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Adjusting for abiraterone-prednisone cross-over in *de novo* metastatic castration-sensitive prostate cancer: a post-hoc analysis of the PEACE-1 trial

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ABSTRACT

Introduction: PEACE-1 is a 2×2 factorial phase III trial evaluating the impact of abiraterone-prednisone and prostate radiotherapy in patients with *de novo* metastatic castration-sensitive prostate cancer (mCSPC). Abiraterone-prednisone significantly improved overall survival (OS) (hazard ratio (HR)= 0.82 [95 %CI, 0.69–0.98]). In the control arm, men often received an androgen receptor pathway inhibitor (ARPI) – either abiraterone-prednisone or enzalutamide – after progression to castration-resistant disease. The use of active drug beyond progression may improve post-progression survival and thereby attenuate the estimated benefit of early use of this drug in intention-to-treat analyses.

Methods: This post-hoc analysis applied three statistical methods to estimate an adjusted HR accounting for abiraterone-prednisone use beyond progression: Two-Stage Estimation (TSE), Inverse Probability of Censoring Weighting (IPCW) and Rank-Preserving Structural Failure Time Models (RPSFTM).

Results: Among 589 patients randomised to the control arm, 183 received abiraterone-prednisone after disease progression. Compared with patients who did not, these men had higher PSA at diagnosis, higher tumour burden, more bone metastases, and were more likely to have received docetaxel for mCSPC. Experiencing biochemical progression was found to be a risk factor for 2nd line abiraterone use. The HR for OS adjusted by RPSFTM, IPCW, and TSE were 0.79 [0.64–0.98], 0.75 [0.62–0.92], and 0.82 [0.67–0.98], respectively. Sensitivity analyses adjusting for ARPI cross-over (abiraterone-prednisone or enzalutamide) yielded consistent results.

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Conclusions: This analysis confirms the survival benefit related to upfront abiraterone-prednisone use for patients with *de novo* mCSPC.

1. Introduction

Prostate cancer is one of the leading cancers in men worldwide, representing 470,000 cases in Europe [1], and men diagnosed with *de novo* metastatic disease have a worse prognosis. Over the last decade, the standard of care (SOC) has evolved substantially with the intensification of androgen deprivation therapy (ADT) by adding docetaxel, a second-generation androgen receptor pathway inhibitor (ARPI) – namely, abiraterone-prednisone, apalutamide, darolutamide, or enzalutamide – or both [2]. PEACE-1 is a 2×2 international randomised controlled trial that assessed the addition of abiraterone-prednisone and that of prostate radiotherapy to SOC in patients with *de novo* metastatic castration-sensitive prostate cancer (mCSPC) [3,4]. During the course of the trial, the SOC evolved from ADT alone to ADT plus docetaxel in fit men able to tolerate chemotherapy. Overall, 1173 patients participated in the trial and overall survival (OS) was significantly improved by abiraterone-prednisone (hazard ratio (HR) = 0.82; 95.1 % confidence interval (CI), 0.69–0.98), with a median follow-up of 4.4 years. The size of the OS effect was smaller than in similar studies also testing abiraterone-prednisone in mCSPC (LATITUDE: HR = 0.66; 95 % CI, 0.56–0.78 [5]); STAMPEDE: HR = 0.61; 95 % CI, 0.49–0.75 [6]), while the effect on radiographic progression-free survival (rPFS) was of similar magnitude across trials: HR = 0.54 (95 % CI, 0.41–0.71) in PEACE-1, HR = 0.47 (95 % CI, 0.39–0.55) in LATITUDE, and HR = 0.40 (95 % CI, 0.34–0.47) in STAMPEDE. In all three trials, patients randomised to the control arm could receive an ARPI, if available, after disease progression: this occurred in 48.4 % in PEACE-1, in 27.5 % in LATITUDE, and 48.2 % in STAMPEDE. The experimental treatment cross-over, also called switch, is a well-known issue in oncology trials, which can negatively impact the apparent magnitude of an OS benefit [7]. In LATITUDE, 8.8 % patients in the control arm switched to abiraterone; in STAMPEDE, 22 % of patients in the control arm with progression switched to abiraterone; and in PEACE-1, 31 % of control-arm patients switched to abiraterone as a second-line treatment. At the time the PEACE-1 trial was conducted, both abiraterone-prednisone and enzalutamide had shown survival benefit and were part of the SOC for metastatic castration-resistant prostate cancer (mCRPC). As an example from another setting, the BREAK-3 trial in metastatic melanoma showed a non-significant OS benefit for dabrafenib (HR = 0.76, 95 % CI 0.48–1.21). In the UK, the National Institute for Health and Care Excellence (NICE) ordered supplementary analysis to grant reimbursement. Thus, the effect of dabrafenib on OS was re-estimated with an HR of 0.50–0.55 after adjusting for the 57 % cross-over rate [8] and the therapy was subsequently approved. Simple methods such as per-protocol analysis (i.e. censoring the data at the time of cross-over) can be used to take into consideration the cross-over. However, they may be prone to bias, because treatment cross-over can be related to prognosis. More advanced statistical methods – including Inverse Probability of Censoring Weighting (IPCW), Rank-Preserving Structural Failure Time Models (RPSFTM), and Two-Stage Estimation (TSE) – are recommended to adjust for treatment cross-over [9]. These methods rely on counterfactual survival times (i.e. survival times that would have been observed in the absence of cross-over). Here we conducted a post-hoc analysis of PEACE-1 to estimate the OS benefit of abiraterone-prednisone plus SOC using these methods.

