original reports

Orteronel for Metastatic Hormone-Sensitive Prostate Cancer: A Multicenter, Randomized, Open-Label Phase III Trial (SWOG-1216)

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abstract

PURPOSE Orteronel (TAK-700) is a nonsteroidal 17,20-lyase inhibitor suppressing androgen synthesis. We evaluated the clinical benefit of orteronel when added to androgen deprivation therapy (ADT) in patients with newly diagnosed metastatic hormone-sensitive prostate cancer.

METHODS In this open-label randomized phase III study, patients with metastatic hormone-sensitive prostate cancer were randomly assigned 1:1 to ADT with orteronel (300 mg oral twice daily; experimental arm) or ADT with bicalutamide (50 mg oral once daily; control arm). The primary objective was the comparison of overall survival (OS), targeting a 33% improvement in median survival. A stratified log-rank test with a one-sided $P \leq .022$ would indicate statistical significance. Secondary end points were progression-free survival (PFS), prostate-specific antigen (PSA) level at 7 months (≤ 0.2 *v* 0.2 to ≤ 4 *v* > 4 ng/mL), and adverse event profile.

RESULTS Among 1,279 patients included in the analysis, 638 were randomly assigned to the ADT plus orteronel arm and 641 to the control arm. The median age was 68 years; 49% had extensive disease. After a median follow-up of 4.9 years, there was a significant improvement in PFS (median 47.6 *v* 23.0 months, hazard ratio 0.58; 95% CI, 0.51 to 0.67; $P < .0001$) and PSA response at 7 months ($P < .0001$), but not in OS (median 81.1 *v* 70.2 months, hazard ratio 0.86; 95% CI, 0.72 to 1.02; $P = .040$, one-sided). More grade 3/4 adverse events occurred in the experimental versus the control arms (43% *v* 14%). Postprotocol life-prolonging therapy was received by 77.4% of patients in the control arm and 61.3% of patients in the orteronel arm.

CONCLUSION The study did not meet the primary end point of improved OS with orteronel. The lack of correlation of PFS and PSA response with OS raises concerns over assumption of their consistent surrogacy for OS in the context of extensive postprotocol therapy in this setting.

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ASSOCIATED CONTENT

Appendix

Data Sharing Statement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

The cornerstone of treatment for metastatic hormone-sensitive prostate cancer (mHSPC) is androgen deprivation therapy (ADT) with medical or surgical castration.[1] However, disease progression universally occurs on ADT, mediated by extragonadal production of androgens or androgen-independent activation of androgen receptor.[1] The treatment paradigm of mHSPC has evolved over the past decade with multiple trials showing improved survival by intensification of ADT with either docetaxel chemotherapy or abiraterone, which inhibits a pivotal enzyme in intra- and extragonadal androgen synthesis (ie, CYP17 [CYP17 hydroxylase, CYP17, 20 lyase]) located in the testes and adrenal glands.[1-5] More recently, two direct, potent, and specific inhibitors of the androgen receptor, apalutamide and enzalutamide, were approved on the basis of improved survival in phase III trials.[1,6,7] Currently, the most common sequencing of these agents in the treatment of metastatic prostate cancer is abiraterone acetate followed by enzalutamide or docetaxel.[8] One challenge with abiraterone acetate is the requirement for coadministration of corticosteroids because of inhibition of CYP17 hydroxylase.[1] This results in diminished cortisol production and leads to secondary mineralocorticoid excess, with symptoms such as electrolyte abnormalities, hypertension, and edema.[1]

Orteronel (TAK-700) is a novel CYP17 inhibitor. In comparison with abiraterone acetate, orteronel inhibits CYP17, 20 lyase with greater specificity compared with CYP17 hydroxylase and does not generally lead to the syndrome of secondary mineralocorticoid excess.[9,10]

CONTEXT

Key Objective

We examined if adding orteronel, a novel androgen axis inhibitor, to androgen deprivation therapy (ADT) would improve outcomes compared with ADT plus bicalutamide in men with metastatic hormone-sensitive prostate cancer in a phase III trial.

Knowledge Generated

Addition of orteronel to ADT resulted in a significant improvement in progression-free survival and prostate-specific antigen response but not in overall survival (OS), the primary end point. Interestingly, the median OS of patients in the control arm of SWOG-1216 was 24 months higher than that in patients with metastatic hormone-sensitive prostate cancer on the SWOG-9346 trial (reported in 2013) who had similar disease severity and also received ADT plus bicalutamide (70.2 *v* 46 months).

Relevance

These results indicate that orteronel is likely not an effective androgen axis inhibitor compared with recently approved agents in this setting. Higher than anticipated OS of patients in the control arm is reflective of therapeutic advancements made over the past decade in men with metastatic prostate cancer.

We hypothesized that the addition of orteronel to ADT would improve overall survival (OS), progression-free survival (PFS), and prostate-specific antigen (PSA) response relative to bicalutamide with ADT among men with mHSPC.

