



# Adjusting Overall Survival Estimates for Treatment Switching in Metastatic, Castration-Sensitive Prostate Cancer: Results from the LATITUDE Study

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## Abstract

**Background** LATITUDE was the first phase 3 trial examining the survival benefit of adding abiraterone acetate (AA) + prednisone (P) to androgen-deprivation therapy (ADT) in newly diagnosed metastatic, castration-sensitive prostate cancer (mCSPC). Due to significant improvement in overall survival after the first interim analysis, patients in the placebos + ADT arm could switch to AA + P + ADT during an open-label extension. As in other studies where switching is allowed, statistical adjustments are needed to assess the real benefit of new drugs.

**Patients and Methods** This was a post hoc analysis to estimate the true survival benefit of AA + P + ADT in patients with newly diagnosed mCSPC by applying statistical adjustments commonly used to adjust for treatment switching.

**Results** Of 112 patients still receiving placebos + ADT at the first interim analysis, 72 switched to AA + P + ADT during the open-label extension. Final analysis was conducted after median follow-up of 51.8 months. Compared to the placebos + ADT arm, the risk of death in the AA + P + ADT arm was 34% lower [hazard ratio (HR) = 0.663 (95% confidence interval 0.566–0.778)] by unadjusted intent-to-treat analysis, 37% lower [HR = 0.629 (95% confidence interval 0.526–0.753)] by rank preserving structure failure time modeling, and 38% lower [HR = 0.616 (95% confidence interval 0.524–0.724)] by inverse probability of censoring weights.

**Conclusions** Analyses adjusting for treatment switching using two different statistical approaches confirm the improved survival benefit of adding AA + P to ADT in patients with newly diagnosed mCSPC.

**Trial Registration** ClinicalTrials.gov identifier NCT01715285.

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## Key Points

The LATITUDE trial showed that adding abiraterone acetate + prednisone to androgen-deprivation therapy (ADT) provided a significant survival benefit in men with newly diagnosed metastatic, castration-sensitive prostate cancer.

Due to significant improvement in overall survival after the first interim analysis, patients receiving placebos + ADT arm could switch to abiraterone acetate + prednisone + ADT during an open-label extension.

This post hoc analysis confirmed the significant benefit of adding abiraterone acetate + prednisone to ADT following adjustment for bias introduced by treatment switching.

## 1 Introduction

Prostate cancer is the second-most common cancer worldwide in men, accounting for 15% of all cancers diagnosed in 2012, and it is the fifth-leading cause of death [1]. The incidence of prostate cancer is highest in developed countries, where it is the most common cancer in men. This high incidence is thought to be mostly due to regular screening for prostate-specific antigen and subsequent biopsy. About 15–25% of patients newly diagnosed with prostate cancer have metastatic disease [2–4], which has a poor prognosis and a 5-year survival rate below 30% [5].

For nearly 80 years, the standard of care for patients with newly diagnosed metastatic prostate cancer has been androgen-deprivation therapy (ADT), which consists of a luteinizing hormone-releasing hormone agonist (medical castration) or orchiectomy (surgical castration) with or without concurrent anti-androgens [6]. However, patients eventually become castration-resistant and need additional drugs to control the cancer. Clinical trials in the early 2000s indicated that docetaxel was effective for treating metastatic castration-resistant prostate cancer, and following trials showed that docetaxel is even more effective for metastatic, castration-sensitive prostate cancer (mCSPC) [6]. Based on this proven survival benefit, the addition of docetaxel to ADT has since become a standard of care for patients with mCSPC [7]. Docetaxel, however, causes frequent grade 3–5 toxicity, including neutropenia, febrile neutropenia, and fatigue, limiting its use, especially in patients with advanced age, poor performance status, or coexisting illnesses [6]. Also, studies have not shown a conclusive survival benefit of adding docetaxel to ADT for patients with low-volume disease [7].

