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Prostate Cancer

Apalutamide and Overall Survival in Prostate Cancer

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Abstract

Background: The phase 3 SPARTAN study evaluated apalutamide versus placebo in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) and prostate-specific antigen doubling time of ≤ 10 mo. At primary analysis, apalutamide improved median metastasis-free survival (MFS) by 2 yr and overall survival (OS) data were immature.

Objective: We report the prespecified event-driven final analysis for OS.

Design, setting, and participants: A total of 1207 patients with nmCRPC (diagnosed by conventional imaging) were randomised 2:1 to apalutamide (240 mg/d) or placebo, plus on-going androgen deprivation therapy. After MFS was met and the study was unblinded, 76 (19%) patients still receiving placebo crossed over to apalutamide.

Outcome measurements and statistical analysis: OS and time to cytotoxic chemotherapy (TTChemo) were analysed by group-sequential testing with O'Brien-Fleming-type alpha spending function.

Results and limitations: At median 52-mo follow-up, 428 deaths had occurred. The median treatment duration was 32.9 mo for apalutamide group and 11.5 mo for placebo group. Median OS was markedly longer with apalutamide versus placebo, reaching prespecified statistical significance (73.9 vs 59.9 mo, hazard ratio [HR]: 0.78 [95% confidence interval {CI}, 0.64–0.96]; $p = 0.016$). Apalutamide also lengthened TTChemo versus placebo (HR: 0.63 [95% CI, 0.49–0.81]; $p = 0.0002$). Discontinuation rates in apalutamide and placebo groups due to progressive disease were 43% and 74%, and due to adverse events 15% and 8.4%, respectively. Subsequent life-prolonging therapy was received by 371 (46%) patients in the apalutamide arm and by 338 (84%) patients in the placebo arm including 59 patients who received apalutamide after crossover. Safety

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was consistent with previous reports; when adverse events were adjusted for treatment exposure, rash had the greatest difference of incidence between the apalutamide and placebo groups.

Conclusions: Extension of OS with apalutamide compared with placebo conferred impactful benefit in patients with nmCRPC. There was a 22% reduction in the hazard of death in the apalutamide group despite 19% crossover (placebo to apalutamide) and higher rates of subsequent therapy in the placebo group.

Patient summary: With data presented herein, all primary and secondary study end points of SPARTAN were met; findings demonstrate the value of apalutamide as a treatment option for nonmetastatic castration-resistant prostate cancer.

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1. Introduction

Patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) are identified by an increasing prostate-specific antigen (PSA) concentration and no distant metastases on conventional imaging in the setting of on-going androgen deprivation therapy (ADT) [1]. Without further treatment, patients with nmCRPC invariably progress to metastatic disease, with significant morbidity and mortality [2–5]. Shorter PSA doubling time (PSADT) is strongly associated with a greater risk of metastases and death in nmCRPC [6,7]. Overarching goals of therapy in patients with nmCRPC are prevention of metastases, maintenance of quality of life, and extension of overall survival (OS) [6,8].

Apalutamide is an androgen signalling inhibitor approved for the treatment of nmCRPC and metastatic castration-sensitive prostate cancer [9–11]. Approval for nmCRPC was based on interim data from the placebo-controlled, phase III SPARTAN study in patients with nmCRPC and PSADT ≤ 10 mo, in which addition of apalutamide to on-going ADT improved median metastasis-free survival (MFS) by 2 yr over placebo plus ADT [12]. At the primary analysis of MFS, the secondary end points of time to metastasis, progression-free survival (PFS), and time to symptomatic progression were all improved with apalutamide versus placebo, while OS data were immature [12,13]. OS data from the first two interim analyses of SPARTAN consistently favoured apalutamide over placebo [12,13]. In this prespecified, event-driven final analysis of SPARTAN, we report results for OS and time to initiation of cytotoxic chemotherapy. Results for time to symptomatic progression, second PFS (PFS2), time to PSA progression, and safety are updated.

2. Patients and methods

2.1. Study design and conduct

The SPARTAN study design and methods of assessment (ClinicalTrials.gov, NCT01946204) have been reported [12,13]. A brief overview is provided in the [Supplementary material](#).