METHODS

Trial Design and Conduct

The S1216 trial was a phase III, randomized, open-label, multicenter trial involving patients with mHSPC. The trial was designed by the SWOG study team and was approved by the National Cancer Institute (NCI). Patients were enrolled from 248 academic and community centers throughout the United States, incorporating three other NCI-funded cooperative groups (ECOG-ACRIN, ALLIANCE, and NRG). The NCI Central Institutional Review Board approved the initial version of the Protocol (online only) and all subsequent amendments. The study was conducted in accordance with the International Conference on Harmonization of Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Signed written consent was obtained from all patients. First and last authors (N.A. and D.I.Q.) and the statisticians (C.M.T. and M.P.) among the authors assume responsibility for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the Protocol.

Patients and Interventions

Eligible patients were required to have histologically confirmed adenocarcinoma of the prostate and metastatic disease as evidenced by soft tissue and/or bony metastases. Enrolled patients had a Zubrod performance status of 0-2; a Zubrod performance status of 3 was allowed if from bone pain only and a PSA $\geq$ 2.0 ng/mL. No other prior systemic therapy for metastatic prostate cancer was allowed (with the exception of up to 30 days of ADT for metastatic disease before registration), and at least 6 months must have elapsed since completion of prior neoadjuvant and/or adjuvant ADT. Concomitant radiotherapy was allowed only for baseline symptoms per investigator's clinical judgment during the first 4 months of protocol treatment. Patients who had not started any therapy with luteinizing hormone-releasing hormone (LHRH) agonist, antagonist, or orchiectomy (early induction group) and patients who had already started therapy with LHRH agonist, antagonist, or orchiectomy within 30 days before registration (late induction group) were eligible. Patients who were deemed to have extensive mHSPC were eligible for enrollment if, on the basis of the judgment of the treating physician, they were unsuitable candidates for docetaxel or if they declined docetaxel therapy.[11]

Exclusion criteria included brain metastases; prior therapy with ketoconazole, abiraterone acetate, or enzalutamide; New York Heart Association class III or IV heart failure at screening or thromboembolic event; unstable angina pectoris; myocardial infarction; or serious uncontrolled cardiac arrhythmia $\leq$ 6 months before registration.

Patients were randomly assigned in a 1:1 ratio to receive orteronel (300 mg) orally twice daily or bicalutamide (50 mg) administered orally once daily, in addition to continuous ADT. Patient assignment was dynamically balanced on three stratification factors: severity of disease (minimal *v* extensive), Zubrod performance status (0-1 *v* 2-3), and preregistration treatment status (early *v* late induction). Severity (or risk) of disease criteria in this study was originally reported in 1989, and since then, it has been used in all SWOG trials in the mHSPC setting to date.[11-13] Minimal disease was defined as involvement of vertebrae and/or pelvic bones and/or lymph nodes, and extensive disease was defined as that with greater than minimal involvement. Dynamic balancing is a general procedure for treatment

assignment, which concentrates on minimizing imbalance in the distribution of treatment assignment within the levels of each individual prognostic factor.[14]

End Points

The primary end point was OS, which was defined as the time from random assignment to the date of death from any cause. Secondary end points were PFS, PSA response rates, and adverse events (AEs) rate. PFS was defined as the time from random assignment to first documentation of PSA progression (≥ 25% increase and an absolute increase of at least 2 ng/mL from the nadir PSA), radiologic progression (two or more new lesions on radionuclide bone scans, per Prostate Cancer Working Group 2 [PCWG2] criteria, and/or soft tissue progression per RECIST version 1.1), clinical progression (symptomatic deterioration) or death, whichever occurred first. PSA response rates were divided into complete response (CR; PSA < 0.2 ng/mL), partial response (PR; PSA between 0.2 and 4.0 ng/mL), and no response (NR; PSA > 4.0 ng/mL) at a 7-month landmark after random assignment.

Assessments

Patients were assessed for efficacy according to the modified RECIST version 1.1 with the use of computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis during screening (≤ 6 weeks before random assignment) and according to PCWG2 criteria with the use of bone scanning.[15] Progression events were assessed by the treating investigator.

Statistical Analysis

The median survival of patients randomly assigned to ADT plus bicalutamide was assumed to be 54 months on the basis of revised estimates from previous SWOG studies (48 months on the basis of the median from SWOG-S9346, the intermittent *v* continuous ADT phase III trial, and an additional 6 months from the newer drug approvals in the castrate-resistant setting, which may extend survival).[11] With 2.75 years to accrue 1,186 eligible patients and an additional follow-up of 3 years, we had a 90% power to determine a 33% improvement in median OS from 54 to 72 months (one-sided $\alpha = .025$). A final analysis was prespecified after 523 deaths in the combined arms using a one-sided $\alpha = .022$ to account for interim analyses.