More recently, abiraterone acetate (AA) plus prednisone (P) in combination with ADT has been added as a standard of care for mCSPC [7] based on a proven overall survival (OS) benefit [8, 9]. AA is a prodrug of abiraterone, a selective inhibitor of testosterone biosynthesis that acts by blocking cytochrome P450 c17 [6]. Network meta-analyses suggest that AA + P + ADT improves survival at least as well as docetaxel + ADT and is better at preventing disease progression and improving quality of life [10, 11]. Current consensus recommendations are that AA + P in combination with ADT should be considered for patients with newly diagnosed mCSPC who are fit enough for the regimen [12, 13]. For patients with mCSPC, the recommended dose of AA is 1,000 mg orally once daily with 5 mg prednisone orally once daily [14].

LATITUDE was the first phase 3 trial examining the survival benefit of adding AA + P to ADT. It was a multinational, double-blind, randomized, placebo-controlled study in 1,199 men with newly diagnosed mCSPC [8]. The study was unblinded shortly after the first interim analysis on 31

October 2016 after a median follow-up of 30.4 months due to significant and clinically meaningful improvement in OS [hazard ratio (HR) = 0.62 (95% confidence interval (CI) 0.51–0.76)] and radiographic progression or death [HR = 0.47 (95% CI 0.39–0.55)]. Patients in the AA + P + ADT arm also had less pain and fatigue and better overall health-related quality of life than patients in the placebos + ADT arm [15]. As a result, patients in the placebos + ADT arm of LATITUDE were allowed to switch to AA + P + ADT during an open-label extension.

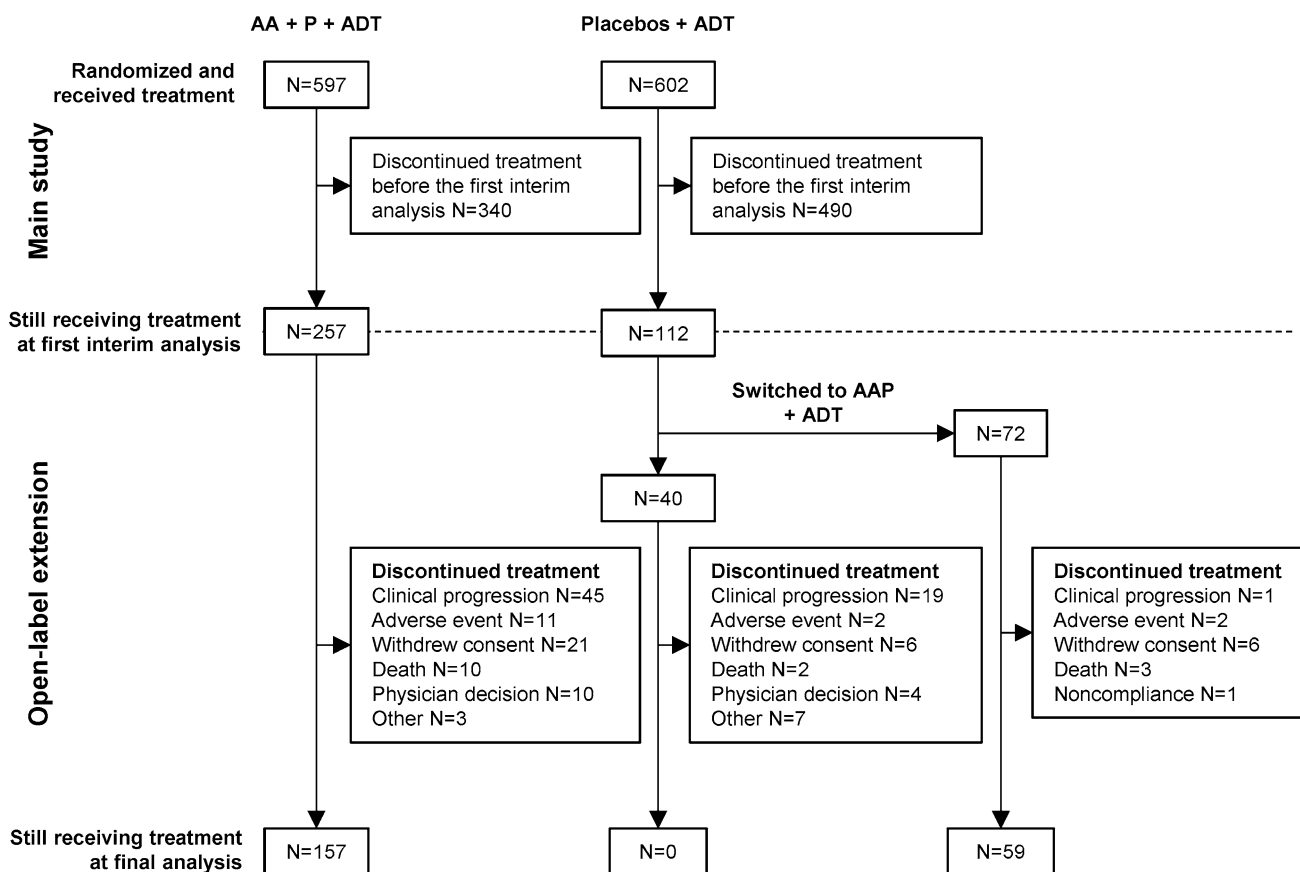
In the final analysis, after a median follow-up of 51.8 months, OS was longer in the AA + P + ADT arm than in the placebos + ADT arm [median, 53.3 months (95% CI 48.2–not reached) vs. 36.5 months (95% CI 33.5–40.0); HR = 0.66 (95% CI 0.56–0.78)] [16]. Because the placebo arm may have gained survival time attributed to AA + P during the open-label extension, the clinical benefit associated with AA + P may have been underestimated. Adjusting OS benefits for treatment switching is common in oncology [17], and a variety of methods are available [18, 19]. Here, we conducted a post hoc analysis to estimate the true OS benefit of AA + P + ADT by applying statistical adjustments to the final results.

