

## Phase III, Randomized, Double-Blind, Multicenter Trial Comparing Orteronel (TAK-700) Plus Prednisone With Placebo Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer That Has Progressed During or After Docetaxel-Based Therapy: ELM-PC 5

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Terms in blue are defined in the glossary, found at the end of this article and online at [www.jco.org](http://www.jco.org).

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### ABSTRACT

#### Purpose

Orteronel (TAK-700) is an investigational, nonsteroidal, reversible, selective 17,20-lyase inhibitor. This study examined orteronel in patients with metastatic castration-resistant prostate cancer that progressed after docetaxel therapy.

#### Patients and Methods

In our study, 1,099 men were randomly assigned in a 2:1 schedule to receive orteronel 400 mg plus prednisone 5 mg twice daily or placebo plus prednisone 5 mg twice daily, stratified by region (Europe, North America [NA], and non-Europe/NA) and Brief Pain Inventory–Short Form worst pain score. Primary end point was overall survival (OS). Key secondary end points (radiographic progression-free survival [rPFS],  $\geq 50\%$  decrease of prostate-specific antigen [PSA50], and pain response at 12 weeks) were to undergo statistical testing only if the primary end point analysis was significant.

#### Results

The study was unblinded after crossing a prespecified OS futility boundary. The median OS was 17.0 months versus 15.2 months with orteronel-prednisone versus placebo-prednisone (hazard ratio [HR], 0.886; 95% CI, 0.739 to 1.062;  $P = .190$ ). Improved rPFS was observed with orteronel-prednisone (median, 8.3 v 5.7 months; HR, 0.760; 95% CI, 0.653 to 0.885;  $P < .001$ ). Orteronel-prednisone showed advantages over placebo-prednisone in PSA50 rate (25% v 10%,  $P < .001$ ) and time to PSA progression (median, 5.5 v 2.9 months,  $P < .001$ ) but not pain response rate (12% v 9%;  $P = .128$ ). Adverse events (all grades) were generally more frequent with orteronel-prednisone, including nausea (42% v 26%), vomiting (36% v 17%), fatigue (29% v 23%), and increased amylase (14% v 2%).

#### Conclusion

Our study did not meet the primary end point of OS. Longer rPFS and a higher PSA50 rate with orteronel-prednisone indicate antitumor activity.

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### INTRODUCTION

Testosterone is essential for prostate-tumor cell growth and perpetuation.<sup>1</sup> Lowering testosterone levels can reduce prostate cancer growth, improve patients' symptoms in metastatic disease, and improve survival rates in patients with high-risk localized disease that is treated with radiotherapy.<sup>2,3</sup> However, over time prostate cancer invariably

evolves to a castration-resistant state.<sup>2,4</sup> Several mechanisms of castration resistance are known, including aberrant androgen-receptor signaling, androgen-receptor mutations or splicing variants, intracrine androgen synthesis, activation of parallel pathways, and cell-cycle activation.<sup>5-8</sup>

A current therapeutic approach in metastatic castration-resistant prostate cancer (mCRPC) is inhibition of CYP17A1, a key enzyme in androgen

synthesis with both 17 $\alpha$ -hydroxylase and 17,20-lyase activities. 17 $\alpha$ -hydroxylase is responsible for generating steroidal precursors necessary for androgen and cortisol syntheses, which then yield androgens through 17,20-lyase conversion.<sup>9,10</sup> 17,20-lyase converts 17-OH-pregnenolone to dehydroepiandrosterone and androstenedione, and its activity is upregulated in mCRPC.<sup>8,9</sup>

In mCRPC, abiraterone acetate with prednisone is established as first-line therapy for chemotherapy-naïve patients and as therapy for patients with up to two prior chemotherapeutic regimens.<sup>11,12</sup> Abiraterone-prednisone demonstrated overall survival (OS) improvements over placebo-prednisone in chemotherapy-naïve patients (hazard ratio [HR], 0.75;  $P = .01$ ) and in postdocetaxel mCRPC (HR, 0.74;  $P < .001$ ).<sup>11-14</sup> Abiraterone-prednisone was generally well-tolerated, with increased frequency of adverse events (AEs) associated with adrenocorticotropic hormone–driven mineralocorticoid excess due to CYP17 blockade compared with placebo in both settings.<sup>10-12</sup>

Orteronel (TAK-700) is an investigational, nonsteroidal, reversible, 17,20-lyase inhibitor.<sup>15,16</sup> In preclinical studies, orteronel demonstrated selectivity for 17,20-lyase over 17 $\alpha$ -hydroxylase inhibition ( $IC_{50}$ : 139 v 760 nmol/L).<sup>16</sup> Phase II experience indicates that orteronel (with or without prednisone) inhibits testosterone and dehydroepiandrosterone-sulfate production, consistent with 17,20-lyase inhibition, and reduces prostate-specific antigen (PSA) levels in mCRPC patients.<sup>17,18</sup> Prednisone was administered to maximize antitumor activity in patients with advanced mCRPC and to minimize the likelihood of adrenal insufficiency owing to 17 $\alpha$ -hydroxylase inhibition with orteronel 400 mg twice daily.<sup>17</sup>

In this article, we report a phase III randomized, double-blind, multicenter study of orteronel plus prednisone in men with mCRPC that has progressed after docetaxel chemotherapy.

## PATIENTS AND METHODS

### Patients

Patients were enrolled onto study from 260 study centers in 42 countries. The study was conducted in accordance with the Helsinki Declaration and Good Clinical Practice; institutional review boards approved all aspects of the study. All participants provided written informed consent.

Eligible patients were at least 18 years old and had histologically or cytologically confirmed adenocarcinoma of the prostate and radiographically documented metastatic disease with evidence of disease progression (per RECIST 1.1<sup>19</sup> for soft tissue lesions or Prostate Cancer Working Group criteria<sup>20</sup> for bone disease, and/or PSA increase) after receiving docetaxel ( $\geq 360$  mg/m<sup>2</sup> within a 6-month period). Patients intolerant to docetaxel or who had progressive disease before receiving  $\geq 360$  mg/m<sup>2</sup> were eligible if they received  $\geq 225$  mg/m<sup>2</sup> of docetaxel within a 6-month period and met other entry criteria. In addition, patient eligibility required surgical/medical castration with testosterone less than 50 ng/dL; PSA  $\geq 2$  ng/mL; Eastern Cooperative Oncology Group performance status of 0 to 2; and adequate renal, hematologic, cardiovascular, and hepatic function.

Exclusion criteria included prior orteronel, ketoconazole, aminoglutethimide, or abiraterone acetate therapy at any time; radioisotope/external-beam radiation therapy within 4 weeks of first dose, investigational drugs within 30 days, or other prostate cancer therapies within 2 weeks; or documented CNS metastasis.

### Study Design and Interventions

Patients were randomly assigned at a 2:1 schedule to receive oral orteronel 400 mg plus prednisone 5 mg or placebo plus prednisone twice daily,

without food restrictions, in 28-day treatment cycles (continuous dosing).<sup>17</sup> Patients in Japan received orteronel 300 mg following a protocol amendment based on preliminary safety results from an ongoing phase I study (Japan, data on file) that suggested generally elevated rates of AEs compared with the phase II study in the United States.

Patients were stratified by region (North America [NA; USA/Canada], Europe, and non-Europe/NA) and Brief Pain Inventory-Short Form (BPI-SF) worst pain score at screening ( $\leq 4$  v  $> 4$ ).<sup>21</sup> Patients could continue treatment until receipt of subsequent antineoplastic therapy or unacceptable AE. An independent data monitoring committee (IDMC) regularly reviewed safety data and results of interim analyses (IAs). After the first IA, the IDMC recommended continuing to the second IA for OS. Following the second IA, with crossing of prespecified futility boundary and per IDMC recommendation, the trial was unblinded.

