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Prior Endocrine Therapy Impact on Abiraterone Acetate Clinical Efficacy in Metastatic Castration-resistant Prostate Cancer: Post-hoc Analysis of Randomised Phase 3 Studies

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Abstract

Background—The duration of prior hormonal treatment can predict responses to subsequent therapy in patients with metastatic castration-resistant prostate cancer (mCRPC).

Objective—To determine if prior endocrine therapy duration is an indicator of abiraterone acetate (AA) sensitivity.

Design, setting, and participants—Post-hoc exploratory analysis of randomised phase 3 studies examining post-docetaxel (COU-AA-301) or chemotherapy-naïve mCRPC (COU-AA-302) patients receiving AA. The treatment effect on overall survival (OS), radiographic progression-free survival (rPFS), and prostate-specific antigen (PSA) response analysed by quartile duration of prior gonadotropin-releasing hormone agonists (GnRHa) or androgen receptor (AR) antagonist.

Intervention—Patients were randomised to AA (1000 mg, orally once daily) plus prednisone (5 mg, orally twice daily) or placebo plus prednisone. Prior endocrine therapy was GnRHa (COU-AA-301, *n* = 1127 [94%]; COU-AA-302, *n* = 1057 [97%], 45.1 mo or 36.7 mo median duration, respectively) and/or orchiectomy (COU-AA-301, *n* = 78 [7%] COU-AA-302, *n* = 44 [4%]); castrated patients received prior AR antagonists (COU-AA-301, *n* = 1015 [85%]; COU-AA-302, *n* = 1078 [99%], 15.7 mo or 16.1 mo median duration, respectively).

Outcome measurements and statistical analysis—Cox model was used to obtain hazard ratio and associated 95% confidence interval with statistical inference by log rank statistic.

Results and limitations—Clinical benefit with AA was observed for OS, rPFS, and PSA response for nearly all quartiles with GnRHa or AR antagonists in both COU-AA-301 and COU-AA-302. In COU-AA-301, patients with a longer duration of prior endocrine therapy tended to have greater AA OS, rPFS, and PSA response benefit, with lead-time chemotherapy bias potentially impacting COU-AA-301 results. Time-to-castration-resistance was not captured. This analysis is limited as a post-hoc exploratory analysis.

Conclusions—In the COU-AA-301 and COU-AA-302 studies, AA produced clinical benefits regardless of prior endocrine therapy duration in patients with mCRPC.

Patient summary—Metastatic castration-resistant prostate cancer patients derived clinical benefits with abiraterone acetate regardless of prior endocrine therapy duration.

Keywords

Abiraterone acetate; Androgen receptor antagonists; Gonadotropin-releasing hormone; Prednisone; Prostate cancer

1. Introduction

Most tumours in men who present with metastatic disease at prostate cancer diagnosis or with disease recurrence after potentially curative local therapy respond to androgen deprivation [1] with luteinising hormone—releasing hormone agonists or antagonists or bilateral orchiectomy, and to first-line androgen receptor antagonists such as bicalutamide [2–5]. In most cases, however, the response is not durable and virtually all tumours eventually progress to a lethal castration-resistant phenotype [1,5].

Abiraterone acetate, a prodrug of abiraterone that is a selective inhibitor of CYP17 [6,7], administered in combination with prednisone/prednisolone (hereafter referred to as abiraterone) is one of several agents indicated for the treatment of patients with metastatic castration-resistant prostate cancer [8–17]. Abiraterone significantly improved overall survival and all secondary and tumour-specific endpoints [9,10], as well as patient-reported fatigue [18] and quality of life [19] in the phase 3 COU-AA-301 trial in patients with metastatic castration-resistant prostate cancer progressing after docetaxel chemotherapy. A similar survival benefit was observed in the pre-chemotherapy COU-AA-302 study along with a significant improvement in radiographic-free survival, all secondary endpoints, and patient-reported outcomes [8,11,16].