## 2 Methods

### 2.1 Study Design

This was a post hoc analysis examining OS following adjustment for treatment switching in patients enrolled in the LATITUDE study (NCT01715285) [8]. The LATITUDE study was conducted at 235 sites in 34 countries in Europe, the Asia–Pacific region, Latin America, and Canada. Patients  $\geq 18$  years of age with high-risk, newly diagnosed mCSPC ( $\leq 3$  months before randomization) and an Eastern Cooperative Oncology Group performance status score of 0–2 were included. Diagnosis of mCSPC had to be demonstrated by a positive bone scan or metastatic lesions at the time of diagnosis on computed tomography or magnetic resonance imaging according to RECIST, version 1.1. Patients were considered at high risk if they had at least two of the following factors associated with poor prognosis: Gleason score  $\geq 8$ ,  $\geq 3$  bone lesions, and presence of measurable visceral metastasis. Patients were randomized in a 1:1 ratio to receive AA (1000 mg once daily as four 250-mg tablets) and P (5 mg once daily) or placebos in addition to ADT. The trial was conducted according to the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent before participating in the trial.

An initial interim analysis was performed after observing 50% of the total number of required death events for the final



**Fig. 1** Disposition. Patients were randomized in a 1:1 ratio to receive AA + P + ADT or placebos + ADT. Because of a positive result at the first interim analysis, patients had the opportunity to enroll in an open-label extension phase in which they received AA + P + ADT for up to 3 years. Patients who had previously received placebos could

switch to the AA + P arm if they met the entry eligibility requirements for hepatic function and cardiovascular disease before starting AA + P. “Deaths” refers to discontinuation of treatment due to death only. AA abiraterone acetate, ADT androgen-deprivation therapy, P prednisone

analysis. Because of a positive result at the first interim analysis, as determined by an independent data and safety monitoring committee, patients remaining in the placebos arm at the time of unblinding were eligible to switch to the active drug (AA + P) in an open-label extension phase for up to 3 years.