2. Methods

2.1. PEACE-1 design

The PEACE-1 trial (NCT01957436) design has been described elsewhere [3]. PEACE-1 is an open-label, randomised, controlled, phase III study, with a factorial design, conducted in seven countries in Western Europe. Patients aged ≥ 18 years with *de novo* metastatic prostate adenocarcinoma (documented by bone scan, CT, or MRI) and Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 (or 2 due to bone pain) were eligible. Eligible patients were randomly assigned in a 1:1:1:1 ratio to: SOC, SOC plus abiraterone-prednisone, SOC plus radiotherapy, or SOC plus radiotherapy plus abiraterone-prednisone. Randomisation used a minimisation algorithm and was stratified by study site, ECOG performance status (0 vs 1–2), type of ADT, planned administration of docetaxel, and disease extent. ADT was continuously maintained; docetaxel consisted of six cycles at a dose of 75mg/m^2, abiraterone was given at 1000 mg once daily plus prednisone 5 mg orally twice daily; and radiotherapy consisted of 74 Gy in 37 fractions. The French Independent Ethics Committee (*Comité de Protection des Personnes Ile de France VII*) approved the initial protocol and subsequent amendments. The study complied with the ethical principles of the Declaration of Helsinki and was approved by institutional Review Boards at each participating site.

2.2. Statistical analysis

The primary endpoint for this post-hoc analysis was OS, defined as the time from randomisation to death from any cause. Patients without a recorded death were censored at the date of their last follow-up. The population of interest was the intention-to-treat population. Survival distribution and median OS were estimated using the Kaplan–Meier method. HRs were estimated using multivariable Cox proportional hazards models. The final outcome model was adjusted for log(PSA), log (haemoglobin), age, country, Gleason score, number of bone metastases, disease extent (lymph nodes only, bone metastases, or visceral metastases)) and docetaxel treatment. The proportional hazards assumption was assessed graphically using Schoenfeld residuals, and the log-linearity assumption was evaluated graphically using Martingale residuals. We followed the reporting guidelines for adjusting survival analyses for treatment cross-over in oncology trials proposed by Sullivan et al. [9]. To account for the effect of treatment switching, HRs were estimated using three methods. A summary of the methods is provided in Table 1, with details below. A comprehensive overview of the methods is available in the Supplementary Methods.

2.2.1. Two-stage estimation

TSE is a recent method for handling treatment cross-over [10]. Here, we defined biological progression as the new baseline. The effect of switching was modelled as a time-dependent variable using a Weibull accelerated failure time (AFT) model, adjusted for log(PSA), log(haemoglobin), age, country, Gleason score, number of bone metastases, disease extent and docetaxel treatment. The inverse of the acceleration factor was used to calculate counterfactual survival times. 95 % CIs were estimated via bootstrapping. Sensitivity analyses were performed with and without re-censoring.