Previous data suggests that the duration of prior hormonal treatment predicts duration to subsequent hormone therapy [20,21]: the longer duration of the response to the first androgen depletion therapy, the longer the duration of response to the second therapy including CYP17 inhibitors [20] such as abiraterone and ketoconazole [21]. Here we report a post-hoc analysis to determine whether the duration of prior endocrine therapy with gonadotropin-releasing hormone (GnRH) agonists or first-generation androgen receptor antagonists was associated with overall survival, radiographic progression-free survival, or prostate-specific antigen (PSA) response rate in patients treated with abiraterone acetate plus prednisone in the post- or the pre-chemotherapy COU-AA-301 and COU-AA-302 trials.

2. Patients and methods

COU-AA-301 (NCT00638690) [9,10] and COU-AA-302 (NCT00887198) [8,11,16] were phase 3, multinational, randomised, double-blind, placebo-controlled studies of post-docetaxel and chemotherapy-naïve patients, respectively, with progressive metastatic castration-resistant prostate cancer (Fig. 1). The review boards at all participating institutions approved the studies, which were conducted according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonisation. All patients provided written informed consent to participate in the studies.

In COU-AA-301 and COU-AA-302, patients were randomised 2:1 and 1:1, respectively, to oral abiraterone acetate 1 g daily and prednisone 5 mg twice daily versus placebo and prednisone 5 mg twice daily. Prednisolone at the same dose was used in place of prednisone at some sites. Patients received continuous GnRH agonist if they had not undergone a surgical orchiectomy to maintain serum testosterone <50 ng/dl. Prior endocrine therapies included GnRH agonists and androgen receptor antagonists as defined in Supplementary Table 1. Duration of prior endocrine therapy from the start of endocrine therapy to the date of randomisation as documented in the case report forms was recorded for each patient and categorised by quartiles as defined in Table 1 and 2 and Figure 2 and 3. Associations with clinical outcomes in the COU-AA-301 and COU-AA-302 studies were associated by quartiles. A study monitor had access to the patients' medical records and was responsible for verifying adherence to the study protocols.

Distributions of time-to-event variables were estimated using the Kaplan-Meier product limits method. The log-rank statistic was used as the primary analysis for treatment comparison. Cox model analysis was used to obtain the hazard ratio and its associated 95% confidence interval. Data shown for COU-AA-301 represent the final analysis of the study before patient crossover from prednisone to abiraterone (775 of the expected 797 death events), with a median follow-up for overall survival of 20.2 mo. Data shown for COU-AA-302 (ie, radiographic progression-free survival and PSA response rate) represent mature data obtained at the third interim analysis conducted at 56% of the expected death events, whereas mature overall survival data were obtained at the final analysis. Results were considered significant if $p \leq 0.05$; no multiplicity adjustments were made for this hypothesis generating post-hoc analysis. An interaction test was performed to assess whether the effect of abiraterone acetate was dependent on prior endocrine therapy duration. This analysis was performed for GnRH agonists given that the majority of patients received prior GnRH agonists (Supplementary Table 2).

3. Results

3.1. Patient characteristics

Patients received prior endocrine therapy with GnRH agonists (COU-AA-301, $n = 1127$ [94%]; COU-AA-302, $n = 1057$ [97%]) and/or orchiectomy (COU-AA-301, $n = 78$ [6.5%]; COU-AA-302, $n = 44$ [4.1%]) (Fig. 1). Pure androgen receptor antagonists (COU-AA-301, $n = 1015$ [85%]; COU-AA-302, $n = 1078$ [99%]) were also used in COU-AA-302. In COU-AA-301, the median duration of prior GnRH agonist and androgen receptor antagonist exposure was 45.1 mo and 15.7 mo, respectively. Median durations of prior GnRH agonist and androgen receptor antagonist exposure in COU-AA-302 were 36.7 mo and 16.1 mo, respectively. These durations represent the duration of prior endocrine therapies, not a single exposure to one form of manipulation.