2.2. End points

The primary end point of SPARTAN was MFS identified on conventional imaging by a blinded independent central review. Secondary end points, in

hierarchical testing order, were time to metastasis, PFS, time to symptomatic progression, OS, and time to initiation of cytotoxic chemotherapy. Exploratory end points included PFS2 and time to PSA progression. PFS2 was defined as the time from randomisation to investigator-assessed disease progression (by PSA, imaging, or symptom development) during or after the first subsequent treatment or death from any cause, whichever occurred first, and time to PSA progression was defined as the time from randomisation to PSA progression according to Prostate Cancer Working Group 2 criteria [14]. Safety is also reported in this final analysis.

At the primary analysis (clinical cut-off date: May 19, 2017), MFS, time to metastasis, PFS, and time to symptomatic progression met statistical significance; therefore, primary analysis was considered the final analysis for these end points [12]. Based on these data, the independent data and safety monitoring committee unanimously recommended unblinding the study and allowing eligible placebo-treated patients without evidence of disease progression to cross over to receive open-label apalutamide. After unblinding, all patients were followed for survival, with crossover patients analysed as part of the intent-to-treat population in the placebo group.

2.3. Statistical analysis

SPARTAN was designed with an ~80% power to detect a 25% reduction in the hazard of death for patients receiving apalutamide. The final OS analysis was scheduled to occur when 427 death events occurred; clinical cut-off was February 1, 2020. Testing of OS was based on the original prespecified O'Brien-Fleming-type alpha-spending function to ensure control of overall type I error with an efficacy boundary of $p \leq 0.046$ at final analysis. If OS was statistically significant, the planned hierarchical testing of time to cytotoxic chemotherapy would occur at an alpha level of 0.0073 (two sided based on 60%, the fraction of total information expected of planned total number of events) based on the O'Brien-Fleming-type alpha-spending function. Kaplan-Meier methods were used to estimate medians. A log-rank test stratified by prespecified factors (PSADT [≤ 6 vs > 6 mo], bone-sparing agent use [yes vs no], and locoregional disease [N0 vs N1]) was used. Hazard ratios (HRs) and respective 95% confidence intervals (CIs) were determined from a stratified proportional hazard model with a single factor of treatment group. Unstratified analyses of OS HRs and respective 95% CIs were evaluated for subgroups and illustrated as a forest plot.

Two exploratory sensitivity analyses of OS accounted for patients who crossed over from placebo to apalutamide. In a naive-censoring approach, crossover patients were censored at the crossover date. Inverse probability of censoring weighted (IPCW) analysis estimated the treatment effect of apalutamide on OS by reweighting patients receiving placebo based on the three stratification factors: PSADT, bone-sparing agent use, and locoregional disease.

Updated analyses were performed for time to symptomatic progression, PFS2, and time to PSA progression. Safety results were reported descriptively. Exposure-adjusted event rates per 100

patient-years of exposure were calculated. Adverse events (AEs) experienced by patients originally randomised to the placebo group while taking apalutamide following crossover were counted independently from AEs experienced while taking placebo. No statistical hypothesis testing was performed for any safety incidences; only descriptive statistics are provided.