2.2.2. Rank-preserving structural failure time model (RPSFTM)

RPSFTM is an intra-subject adjustment [11], using a g-estimation to estimate the treatment switching effect. This estimation was

Table 1
Description and assumptions of statistical methods.

Method	Description	Assumption
Two-stage estimation (TSE)	Treatment's effect ψ is defined as the Acceleration Factor of switch in an Accelerated Failure Time Model modeling post progression survival. Counterfactual survival is calculated in control arm with the time after switch multiplied by exp (-ψ).	**No unmeasured confounders:** all potential baseline and time-dependent confounders covariates to be included. A confounder is a variable associated with both prognosis and switch of treatment.
Rank PreservingStructural Failure TimeModel (RPSFTM)	Treatment's effect ψ is estimated by g-estimation. Counterfactual survival is calculated in control arm with survival after switch multiplied by exp (ψ).	**Perfect randomization assumption:** two arms are comparable at baseline.**Common treatment effect assumption:** experimental treatment effect is the same regardless of the timing of initiation
Inverse Probability of Censoring Weights (IPCW)	Patients who switched are censored at the time they switched. Patients who didn't switch are weighted by the inverse of the probability of remaining uncensored. Treatment effect is estimated with a weighted Cox proportional hazards model.	**No unmeasured confounders:** all potential baseline and time-dependent confounders covariates to be included. A confounder is a variable associated with both prognosis and switch of treatment.

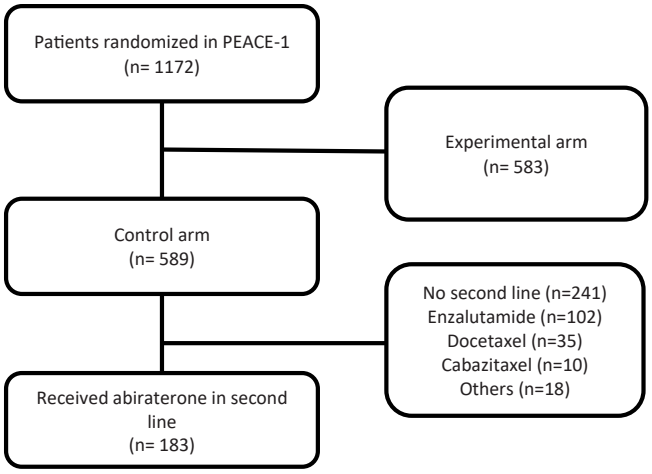

Fig. 1. Flow Chart.

subsequently used to calculate counterfactual survival times [12]. G-estimation was performed with a Cox model adjusted for log(PSA), log (haemoglobin), age, country, Gleason score, number of bone metastases, disease extent and docetaxel treatment. 95 % CI were estimated via bootstrapping. Sensitivity analyses were performed to evaluate the impact of re-censoring (presence or absence), the choice of test for g-estimation (Cox, log-rank, or Weibull), and the validity of common treatment effect assumption through weighted analysis.

2.2.3. *Inverse probability of censoring weighting*

IPCW is an inter-subject adjustment method [11] in which patients who switch treatments are censored at the time of switch and patients who did not switch are weighted by the inverse probability of remaining on the allocated treatment (i.e. the treatment assigned at randomization) [13]. Stabilised weights were computed using a Cox model adjusted for log(PSA), log(haemoglobin), age, country, Gleason score, number of bone metastases, disease extent, docetaxel treatment, time-dependent severe adverse events, time-dependent ECOG status, time-dependent mean score of the Brief Pain Inventory (BPI), and the time-dependent score of the Functional Assessment of Cancer Therapy-Prostate (FACT-P). Sensitivity analyses assessed the impact of truncating weights and the inclusion or exclusion of biological progression in the censoring model.

Additional sensitivity analyses were conducted on the definition of cross-over: abiraterone-prednisone in second line vs ARPI (abiraterone-prednisone or enzalutamide) in second line. Another sensitivity analysis used a stepwise multivariable procedure to identify factor associated with a higher probability of cross-over. This stepwise procedure, selecting variables at randomization, was bi-directional and selected models by Akaike information criterion. Statistical significance was set at P-value < 0.05. Statistical analyses were performed using R software

Table 2
Patients characteristics in the control arm, at baseline.