Demographic and clinical characteristics at baseline were summarized with the use of descriptive statistics. The primary statistical method comparing time-to-event end points was a stratified log-rank test, with stratification according to prespecified factors. The Kaplan-Meier product-limit method was used to generate the survival and PFS curves in Figures 1, 2, Appendix Figure A2 (online only), and the Cox proportional hazards model with covariate adjustment for stratification factors was used to estimate treatment hazard ratios (HRs) and associated CIs for survival and PFS. Homogeneity of treatment effect was descriptively evaluated with a forest plot showing the survival HR and 95% CI for each subgroup defined by the stratification factors and race using a Cox regression model with no covariate adjustment. The

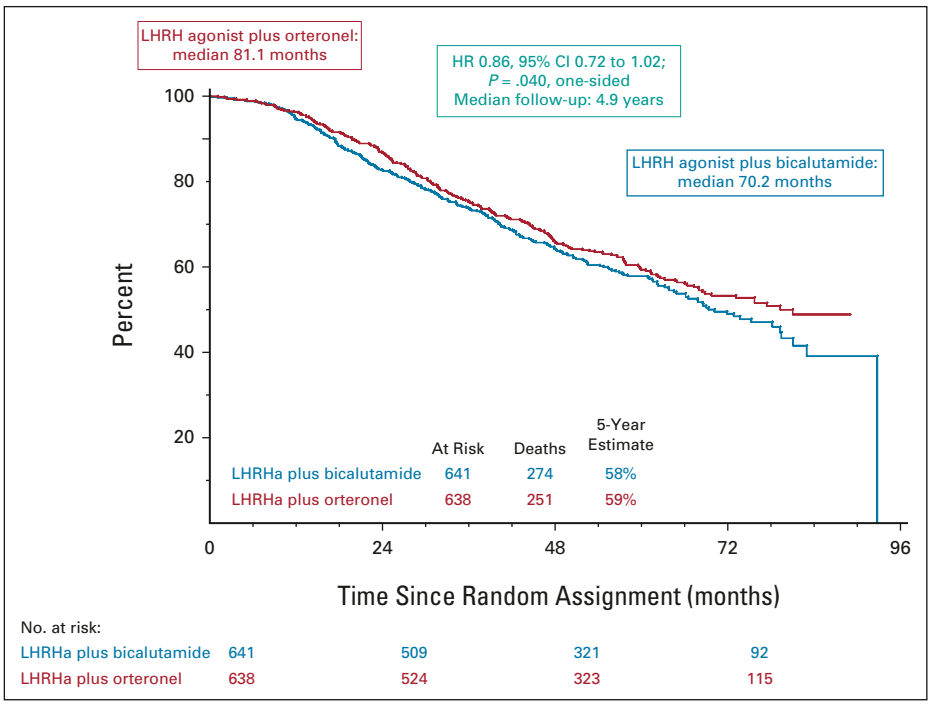

FIG 1. Intention-to-treat comparison of overall survival by arm. HR, hazard ratio; LHRH, luteinizing hormone-releasing hormone.

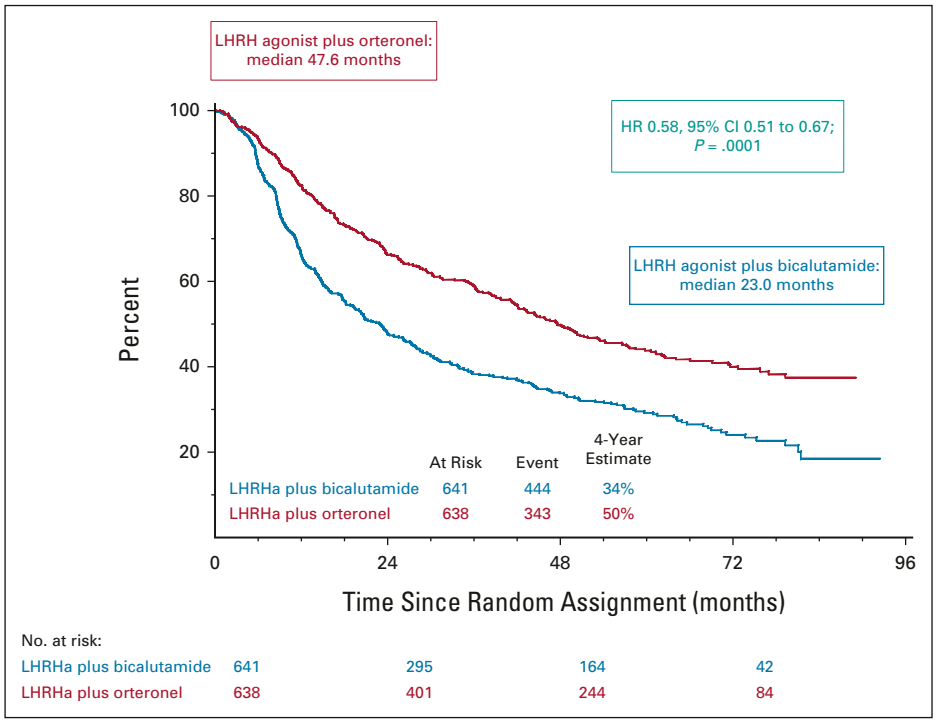

FIG 2. Intention-to-treat comparison of progression-free survival by arm. HR, hazard ratio; LHRH, luteinizing hormone-releasing hormone.

interaction of the stratification factor with treatment, evaluating heterogeneity between levels of a factor, was tested using a residual chi-square from the Cox model. A two-sided Cochrane-Mantel-Haenszel test was used to compare three-category PSA response rates between the two treatment arms.