### 2.2 Statistical Analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) in the intent-to-treat population, which included all randomized patients. The endpoint in this post hoc analysis was OS, a co-primary endpoint in the LATITUDE trial. OS was defined as the time from randomization to death from any cause. Survival distribution and median OS were estimated by Kaplan–Meier analysis. HRs and associated 95% CIs were estimated using an unstratified Cox proportional hazards model. Rank preserving structure failure time modeling (RPSFTM) [20] and inverse probability of censoring weights (IPCW) [21] were used to adjust survival estimates for treatment switching from the placebos

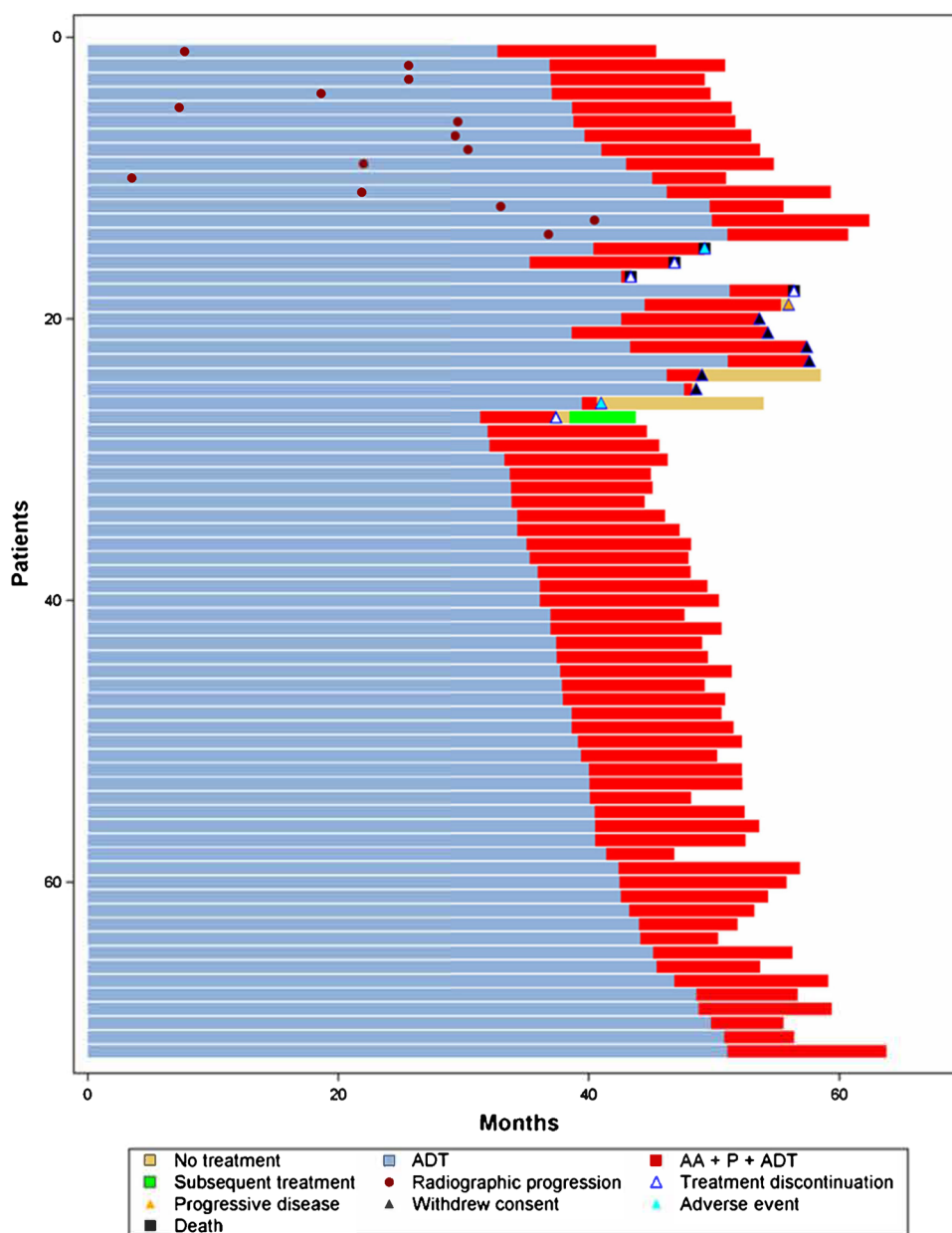
to AA + P. The cut-off for statistical significance was a *P* value < 0.05. Details of RPSFTM and IPCW development and conduct are provided in the Supplemental Methods.

