13 (2%)	1 (<1%)	0	13 (2%)	3 (<1%)	0	0
Pancreatitis (acute and chronic)	15 (2%)	7 (<1%)	0	0	0	0	0	0
Pulmonary embolism	9 (1%)	35 (4%)	5 (<1%)	0	2 (<1%)	21 (3%)	5 (<1%)	1 (<1%)

Data are numbers of patients (%); patients with multiple events were counted only once per row. AE=adverse event. ALT=alanine aminotransferase. AST=aspartate aminotransferase. *The safety population was defined as all patients who received at least one dose of any study drug, which differed from the intention-to-treat population because (1) four patients randomised to the orteronel plus prednisone group and two patients in the placebo plus prednisone group did not receive any study drug and (2) seven patients randomised to receive placebo may have received at least one dose of orteronel and thus they are summarised in the orteronel plus prednisone group. †Only events that occurred at a frequency of 10% of higher (as rounded to the nearest 1%) in either treatment group are shown. †Grade ≥3 increased lipase levels were seen in 12% of patients (n/N = 92/784) in the orteronel plus prednisone group during cycles 1–3, 8% (n/N = 50/713) during cycles 4–7, <1% (n/N = 6/620) during cycles 8–12, and three patients beyond cycle 13. Overall, ten patients (1%) in the orteronel plus prednisone group discontinued due to increased lipase; there were no discontinuations in the placebo plus prednisone group. ‡Grade ≥3 increased amylase levels were seen in 6% of patients (n/N = 50/784) in the orteronel plus prednisone group during cycles 1–3, 6% (n/N = 30/713) during cycles 4–7, no patients during 8–12, and two patients beyond cycle 13. Overall, nine patients (1%) in the orteronel plus prednisone group discontinued due to increased amylase; there were no discontinuations in the placebo plus prednisone group.

Table 3: **Summary of on-study adverse events**

more available through expanded access studies or post-regulatory approval. Abiraterone plus prednisone significantly improved radiographic progression-free survival (median 16·5 months *vs* 8·2 months; HR 0·52; p<0·0001), and prolonged overall survival (median 34·7 months *vs* 30·3 months; HR 0·80; p=0·0027).[23,24] Enzalutamide, which affects androgen-receptor signalling rather than the androgen synthesis pathway, also significantly improved radiographic progression-free survival (median not reached *vs* 3·9 months; HR 0·19; p<0·001) and overall survival (median 32·4 months *vs* 30·2 months; HR 0·71; p<0·001) compared with placebo.[4] More recently, promising activity has been reported in early clinical trials testing other androgen-receptor inhibitors including ODM-201[26] and ARN-509,[27] which are now in being tested in phase 3 trials (ClinicalTrials.gov, NCT02200614 and NCT01946204).

The availability of new, life-prolonging therapies increased the likelihood of patient crossover to an

effective treatment as the ELM-PC 4 trial matured. This finding, together with the results of the ELM-PC 5 trial assessing orteronel post-chemotherapy in patients with metastatic castration-resistant prostate cancer,[13] indicated that achieving a significant overall survival improvement in the ELM-PC 4 trial would be challenging. To address this, the final analysis for overall survival in ELM-PC 4 was brought forward with some loss of statistical power, with regulatory acknowledgment. At this final analysis (611 events), there was no significant difference in overall survival between the treatment groups. On the basis of these two studies, orteronel is not undergoing further development in metastatic castration-resistant prostate cancer.

The frequency of use of subsequent therapies was slightly higher in the placebo plus prednisone group than in the orteronel plus prednisone group. The most frequently used subsequent therapy was docetaxel, at similar frequency between the two groups, whereas the use of abiraterone was lower in the orteronel plus prednisone than in the placebo plus prednisone group. However, the activity of these alternative treatments when given post-orteronel has not been established. Additionally, findings from a pre-specified sensitivity analysis of overall survival, which censored patients at the start of any subsequent therapy, showed that treatment with orteronel plus prednisone was not associated with improved overall survival, and little substantive evidence exists regarding the effect of subsequent therapies on overall survival in this study.