3. Results

Between October 14, 2013 and December 15, 2016, 1207 patients were randomised 2:1 to apalutamide ($n = 806$) or placebo ($n = 401$). Patient disposition is summarised in [Supplementary Figure 1](#). Patient demographics and disease characteristics have been described [\[12\]](#) and are included in [Supplementary Table 1](#). MFS was previously reported, and the location of metastases was assessed at progression; most cases were identified with a single-site metastasis, with the majority localised to bone [\[15,16\]](#). After unblinding, 76 (19%) patients in the placebo group without disease progression crossed over to receive open-label apalutamide (“crossover group”). At final analysis data cut, 237 (30%) of 803 patients originally randomised to apalutamide and 46 (61%) of 76 crossover patients continued treatment with apalutamide. Progressive disease was the most common reason for treatment discontinuation ([Supplementary Table 2](#)). The median follow-up was 52.0 mo for all patients and 20.3 mo at the first interim analysis [\[12\]](#). Median treatment duration was 32.9, 11.5, and 26.1 mo in the apalutamide, placebo, and crossover groups, respectively ([Table 1](#)). In the intent-to-treat population, life-extending subsequent therapy was used more frequently in the placebo group. Before unblinding, 217 patients from the placebo group and 165 from the apalutamide group had discontinued and were receiving subsequent treatment with a US Food and Drug Administration–approved therapy for metastatic CRPC. At final analysis, 285 patients in the placebo group and 386 in the apalutamide group had received a first subsequent therapy ([Supplementary Table 3](#)). Overall, of the 401 patients initially randomised to the placebo group, 338 (84%) received either life-prolonging active therapy as the first subsequent therapy upon disease progression or apalutamide as a crossover treatment option without progression after study unblinding. Abiraterone acetate plus prednisone was the most common postprogression treatment; 73% and 72% patients of the apalutamide and placebo groups, respectively, who received subsequent therapy, received abiraterone acetate plus prednisone as a first subsequent therapy.

Of 428 death events, 274 (of 806 patients) occurred in the apalutamide group and 154 (of 401) in the placebo group; 779 patients were censored without event, with a median follow-up time of 50.4 mo. Compared with placebo, apalutamide decreased the hazard of death by 22% in the intent-to-treat population (HR: 0.78 [95% CI, 0.64–0.96]; $p = 0.016$). The p value for OS confirmed a statistically significant improvement of OS, crossing the prespecified O’Brien-Fleming boundary of 0.046 ([Fig. 1A](#)). The median OS (95% CI) was 73.9 (61.2–not reached [NR]) mo for

apalutamide and 59.9 (52.8–NR) mo for placebo (median OS was estimated with limitation since only a small number of patients were at risk and the CI for the median was not estimable). Note a limitation for median OS was estimates with longer follow-up had CIs that were not estimable due to a smaller number of patients at risk.

Two exploratory sensitivity analyses of OS accounting for patients who crossed over from placebo to apalutamide revealed similar results ([Fig. 1B](#)). With naive censoring, median OS was 73.9 (95% CI, 61.2–NR) mo in the apalutamide group and 52.8 (48.5–61.1) mo in the placebo group (HR: 0.69 [95% CI, 0.56–0.84]; nominal $p = 0.0002$). Similarly, with the inverse probability of censoring weighted analysis, median OS was 73.9 mo with apalutamide and 52.8 mo with placebo (HR: 0.69 [95% CI, 0.56–0.84]; nominal $p = 0.0003$). Both sensitivity analyses demonstrated an increase of OS by 21.1 mo with apalutamide versus placebo. When naive censoring was used to account for crossover, the 6-yr survival rate was 40% (95% CI, 32–48) in the placebo group (vs 46% in the intent-to-treat population analysis) versus 50% (44–56) in the apalutamide group.

The treatment effect of apalutamide was generally consistent in the study subpopulations analysed ([Fig. 1C](#)). However, in some subpopulations with smaller sample sizes, the 95% CI included 1.0.

At the time of final analysis, 258 patients had initiated cytotoxic chemotherapy: 155 of 806 receiving apalutamide and 103 of 401 receiving placebo. Apalutamide decreased the hazard of initiating cytotoxic chemotherapy by 37% versus placebo (HR: 0.63 [95% CI, 0.49–0.81]; $p = 0.0002$), and median time to cytotoxic chemotherapy was not reached in either group ([Fig. 2A](#)). The p value for time to cytotoxic chemotherapy was below the prespecified boundary for statistical significance.

The statistical significance of time to symptomatic progression was achieved at the first interim analysis, when final analysis of MFS (primary end point) was performed [\[12\]](#). For this report, we performed an updated analysis of time to symptomatic progression. In total, 264 patients experienced symptomatic progression, 156 of 806 in the apalutamide group and 108 of 401 of the placebo group. Updated analysis confirmed the benefit observed with apalutamide in hazard reduction of symptomatic progression compared with placebo (HR: 0.57 [95% CI, 0.44–0.73]; nominal $p < 0.0001$; [Fig. 2B](#)). Median was not reached in either group.