### 3 Results

The LATITUDE study included 1,199 patients, of whom 597 were randomized to AA + P + ADT and 602 to placebos + ADT [8]. The first interim analysis of OS was performed when 406 deaths had occurred (31 October 2016) with a median follow-up time of 30.4 months [8]. The final analysis of OS was performed on 15 August 2018, with a median follow-up of 51.8 months [16].

Baseline characteristics, patient disposition, and reasons for discontinuation for the LATITUDE trial were previously published [8, 16]. Briefly, at the first interim analysis, treatment was ongoing for 257 of 597 (43.0%) patients in the AA + P + ADT arm and 112 of 602 (18.6%) patients in the placebos + ADT arm (Fig. 1). Of the 112 patients still receiving

**Fig. 2** Treatment timeline of patients who switched from placebo + ADT to AA + P + ADT. Clinical progression was defined as deterioration of ECOG performance status to grade 3 or higher or need to initiate any of the following because of tumor progression (even in the absence of radiographic evidence of disease): anticancer therapy for prostate cancer; radiation therapy or surgical interventions for complications due to tumor progression; or cancer pain requiring immediate administration of chronic opioid analgesics. If a patient had radiographic progression (without clinical progression) and alternate therapy was not initiated, treatment could continue at the discretion of the investigator. “Death” refers to discontinuation of treatment due to death only. Radiographic progression was defined as detection of soft tissue lesions by computed tomography/magnetic resonance imaging per RECIST 1.1 or by bone lesion progression on bone scans per modified Prostate Cancer Working Group 2 criteria. AA abiraterone acetate, ADT androgen deprivation therapy, ECOG Eastern Cooperative Oncology Group, P prednisone



placebos + ADT, 72 switched over to the AA + P + ADT during the open-label extension after a median of 40.07 months (interquartile range 36.98–44.34). Between the first interim analysis and the final analysis, 13 of the 72 patients who switched from placebo + ADT discontinued AA + P + ADT, and the remaining 59 were still receiving AA + P + ADT at the time of the final analysis (Fig. 2). The median for time from switching to death or end of the trial was 11.78 months (interquartile range 9.85–13.71). The 40 patients who did not switch to AA + P + ADT remained on placebo + ADT. Of these 40, none were still receiving treatment at the end of the study. In all groups, the main reason for discontinuation was clinical progression.

Patients who switched from the placebo + ADT arm to the AA + P + ADT arm resided in all regions and were in all age groups (Table 1). Eastern Cooperative Oncology Group performance status, total Gleason scores, serum prostate-specific antigen, lactate dehydrogenase, and presence of visceral disease were similar between switchers, non-switchers, and patients originally randomized to the AA + P + ADT arm. Pain scores and numbers of bone lesions, however, were lower in switchers than non-switchers and patients in the AA + P + ADT arm.