### End Points and Assessments

The primary end point was OS. Key secondary end points were radiographic progression-free survival (rPFS), PSA  $\geq 50\%$  decrease (PSA50) at 12 weeks, and pain response at 12 weeks. Other secondary end points included response by RECIST 1.1, time to PSA progression, duration of pain response, time to pain progression, and safety. Radiographic changes were assessed by independent central review, per RECIST 1.1 and Prostate Cancer Working Group criteria.

Pain response was defined as a reduction of at least two points from baseline in BPI-SF worst pain score without an increase in analgesic use or  $\geq 25\%$  reduction in analgesic use from baseline without an increase in worst pain score from baseline, confirmed by an additional assessment 3 to 5 weeks later. Toxicity was evaluated according to National Cancer Institute Common Terminology Criteria for AEs version 4.02.<sup>22</sup>

### Statistical Methods

Assuming an exponential distribution for OS, 639 OS events were calculated to provide approximately 90% power to detect an HR of 1.32 (median OS, 15.8 v 12.0 months, orteronel-prednisone v placebo-prednisone) using a two-sided log-rank test at a 5% overall significance level; 1,083 patients were planned for random assignment. Two formal IAs were planned at 320 OS events (50% expected events) and 426 OS events (67% expected events; futility boundary  $P \geq .4275$ ), with the actual second IA conducted at 507 events (futility boundary  $P \geq .1775$ ).

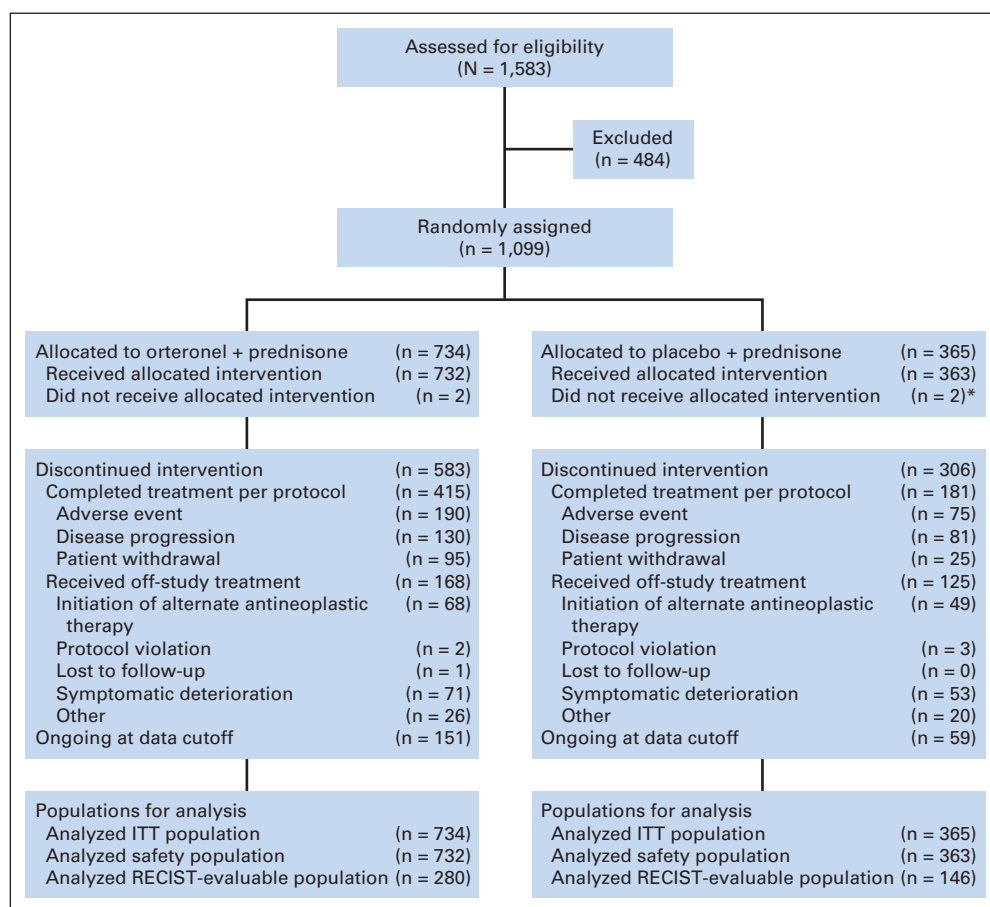
Randomization and stratification were undertaken centrally using an interactive voice response system. A stratified log-rank test was used to compare OS between treatment groups, stratified by the randomization stratification factors. HRs and 95% CIs were estimated using the stratified Cox model with treatment as the explanatory variable. Kaplan-Meier survival curves and medians, with two-sided 95% CIs, are provided.

PSA50 and pain response rates were compared using the Cochran-Mantel-Haenszel  $\chi^2$  test stratified by randomization stratification factors. rPFS (time from randomization to centrally confirmed radiographic disease progression or death from any cause) was analyzed per OS. Regardless of discontinuation reasons, all patients with protocol-specified radiographic progressive disease (rPD) or who died before data cutoff were included as rPFS events.

## RESULTS

### Patients and Disposition

In our study, 1,099 patients were randomly assigned (orteronel-prednisone,  $n = 734$ ; placebo-prednisone,  $n = 365$ ; Fig 1). Patient demographics and disease characteristics were generally balanced between treatment groups (Table 1), and across regions (Appendix Table A1, online only), except for BPI-SF worst pain score, two or more prior chemotherapies, PSA, and lactate dehydrogenase.



**Fig 1.** CONSORT diagram. (\*) One patient allocated to placebo-prednisone received orteronel plus prednisone. This patient is included in the orteronel plus prednisone safety population. ITT, intent to treat.

Median treatment duration was 6.2 cycles (range, 0 to 26.4 cycles) and 5.7 months (range, 0.03 to 24.3 months) with orteronel-prednisone versus 5.0 cycles (range, 0.3 to 29.4 cycles) and 4.6 months (range, 0.3 to 27.0 months) with placebo-prednisone. Median follow-up at data cutoff (May 16, 2013) was 10.6 months (range, 0.2 to 29.5 months) and 10.7 months (range, 0.4 to 27.1 months) in the orteronel-prednisone and placebo-prednisone groups. Overall, 583 patients (79%) and 306 patients (84%) discontinued treatment in the orteronel-prednisone and placebo-prednisone groups, respectively, with the primary reasons recorded as AEs (26% v 21%), disease progression (18% v 22%), and patient withdrawal (13% v 7%; Fig 1).

### Study Unblinding

At the second IA (507 deaths; 79% of 639 deaths required for final analysis), the IDMC determined that the futility boundary ( $P \geq .1775$ ) had been crossed, indicating that the orteronel-prednisone group would likely not meet the primary end point of improved OS versus the placebo-prednisone group if continued to final analysis. This led to the recommendation that the study be unblinded. Patients randomly assigned to orteronel-prednisone were allowed to continue therapy.

### Efficacy

At data cutoff, 512 patients died (Fig 2A). The OS HR was 0.886 (95% CI, 0.739 to 1.062;  $P = .190$ ; Fig 2A); median OS was 17.0 months versus 15.2 months with orteronel-prednisone versus placebo-prednisone, respectively. The treatment effect across protocol-specified

subgroups seemed consistent with overall findings, with observed variances including baseline pain and PSA levels (Fig 3). Differences in treatment effects were seen between subgroups with (HR, 1.104;  $P = .928$ ) or without baseline visceral disease (HR, 0.821;  $P = .084$ ) and between regions (Fig 3; Appendix Fig A1, online only). Regional differences in OS were seen between Europe (HR, 1.048;  $P = .721$ ), non-Europe/NA (HR, 0.709;  $P = .019$ ), and NA (HR, 0.889;  $P = .680$ ).