A total of 572 patients experienced PSA progression: 235 of 806 received apalutamide and 337 of 401 received placebo. Median times to PSA progression for the apalutamide and placebo groups were 40.5 and 3.7 mo, respectively ([Fig. 2C](#)). Apalutamide reduced the hazard of PSA progression by 93% compared with placebo (HR: 0.07 [95% CI, 0.06–0.09]; nominal $p < 0.0001$).

As reported previously, at 12 wk after randomisation, median PSA had decreased by 90% in the apalutamide group and had increased by 40% in the placebo group [\[12\]](#). The proportions of patients achieving a PSA decline from baseline of $\geq 50\%$ (PSA50) were 93% (753 of 806 patients [724 confirmed]) in the apalutamide group and 3.5% (14 of

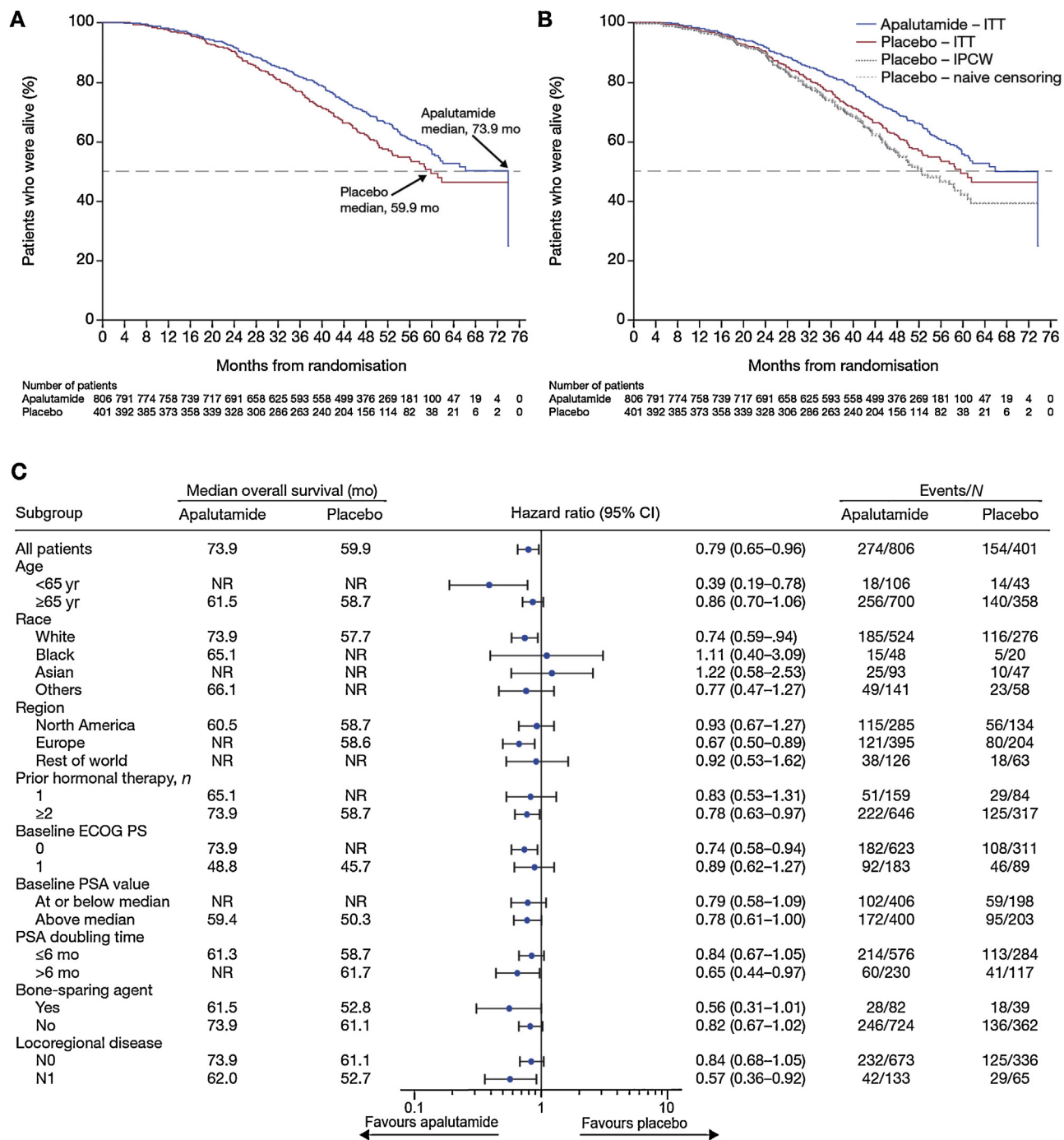


Fig. 1 – Overall survival (OS): (A) Kaplan-Meier estimate of OS, (B) Kaplan-Meier estimate of OS adjusted for patient crossover from placebo to apalutamide, and (C) forest plot subgroup analysis by OS by baseline patient characteristics. Analyses for the Kaplan-Meier estimate of OS (A) were stratified, while analyses for the forest plot were unstratified. In (B), inverse probability of censoring weighted (IPCW) and naive-censored Kaplan-Meier estimates of OS for the placebo group are presented along with the standard Kaplan-Meier estimates of OS for both the apalutamide and the placebo group. Patients at risk are presented for the naive-censored curve. Patients at risk for the IPCW curve are not included because of a lack of clear clinical interpretation of the number of patients at risk associated with the weighted methodology. CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; ITT = intent to treat; NR = not reached; PSA = prostate-specific antigen.

401 patients [nine confirmed]) in the placebo group. The relative PSA response rate (95% CI), based on the confirmed response, was 40.2 (21–77; nominal $p < 0.001$) with apalutamide versus placebo. In the apalutamide group, 38% (303 of 806) of patients attained a confirmed PSA level

of ≤ 0.2 ng/ml compared with no patients in the placebo group.

Progression on or after the first subsequent therapy or death (PFS2) occurred in 319 of 806 apalutamide-treated patients and in 190 of 401 placebo-treated patients.