		No cross-over to abirateroneN = 406	**Cross-over to abirateroneN = 183**
Age	Min / Max	43.0 / 87.0	44.0 / 84.0
	Med [IQR]	66.5 [60.0;71.0]	66.0 [59.0;72.0]
	Mean (std)	65.9 (8.2)	65.3 (8.7)
ECOG	0	284 (69.9 %)	128 (69.9 %)
	1	118 (29.1 %)	54 (29.5 %)
	2	4 (0.99 %)	1 (0.55 %)
Gleason	< 8	94 (23.6 %)	39 (22.2 %)
	≥ 8	304 (76.4 %)	137 (77.8 %)
	Missing	8	7
PSA	Min / Max	0.1 / 1752.0	0.2 / 2942.0
	Med [IQR]	9.4 [2.6;43.7]	17.6 [3.9;67.0]
	Mean (std)	76.3 (196.4)	103.5 (294.0)
	Missing	4	0
Country	BELGIUM	15 (3.7 %)	10 (5.5 %)
	FRANCE	314 (77.3 %)	148 (80.9 %)
	IRELAND	22 (5.4 %)	8 (4.4 %)
	ITALY	2 (0.49 %)	1 (0.55 %)
	ROMANIA	4 (0.99 %)	1 (0.55 %)
	SPAIN	44 (10.8 %)	12 (6.7 %)
	SWITZERLAND	5 (1.2 %)	3 (1.7 %)
High tumour burden	No	186 (45.8 %)	67 (36.6 %)
	Yes	220 (54.2 %)	116 (63.4 %)
Disease extension	Lymph node only	37 (9.1 %)	15 (8.2 %)
	Bone metastasis	327 (80.5 %)	148 (80.9 %)
	Visceral metastasis	42 (10.3 %)	20 (10.9 %)
Number of bone metastases	Min / Max	0 / 111.0	0 / 40.0
	Med [IQR]	4.0 [2.0;11.0]	7.0 [3.0;11.0]
	Mean (std)	7.2 (10.7)	7.9 (6.3)
	Missing	22	12
Diabetes	No	327 (85.8 %)	149 (85.1 %)
	Yes	54 (14.2 %)	26 (14.9 %)
	Missing	25	8
High blood pressure	No	218 (56.6 %)	103 (58.2 %)
	Yes	167 (43.4 %)	74 (41.8 %)
	Missing	21	6
Radiation therapy	No	195 (48.0 %)	101 (55.2 %)
	Yes	211 (52.0 %)	82 (44.8 %)
Docetaxel	No	179 (44.3 %)	59 (32.2 %)
	Yes	225 (55.7 %)	124 (67.8 %)
	Missing	2	0
Denosumab	No	203 (96.7 %)	181 (98.9 %)
	Yes	7 (3.3 %)	2 (1.1 %)
	Missing	196	0
Radiological progression	No	172 (42.4 %)	39 (21.3 %)
	Yes	234 (57.6 %)	144 (78.7 %)
Biological progression	No	164 (40.4 %)	11 (6 %)
	Yes	242 (59.6 %)	172 (94 %)