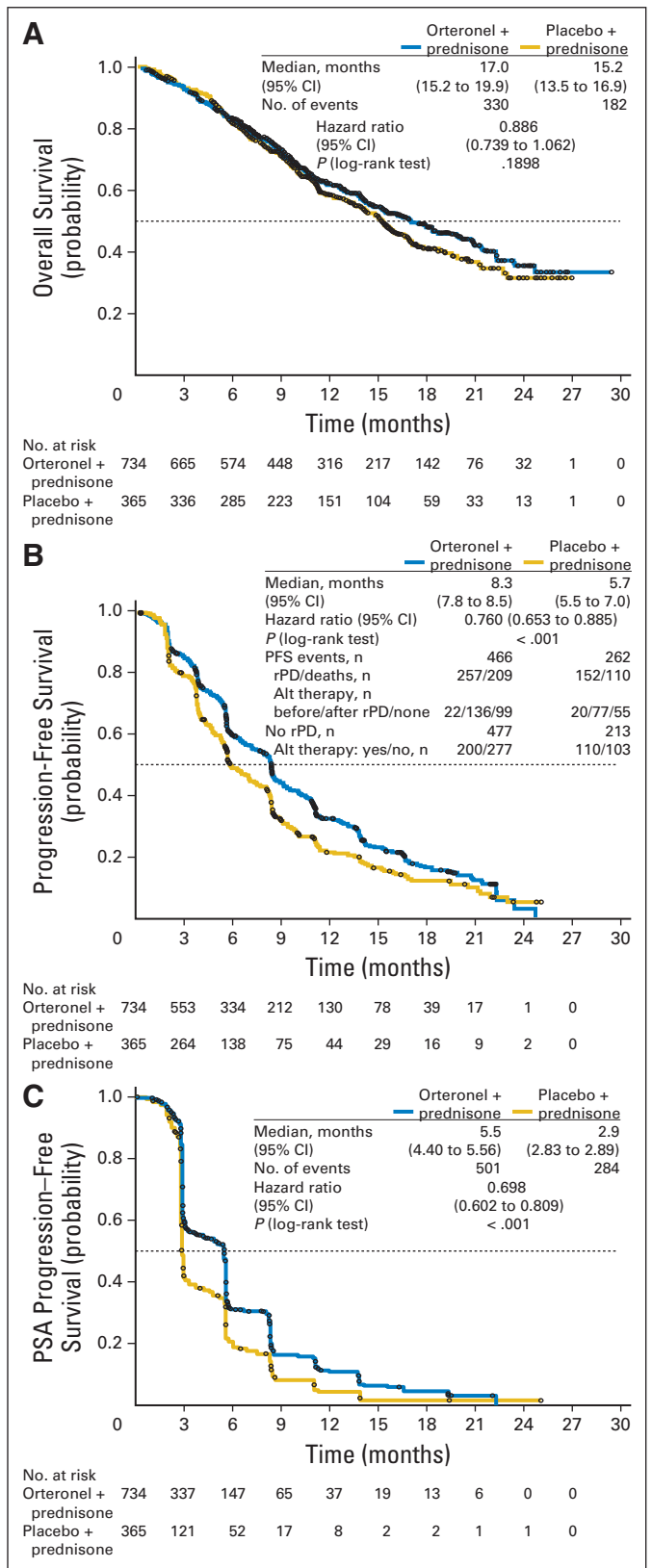
Secondary efficacy end points were only to be analyzed by a sequential testing procedure if the primary end point comparison was significant. Because the study did not meet the OS end point, formal hypothesis testing could not be performed for the ranked secondary end points. Results, observed  $P$  values, and HRs are for descriptive purposes.

In the analysis of rPFS, 466 and 262 patients in the orteronel-prednisone and placebo-prednisone groups, respectively, had events of rPD (orteronel-prednisone,  $n = 257$ ; placebo-prednisone,  $n = 152$ ) or death (orteronel-prednisone,  $n = 209$ ; placebo-prednisone,  $n = 110$ ); 268 and 103 patients, respectively, were censored. Within the rPD events, 22 of 257 orteronel-prednisone patients and 20 of 152 placebo-prednisone patients received alternate therapy before rPD (Fig 2B). In patients without rPD, 200 of 477 orteronel-prednisone patients and 110 of 213 placebo-prednisone patients received alternate therapy. Numerically longer rPFS was seen with orteronel-prednisone patients (HR, 0.760; 95% CI, 0.653 to 0.885;  $P < .001$ ; Fig 2B); median rPFS was 8.3 months with orteronel-prednisone versus 5.7 months with placebo-prednisone. Regional differences in rPFS subgroup

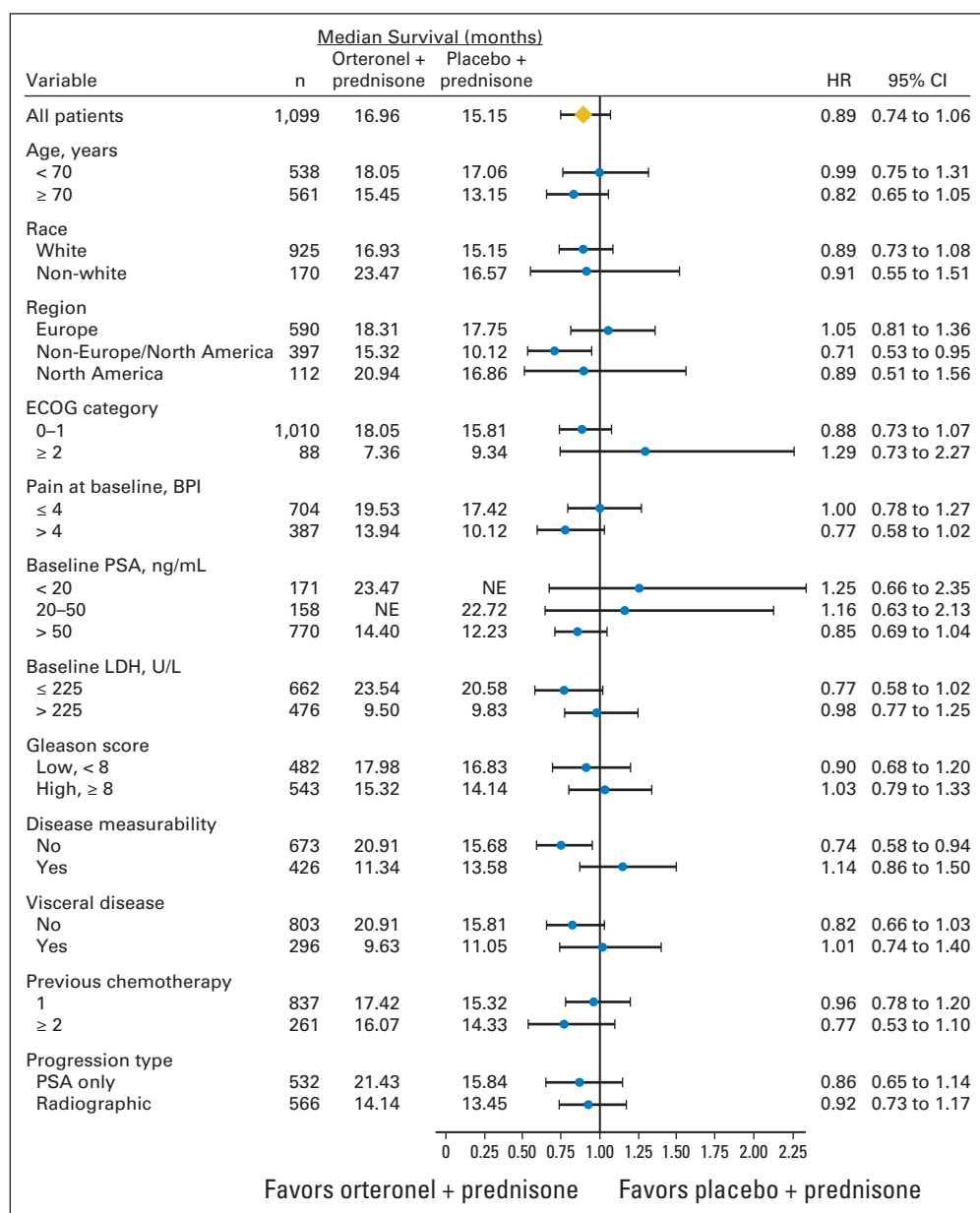
**Table 1. Patient Demographics and Disease Characteristics**