3.2. Outcomes

Overall survival was improved in the abiraterone group versus the prednisone group in all quartiles of duration of prior endocrine therapy studied in COU-AA-301 (Table 1 and Supplementary Fig. 1) and all except quartile 3 in COU-AA-302 (Table 2 and

Supplementary Fig. 2). However, there were inconsistencies across quartiles in demonstrating a significant treatment benefit with abiraterone acetate in this post-hoc exploratory analysis. In both trials, patients who experienced a longer duration (quartile 4 equals the longest duration) of prior endocrine therapy had a longer overall survival, whether measured against quartile exposure of GnRH agonists or androgen receptor antagonists. This was observed regardless of assignment with few exceptions for both the abiraterone and prednisone groups.

Radiographic progression-free survival was significantly improved in the abiraterone group versus the prednisone group in patients for all quartiles of prior GnRH agonists or androgen receptor antagonists treatment in both COU-AA-301 (Table 1 and Fig. 2) and COU-AA-302 (Table 2 and Fig. 3). The PSA response proportions were also superior independent of the type and duration of prior endocrine therapy (Supplementary Fig. 3).

Results from an interaction analysis to examine whether the effect of abiraterone acetate was dependent on prior endocrine therapy duration were not significant in both COU-AA-301 and COU-AA-302 for both overall survival and radiographic progression-free survival (Table 3). Analysis by GnRH agonist quartiles yielded similar results, with none of the interaction tests on outcome measures showing significance.

Treatment with abiraterone acetate and prednisone was well tolerated by patients, as previously reported for both COU-AA-301 [9,10] and COU-AA-302 [8,11,16].

4. Discussion

The clinical benefit of abiraterone was maintained regardless of type and duration of prior endocrine therapy at nearly all quartiles examined, as shown in this post-hoc analysis of the phase 3 COU-AA-301 and COU-AA-302 studies in patients with metastatic castration-resistant prostate cancer progressing post-docetaxel or without prior chemotherapy, respectively. The clinical benefit of abiraterone was maintained despite the fact that longer exposure of prior endocrine therapy in COU-AA-301 and COU-AA-302 was associated with a longer time-to-death and radiographic progression-free survival regardless of treatment assignment. The results show the importance of considering the duration of prior hormone therapy in trial design, both as a stratification factor and a predictive factor in the evaluation of patients with castration-resistant prostate cancer who are progressing in the pre- or post-chemotherapy setting. When interpreting these results, it should be evident that prior endocrine therapy exposure in the setting of this post-hoc analysis equates with the duration of prior hormone therapy and not with hormone sensitivity or hormone response.

Previous data using other hormonal agents suggested that a short response to first-line androgen deprivation therapy (ADT) predicts poor response both in frequency and duration to a subsequent hormone therapy [20–23]. In one retrospective study of 57 patients with progressing castration-resistant prostate cancer treated with post-docetaxel enzalutamide from the AFFIRM trial, the median time-to-progression-free survival was significantly shorter (2.8 mo vs 8.6 mo, $p = 0.002$) and PSA response rate was significantly lower (8% vs 58%, $p < 0.001$) in patients with a less than 12-mo median duration versus greater than 12-

mo median duration of response to first-line ADT [22]. The results are consistent with the current analysis which showed that the patients in the lowest quartile of duration of prior endocrine therapy had the shortest overall survival and radiographic progression-free survival. The effects of abiraterone acetate and prednisone, however, were seen in patients with short and long durations of exposure by quartile with the exception of the lowest quartile for overall survival and radiographic progression-free survival in COU-AA-301. This is consistent with results shown in a single-site analysis limited to 37 patients with metastatic castration-resistant prostate cancer post-docetaxel with varying duration of enzalutamide therapy, in which PSA response to subsequent abiraterone was similar for patients who received enzalutamide for ≤3 mo or >3 mo [24]. As reported recently [23], earlier treatment with docetaxel might not have a large impact on the subsequent activity of hormonal treatment, as comparable outcomes from enzalutamide after abiraterone were observed irrespective of prior docetaxel use [25]. Cabazitaxel was also shown to significantly improve overall survival compared with mitoxantrone regardless of the duration of prior ADT separated by tertiles of <2.5 yr, 2.5–5.0 yr, and ≥5 yr [26]. Although beyond the scope of this study, it would be of clinical value to examine whether patients with a particular duration of prior endocrine therapy before developing castration-resistance might be optimally sequenced with a particular second-line treatment of abiraterone acetate plus prednisone versus enzalutamide versus docetaxel.