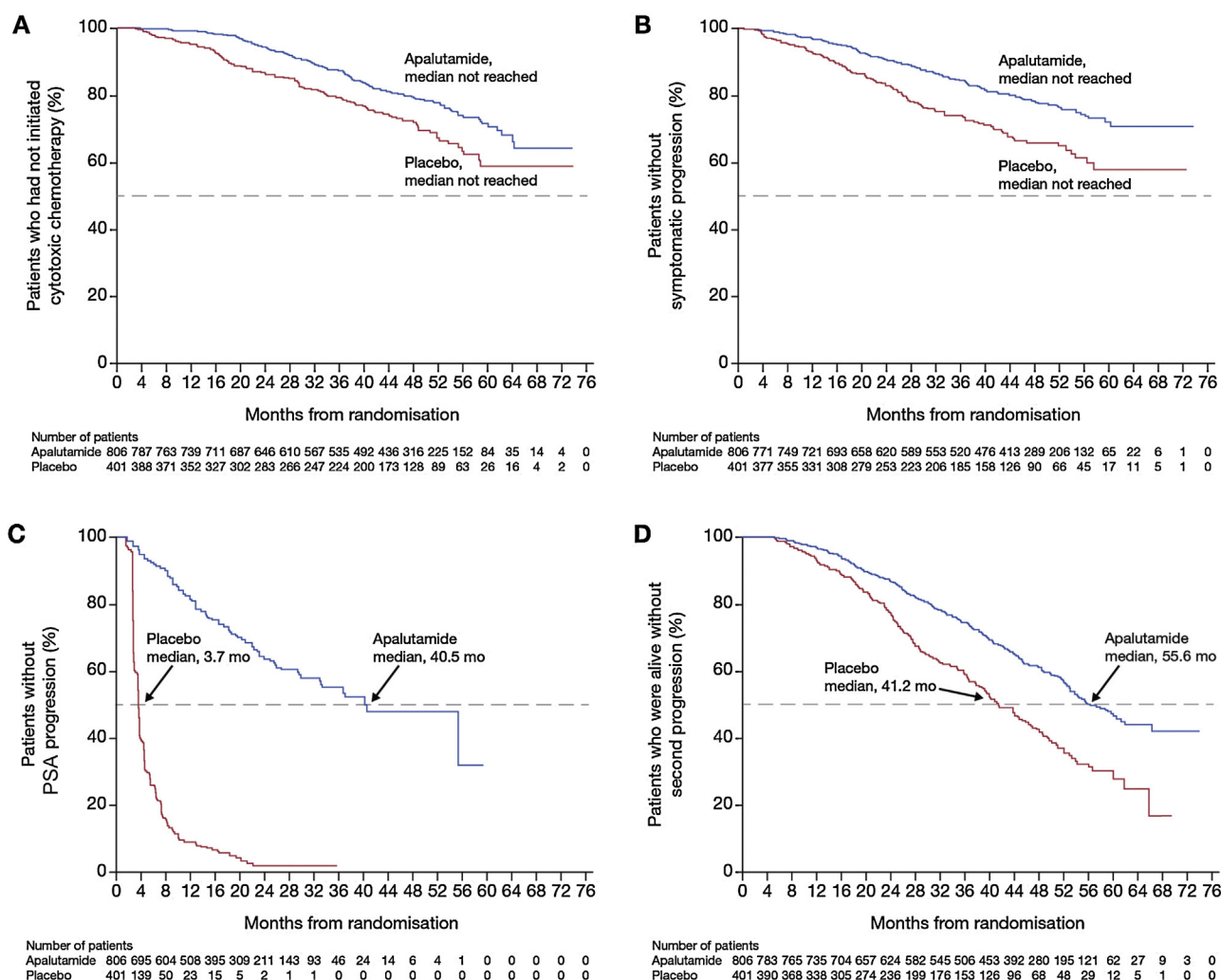


Fig. 2 – Kaplan-Meier estimates of (A) time to initiation of cytotoxic chemotherapy, (B) time to symptomatic progression, (C) time to PSA progression, and (D) second progression-free survival. PSA = prostate-specific antigen.

Apalutamide extended median PFS2 by 14.4 mo versus placebo (apalutamide, 55.6 mo; placebo, 41.2 mo) and reduced the hazard of second progression or death by 45% versus placebo (HR: 0.55 [95% CI, 0.46–0.66]; nominal $p < 0.0001$; Fig. 2D).

The median treatment duration was 21.4 mo longer in the apalutamide group than in the placebo group (apalutamide, 32.9 mo; placebo, 11.5 mo). Median treatment duration with apalutamide in the crossover group was 26.1 mo (Table 1). The overall incidence of any AEs was similar between the apalutamide and placebo groups. AEs (all grades) were observed in 97% of patients receiving apalutamide, 94% of patients receiving placebo, and 90% of patients in the crossover group (Table 1). Exposure-adjusted serious AE (SAE) rates per 100 patient-years were 13.7 in the apalutamide group and 22.2 in the placebo group. No AE or SAE rates had a notable increase with increased apalutamide exposure/follow-up. One AE leading to death (myocardial infarction) was considered potentially related

to apalutamide treatment. Additional safety details are provided in the [Supplementary material](#).

4. Discussion

In this prespecified, event-driven final analysis of SPARTAN, apalutamide improved OS compared with placebo in patients with nmCRPC reaching prespecified statistical significance, with 22% reduction in the hazard of death and a 14-mo increase in median OS. The survival benefit of apalutamide added to on-going ADT was observed despite the crossover of 19% of placebo-treated patients to apalutamide and the frequent use of subsequent life-prolonging therapy for metastatic prostate cancer in the placebo group (84%). Moreover, after crossover from placebo to apalutamide, the median treatment duration with apalutamide exceeded 2 yr (26.1 m), which is approximately double the median time on treatment reported for crossover patients in other studies in nmCRPC