Characteristic	Orteronel Plus Prednisone (n = 734)		Placebo Plus Prednisone (n = 365)	
	No. of Patients	%	No. of Patients	%
<b>Age, years</b>				
Median	69.5		70.0	
Range	43-89		48-87	
Age ≥ 70	367	50	194	53
<b>Race</b>				
White	620	84	305	84
Black/African American	18	2	9	2
Asian	77	10	48	13
American Indian or Alaskan Native	4	< 1	1	< 1
Other/not reported	15	2	2	< 1
<b>Region</b>				
Europe	394	54	196	54
Non-Europe/North America	265	36	132	36
North America	75	10	37	10
<b>Time since initial diagnosis, years</b>				
Median	5.5		5.7	
Range	0-22		0.1-29	
<b>ECOG PS, %</b>				
0		42		40
1		50		53
2		9		7*
<b>BPI-SF worst pain score</b>				
Median	3.0		3.0	
Range	0-10		0-10	
<b>PSA at baseline, ng/mL</b>				
Median	122.5		134.0	
Range	0-8,456		1-19,009	
<b>Testosterone at baseline, ng/dL</b>				
Median	4.65		4.2	
Range	0.2-99.9		0.2-138.9	
<b>Gleason score at diagnosis</b>				
≤ 6	102	14	62	17
7	213	29	105	29
8-10	372	51	171	47
Unknown/missing	47	6	27	7
<b>Extent of disease at baseline</b>				
Bone metastases	699	95	340	93
Lymph node metastases	344	47	171	47
Lung metastases	90	12	39	11
Liver metastases	64	9	44	12
Other metastases†	124	17	60	16*
Visceral disease‡	197	27	99	27
<b>Prior chemotherapy regimens</b>				
1	574	78	263	72
≥ 2	160	22	101	28*
<b>Prior radiation therapy</b>	490	67	224	61
<b>Prior surgery</b>	390	53	190	52
<b>Prior ADT</b>	702	96	347	95

Abbreviations: ADT, androgen deprivation therapy; BPI-SF, Brief Pain Inventory–Short Form; ECOG PS, Eastern Cooperative Oncology Group performance status; PSA, prostate-specific antigen.  
 \*One missing value.  
 †Other metastases include patients with metastases identified in locations other than the bone, lymph node, lung, and liver.  
 ‡Visceral disease includes patients with metastases identified in one of the following locations: abdomen, adrenal gland, bladder, bowel, colon, kidney, liver, lung, pancreas, peritoneum, pleura, spleen, and ureter.



**Fig 2.** Kaplan-Meier estimates of (A) overall survival, (B) radiographic progression-free survival (PFS), and (C) time to prostate-specific antigen (PSA) progression. (B) Radiographic progressive disease (rPD) was determined by a central imaging center based on protocol definition, not per identification by investigator. Alt, alternate.



**Fig 3.** Overall survival by subgroups. BPI, Brief Pain Inventory; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; NE, not estimable; PSA, prostate-specific antigen.

analyses were noted between Europe (orteronel-prednisone *v* placebo-prednisone: median, 8.3 *v* 6.4 months; HR, 0.827; *P* = .075), non-Europe/NA (orteronel-prednisone *v* placebo-prednisone: median, 6.7 *v* 5.2 months; HR, 0.660; *P* < .001), and NA (orteronel-prednisone *v* placebo-prednisone: median, 11.0 *v* 8.3 months; HR, 0.849; *P* = .539; Appendix Fig A2, online only). Exploratory analysis in all patients suggested longer rPFS in the orteronel-prednisone group was observed only in patients without (HR, 0.712; *P* < .001) but not with (HR, 0.837; *P* = .232), visceral disease at baseline (Appendix Fig A2).

Median time to PSA progression was 5.5 months versus 2.9 months with orteronel-prednisone versus placebo-prednisone (HR, 0.698; *P* < .001; Fig 2C). PSA50 responses at 12 weeks were 25% *v* 10% with orteronel-prednisone versus placebo-prednisone (*P* < .001; Table 2; Fig 4). In RECIST-evaluable patients, response rates

were 17% versus 3%, respectively (*P* < .001; Table 2). No differences in pain response were observed (Table 2).

### Safety

The most common all-cause, all-grade AEs were nausea (orteronel-prednisone *v* placebo-prednisone, 42% *v* 26%), vomiting (orteronel-prednisone *v* placebo-prednisone, 36% *v* 17%), and fatigue (orteronel-prednisone *v* placebo-prednisone, 29% *v* 23%; Table 3). Other AEs included worsening hypertension (orteronel-prednisone *v* placebo-prednisone, 11% *v* 6%), hypokalemia (orteronel-prednisone *v* placebo-prednisone, 6% *v* 4%), overall adrenal insufficiency (orteronel-prednisone *v* placebo-prednisone, 2% *v* < 1%), and congestive heart failure (16% each). Most of these events were grade 1 or 2.

Common grade ≥ 3 AEs included lipase increases (orteronel-prednisone *v* placebo-prednisone, 13% *v* < 1%), amylase increases

**Table 2.** Secondary Efficacy End Points

End Point	Orteronel Plus Prednisone (n = 734)		Placebo Plus Prednisone (n = 365)		Log-Rank P
	No. of Patients	%	No. of Patients	%	
PSA50 response at 12 weeks	183	25	36	10	< .001
Absolute difference	15.1				
95% CI	10.5 to 19.7				
Odds ratio	2.93				< .001
95% CI	1.97 to 4.37				
Duration of PSA50 response, months					
Median	5.6		5.7		
Range	0-19.5		0-22.6		
95% CI	5.5 to 5.6		4.9 to 6.5		
Pain response at 12 weeks*	89	12	33	9	.128
Absolute difference	3.1				
95% CI	-0.9 to 7.1				
Odds ratio	1.5				.092
95% CI	0.9 to 2.3				
Duration of pain response, months					
Median	13.0		12.6		
Range	0-23.3		0-24.3		
95% CI	11.0 to 14.6		6.9 to 16.8		
Pain response for patients with significant pain at baseline†					
Total No. of patients	336		171		
Patients with significant pain	66	20	24	14	.134
Absolute difference	5.6				
95% CI	-1.6 to 12.8				
Odds ratio	1.5				.124
95% CI	0.9 to 2.7				
Time to pain progression, months					.327
Median	24.2		22.0		
Range	0-24.2		0-25.1		
95% CI	18.2 to 24.2		20.5 to NE		
HR	0.885				
95% CI	0.693 to 1.131				
Response by RECIST					
Total No. of patients	280		146		
Complete response	1	0.4	0		
Partial response	47	17	4	3	
Overall response rate (CR plus PR)	48	17	4	3	< .001
Absolute difference	14.4				
95% CI	8.7 to 20.1				
Odds ratio	11.2				< .001
95% CI	3.3 to 37.8				

Abbreviations: BPI-SF, Brief Pain Inventory–Short Form; CR, complete response; HR, hazard ratio; NE, not estimable; PR, partial response; PSA50, prostate-specific antigen decrease of  $\geq 50\%$  from baseline.

\*Defined 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: a  $\geq$  two-point reduction from baseline in BPI-SF worst pain score without an increase in analgesic use or a 25% or more reduction in analgesic use from baseline without an increase in worst pain score from baseline.

†Defined as baseline pain score  $\geq 4$ .