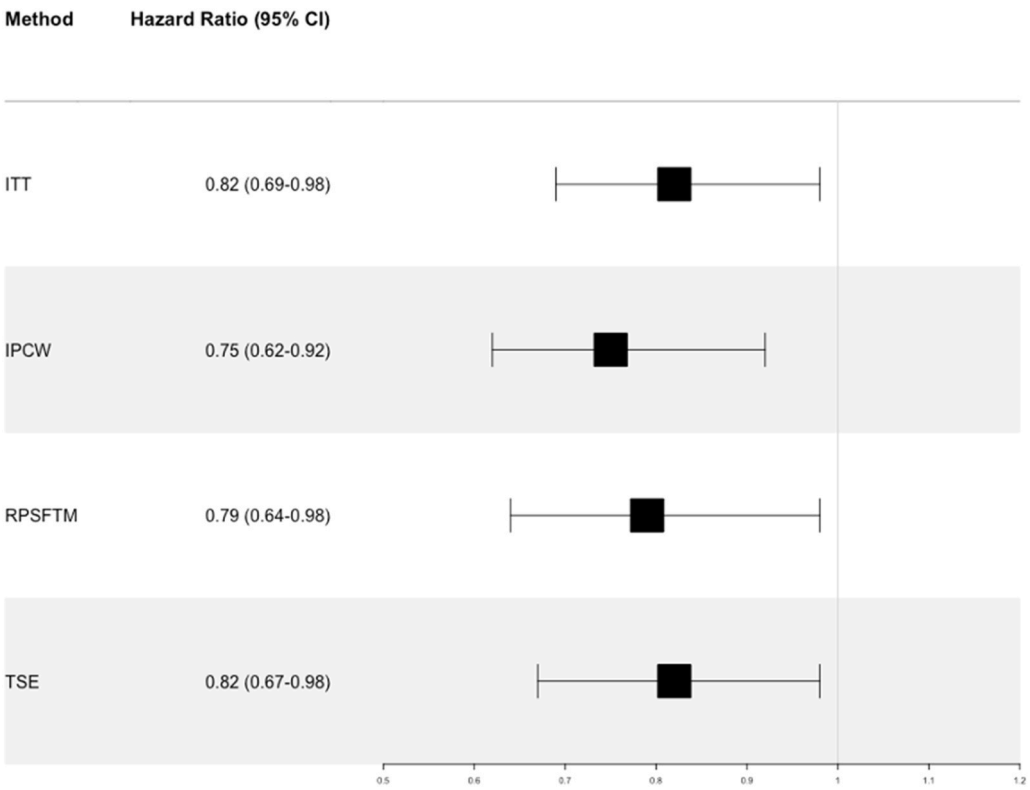

Fig. 2. Hazard Ratios adjusted on abiraterone-prednisone cross-over. ITT: intention to treat; IPCW: Inverse probability of censoring weighting; RPSFTM: rank preserving structural failure time model; TSE: Two-stage estimation.

(version 4.1.1).

3. Results

3.1. Population

Of the 1172 patients included in the PEACE-1 study, 583 were randomised to the abiraterone arm. In the overall population, the final ITT analysis performed after a median follow-up of 4.4 years, found a HR of 0.82 (95.1 % CI, 0.69–0.98) for OS in favour of the addition of abiraterone. Of the 589 patients randomised to the control arm, 285 received second-line ARPI (Figure S1), including 183 who switched to abiraterone (Fig. 1).

3.2. Analysis adjusted for abiraterone-prednisone switch

Baseline characteristics of patients in the control arm are detailed in Table 2. Patients who switched to abiraterone-prednisone tended to have higher PSA levels at diagnosis, higher tumour burden, higher number of bone metastases, received docetaxel more frequently in the first line, and harbored more disease progression. In stepwise multivariable analysis, biological progression (OR=3.18 [95 % CI, 1.18–6.57]) and docetaxel in first line (OR=1.77 [95 % CI, 1.19–2.64]) were associated with switching. The median OS was 4.27 years (95 % CI, 4.40-not reached) in the cross-over group and 5.16 years (95 % CI, 4.00–5.19) in the no-cross-over group. The median time to cross-over to abiraterone-prednisone was 1.38 years (95 % CI, 1.26–1.56). The HRs for OS adjusted by RPSFTM, IPCW, and TSE were 0.79 (95 % CI, 0.64–0.98), 0.75 (95 % CI, 0.62–0.92) and 0.82 (95 % CI, 0.67–0.98), respectively. The estimates were consistent in all sensitivity analyses for RPSFTM, TSE, and IPCW, except for the one including the variable "biological progression" in the IPCW model, which improved the HR to 0.65 [95 %CI, 0.53–0.77]. All HR estimates are detailed in Fig. 2 and Figure S2, and adjusted survival curves are presented in Fig. 3. In another sensitivity analysis, inclusion of radiotherapy in models did not change the results, with HR for RPSFTM, IPCW, and TSE of 0.80 [0.64–0.98], 0.76 [0.62–0.92] and 0.82 [0.67–0.98], respectively.