Table 1 – Summary of AEs and most frequent treatment-emergent AEs (occurring in 15% of the apalutamide group)

	Apalutamide with on-going ADT (n = 803)		Placebo with on-going ADT (n = 398)		Placebo group to apalutamide group (n = 76)	
Treatment duration (mo), median (range)	32.9 (0.1–74.5)		11.5 (0.1–37.2)		26.1 (1.0–28.9) ^a	
Any AE, n (%)	781 (97)		373 (94)		68 (89)	
Grade 3 or 4 AE	449 (56)		145 (36)		29 (38)	
Any serious AE	290 (36)		99 (25)		19 (25)	
Any AE leading to treatment discontinuation ^b	120 (15)		29 (7.3)		8 (11)	
AE leading to death	24 (3.0)		2 (0.5)		2 (2.6)	
AE by preferred term	All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4
Fatigue (%)	33	0.9	21	0.3	16	1.3
Hypertension (%)	28	16	21	12	11	5.3
Diarrhoea (%)	23	1.5	15	0.5	13	1.3
Fall (%)	22	2.7	9.5	0.8	11	2.6
Nausea (%)	20	0	16	0	6.6	0
Arthralgia (%)	20	0.4	8.3	0	12	1.3
Weight decreased (%)	20	1.5	6.5	0.3	11	1.3
Back pain (%)	18	1.4	15	1.5	11	0
Hot flush (%)	15	0	8.5	0	9.2	0

ADT = androgen deprivation therapy; AE = adverse event.

Data are n (%) unless otherwise noted.

^a Duration on apalutamide after crossover.^b All AEs leading to discontinuation are reported. However, reported AEs may not be the primary reason for discontinuation. Total patient-years of exposure were 2117.9 for the apalutamide group, 446.0 for the placebo group, and 134.5 for the crossover group. Patients are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the patient with the worst toxicity grade is used. If a patient has all AEs with missing toxicity grades, the patient is counted only in the total column.

(ie, 14.5 mo in PROSPER and 11.0 mo in ARAMIS) [17–19]. In our study, two sensitivity analyses using independent methods (naïve censoring and IPCW), to account for the patients receiving placebo crossing over to apalutamide, demonstrated consistent results and a 21-mo increase in median OS. These analyses delineated the impact of crossover treatment in the placebo arm. The treatment effect of apalutamide on survival was generally observed in the subpopulations evaluated, with exceptions in those with small numbers of patients. Additionally, treatment with apalutamide decreased the hazard of initiating cytotoxic chemotherapy by 37% compared with placebo.

Taken together with data from the primary analysis, all end points in the SPARTAN study favoured treatment of patients with nmCRPC using apalutamide. This includes MFS, the primary end point, all secondary end points (time to metastasis, PFS, time to symptomatic progression, OS, and time to initiation of cytotoxic chemotherapy), as well as all exploratory end points (PFS2, PSA responses, and hazard of PSA progression), while preserving patient health-related quality of life [8,12,13].

In SPARTAN, patients who progressed to metastatic disease were offered treatment with abiraterone acetate plus prednisone; >70% of patients in either arm received study-sponsored abiraterone acetate plus prednisone as the first subsequent therapy after progression (Supplementary Table 3). Among these patients, approximately half of the men progressing in either group received taxane chemotherapy. Of note, in terms of survival after metastasis in the apalutamide arm, the difference between median MFS and