(orteronel-prednisone *v* placebo-prednisone, 8% *v* < 1%), and anemia (orteronel-prednisone *v* placebo-prednisone, 7% *v* 10%; Table 3). Most events of lipase or amylase elevations were transient and subsided by cycle 7 of the study period. Seven patients (< 1%) in the orteronel-prednisone group experienced pancreatitis (five serious events requiring dose modifications). The most common serious AEs with orteronel-prednisone were pulmonary embolism (n = 19), general physical health deterioration (n = 17), pneumonia (n = 16), urinary tract infection (n = 16), vomiting (n = 16), spinal cord compression (n = 16), anemia (n = 15), sepsis (n = 13), increased lipase (n = 12), nausea (n = 11), dehydration (n = 11), and urosepsis and urinary retention (n = 11). Regional differences in safety profiles were observed in non-Europe/NA versus Europe and NA, including numerically higher rates of grade  $\geq 3$  AEs, serious AEs, AEs resulting in discontinuation, and on-study deaths in both treatment groups, plus relatively higher rates of serious AEs, AEs resulting in discontinuation, and on-study deaths in the placebo-prednisone versus orteronel-prednisone groups (Appendix Table A2, online only).

Incidence of AEs resulting in treatment discontinuation was similar between the orteronel-prednisone and placebo-prednisone groups (30% and 24%, respectively). In addition to disease progression recorded as an AE (n = 13 in each group), the most common AEs resulting in treatment discontinuation were vomiting (n = 19 *v* n = 2) and other gastrointestinal disorders, nausea (n = 14 *v* n = 1), and diarrhea (n = 8 *v* n = 0). Dose modifications because of AEs were required by 43% and 23% of patients in the orteronel-prednisone and prednisone groups, respectively, the most common AEs being gastrointestinal disorders (vomiting [7% *v* < 1%], nausea [7% *v* 2%], diarrhea [5% *v* 2%]), increased lipase (9% *v* < 1%), and increased amylase (7% *v* < 1%).

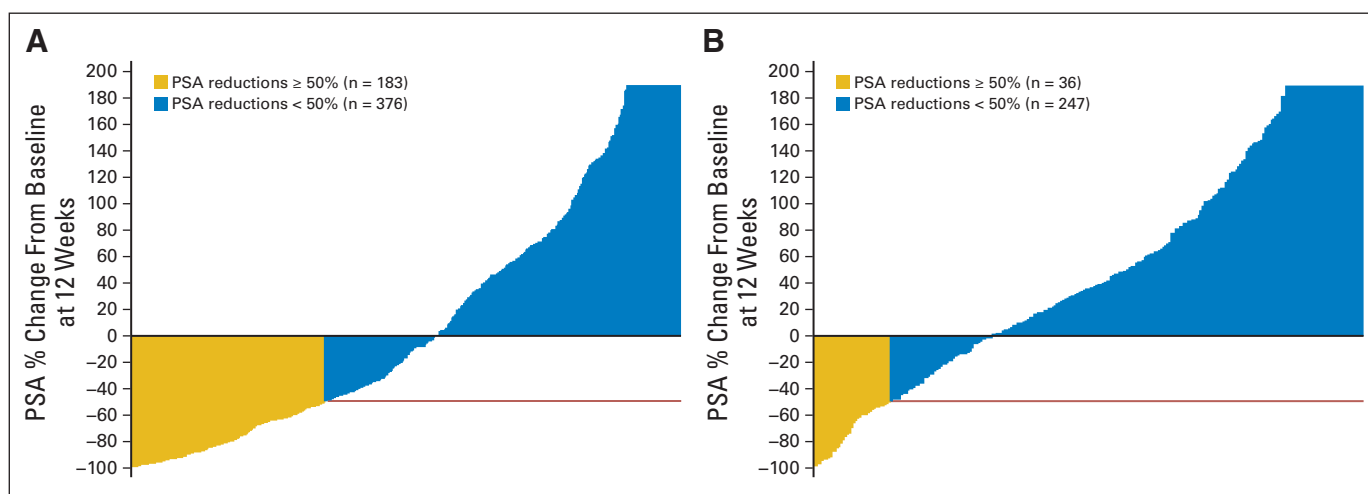
Overall, 47% of patients died (orteronel-prednisone, 45% *v* placebo-prednisone, 50%); most deaths (orteronel-prednisone, 226 patients; 69%; *v* placebo-prednisone, 127 patients; 70%) were related to prostate cancer and/or its complications.

### Subsequent Therapies

Overall, 45% (n = 326) and 54% (n = 197) of patients in the orteronel-prednisone and placebo-prednisone groups, respectively, received alternate therapy for prostate cancer. Patients in the orteronel-prednisone and placebo-prednisone groups subsequently received abiraterone acetate (20% *v* 21%), cabazitaxel (15% *v* 18%), docetaxel (5% *v* 9%), or enzalutamide (5% *v* 4%) therapies. Types of subsequent therapies varied across the protocol-specified regional subgroups (Appendix Table A3, online only).

## DISCUSSION

This phase III study of orteronel in patients with mCRPC who had received prior chemotherapy did not meet the primary end point of OS in the overall population. However, longer rPFS ( $P = .0004$ ) with orteronel-prednisone suggests antitumor activity. Furthermore, patients receiving orteronel-prednisone had delays in PSA progression and a higher rate of  $\geq 50\%$  PSA decrease, but no improvement in pain, versus patients receiving placebo-prednisone. Similar to other studies of endocrine therapies for mCRPC, these results support androgen signaling pathway inhibition for reducing disease symptoms and progression.<sup>12,13,23</sup>



**Fig 4.** Waterfall plots of prostate-specific antigen (PSA) response at 12 weeks in the evaluable patients with baseline and postbaseline assessments in the (A) orteronel-prednisone group ( $n = 559$ ) and the (B) placebo-prednisone group ( $n = 283$ ). Plots are truncated at 200%.

Orteronel had limited activity in terms of prolonging OS in patients with mCRPC that progressed after prior chemotherapy. However, numerical improvements in secondary end points and activity seen in phase II investigation suggest that orteronel seems to have antitumor activity in mCRPC alone or with prednisone.<sup>17,18</sup> OS may have been negatively affected by short treatment duration (orteronel-prednisone *v* placebo-prednisone, 5.7 *v* 4.6 months). The abiraterone study in a similar mCRPC setting reported treatment durations of 8 months versus 4 months with abiraterone-prednisone versus placebo-prednisone.<sup>12</sup> The short treatment duration in our study may be correlated with high rates of study discontinuations owing to various factors, including AEs (orteronel-prednisone *v* placebo-prednisone, 30% *v* 24%), notably gastrointestinal-related AEs, and initiation of subsequent therapy (45% *v* 54%). In the abiraterone study, AEs resulting in treatment discontinuation occurred in 19% and 23% of the abiraterone-prednisone and placebo-prednisone groups, respectively.<sup>12</sup> At the time the abiraterone trial was initiated, there was limited survival-prolonging therapy available for men with mCRPC after docetaxel therapy.

During the course of this trial, the US and European treatment landscape included two novel androgen-directed agents, abiraterone and enzalutamide, and a new taxane, cabazitaxel (either as approved agents or through an expanded access program).<sup>13,23,24</sup> These agents have demonstrated OS benefit in mCRPC and could have been received subsequent to study treatment, and may thus have affected OS comparisons. Furthermore, the impact of prior orteronel treatment followed by another CYP17A1 inhibitor (such as, abiraterone) on efficacy outcomes in mCRPC is unknown.

An OS advantage with orteronel-prednisone observed in non-Europe/NA ( $P = .019$ ) but not in Europe or NA could be associated with the lower rate of subsequent novel therapy use (Fig 3; Appendix Table A3). Similarly, a numerical rPFS benefit was observed with orteronel-prednisone in non-Europe/NA ( $P = .0008$ ) but not in Europe or NA (Appendix Fig A2); this end point is less affected by subsequent therapy. Though there were overall differences between regions, subsequent therapy use was generally similar between treatment groups and within regions. Furthermore, the less favorable baseline characteristics (higher BPI-SF worst pain score, more patients

with two or more prior chemotherapies, and higher baseline PSA and lactate dehydrogenase) in patients in non-Europe/NA versus Europe or NA may indicate that these patients were sicker at baseline, and possibly more susceptible to AEs or more likely to discontinue treatment (Appendix Table A1). These factors (regional differences, use of subsequent therapy, and baseline characteristics) represent possible limitations of the study.