3.3. Analysis adjusted for abiraterone-prednisone + enzalutamide switch

Baseline characteristics of patients in the control arm are detailed in Table S1. The HRs for OS adjusted by RPSFTM, IPCW, and TSE were 0.78 (95 %CI, 0.61–1.00), 0.77 (95 %CI, 0.63–0.95), and 0.83 (95 %CI, 0.66–1.01), respectively. The estimates were also consistent in sensitivity analyses for RPSFTM, TSE and IPCW except when biological progression was included in the IPCW model, which improved the HR to 0.62 (95 %CI, 0.50–0.77). All HR estimates are detailed in Figure S3 and adjusted survival curves are presented in Figure S4. Overall, this sensitivity analysis was consistent with our main analysis, which focused on the switch to abiraterone-prednisone alone.

4. Discussion

PEACE-1 was the first trial to demonstrate the benefit (both in rPFS and OS) of adding abiraterone-prednisone to ADT-docetaxel in mCSPC [3]. The trial also showed that early prostate radiotherapy does not improve survival in patients with upfront mCSPC treated with modern intensified systemic treatment, although it efficiently prevents the onset of symptomatic local CRPC progression requiring intervention, regardless of metastatic burden [4]. Finally, it further confirmed data from LATITUDE and STAMPEDE regarding the benefit of abiraterone-prednisone in mCSPC, irrespective of the standard of care [5]. This post-hoc analysis confirmed this benefit after adjusting for abiraterone-prednisone cross-over and after adjusting for abiraterone-prednisone or enzalutamide cross-over.

The IPCW method gives greater weight to patients who do not cross-over but have similar characteristics than those who cross-over [13], and requires the no-unmeasured confounder (NUC) assumption, from