The current study has several important limitations. Some patients might have received short courses of androgen receptor antagonists to prevent tumour flare in the castrate setting. This short course of therapy would not necessarily be expected to affect outcomes. There is also uncertainty with respect to the analysis of the lowest quartile with presumably more aggressive disease as evidenced by a short duration of 0–12 mo of prior GnRH agonist therapy, as the number of patients in this group was too low to analyse definitively. An additional concern is whether duration of exposure is an appropriate surrogate for sensitivity, given that there are no standards for reporting the response to ADT. Time-to-castration-resistance, which probably better describes sensitivity to ADT, could not be tested as a potential predictor of abiraterone clinical benefit in this study because this parameter was not available in the database. It should be noted that in the current study duration of prior hormonal treatment comprised time-to-castration-resistance and time-with-castration-resistance on hormonal treatment. Moreover, the onset of castration-resistance could have started earlier than indicated by the addition of abiraterone acetate and prednisone, reflecting individual physicians' management philosophy and preferences. The effects of abiraterone acetate and prednisone on further outcomes are valid given that patients were randomised between the two treatment groups, as this analysis is reporting phase 3 randomised trials.

5. Conclusion

In general, the efficacy outcomes favoured the abiraterone treatment groups compared with prednisone groups regardless of prior endocrine therapy exposure in metastatic castration-resistant prostate cancer patients either post-docetaxel or without prior chemotherapy. Consistent with other studies, a longer duration of prior endocrine therapy in less pre-treated patients (ie, chemotherapy-naïve) tended to have a greater benefit. There were too few patients in the subgroup with a short initial sensitivity to androgen deprivation (eg, 6–12 mo)