OS is 33.4 mo, which is similar to the previously reported median OS of 34.7 mo for the abiraterone acetate plus prednisone arm in the COU-AA-302 study of first-line treatment for metastatic CRPC [20]. In addition, the difference between median MFS and PFS2 in SPARTAN is 15.1 mo, which is close to the median radiographic PFS of 16.5 mo reported in COU-AA-302 [21]. Thus, early treatment of nmCRPC with apalutamide delays metastasis and, as shown by PFS2 and OS, lays the foundation for long-term clinical benefits. Baseline characteristics and biology of patients progressing after treatment with apalutamide who received abiraterone acetate plus prednisone as the first subsequent therapy in SPARTAN certainly have significant differences compared with baseline characteristics of patients included in the COU-AA-302 study, who had prior exposure to ADT alone. To understand continued benefit from different treatments, further investigations of cross-resistance mechanisms of androgen signalling inhibitors are needed. Recent in vitro studies highlighted potential cross-resistance in cells with high expression of androgen receptor variant 7 (ARv7) and aldo-keto reductase family 1 member C3 (AKR1C3) [22]. Preliminary results of the assessment of end-of-study-treatment patient samples from the apalutamide and placebo groups in SPARTAN demonstrated that in vivo rates of ARv7 expression in circulating free RNA were similar for apalutamide and placebo groups. No difference was observed between groups with respect to any other androgen receptor anomalies tested [23,24]. Further research on resistance mechanisms to apalutamide is under way.

At 52 mo of median follow-up, the safety profile of apalutamide remained consistent with that in prior reports [12,13]. Rates of AEs leading to permanent treatment discontinuation were low, and disease progression was the most common reason for discontinuation in both groups. Although the median duration of treatment on study was almost three times longer (32.9 vs 11.5 mo) in the apalutamide group than in the placebo group, the rate of exposure-adjusted AEs in the apalutamide group (event rates/100 patient-years) did not change substantially. No new safety signals were detected with additional follow-up. These results suggest that early use of apalutamide before development of distant metastases on conventional imaging confers an overall advantage in oncologic outcome and extends survival. Conventional imaging is less sensitive than newer approaches such as prostate-specific membrane antigen ligand positron-emission tomography (PSMA-PET). Therefore, it is possible that some patients in SPARTAN whose disease was classified as nmCRPC by conventional imaging could have had low-volume metastatic disease. In a study by Fendler et al [25], a retrospective analysis of PSMA-PET imaging conducted in 200 patients diagnosed with nmCRPC by conventional imaging showed that 55% had M1 disease, based on a PSMA-PET assessment. Therefore, given the favourable outcomes for SPARTAN patients, and as also suggested in a recent editorial by van der Poel [26], apalutamide may also likely improve outcomes for patients with early M1 disease detectable with sensitive next-generation imaging techniques.

The SPARTAN results, corroborated by other data from PROSPER (enzalutamide) and ARAMIS (darolutamide), show the benefit of adding an androgen signalling inhibitor to ADT for patients with nmCRPC and represent a major advance in treatment [12,27,28]. SPARTAN, PROSPER, and ARAMIS all met their primary end point of MFS. Each of the three studies also assessed the secondary end point of OS with longer follow-up recently [17–19]. Based on the results of these large randomised prospective studies and the maturation rate of data for MFS (earlier) versus OS (later), MFS appears to be relevant as an early indicator of long-term outcome in patients with nmCRPC. The findings support the US Food and Drug Administration's guidance on the use of MFS as a study end point [29]. A retrospective analysis of the relationship between MFS and OS in high-risk patients with nmCRPC concluded that metastasis development, regardless of time, is associated with a significantly greater hazard of death, and hence, MFS is predictive of OS [30].

5. Conclusions

The final analysis of SPARTAN demonstrated that, in addition to improved MFS and time to symptomatic progression reported previously [12], the addition of apalutamide to ADT improves OS and lengthens time before initiation of cytotoxic chemotherapy in patients with nmCRPC; all primary and secondary end points were improved with apalutamide. With longer follow-up, the

safety profile of apalutamide was similar to that shown in earlier reports.

Portions of the data were presented at the 2020 ASCO virtual conference.

Author contributions: Matthew R. Smith had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Smith, Small.

Acquisition of data: Smith, Saad, Chowdhury, Oudard, Hadaschik, Graff, Olmos, Mainwaring, Lee, Uemura, Small.

Analysis and interpretation of data: Smith, Saad, Chowdhury, Oudard, Hadaschik, Graff, Olmos, Mainwaring, Lee, Uemura, De Porre, Smith, Brookman-May, Li, Zhang, Rooney, Lopez-Gitlitz, Small.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at <https://doi.org/10.1016/j.eururo.2020.08.011>.

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