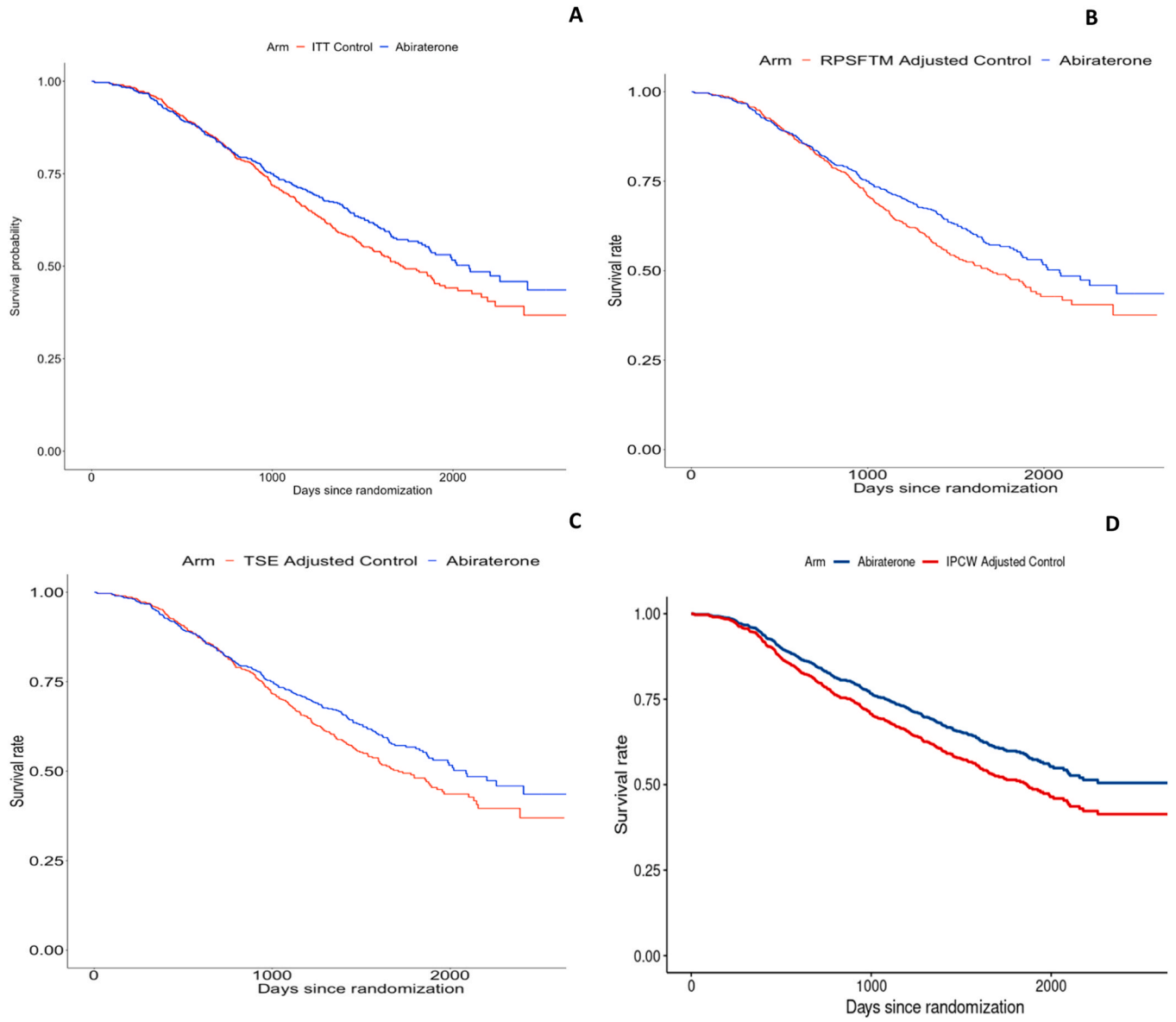

Fig. 3. Adjusted Kaplan-Meier survival curves. A: Intention to treat; B: Rank preserving structural failure time model; C: two-stage estimation; D: inverse probability of censoring weighting.

baseline to cross-over. We considered various confounding factors, including time-dependent quality of life, but we cannot exclude the possibility that some confounders were not accounted for. One of the specificities of IPCW is the ability to adjust for time-dependent covariates, which could explain why the adjustment was slightly more impactful with this method. It is unclear whether including disease progression in the model is recommended or not. In our analysis, this had a clear impact on estimates, but progression closely relates to both survival and treatment switch, thus it might not be recommended to include it in the model. The same NUC assumption applies to two-stage estimation. RPSFTM is valid under the assumptions of correct randomization and a common treatment effect (CTE). The CTE assumption implies that abiraterone-prednisone's effect is the same when used in mCSPC and mCRPC settings. Our sensitivity analyses did not show major changes in the treatment effect estimates, but this CTE assumption is always debatable in oncology trials. Sensitivity analyses with recensoring produced consistent results, suggesting a low level of informative recensoring. In the LATITUDE trial, 72 patients switched to abiraterone/prednisone and the adjusted for crossover HR were 0.63 [0.53–0.75] with RPSFTM and 0.61 [0.52–0.72] with IPCW, whereas it was 0.66 [0.57–0.78] in the unadjusted intent-to-treat analysis [14]. As in our analysis, in the post of analysis of the LATITUDE trial, all the confidence intervals of various methods overlap. Another post hoc analysis of the LATITUDE trial used IPCW to adjust for patients in the placebo group who switch to any life-extending subsequent therapies and found a HR of 0.73 [0.60–0.89] [15]. As far as we know, no analysis adjusting for crossover is available for the STAMPEDE abiraterone/prednisone trial. In the ARANOTE trial [16], 42.5 % of patients from the standard treatment arm received a life-extending subsequent therapy, but no adjusted analysis is published yet.

In PEACE-1, 95 % of patients in the control arm who experienced cancer progression received at least one life-prolonging treatment beyond progression (an ARPI, taxanes, Radium-223, or Lu-PSMA) and 48.4 % of those who developed mCRPC subsequently received an ARPI [3]. This is in marked contrast with the LATITUDE phase III abiraterone-prednisone trial, where only 27.5 % of patients in the control arm with cancer progression received an ARPI for mCRPC, and similar to STAMPEDE where the rate was 48.2 % [5,6]. This difference may partly explain the discrepancy in survival magnitude across these three trials. Of note, the available methods are not designed to take into

account multiple sequential life-prolonging treatments, and this may partly explain the limited impact of the adjusted analysis in this study, because patients from the standard arm received more subsequent treatments than patients from the experimental arm (supplementary table S2). Moreover, many patients in PEACE-1 who did not cross-over simply did not experience progression, underscoring that patients who crossed-over had a worse prognosis.