Improvements in most of the secondary efficacy endpoints were noted with orteronel plus prednisone versus placebo plus prednisone, including PSA50 response and favourable CTC response rates at 12 weeks, time to PSA progression, time to docetaxel-based chemotherapy, and time to subsequent prostate cancer therapy. Although reported for descriptive purposes only, these improvements build on earlier phase 2 data that were indicative of antitumour activity of orteronel in this patient population.[12] Orteronel plus prednisone also reduced androgen concentrations to undetectable levels, but how these effects compare with other androgen synthesis inhibitors in this regard cannot be assessed. Direct comparisons with abiraterone have not been done in the clinic, and it is not known whether subtle differences in androgen synthesis inhibition, which are not directly reflected in clinical endocrine or biomarker data, might have contributed to differences in trial outcomes. Another possibility is that abiraterone is simply more effective clinically in this setting.

The safety profile of orteronel in this study was similar to that previously reported in patients with progressive metastatic castration-resistant prostate cancer following chemotherapy.[13] Most common adverse events with orteronel plus prednisone were grade 1 or 2 with the exception of increased lipase and amylase concentrations, consistent with previous observations of an increased rate of gastrointestinal-related toxic effects.[13] Treatment with orteronel was not associated with symptoms of mineralocorticoid excess, increased risk of cardiovascular complications, or hepatotoxic effects.

The tolerability profile of orteronel might have been one additional factor in its modest activity in prolonging overall survival in this study. The treatment duration in the orteronel plus prednisone group was similar to that in the placebo plus prednisone group. In similar settings, treatment durations were reported of 13·8 months for abiraterone versus 8·3 months for prednisone,[23] and of 16·6 months with enzalutamide versus 4·6 months with placebo.[4] The short treatment duration with orteronel plus prednisone in the present study was associated with a somewhat high number of study discontinuations due to adverse events (26%), whereas treatment discontinuations because of adverse events were low with abiraterone (8%)[23] and enzalutamide (6%).[4] The likely effect of orteronel tolerability on treatment duration and study discontinuation could have been accentuated by the availability of alternative therapies to the patient (and investigators)

Panel: Research in context

Systematic review

We searched PubMed for English-language reports published until Jan 15, 2015, using the MeSH terms "metastatic castration-resistant prostate cancer", "chemotherapy-naive", "survival", "abiraterone", and "enzalutamide". Preparation for this report incorporated inclusive reviews of the scientific literature and cited key primary publications for these agents. Our findings are discussed in the context of recent publications and compare to key endpoints in other studies. At the initiation of the ELM-PC 4 trial, docetaxel-based chemotherapy was an approved treatment for castration-resistant prostate cancer but it was associated with toxic effects—there remained an unmet need for safe and effective treatment for patients with metastatic castration-resistant prostate cancer. To target the intratumoural androgen concentrations and increased signalling activities observed in metastatic castration-resistant prostate cancer, the concept of CYP17A1 inhibition to deplete intra-tumoural and extragonadal androgen sources led to the investigation of orteronel (which selectively inhibits the 17,20-lyase enzyme in the biosynthesis pathway) as a potential therapeutic agent.

Interpretation

Orteronel prolongs radiographic progression-free survival, but not overall survival, in chemotherapy-naive patients with progressive metastatic castration-resistant prostate cancer. The lack of effect on overall survival might be a consequence of recent availability of androgen-targeted alternative therapies for metastatic castration-resistant prostate cancer or inadequate patient toleration and time on therapy.[25] Orteronel is not undergoing further development in metastatic castration-resistant prostate cancer.

In conclusion, orteronel plus prednisone significantly improved the primary endpoint of radiographic progression-free survival in patients with chemotherapy-naive metastatic castration-resistant prostate cancer compared with placebo plus prednisone. However, we noted no significant improvement in the co-primary endpoint of overall survival, which might have been due to both the tolerability and safety profile of orteronel as well as the availability of new alternative therapies. Orteronel is not undergoing further development in metastatic castration-resistant prostate cancer.