to draw the definitive conclusion highlighting the need of further studies in this specific patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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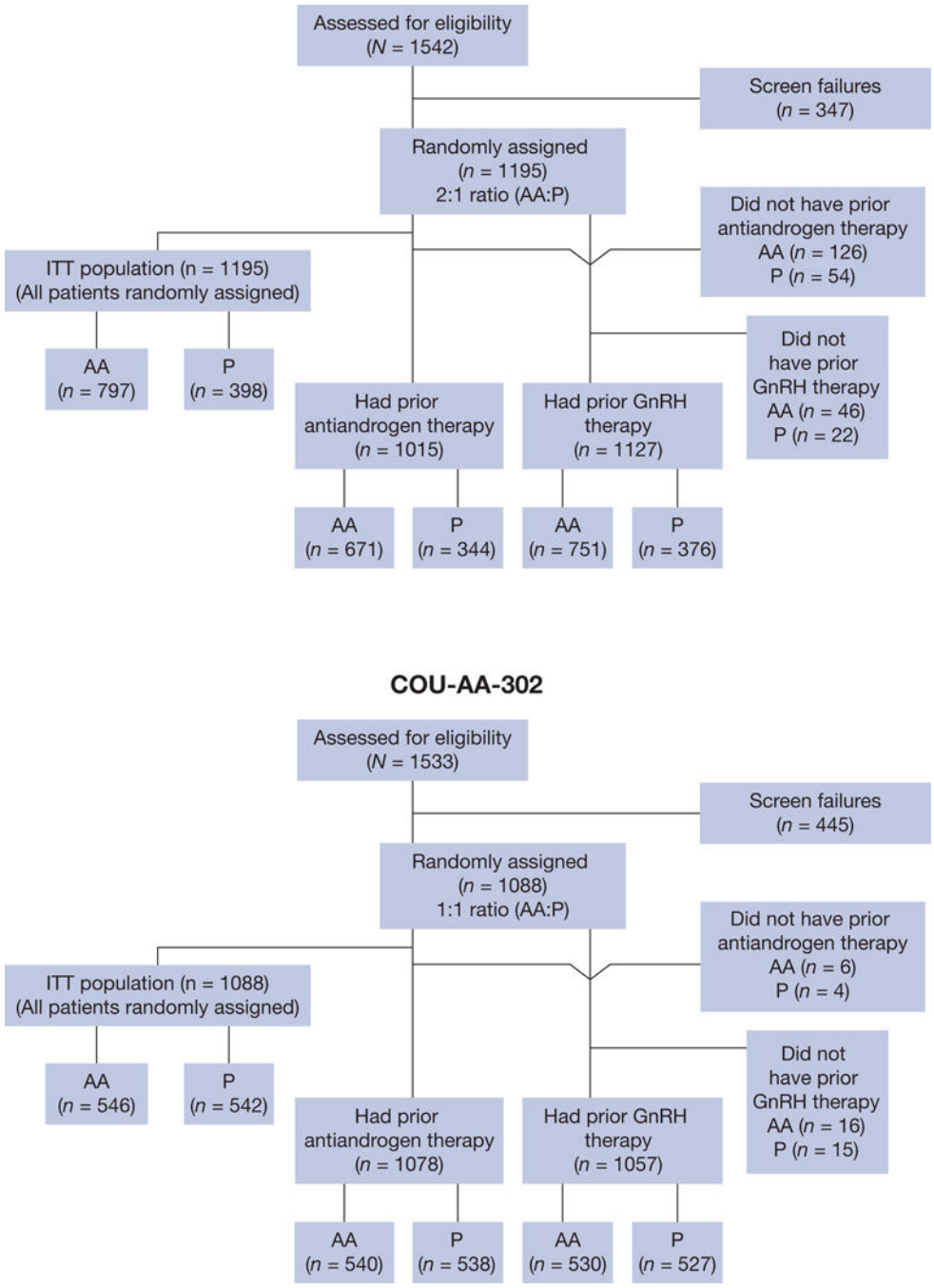

Fig.1.

Consolidated Standards of Reporting Trials diagram for (A) COU-AA-301 and (B) COU-AA-302.

AA = abiraterone acetate; GnRH = gonadotropin-releasing hormone; ITT = intention-to-treat; P = prednisone.