In a randomized controlled trial, the experimental treatment cross-over, or switch, can attenuate the treatment effect estimated on OS between arms (contrary to PFS which is calculated before the event of cross-over). As the OS benefit of abiraterone in PEACE-1 was slightly lower than in other published trials, we hypothesized that treatment crossover could explain this discrepancy. However, our results do not match this hypothesis. Potential explanations are unmeasured confounding, especially after randomization such as impact of other life-prolonging therapies; or a difference in the PEACE-1 population compared to LATITUDE or STAMPEDE.

5. Conclusion

In men with *de novo* metastatic prostate cancer, abiraterone-prednisone is the new standard of care in combination with ADT and docetaxel, and the its survival benefit is confirmed even after adjusting for cross-over and subsequent ARPI treatment. This analysis, after adjusting for almost 50 % cross-over or subsequent ARPI treatment, reinforces the survival benefit associated with upfront abiraterone-prednisone use for *de novo* metastatic castration-sensitive prostate cancer. However, the dilution effect of cross-over or ARPI beyond progression appeared to be mild, likely owing to the intensified systemic therapy received in the control arm (ADT + docetaxel).

CRediT authorship contribution statement

Foulon Stephanie: Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Bertrand Tombal:** Writing – review & editing, Investigation. **Philippe Ronchin:** Writing – review & editing, Investigation. **Sophie Tartas:** Writing – review & editing, Investigation. **Xavier Maldonado:** Writing – review & editing, Investigation. **Xavier Muracciole:** Writing – review & editing, Investigation. **Stephane Supiot:** Writing – review & editing, Investigation. **Helene Ribault:** Project administration. **Ray McDermott:** Writing – review & editing, Investigation. **Karim Fizazi:** Writing – review & editing, Supervision, Investigation. **Aude Flechon:** Writing – review & editing, Investigation. **Jean-François Berdah:** Writing – review & editing, Investigation. **Adrien Rousseau:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Gabriel Kacso:** Writing – review & editing, Investigation. **Maryam Karimi:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Gwenaelle Gravis:** Writing – review & editing, Investigation. **Stefan Michiels:** Writing – review & editing, Methodology, Conceptualization. **Fabio Calabro:** Writing – review & editing, Investigation. **Guilhem Roubaud:** Writing – review & editing, Investigation. **Dominik Berthold:** Writing – review & editing, Investigation.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: AR: No competing interest. Received a public granted from Fonds d'Etudes et de Recherche du Corps Médical (FERCM). MK: No competing interest. SM: Did not declare competing interest. GR: Advisory Boards: Astellas, Astra Zeneca, Bayer, Pfizer; Consulting: AAA Novartis, Astra Zeneca, Janssen, Merck, Pfizer; Funding research Bayer; Travel expensesAAA Novartis, Astra Zeneca, Bayer, Janssen. XM: No competing interest. SS: Janssen: Research grants and advisory board member; Astellas: Research grants and advisory board member; Bayer: Research grants and advisory board member. RM: Did not declare competing interest. AF: Honorarium and travel expenses: Janssen, Astra Zeneca, AAA, Novartis, Pfizer Bayer, Astellas. BT: Paid advisor or consultant for Amgen, Astellas, AstraZeneca, Bayer, Janssen, Ferring, Myovant, Novartis, and Pfizer; Investigator for Astellas, Bayer, Janssen, Ferring, Myovant, Novartis, Pfizer. PR: No competing interest. DB: Did not declare competing interest. JFB: No competing interest. GK: No competing interest. GG: Did not declare competing interest. FC: Advisory boards: Pfizer, BMS, Ipsen, MSD, Astra Zeneca, Merck, Accord, Gilead, Novartis, AAA, J&J, Astellas; Consulting: Johnson & Johnson. ST: Did not declare competing interest. XM: No competing interest. HR: Did not declare competing interest. KF: Participation to advisory boards and talks for:cAmgen, Astellas, Astrazeneca, Bayer, Clovis, Daiichi Sankyo, Janssen, MSD, Novartis/AAA, Pfizer, Sanofi; Arvinas, CureVac, Macrogenics and Orion. SF: No competing interest

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Declaration

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.116024.

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