RESULTS

Patients

Between March 1, 2013, and July 15, 2017, 1,313 patients were randomly assigned and 1,279 were included in the intention-to-treat analysis (32 patients were ineligible, and two patients withdrew all consent before starting treatment—see Appendix Fig A1, online only for details). Six hundred thirty-eight patients were randomly assigned to the orteronel arm, and 641 were randomly assigned to the control arm. At the cutoff date (February 5, 2021) for the final analysis after 525 deaths (and 787 PFS events), the median follow-up time was 4.9 years. Demographic and clinical characteristics at baseline were well balanced (Table 1). The median age of the patients for the orteronel and control arms was 67.6 and 68.1 years, respectively. Across both groups, approximately 10% of the patients were African American, 49% had extensive disease, and 96% had a Zubrod performance status of 0 or 1.

Primary End Point

Analysis for OS occurred after the prespecified 525 deaths were observed (251 in the orteronel group and 274 in the control group). The median OS in the orteronel group was 81.1 months as compared with 70.2 months in the control group. The OS rate at 5 years was 59.7% in the orteronel group and 57.9% in the control group (HR for death 0.86; 95% CI, 0.72 to 1.02; $P = .040$, one-sided). No statistically significant improvement in OS was observed with orteronel compared with control (Fig 1). This lack of treatment effect on OS seemed consistent across stratification factors, including disease severity, and by race (Fig 3 and Appendix Table A3, online only).

Secondary End Points

Analysis of PFS occurred after 787 events were observed (343 in the orteronel group and 444 in the control group). The median PFS in the orteronel group was 47.6 months compared with 23.0 months in the control group (Fig 2). The PFS at 4 years was 50.2% in the orteronel group and 33.9% in the control group (HR, 0.58; 95% CI, 0.51 to 0.67; $P < .001$).

The PSA response rates at month 7 were significantly improved with orteronel (CR 58%; PR: 22%, NR: 19%) versus bicalutamide (CR: 44%; PR: 31%; NR: 25%; $P < .0001$).

Safety

More grade 3 and 4 AEs occurred in the orteronel group versus the control group (43% *v* 13%). Notable differences included the frequency of hypertension (20% with orteronel *v* 5% with control) and fatigue (5% in orteronel *v* 2% in the control group). Five patients in the experimental arm and

TABLE 1. Baseline Characteristics of Patients Included in the Primary Intention-To-Treat Analysis (N = 1,279)

Characteristic	Orteronel (n = 638)	Bicalutamide (n = 641)
Median age, years (range)	67.6 (46.1-90.0)	68.1 (19.4-92.3)
Race, No. (%)		
White	539 (84)	538 (84)
Black	64 (10)	71 (11)
Others	35 (6)	32 (5)
Zubrod PS,[a] No. (%)		
0	416 (65)	442 (69)
1	197 (31)	175 (27)
2	21 (3)	21 (3)
3	3 (< 1)	2 (< 1)
Missing	1 (< 1)	1 (< 1)
Gleason score at initial diagnosis, No. (%)		
< 7	46 (7)	39 (6)
7	165 (26)	168 (26)
8	123 (19)	118 (19)
9-10	249 (39)	264 (41)
Missing	55 (9)	52 (8)
Median PSA level, ng/mL (range)	27.2 (2.0-6,710.0)	31.8 (2.0-6,651.2)
Bone pain, No. (%)		
Yes	158 (25)	143 (22)
No	480 (75)	498 (78)
Bone metastases, No. (%)		
Yes	470 (74)	482 (75)
No	168 (26)	159 (25)
Liver metastases, No. (%)		
Yes	16 (3)	14 (2)
No	622 (97)	627 (98)
Other visceral metastases, No. (%)		
Yes	82 (13)	72 (11)
No	556 (87)	569 (89)
Disease severity, No. (%)		
Minimal	328 (51)	328 (51)
Extensive	310 (49)	313 (49)
Preregistration LHRH suppression, No. (%)		
Yes	330 (52)	331 (52)
No	308 (48)	310 (48)
Bisphosphonate use at study entry, No. (%)		
Yes	39 (6)	35 (5)
No	599 (94)	606 (95)
Prior radical prostatectomy, No. (%)		
Yes	167 (26)	148 (23)
No	471 (74)	493 (77)
Prior bilateral orchiectomy, No. (%)		
Yes	4 (1)	3 (1)
No	634 (99)	638 (99)

Abbreviations: LHRH, luteinizing hormone-releasing hormone; PS, performance score; PSA, prostate-specific antigen.
[a]Zubrod performance status scores range from 0 to 3, with higher scores reflecting greater disability.