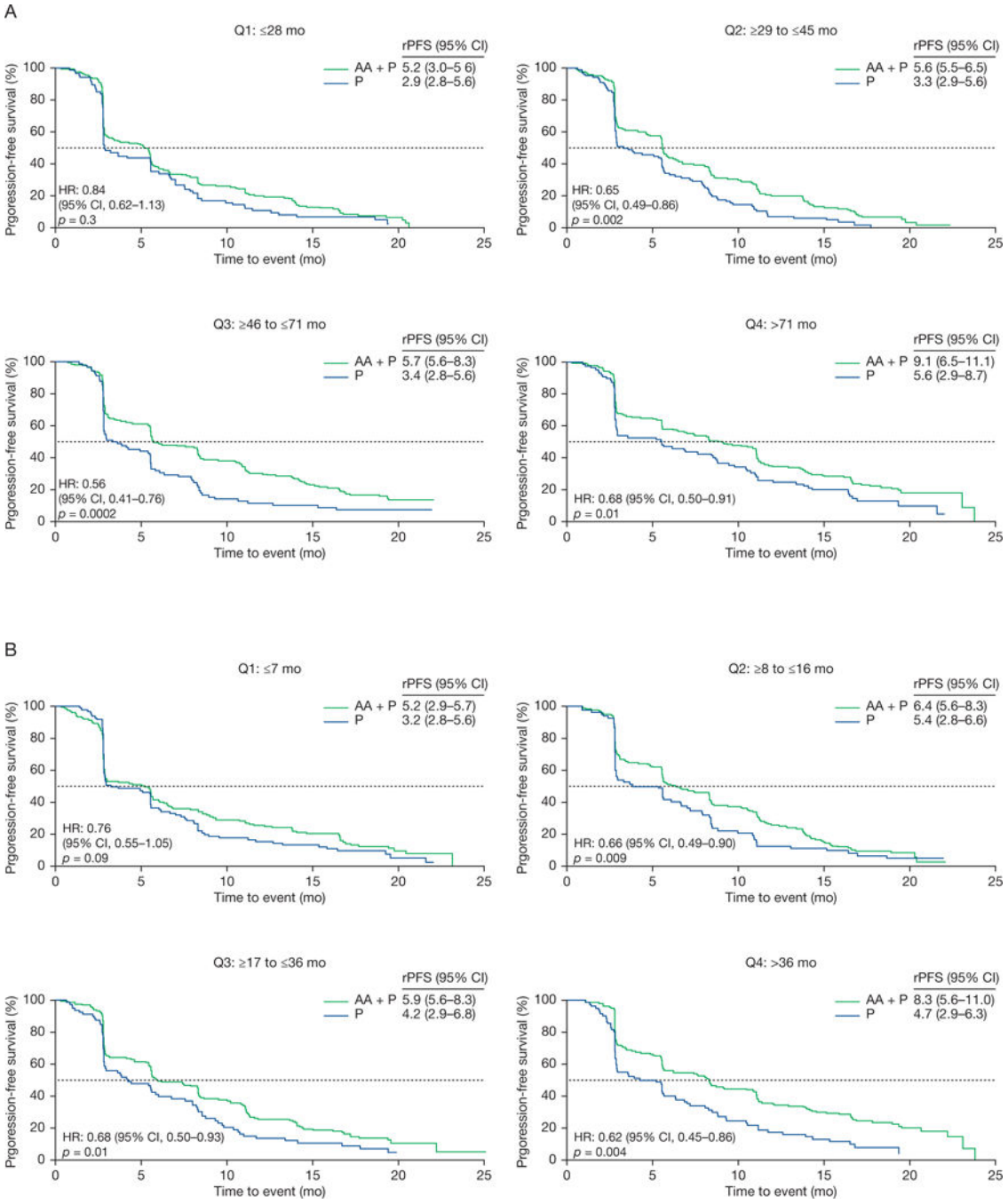

Fig. 2.

Radiographic progression-free survival Kaplan-Meier estimates in COU-AA-301 patients with prior endocrine therapy exposure by duration in quartiles for (A) gonadotropin-releasing hormone agonists and (B) androgen receptor antagonists.

AA = abiraterone acetate; CI = confidence interval; HR = hazard ratio; P = prednisone; rPFS = radiographic progression-free survival; Q = quartile.