In a recent phase III trial of orteronel in chemotherapy-naïve patients with mCRPC (ELM-PC 4), rPFS was prolonged with orteronel-prednisone versus placebo-prednisone (13.8 months *v* 8.7 months; HR, 0.71;  $P < .001$ ).<sup>25</sup> However, there was no improvement in the primary end point of OS (31.4 months with orteronel-prednisone *v* 29.5 months with placebo-prednisone; HR, 0.92;  $P = .314$ ).<sup>25</sup> Though the enrollment period for the ELM-PC 4 trial overlapped with this study, there were no regional differences observed in the prespecified subgroup analyses for either primary end point (OS and rPFS) in the ELM-PC 4 trial. Thus, the actual impact of regional differences is unclear and the failure to prolong OS in mCRPC after docetaxel-based chemotherapy may result from insufficient clinical activity of orteronel in this patient population.

In this study, the safety profile observed with orteronel-prednisone consisted of predominantly grade 1 or 2 AEs, except for amylase elevations, lipase elevations, and anemia. Notably, there was a higher rate of grade  $\geq 3$  gastrointestinal-related toxicities (lipase and amylase elevations) with limited clinical symptoms, consistent with observations from the phase I/II trial.<sup>17</sup> However, these laboratory elevations were transient, often resolving by cycle 7. Furthermore, gastrointestinal-related AEs most commonly contributed to the increased frequencies of dose discontinuations and modifications in the orteronel-prednisone group. All-cause, all-grade gastrointestinal-related AEs were observed in the abiraterone study, including diarrhea (abiraterone-prednisone *v* placebo-prednisone, 20% *v* 15%), nausea (abiraterone-prednisone *v* placebo-prednisone, 33% *v* 33%), and vomiting (abiraterone-prednisone *v* placebo-prednisone, 24% *v* 26%).<sup>13</sup>

As the treatment landscape for prostate cancer continues to expand, OS alone may no longer be a fair indicator of treatment efficacy because it is not only confounded by other causes of mortality but also

**Table 3.** Safety Profiles and Summaries of the Most Common All-Cause Adverse Events (any grade in > 10% of patients overall and grade ≥ 3 in ≥ 2%) and Other Adverse Events of Interest

Adverse Events	Orteronel Plus Prednisone (n = 732)				Placebo Plus Prednisone (n = 363)			
	Any Grade		Grade ≥ 3		Any Grade		Grade ≥ 3	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Any AE	717	98	506	69	345	95	199	55
Any drug-related AE	571	78	269	37	217	60	67	18
Any serious AE	351		48		143		39	
Any drug-related serious AE	113		15		27		7	
<b>Most common AEs</b>								
Nausea	304	42	23	3	93	26	5	1
Vomiting	261	36	27	4	61	17	8	2
Fatigue	215	29	42	6	82	23	17	5
Constipation	212	29	11	2	67	18	5	1
Decreased appetite	200	27	17	2	67	18	10	3
Diarrhea	194	27	26	4	54	15	5	1
Back pain	125	17	24	3	65	18	13	4
Increased lipase*	120	16	98	13	6	2	3	< 1
Decreased weight	107	15	4	< 1	32	9	4	1
Muscle spasms	107	15	1	< 1	26	7	1	< 1
Arthralgia	105	14	19	3	55	15	8	2
Asthenia	105	14	18	2	42	12	11	3
Increased amylase†	103	14	61	8	6	2	1	< 1
Anemia	102	14	52	7	64	18	37	10
Bone pain	87	12	32	4	59	16	22	6
Pain in extremity	80	11	10	1	44	12	10	3
Dizziness	76	10	3	< 1	16	4	2	< 1
<b>Additional AEs of interest</b>								
Hypertension	83	11	24	3	21	6	6	2
Peripheral edema	72	10	5	< 1	46	13	1	< 1
Hot flashes	63	9	0		20	6	0	
Hypokalemia	44	6	16	2	14	4	1	< 1
Decreased blood potassium	1	< 1	1	< 1	2	< 1	0	
ALT increased	23	3	6	< 1	9	2	2	< 1
AST increased	17	2	2	< 1	9	2	1	< 1

Abbreviation: AE, adverse event.

\*Elevations in lipase levels were observed in 12% of patients (88 of 732 patients) in the orteronel plus prednisone group during cycles 1-3, 8% of patients (46 of 585 patients) during cycles 4-7, < 1% of patients (three of 412 patients) during cycles 8-12, and in two patients beyond cycle 13.

†Increase in amylase levels were seen in 10% of patients (74 of 732 patients) in the orteronel plus prednisone group during cycles 1-3, 6% of patients (38 of 585 patients) during cycles 4-7, and < 1% of patients (three of 412 patients) during cycles 8-12, and in two patients beyond cycle 13.

the impact of effective post-trial therapy. Time to disease progression and rPFS may contribute significant insight as primary efficacy parameters, as these data are available earlier than OS, are less influenced by competing causes of death, and are not affected by alternative treatments administered after progression. When several effective therapies are available in clinical practice, as for mCRPC, multiple parameters should be considered in public health decisions as long as the novel agents display favorable safety profiles.<sup>26-28</sup>

In conclusion, there was no statistically significant improvement in OS with orteronel-prednisone versus placebo-prednisone. Furthermore, the longer rPFS and higher rate of ≥ 50% PSA decrease suggest that orteronel may have antitumor activity in mCRPC after docetaxel therapy.

**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Disclosures provided by the authors are available with this article at [www.jco.org](http://www.jco.org).

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## GLOSSARY TERMS

**metastatic castration-resistant prostate cancer**

**(mCRPC):** progressive disease despite surgical castration or ongoing use of gonadotropin-releasing hormone agonists with confirmed castrate levels of testosterone.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Phase III, Randomized, Double-Blind, Multicenter Trial Comparing Orteronel (TAK-700) Plus Prednisone With Placebo Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer That Has Progressed During or After Docetaxel-Based Therapy: ELM-PC 5**

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### Appendix

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The following investigators, listed in alphabetical order per country, participated in the ELM-PC 5 study. (Investigators at study sites with zero subjects enrolled are not listed, unless they were a Steering Committee member.)