Contributors

HA, RdW, RD, KF, DBM, JN, FS, HIS, KS, IJW, and MW participated in the study conception and design. RdW, RD, EE, KF, PCF, LLH, VJ, RJ, FS, KS, LW, and MW participated in the data collection and assembly. HA, RdW, RD, EE, KF, PCF, LLH, RJ, DBM, JN, FS, HIS, KS, LW, IJW, and MW participated in the data analysis and interpretation. RdW, EE, KF, PCF, LLH, RJ, RM, FS, KS, and MW participated in the provision of study materials or patients. All authors contributed to drafting or revising the report, and reviewed and approved its final version.

Declaration of interests

DBM, LW, and IJW are employees of Millennium Pharmaceuticals Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. FS is a consultant for Millennium Pharmaceuticals Inc, Astellas, Janssen, and Sanofi; has received research funding from Astellas, Janssen, Millennium Pharmaceuticals Inc, and Sanofi; and has received honoraria from Astellas and Janssen. KF has received personal fees from Takeda; has participated in the advisory board of Millennium Pharmaceuticals Inc; and has been a consultant or held an advisory role for Millennium Pharmaceuticals Inc, Amgen, Astellas, Bayer, BMS, Dendreon, Ipsen, Janssen, Medivation, Novartis, and Sanofi-Aventis). VJ has received personal fees from Takeda; and honoraria from Millennium Pharmaceuticals, Astellas, and Janssen. EE has received research funding from Millennium Pharmaceuticals Inc, Janssen, Sanofi-Aventis, and Viamet; has received speaker honoraria from Millennium Pharmaceuticals Inc, Janssen, Sanofi-Aventis; and has been a consultant or held an advisory role for Janssen, Medivation, Sanofi-Aventis, Millennium Pharmaceuticals Inc, and Bayer. PCF has been a member of the advisory board of Janssen and Astellas. LLH has received research funding to institution from Millennium Pharmaceuticals Inc. RJ has received research funding from Millennium Pharmaceuticals, Astellas, Medivation, Janssen, and Sanofi; has received speaker honoraria from Millennium Pharmaceuticals Inc, Astellas, Janssen, and Sanofi); and has been a member of the advisory board of Astellas, Janssen, Millennium Pharmaceuticals Inc, Bayer, and Dendreon. RM has received research funding from Millennium Pharmaceuticals Inc and personal fees from Pfizer, GlaxoSmithKline, Janssen, Astellas, and Bayer. MW has received personal fees from Millennium Pharmaceuticals Inc, Apogepha, Bayer, Janssen, Merck, Roche, Sanofi-Aventis, Dendreon, Ferring, Ipsen, Pfizer, Teva, Orion, and Farco Pharma. KS has received research grant and personal fees from Millennium Pharmaceuticals Inc and has been a consultant or held an advisory role for Millennium Pharmaceuticals Inc. HA has received research funding or grants from the Ministry of Education, Culture, Sports, Science and Technology and has received personal fees from Millennium Pharmaceuticals Inc, Janssen, and Astellas). HIS has been a consultant (uncompensated) for AstraZeneca, Bristol Myers Squibb, Celgene, Endocyte, Exelixis, Foundation Medicine, Genentech, Janssen, Medivation, Pfizer, Ventana/Roche, and Novartis) and a consultant (compensated) for Astellas, BIND, Chugai Academy for Advanced Onvology, Endo/Orion Pharmaceuticals, Ferring, OncologySTAT, Sanofi-Aventis, and Millennium Pharmaceuticals Inc; and he has received speaker fees from WebMD and research funding or grants to institution from BIND, Exelixis, Janssen, and Medivation. RD has been in the advisory board or a consultant for Millennium Pharmaceuticals Inc, Janssen, Medivation, Astellas, Roche, Merck, Dendreon, and Endo Pharma; received honoraria from Janssen and Dendreon; and research funding from Millennium Pharmaceuticals Inc, Dendreon, Progenics, and BIND. RdW has received research funding and advisory or consultant fees from Millennium Pharmaceuticals Inc, and research funding, speaker and advisory fees from Sanofi, Janssen, and Astellas. JN declares no competing interests.

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