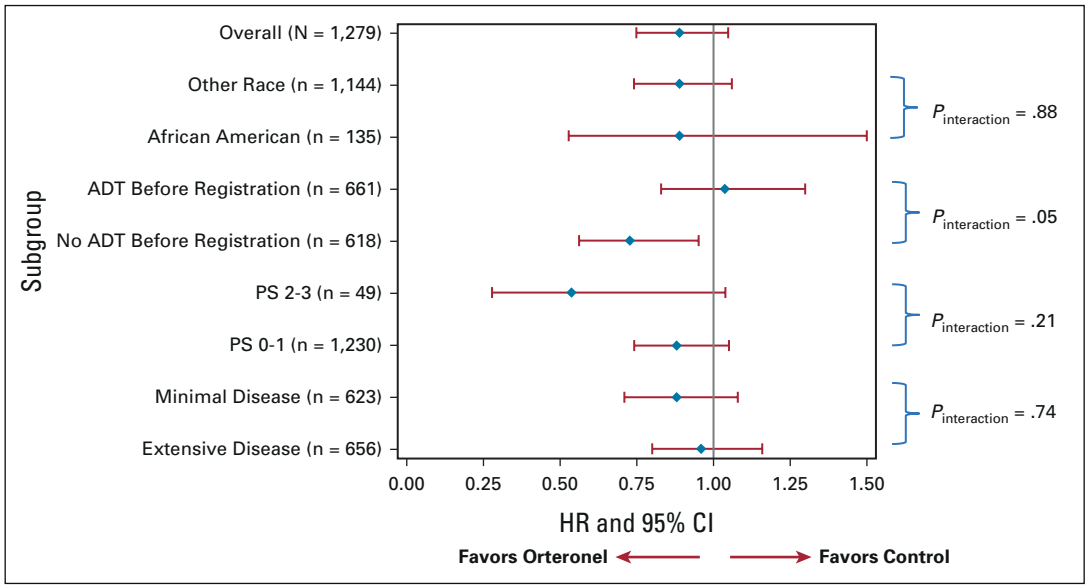

FIG 3. Estimated treatment HRs for overall survival by subgroup (survival forest plot for S1216). ADT, androgen deprivation therapy; HR, hazard ratio; PS, performance score.

one patient in the control arm had grade 5 AEs, including two patients experiencing myocardial infarction and one experiencing a stroke in the orteronel arm (Table 2).

Subsequent Life-Prolonging Anticancer Therapy

Treatment after discontinuation of protocol therapy was initiated per patient's choice and as per local standard of care. At the time of this report, receipt of at least one approved life-prolonging therapy after discontinuation of protocol therapy was evaluable in 331 patients in the orteronel arm and 402 patients in the control arm. A higher proportion of patients in the control arm received postprotocol therapy, which was consistent with a higher incidence of disease progression in the control arm. Of these, 203 (61.3%) patients in the orteronel arm and 311 (77.4%) patients in the control arm received one or more life-prolonging anticancer therapies (Appendix Table A1, online only).

DISCUSSION

In this study, addition of orteronel to ADT compared with bicalutamide led to a statistically significant improvement in PFS and PSA response. Although the approximately 11-month improvement in median OS with orteronel appears clinically meaningful, it did not reach the prespecified requirement for statistical significance. The assumption of 54-month OS for the control arm was a substantial underestimate, exceeded by 16 months in the actual results, challenging the probability of a statistically significant result.

The discrepancy between improvement in PFS but not in OS might have occurred because of receipt of subsequent life-prolonging therapy in a large proportion of patients in the control arm. The primary end point of OS evaluated not only the benefit of early addition of orteronel but also the impact of subsequent life-prolonging therapies including abiraterone acetate, enzalutamide, docetaxel, cabazitaxel, sipuleucel-T, and radium-223.[16-23] In this study, 77.4% of the patients who progressed in the control arm received subsequent life-prolonging therapies compared with 21%-64% of patients in phase III studies in this setting reported since 2013 where the control arm comprised ADT only without recently approved novel agents (nonintensified ADT; Appendix Table A2, online only). The receipt of subsequent life-prolonging therapies by the majority of patients on the control arm might have also resulted in an absolute median OS of 70 months, the highest ever reported for patients on a nonintensified ADT control arm of contemporary trials in mHSPC. It is also possible that the results from the CHAARTED trial, which reported approximately 1 year after activation of SWOG-1216 and showed significant improvement in OS with docetaxel in patients with high-volume disease, prompted a preferential recruitment of patients with low-volume disease on the SWOG-1216 trial, leading to an unexpected improvement in the OS in both arms, especially in the control arm. For example, the median OS in patients with low-volume mHSPC in the CHAARTED trial had not been reached after a median follow-up of 53.7 months and was 83.4 months in the GETUG AFU-15 trial.[24,25] Nonetheless, when compared with the median OS of men on the SWOG-9346 trial in the mHSPC setting (reported in 2013), where all patients received ADT plus bicalutamide and which had almost an identical proportion of men with extensive disease by SWOG criteria of disease severity (48% *v* 49%), the median OS in the control arm of SWOG-1216 was 24 months higher (46 *v* 70.2 months) (Appendix Figure A2).[11]