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Nakagawa (Kagoshima), T. Nakatani (Osaka), K. Nishimura (Osaka), M. Niwakawa (Shizuoka), F. Sato (Yufu), M. Sugimoto (Kagawa), T. Takayama (Shizuoka), A. Yokomizo (Fukuoka), K. Yoshimura (Osaka); Republic of Korea: J.B. Ahn (Seoul), B.H. Chung (Seoul), T.W. Kang (Gwangju), C. Kwak (Seoul), C. Kim (Seoul), S.W. Kim (Seoul), K.H. Lee (Goyang); Lithuania: F. Jankevicius (Vilnius), G. Jocys (Klaipeda), D. Milonas (Kauans), A. Ulys (Vilnius); Mexico: G. Garcia Jaliffe (Colonia Santa Cruz Atoyac), J.A. Rodriguez Rivera (Jalisco); the Netherlands: R. de Wit (Rotterdam), A.P. Hamberg (Rotterdam), I.M. Van Oort (Nijmegen), J.J.E.J. Vrijhof (Eindhoven); New Zealand: P.C.C. Fong (Auckland); Poland: T. Demkow, Z. Jablonska (Wroclaw), E. Kalinka-Warzocha (Lodz), R. Kmiecik (Wroclaw); Portugal: J. Coelho (Lisboa), G. Sousa (Coimbra), N. Sousa (Porto); Romania: C.L. Cebotaru (Cluj-Napoca), T. Ciuleanu (Cluj-Napoca), D. Lungulescu (Craiova), S. Mihutiu (Oradea); Russia: S. Ivanov (Moscow), A. 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(Kaohsiung); United Kingdom: A. Bahl (Bristol), S. Chowdhury (London), J. De Bono (Sutton), S. Dixit (Grimsby), P. Elliott (Manchester), J. Graham (Somerset), P. Hoskin (Northwood), R. Jones (Glasgow), A. MacDonald (Aberdeen), Z. Malik (Wirral), D. McLaren (Edinburgh), J. O'Sullivan (Belfast), H. Payne (London); United States: N. Agarwal (Salt Lake City, UT), D. Agus (Los Angeles, CA), R. Alter (Hackensack, NJ), J. Bailen (Jeffersonville, IN), J. Bellmunt (Boston, MA), W. Berry (Raleigh, NC), K. Chang (Anchorage, AK), W. Clark (Anchorage, AK), C. Cowey (Corona, CA), R. Dreicer (Cleveland, OH), M. Fleming (Canandaigua, NY), L. Forero (East Syracuse, NY), S. Goel (San Diego, CA), J. Haluschak (Cleveland, OH), L. Hart (San Juan, Puerto Rico), E. Heath (Pittsburgh, PA), P. Lara Jr. (Sacramento, CA), S. Mao (Pittsburgh, PA), L. Norquist (New Orleans, LA), D. Petrylak (Los Angeles, CA), T. Rado (Sacramento, CA), D. Richards (Riverside, CA), A. Rodney (Highland, CA), A. Sartor (New Orleans, LA), I. Schnadig (Hackensack, NJ), P. Sieber (Lancaster, PA), R. Singal (Deerfield Beach, FL), B. Somer (Memphis, TN), G. Srkalovic (Dickson, TN), M. Wertheim (Port St Lucie, FL), N. Vogelzang (Jeffersonville, IN).

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Table A1. Patient Demographics and Disease Characteristics by Region

Characteristic	Europe				Non-Europe/NA				NA			
	Orteronel Plus Prednisone (n = 394)		Placebo Plus Prednisone (n = 196)		Orteronel Plus Prednisone (n = 265)		Placebo Plus Prednisone (n = 132)		Orteronel Plus Prednisone (n = 75)		Placebo Plus Prednisone (n = 37)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years												
Median	69.0		69.0		70.0		71.0		71.0		72.0	
Range	45-89		50-86		43-87		50-87		48-84		48-85	
≥ 70	187	47	92	47	138	52	75	57	42	56	27	73
Race												
White*	388	98	193	98	169	64	79	60	63	84	33	89
Black/African American	3	< 1	2	1	8	3	5	4	7	9	2	5
Asian*	1	< 1	1	< 1	72	27	46	35	4	5	1	3
American Indian or Alaskan Native	0		0		4	2	1	< 1	0		0	
Other/not reported	2	< 1	0		12	5	1	< 1	1	1	1	3
Time since initial diagnosis, years*												
Median	5.3		5.7		5.3		5.6		7.5		7.3	
Range	0-22		0.2-28.8		0.1-16.8		0.1-20.7		1.4-19.6		1.6-20	
ECOG PS, %†												
0		43		43		41		37		35		35
1		49		52		49		52		57		62
2		7		5		11		11		8		3
BPI-SF worst pain score*												
Median	3.0		3.0		4.0		3.5		2.0		2.5	
Range	0-10		0-10		0-10		0-10		0-10		0-10	
PSA at baseline, ng/mL*												
Median	138.0		127.5		131.0		169.0		53.6		51.6	
Range	3-7,992		3-9,263		1-8,456		2-19,009		0-3,534		1-1,164	
Testosterone at baseline, ng/dL												
Median	4.7		5.0		4.7		3.7		4.2		4.5	
Range	0.2-99.9		0.2-36.1		0.2-99.9		0.2-138.9		0.3-60.7		0.4-19.7	
Gleason score at diagnosis												
≤ 6	55	14	39	20	37	14	19	14	10	13	4	11
7	108	27	56	29	82	31	34	26	23	31	15	41
8-10	191	48	81	41	142	54	74	56	39	52	16	43
Unknown/missing	40	10	20	10	4	2	5	4	3	4	2	5
Extent of disease at baseline												
Bone metastases	379	96	184	94	249	94	123	93	71	95	33	89
Lymph node metastases	185	47	90	46	126	48	60	45	33	44	21	57
Lung metastases	44	11	22	11	36	14	12	9	10	13	5	14
Liver metastases	37	9	24	12	19	7	17	13	8	11	3	8
Other metastases/missing	71	18	36	18	38	14	21	16‡	15	20	3	8
Visceral disease	106	27	55	28	69	26	35	27	22	29	9	24
Prior chemotherapy regimens*												
1	325	82	149	76	179	68	87	66	70	93	27	73
≥ 2	69	18	46	23	86	32	45	34	5	7	10	27
Prior radiation therapy	257	65	118	60	181	68	82	62	52	69	24	65
Prior surgery	184	47	96	49	152	57	75	57	54	72	19	51
Prior ADT	380	96	185	94	249	94	126	95	73	97	36	97

Abbreviations: ADT, androgen-deprivation therapy; BPI-SF, Brief Pain Inventory–Short Form; ECOG PS, Eastern Cooperative Oncology Group performance status; NA, North America; PSA, prostate-specific antigen.

\*Differences in baseline characteristics across regions.

†Percentages may not add up to 100% because of rounding.

‡One missing.

**Table A2.** Summary of Adverse Events by Regional Subgroup Analyses

Category	Europe				Non-Europe/NA				NA			
	Orteronel Plus Prednisone (n = 392)		Placebo Plus Prednisone (n = 194)		Orteronel Plus Prednisone (n = 265)		Placebo Plus Prednisone (n = 132)		Orteronel Plus Prednisone (n = 75)		Placebo Plus Prednisone (n = 37)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
All TEAEs	382	97	183	94	261	98	125	95	74	99	37	100
Grade $\geq$ 3 TEAEs	263	67	89	46	196	74	91	69	47	63	19	51
Drug-related TEAEs	298	76	115	59	210	79	76	58	63	84	26	70
Grade $\geq$ 3 drug-related TEAEs	126	32	28	14	115	43	32	24	28	37	7	19
Serious AEs	190	48	57	29	134	51	75	57	27	36	11	30
AEs leading to discontinuation	108	28	35	18	49	18	15	11	9	12	3	8
On-study deaths	37	9	15	8	86	32	46	35	22	29	5	14

Abbreviations: AE, adverse event; NA, North America; TEAEs, treatment-emergent adverse events.

**Table A3.** Subsequent Therapies Received, Overall and Across Regions

Therapy	Global				Europe				non-Europe/NA				NA			
	Orteronel Plus Prednisone (n = 732)		Placebo Plus Prednisone (n = 363)		Orteronel Plus Prednisone (n = 392)		Placebo Plus Prednisone (n = 194)		Orteronel Plus Prednisone (n = 265)		Placebo Plus Prednisone (n = 132)		Orteronel Plus Prednisone (n = 75)		Placebo Plus Prednisone (n = 37)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Patients with one or more subsequent therapies, %	326	45	197	54	192	49	119	61	94	35	58	44	40	53	20	54
Abiraterone	146	20	78	21	103	26	62	32	23	9	7	5	20	27	9	24
Cabazitaxel	107	15	66	18	65	17	42	22	28	11	16	12	14	19	8	22
Dexamethasone	85	12	52	14	38	10	16	8	39	15	32	24	8	11	4	11
Docetaxel	40	5	32	9	22	6	21	11	14	5	9	7	4	5	2	5
Enzalutamide	35	5	13	4	24	6	11	6	0	0	0	0	11	15	2	5
Abiraterone, cabazitaxel, or enzalutamide	222	30	129	36	149	38	93	48	41	15	21	16	33	44	15	41

Abbreviation: NA, North America.