In the final unadjusted intent-to-treat analysis, the median OS was 53.3 months (95% CI 48.2–not reached) in the AA + P + ADT arm and 36.5 months (95% CI 33.5–40.0) in the placebo + ADT arm (Fig. 3). This corresponded to a 34%

**Table 1** Patient characteristics

Characteristics	AA + P + ADT	Placebos + ADT	
	Did not switch	Did not switch	Switched to AA + P + ADT
	<i>N</i> = 597	<i>N</i> = 530	<i>N</i> = 72
Age (years), mean (SD)	67.3 (8.48)	66.8 (8.69)	67.2 (8.96)
Age category (years), <i>n</i> (%)			
< 65	221 (37.0)	209 (39.4)	24 (33.3)
65–69	112 (18.8)	113 (21.3)	21 (29.2)
70–74	141 (23.6)	105 (19.8)	10 (13.9)
≥ 75	123 (20.6)	103 (19.4)	17 (23.6)
ECOG performance status at baseline, <i>n</i> (%)			
0 or 1	573 (96.0)	515 (97.2)	71 (98.6)
2	24 (4.0)	15 (2.8)	1 (1.4)
Region, <i>n</i> (%)			
Asia	124 (20.8)	103 (19.4)	18 (25.0)
Eastern Europe	214 (35.8)	192 (36.2)	25 (34.7)
Rest of world	104 (17.4)	84 (15.8)	18 (25.0)
Western Europe	155 (26.0)	151 (28.5)	11 (15.3)
Total Gleason score, mean (SD)	8.6 (0.68)	8.6 (0.67)	8.4 (0.6)
Gleason score category, <i>n</i> (%)			
< 8	13 (2.2)	15 (2.8)	1 (1.4)
≥ 8	584 (97.8)	515 (97.2)	71 (98.6)
Presence of visceral disease, <i>n</i> (%)			
Yes	114 (19.1)	103 (19.4)	11 (15.3)
No	483 (80.9)	427 (80.6)	61 (84.7)
Baseline pain score category, <i>n</i> (%) <sup>a</sup>			
0–1	284 (49.7)	247 (48.1)	41 (60.3)
2–3	125 (21.9)	120 (23.4)	18 (26.5)
≥ 4	163 (28.5)	146 (28.5)	9 (13.2)
Bone lesions at baseline, <i>n</i> (%)			
≤ 10	211 (35.3)	180 (34.0)	41 (56.9)
> 10	386 (64.7)	350 (66.0)	31 (43.1)
Log baseline serum PSA (ng/mL), mean (SD)	3.3 (2.33)	3.2 (2.18)	3.1 (2.33)
Log baseline lactate dehydrogenase (U/L), mean (SD)	5.2 (0.3)	5.2 (0.3)	5.1 (0.17)
Log baseline hemoglobin (g/L), mean (SD)	4.9 (0.14)	4.9 (0.14)	4.9 (0.11)

For some characteristics, the total number of patients was less than *N* due to missing values