TABLE 2. No. and Percent of Patients With a Given Type and Grade of AE

	LHRHa Plus Orteronel (n = 627), No. (%)		LHRHa Plus Bicalutamide (n = 629), No. (%)	
AEs	**Any Grade**	**Grade 3-5**	**Any Grade**	**Grade 3-5[a]**
ALT increased	142 (22.6)	10 (1.6)	65 (10.3)	2 (0.3)
Anemia	188 (30)	1 (0.2)	147 (23.4)	2 (0.3)
Anorexia	84 (13.4)	4 (0.6)	23 (3.7)	1 (0.2)
Arthralgia	83 (13.2)	5 (0.8)	44 (7)	2 (0.3)
AST increased	138 (22)	7 (1.1)	60 (9.5)	3 (0.5)
Constipation	123 (19.6)	2 (0.3)	55 (8.7)	0 (0.0)
Depression	64 (10.2)	7 (1.2)	38 (6)	2 (0.3)
Diarrhea	117 (18.7)	10 (1.6)	44 (7)	2 (0.3)
Dizziness	65 (10.4)	3 (0.5)	33 (5.2)	1 (0.2)
Edema limbs	83 (13.2)	4 (0.6)	41 (6.5)	0 (0)
Fatigue	402 (64.1)	34 (5.4)	291 (46.3)	11 (1.7)
Generalized muscle weakness	74 (11.8)	4 (0.6)	42 (6.7)	1 (0.2)
Gynecomastia	39 (6.2)	1 (0.2)	68 (10.8)	0 (0.0)
Headache	105 (16.7)	3 (0.5)	38 (6)	1 (0.2)
Hot flashes	416 (66.3)	5 (0.8)	434 (69)	5 (0.8)
Hyperglycemia	107 (17.1)	11 (1.8)	65 (10.3)	6 (1.0)
Hypertension	267 (42.6)	126 (20.1)	87 (13.8)	28 (4.5)
Hypokalemia	75 (12)	20 (3.1)	9 (1.4)	1 (0.2)
Insomnia	94 (15)	2 (0.3)	55 (8.7)	1 (0.2)
Nausea	156 (24.9)	5 (0.8)	44 (7)	0 (0.0)
Vomiting	67 (10.7)	4 (0.6)	10 (1.6)	0 (0.0)
Weight loss	70 (11.2)	4 (0.6)	12 (1.9)	1 (0.2)

NOTE. AEs unlikely or not related to treatment were excluded. Including all toxicities with 10% incidence of combined grades on one arm.

Abbreviations: AE, adverse event; LHRHa, luteinizing hormone-releasing hormone agonist.

[a]Grade 5 AEs include multiorgan failure (one) in the LHRHa plus bicalutamide arm and myocardial infarction (two), stroke (one) and bronchiectasis (one) and is nonspecified (one) in the LHRHa plus orteronel arm.

SWOG-1216 is the third phaseIII trial investigating the use of orteronel in the metastatic prostate cancer setting after the ELM-PC5 and ELM-PC4 trials failed to meet their primary end point of OS. The ELM-PC5 trial was conducted in the postdocetaxel metastatic castration-resistant prostate cancer (mCRPC) setting, whereas ELM-PC4 trial was conducted in the predocetaxel mCRPC setting.[26,27] Results of these three trials, which combined and enrolled more than 3000 patients with metastatic prostate cancer, suggest that orteronel is likely not an effective androgen axis inhibitor compared with recently approved agents such as abiraterone, apalutamide, and enzalutamide. Furthermore, both PFS and OS were significantly improved with addition of abiraterone, apalutamide, and enzalutamide to ADT compared with ADT alone in the LATITUDE, TITAN, and the ARCHES trials, respectively, all conducted in the mHSPC setting (Appendix Table A2).

The strengths of this study include enrollment of patients from academic and community centers across the United States, proportionate representation of African-American patients (highest to date among all contemporary trials), and a representative patient population as evident by the risk status (approximately 50% high risk). These results emphasize the need to account for receipt of subsequent life-prolonging therapy and a need for validated surrogate intermediate end points to expedite drug development in a time where the treatment paradigm in the mCRPC setting is rapidly changing. Given the improved OS in men with mHSPC receiving nonintensified therapy, it may also be prudent to focus on designing trials for those at the highest risk of early disease progression and death. The results of SWOG-1216 indicate that access to life-prolonging therapies, approved over the past decade, has significantly improved outcomes in patients with metastatic prostate cancer. Furthermore, this trial provides survival estimates in the contemporary era when patients with mHSPC have access to multiple approved life-prolonging therapies. These contemporary survival data will be invaluable for counseling of patients with newly diagnosed mHSPC and for design of future clinical trials in this setting.