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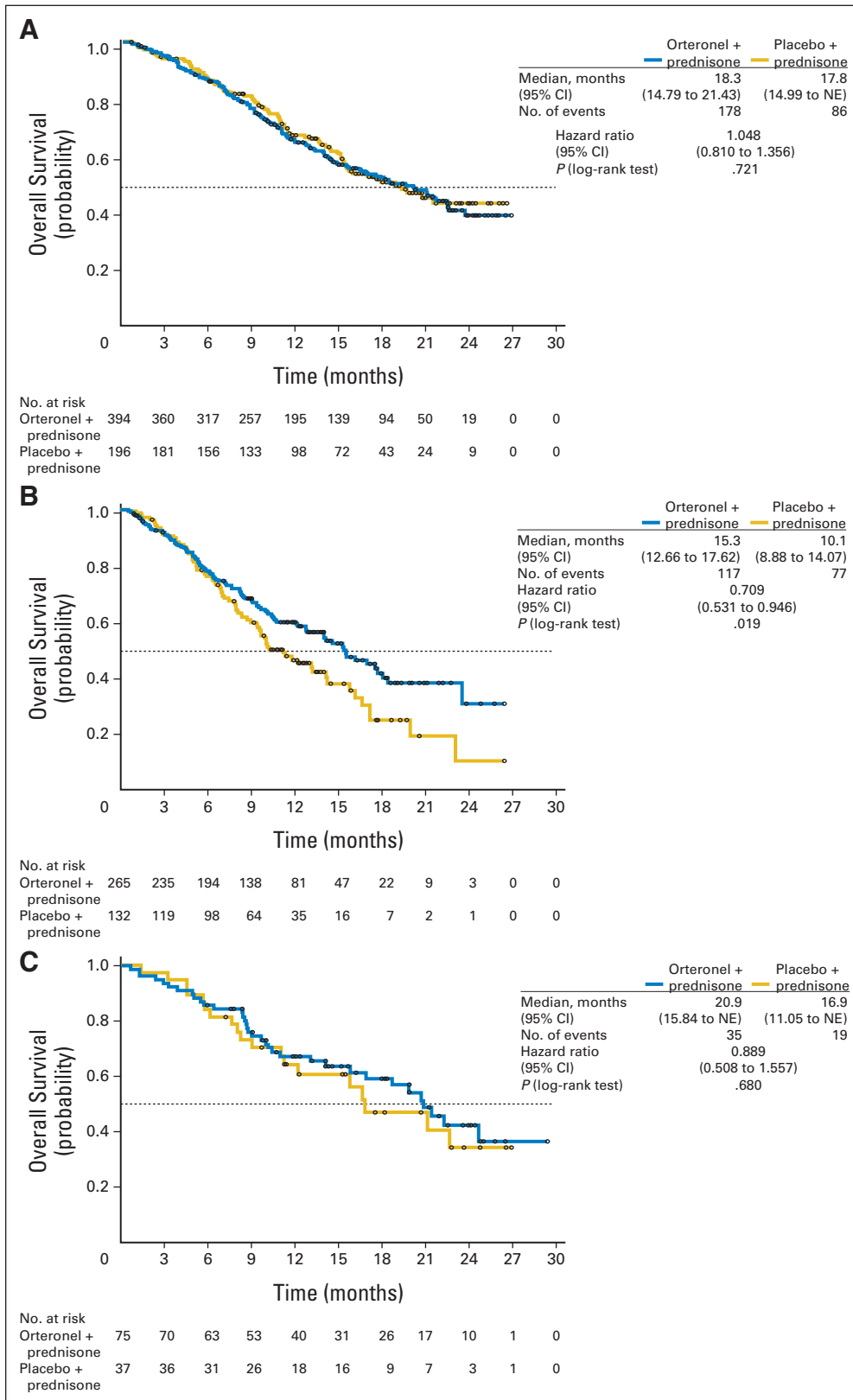
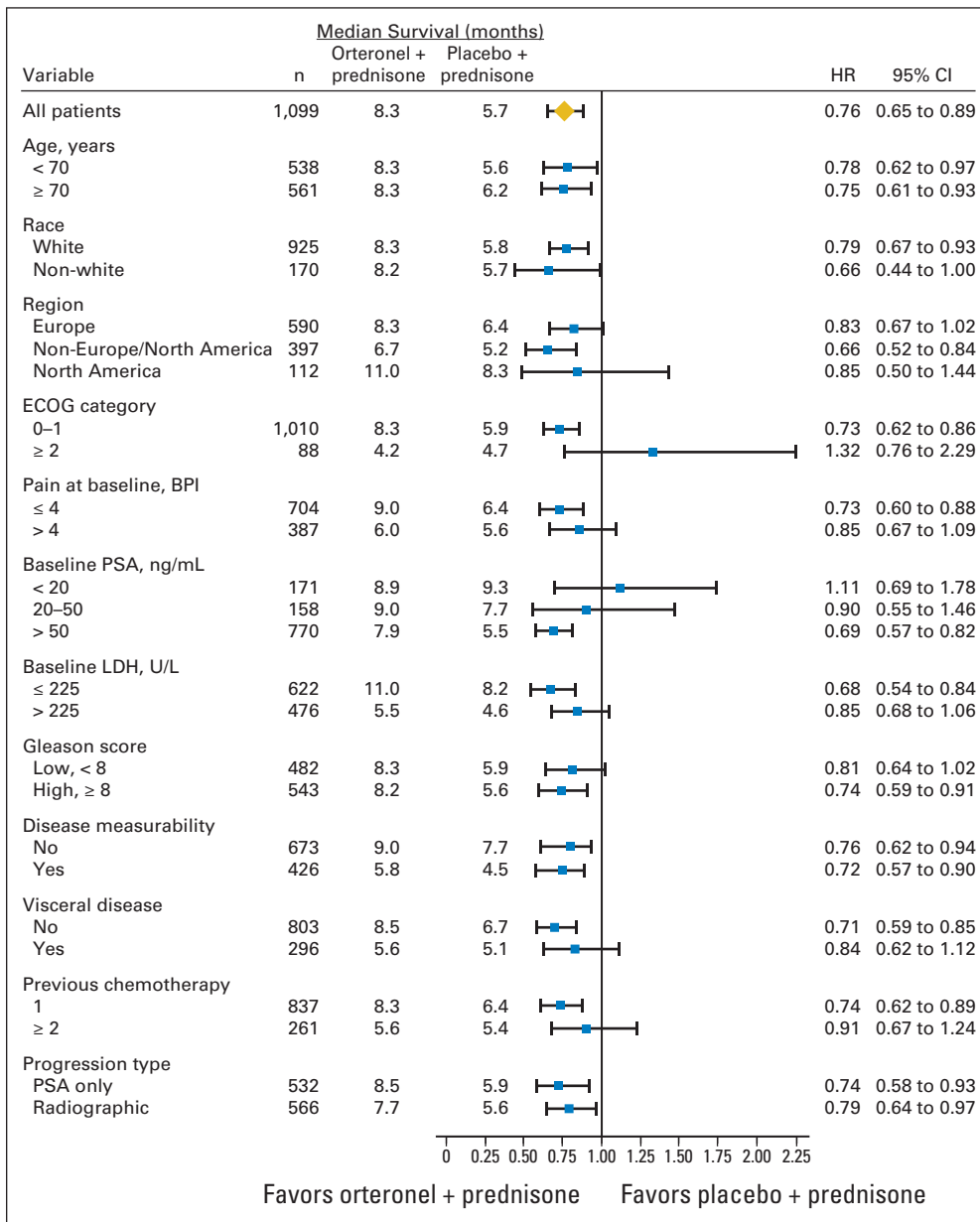


Fig A1. Kaplan-Meier estimates of overall survival in (A) Europe, (B) non-Europe/North America, and (C) North America. NE, not evaluable.



**Fig A2.** Radiographic progression-free survival by subgroups. BPI, brief pain inventory; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; PSA, prostate-specific antigen.