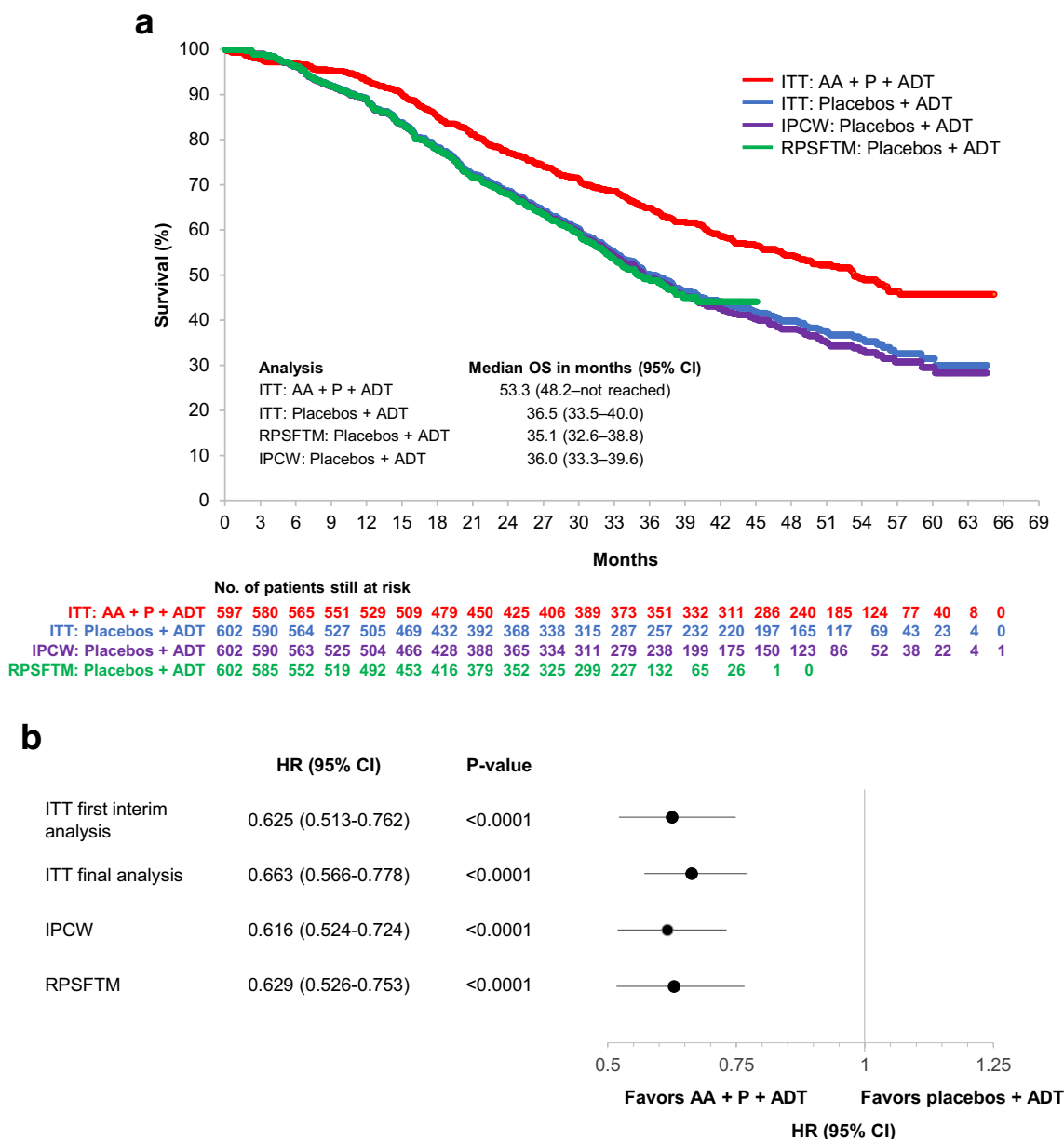
AA abiraterone acetate, ADT androgen-deprivation therapy, ECOG Eastern Cooperative Oncology Group, P prednisone, PSA prostate-specific antigen, SD standard deviation

<sup>a</sup>Two patients in each trial arm with missing values at the first interim analysis have updated values at the second interim analysis

lower risk of death in the AA + P + ADT arm than in the placebo + ADT arm [HR = 0.663 (95% CI 0.566–0.778)]. When adjusted by RPSFTM, the median OS in the placebo + ADT arm was 35.1 months (95% CI 32.6–38.8), corresponding to a 38% lower risk of death in the AA + P + ADT arm than in the placebo + ADT arm (HR = 0.616 (95% CI, 0.524–0.724)). When adjusted by IPCW, the median OS was 36.0 months (95% CI 33.3–39.6) in the placebo + ADT arm, corresponding to a 37% lower risk of death in the AA + P + ADT arm than in the placebo + ADT arm [HR = 0.629 (95% CI 0.526–0.753)].

## 4 Discussion

The final analysis of LATITUDE indicated a significant OS benefit from adding AA + P to ADT in men with newly diagnosed mCSPC [16]. The current post hoc analysis confirmed the significant benefit of adding AA + P to ADT after adjustment for bias introduced by switching from placebo to AA + P during the open-label extension.