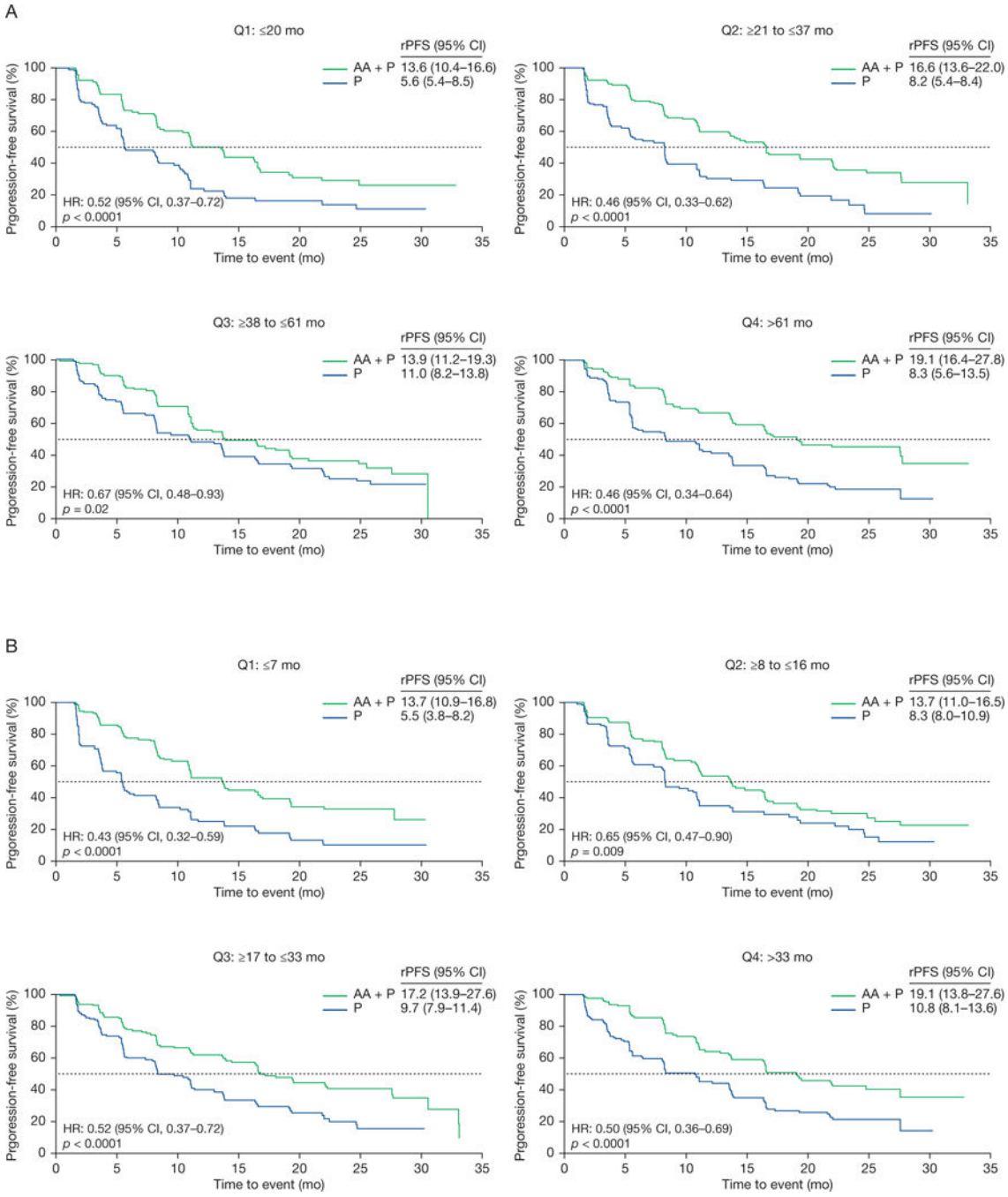

Fig. 3.

Radiographic progression-free survival Kaplan-Meier estimates in COU-AA-302 patients with prior endocrine therapy exposure by duration in quartiles for (A) gonadotropin-releasing hormone agonists and (B) androgen receptor antagonists.

AA = abiraterone acetate; CI = confidence interval; HR = hazard ratio; P = prednisone; rPFS = radiographic progression-free survival; Q = quartile.

Table 1

Clinical outcomes in COU-AA-301 patients with prior endocrine therapy exposure by duration in quartiles