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DISCLAIMER

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Orteronel for Metastatic Hormone-Sensitive Prostate Cancer: a Multicenter, Randomized, Open-Label Phase III Trial (SWOG-1216)

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APPENDIX

TABLE A1. Post Hoc Analysis of Subsequent Life-Prolonging Therapy

Protocol/Postprotocol Treatment Status	LHRH Agonist Plus Orteronel (n = 638)	LHRH Agonist Plus Bicalutamide (n = 641)
Patients still on protocol treatment	192	100
Patients off protocol treatment	446	541
Data unavailable	115	139
Postprotocol treatment or death, No. (%)	331 (100)	402 (100)
Died on treatment or within 1 month of going off treatment	33 (10)	19 (4.7)
Receiving non–life-prolonging treatment only	95 (28.7)	72 (17.9)
Receiving life-prolonging treatment[a]	203 (61.3)	311 (77.4)
Receiving subsequent androgen axis inhibitor therapy	138 (68)	237 (76.2)

Abbreviation: LHRH, luteinizing hormone-releasing hormone.

[a]Receipt of approved systemic therapy known to improve survival outcomes in metastatic prostate cancer, as reported by treating investigators.

TABLE A2. Comparison of Contemporary Phase III Trials

	Experimental Arm	Control Arm With Nonintensified ADT	HR		Treatment Arm	Control Arm	
Trial[a]	Subsequent Therapy, %	Subsequent Therapy, %	PFS	OS	High Volume/ Risk,[b] %	High Volume/ Risk,[b] %	Median Follow-Up (months)
ARCHES[28]	8	23.10	0.39 (0.30-0.50) (rPFS)	0.81 (0.53-1.25)	61.7	64.8	14.4
CHAARTED[24]	37.8	47.60	0.61 (0.51-0.72)	0.72 (0.59-0.89)	66.2	63.6	28.9
LATITUDE[4]	30	57	0.47 (0.39-0.55) (rPFS)	0.62 (0.51-0.76)	81.6	77.7	30.4
STAMPEDE abiraterone[5]	53	58	0.31 (0.25-0.39)	0.61 (0.49-0.79)	48.7	51.3	40
STAMPEDE docetaxel[29]	21	21	0.69 (0.59-0.81)	0.81 (0.69-0.95)	41	44	78.2
TITAN[7]	48.6	64.1	0.48 (0.39-0.60) (rPFS)	0.67 (0.51-0.89)	61.9	63.6	22.7
SWOG S1216	61.3	77.4	0.58 (0.51-0.67)	0.86 (0.72-1.02)	49	49	58.8

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; rPFS, radiographic progression-free survival.

[a]The ENZAMET trial was not included as 44% of patients on the control arm received early docetaxel therapy.

[b]In S1216, extensive (high) risk was defined as metastatic disease beyond axial skeleton and/or lymph nodes; in LATITUDE, high-risk disease was defined as having any two of the following: three or more bone metastases on bone scan, Gleason sum ≥ 8, and any visceral metastases; in the other trials, high-volume disease was defined as having four or more bone metastases on bone scan, including one or more outside the vertebral bodies or pelvis and/or visceral metastases.

TABLE A3. Treatment Outcomes by Disease Severity

Disease Group	Control Arm	Orteronel Arm	PFS Control Median/5 Year	PFS Orteronel Median/5 Year	HR (95% CI)	OS Control Median/5 Year	OS Orteronel Median/5 Year	HR (95% CI)
Extensive	313	310	1.1 years/20%	2.2 years/29%	0.66 (0.55 to 0.79)	4.1 years/44%	4.8 years/47%	0.88 (0.71 to 1.10)
Minimal	328	328	3.6 years/38%	NR/58%	0.53 (0.42 to 0.66)	NR/71%	NR/71%	0.89 (0.67 to 1.18)