**Fig. 3** Kaplan-Meier curves for overall survival. **a** Survival distribution and median overall survival were estimated by Kaplan–Meier analysis. **b** HRs and associated 95% CIs were estimated using an unstratified Cox proportional hazards model. AA abiraterone acetate,

ADT androgen-deprivation therapy, CI confidence interval, HR hazard ratio, IPCW inverse probability of censoring weights, ITT intent to treat, OS overall survival, P prednisone, RPSFTM rank preserving structure failure time model

Adjusting for treatment switching is necessary to assess the real benefit of new drugs, especially in oncology [17]. For example, when patients switch from placebo to an active therapy, as in this study, the true OS benefit may be underestimated. Several methods can be used to adjust for bias due to treatment switching [18, 19]. In the current analysis, we employed RPSFTM and IPCW, which have been used to adjust for treatment switching in clinical trials of antineoplastic agents [22–25]. IPCW works by censoring patients when they switch from placebo to experimental treatment

and then, to adjust for any differences in characteristics from the original study population, up-weighting any patients who did not switch and who had similar characteristics as the patients who switched [21]. For this to be valid, all prognostic covariates must be taken into account, which is referred to as the “no unmeasured confounders” assumption. Although we took a wide range of confounders into account in the current analysis, it is not possible to be certain that there were no unmeasured confounders. RPSFTM, in contrast, attempts to estimate the “counterfactual” survival



times that would have been observed had treatment switching not occurred [22]. The main assumption for RPSFTM is that there is a “common treatment effect” [20]. For this study, that means that the benefit of AA + P was assumed to be similar for patients in the placebo arm who later switched to AA + P as for patients who received AA + P starting from baseline. The common treatment effect may be a reasonable approximation here because adding AA + P to ADT should have had a similar effect in patients randomized to AA + P + ADT at the beginning of the trial as in patients whose disease had not progressed while receiving placebo + ADT and who switched to AA + P + ADT. Although it is possible that patients who switched from placebo benefited more from AA + P because they had a better response to ADT alone, it is also possible that they had a worse outcome because of receiving AA + P later in the course of the disease [26]. In any case, the effect of adjustment was small and similar to that obtained using IPCW. Finally, because all patients eligible to switch did so, we could not apply the two-stage method, another common method for adjusting for switching. We also did not use iterative parameter estimation because it is a minor variation of RPSFTM and was not expected to provide significant additional information.

Although adjustment methods may provide estimates that are less biased than intent-to-treat analysis, they can be less precise, and the underlying assumptions may be difficult to verify [18, 19]. However, the adjusted OS benefits were close to the OS benefits determined at the first interim analysis before treatment switching occurred. Overall, the adjustment had little impact because relatively few patients switched from placebo to AA + P and because exposure to AA + P was short.

In conclusion, this post hoc analysis confirmed that adding AA + P to ADT in patients with newly diagnosed high-risk mCSPC reduces the risk of death by 37–38% and provides 17–18 months of additional survival. The combination of AA + P and ADT adds to the options available to these patients who would otherwise survive for only around 3 years with ADT alone.

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**Author Contributions** All authors helped interpret results, helped write or edit the manuscript, and approved the final version. N.J. Perualila, J. Diels, and T. Ito also helped conceive and design the study, and N.J. Perualila performed the analyses.

## Compliance with Ethical Standards

**Funding** This study was funded by Janssen Pharmaceutica NV.

**Conflicts of interest** S Feyerabend has nothing to disclose. F. Saad reports grants, personal fees, and non-financial support from Janssen

and Sanofi related to the conduct of the study, and grants, personal fees, and non-financial support from Astellas and Bayer unrelated to the submitted work. N.J. Perualila, S. Van Sanden, J. Diels, T. Ito, and P. De Porre are employees of Janssen. S. Van Sanden, T. Ito, and P. De Porre are shareholders of Janssen’s parent company, Johnson & Johnson. K. Fizazi reports financial support for participation in advisory boards for Amgen, AstraZeneca, Astellas, Bayer, Janssen, Sanofi, Orion, and CureVac.

**Research involving human participants and/or animals** All procedures performed in studies involving human participants were in accordance with the ethical standards of the local Institutional Review Boards for each site and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the LATITUDE study (ClinicalTrials.gov identifier NCT01715285).

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