GnRH agonists								
	Q1		**Q2**		**Q3**		**Q4**	
	≤28 mo		**≥29 to ≤45 mo**		**≥46 to ≤71 mo**		**>71 mo**	
Treatment	**AA + P**	**P**	**AA + P**	**P**	**AA + P**	**P**	**AA + P**	**P**
	(*n* = 191)	**(*n* = 87)**	**(*n* = 174)**	**(*n* = 109)**	**(*n* = 191)**	**(*n* = 91)**	**(*n* = 195)**	**(*n* = 89)**
Overall survival								
HR	0.99		0.61		0.73		0.68	
(95% CI)	(0.71–1.37)		(0.46–0.82)		(0.53–1.00)		(0.48–0.97)	
Radiographic progression-free survival								
HR	0.84		0.65		0.56		0.68	
(95% CI)	(0.62–1.13)		(0.49–0.86)		(0.41–0.76)		(0.50–0.91)	
Androgen receptor antagonists								
	Q1		Q2		Q3		Q4	
	≤7 mo		≥8 to ≤16 mo		≥17 to ≤36 mo		>36 mo	
Treatment	AA + P	P	AA + P	P	AA + P	P	AA + P	P
	(*n* = 155)	(*n* = 95)	(*n* = 179)	(*n* = 85)	(*n* = 167)	(*n* = 82)	(*n* = 170)	(*n* = 82)
Overall survival								
HR	0.78		0.99		0.73		0.57	
(95% CI)	(0.56–1.08)		(0.71–1.38)		(0.51–1.03)		(0.40–0.81)	
Radiographic progression-free survival								
HR	0.76		0.66		0.68		0.62	
(95% CI)	(0.55–1.05)		(0.49–0.90)		(0.50–0.93)		(0.45–0.86)	

AA = abiraterone acetate; CI = confidence interval; GnRH = gonadotropin-releasing hormone; HR = hazard ratio; P = prednisone; Q = quartile.

Table 2

Clinical outcomes in COU-AA-302 patients with prior endocrine therapy exposure by duration in quartiles

	GnRH agonists							
	Q1		**Q2**		**Q3**		**Q4**	
	≤20 mo		**≥21 to ≤37 mo**		**≥38 to ≤61 mo**		**>61 mo**	
Treatment	**AA + P**	**P**	**AA + P**	**P**	**AA + P**	**P**	**AA + P**	**P**
	(*n* = 119)	**(*n* = 133)**	**(*n* = 145)**	**(*n* = 137)**	**(*n* = 127)**	**(*n* = 127)**	**(*n* = 139)**	**(*n* = 130)**
Overall survival								
HR	0.79		0.69		1.05		0.78	
(95% CI)	(0.59–1.04)		(0.52–0.91)		(0.76–1.43)		(0.57–1.06)	
Radiographic progression-free survival								
HR	0.52		0.46		0.67		0.46	
(95% CI)	(0.37–0.72)		(0.33–0.62)		(0.48–0.93)		(0.34–0.64)	
	Androgen receptor antagonists							
	Q1		Q2		Q3		Q4	
	≤7 mo		≥8 to ≤16 mo		≥17 to ≤33 mo		>33 mo	
Treatment	AA + P	P	AA + P	P	AA + P	P	AA + P	P
	(*n* = 138)	(*n* = 134)	(*n* = 132)	(*n* = 132)	(*n* = 138)	(*n* = 131)	(*n* = 132)	(*n* = 141)
Overall survival								
HR	0.68		0.83		0.97		0.88	
(95% CI)	(0.47–0.82)		(0.62–1.11)		(0.72–1.31)		(0.65–1.20)	
Radiographic progression-free survival								
HR	0.43		0.65		0.52		0.5	
(95% CI)	(0.32–0.59)		(0.47–0.90)		(0.37–0.72)		(0.36–0.69)	

AA = abiraterone acetate; CI = confidence interval; GnRH = gonadotropin-releasing hormone; HR = hazard ratio; P = prednisone; Q = quartile.

Table 3

Interaction analysis of abiraterone acetate treatment and prior endocrine therapy duration for overall survival and radiographic progression-free survival in COU-AA-301 and COU-AA-302

COU-AA-301	
Parameter	*p* value
Overall survival	
Treatment	0.1
Duration	0.009
Treatment × duration	0.4
Radiographic progression-free survival	
Treatment	0.0006
Duration	<0.0001
Treatment × duration	0.7
COU-AA-302	
Parameter	*p* value
Overall survival	
Treatment	0.4
Duration	0.002
Treatment × duration	0.6
Radiographic progression-free survival	
Treatment	<0.0001
Duration	0.04
Treatment × duration	0.7