Abbreviations: HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

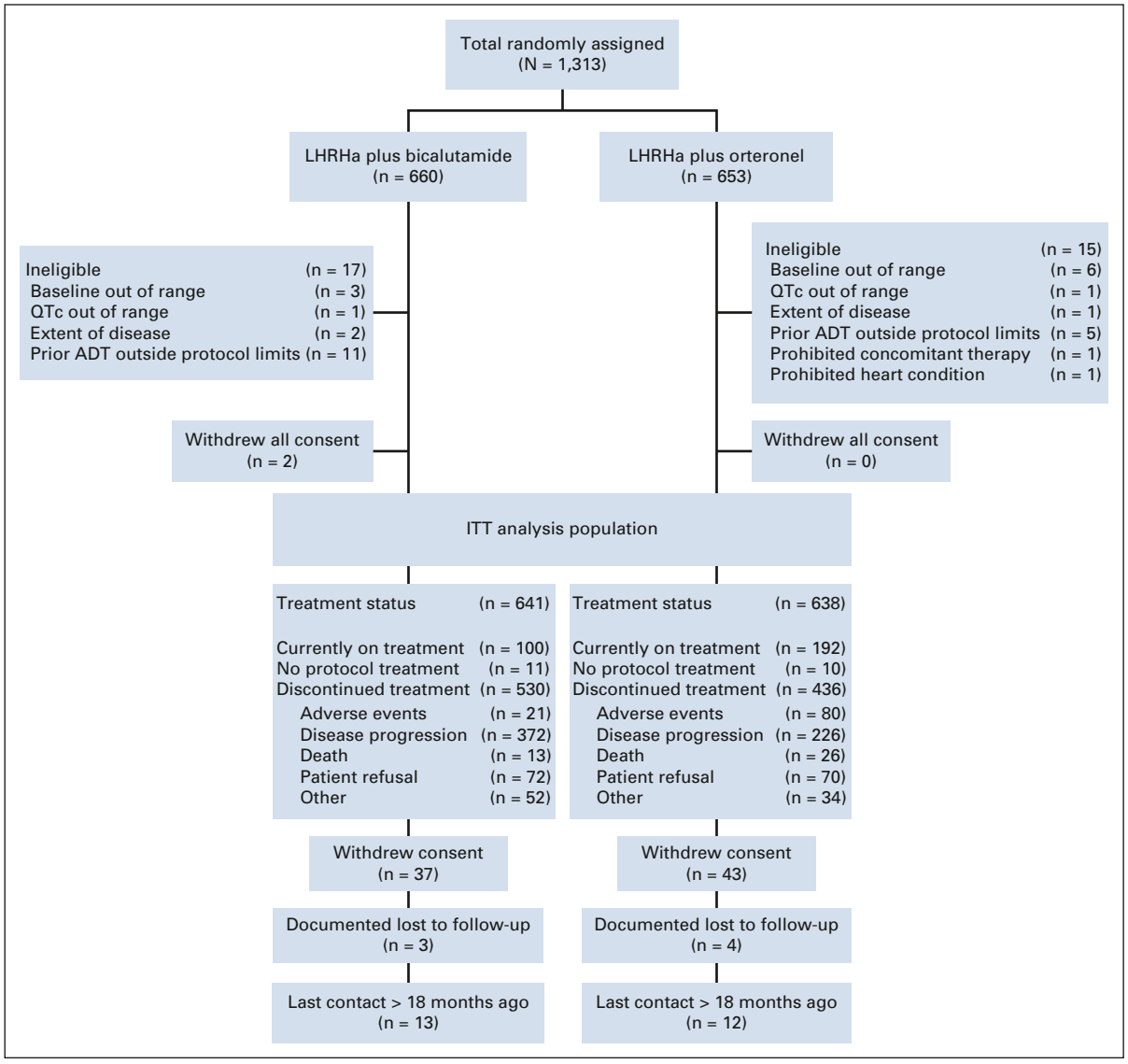

FIG A1. CONSORT diagram for the S1216 trial. ADT, androgen deprivation therapy; ITT, intention-to-treat; LHRHa, luteinizing hormone-releasing hormone agonist; QTc, corrected QT interval.

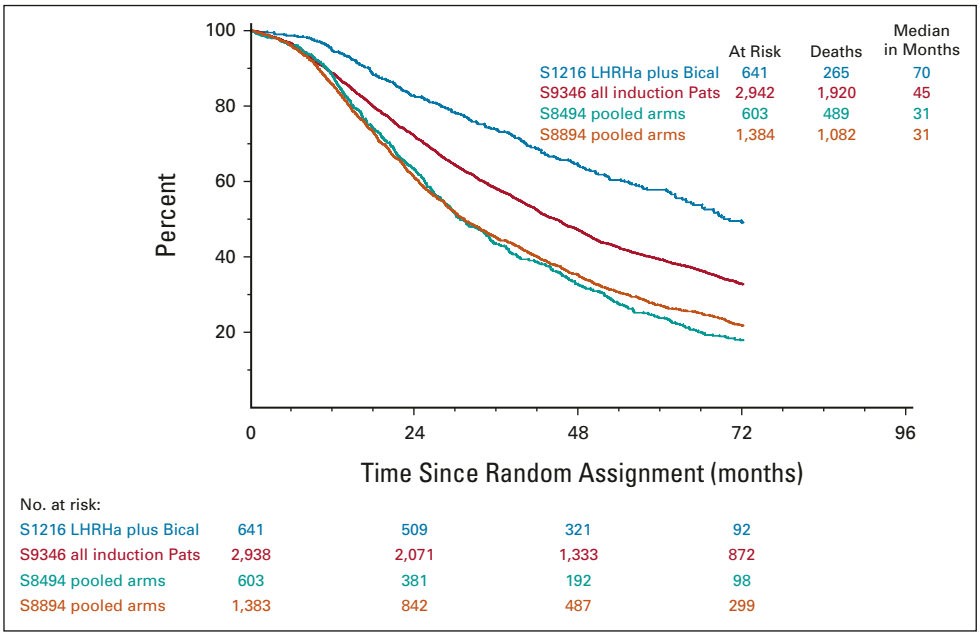

FIG A2. Overall survival curves of different SWOG trials (stratified by trial, follow-up truncated at 6 years). Bical, bicalutamide; LHRHa, luteinizing hormone-releasing hormone agonist; Pats, patients.