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

Joaquim Bellmunt, MD, PhD[a, *], Thian Kheoh, PhD[b], Margaret K. Yu, MD[c], Matthew R. Smith, MD, PhD[d], Eric J. Small, MD[e], Peter F.A. Mulders, MD, PhD[f], Karim Fizazi, MD, PhD[g], Dana E. Rathkopf, MD[h], Fred Saad, MD FRCS[i], Howard I. Scher, MD[h], Mary-Ellen Taplin, MD[a], Ian D. Davis, MBBS, PhD, FRACP, FAChPM[j], Dirk Schrijvers, MD, PhD[k], Andrew Protheroe, MD, PhD[l], Arturo Molina, MD[m], Peter De Porre, MD[n], Thomas W. Griffin, MD[c], Johann S. de Bono, MB, ChB, PhD[o], Charles J. Ryan, MD[e], Stéphane Oudard, MD, PhD[p]

[a] Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA; [b] Janssen Research & Development, San Diego, California, USA; [c] Janssen Research & Development, Los Angeles, California, USA; [d] Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA; [e] Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, California, USA; [f] Radboud University Medical Centre, Nijmegen, The Netherlands; [g] Institut Gustave Roussy, University of Paris Sud, Villejuif, France; [h] Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, New York, New York, USA; [i] University of Montréal, Montréal, Québec, Canada; [j] Monash University and Eastern Health, Victoria, Australia; [k] ZNA Middelheim Oncology Clinic, Medical Oncology, Antwerp, Belgium; [l] Churchill Hospital, Oxford, UK; [m] Janssen Research & Development, Menlo Park, California, USA; [n] Janssen Research & Development, Beerse, Belgium; [o] The Institute of Cancer Research and The Royal

Marsden Hospital, Sutton, UK; [p] Georges Pompidou Hospital, University René Descartes, Paris, France

***** Corresponding author. Harvard Medical School, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215-5450, USA; Phone: (617) 632-3237; Fax: (617) 632-2165; Joaquim_Bellmunt@dfci.harvard.edu

Previous presentations: These data were presented in part at the 2013 European Cancer Congress (ECCO-ESMO-ESTRO), Amsterdam, the Netherlands, September 27 – October 1, 2013; the 2014 Genitourinary Cancers Symposium, San Francisco, CA, USA, January 30 – February 1, 2014; the 2014 European Association of Urology Congress, Stockholm, Sweden, April 11– 15, 2014; and the 2014 American Urological Association Annual Meeting, Orlando, FL, USA, May 16 – 21, 2014.

Funding: These clinical trials were supported by Ortho Biotech Oncology Research & Development, unit of Cougar Biotechnology (now Janssen Research & Development).

Registration number at ClinicalTrials.gov: COU-AA-301: NCT00638690; COU-AA-302: NCT00887198

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

Word count of text: 1883

Word count of the abstract: 300

Abstract (Maximum: 300 words; current: 300 words)

***Background*:** Duration of prior hormonal treatment can predict response 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. 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 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 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 or 16.1 mo median duration, respectively).

Outcome measurements and statistical analysis: Cox model used to obtain HR and associated 95% CI 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 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 benefit regardless of prior endocrine therapy duration in patients with mCRPC.

Patient Summary: mCRPC patients derived clinical benefit with AA regardless of prior endocrine therapy duration.

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 suggest 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 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 Supporting Table 1. Duration of prior endocrine therapy from the start of endocrine therapy to the date of randomization as documented in the case report forms was recorded for each patient and categorised by quartiles as defined in Tables 1 and 2

and Figures 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 the majority of patients received prior GnRH agonists (Supporting 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, 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 duration of prior endocrine therapies, not a single exposure to one form of manipulation.

3.2. Outcomes

Median overall survival was longer 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 Supporting Fig. 1) and all except quartile 3 in COU-AA-302 (Table 2 and Supporting 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 longer duration (quartile 4 equals longest duration) of prior endocrine therapy had 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 longer 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

182 superior independent of the type and duration of prior endocrine therapy (Fig. 4A,
183 Fig. 4B).
184
185 Results from an interaction analysis to examine whether the effect of abiraterone
186 was dependent on prior endocrine therapy duration were not significant in both COU-
187 AA-301 and COU-AA-302 for both overall survival and radiographic progression-free
188 survival (Supporting Table 2). Analysis by GnRH agonist quartiles yielded similar
189 results, with none of the interaction tests on outcome measures showing
190 significance.
191
192 Treatment with abiraterone acetate and prednisone was well tolerated by patients,
193 as previously reported for both COU-AA-301 [9,10] and COU-AA-302 [8,11,16].
194
195 **4. Discussion**
196 Clinical benefit of abiraterone was maintained regardless of type and duration of
197 prior endocrine therapy at nearly all quartiles examined, as shown in this post hoc
198 analysis of the phase 3 COU-AA-301 and COU-AA-302 studies in patients with
199 metastatic castration-resistant prostate cancer progressing post docetaxel or without
200 prior chemotherapy, respectively. The clinical benefit of abiraterone was maintained
201 despite the fact that longer exposure of prior endocrine therapy in COU-AA-301 and
202 COU-AA-302 was associated with a longer time to death and radiographic
203 progression-free survival regardless of treatment assignment. The results show the
204 importance of considering the duration of prior hormone therapy in trial design, both
205 as a stratification factor, and predictive factor in the evaluation of patients with CRPC
206 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 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 predicts poor response both in frequency and duration to a subsequent hormone therapy [20-23]. In one retrospective study of 57 patients with progressing CRPC 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 month versus greater than 12 month 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 androgen deprivation therapy 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 whether 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 short duration of 0–12 months 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, 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 outcome

are valid given that patients were randomized between the two treatment groups, as this analysis is reporting phase 3 randomized 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, longer duration of prior endocrine therapy in less pre-treated patients (ie, chemotherapy-naive) tended to have greater benefit. There were too few patients in the subgroup with short initial sensitivity to androgen deprivation (eg, 6-12 months) to draw the definitive conclusion highlighting the need of further studies in this specific patient population.

Acknowledgements

Author contributions: Joaquim Bellmunt 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: Bellmunt, Oudard, Yu, Kheoh, Molina, Griffin.

Acquisition of data: Kheoh, Yu, Molina, De Porre, Griffin.

Analysis and interpretation of data: Bellmunt, Oudard, Saad, Schrijvers, Yu, Kheoh, Molina, De Porre, Griffin.

Drafting of the manuscript: All.

Critical revision of the manuscript for important intellectual content: All.

Statistical analysis: Kheoh.

Obtaining funding: Molina.

Administrative, technical, or material support: Molina.

Supervision: Molina.

Other (specify): None.

Financial disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Bellmunt has received honoraria and has served as a consultant for Janssen Research & Development. Drs. Kheoh, Yu, Molina, De Porre, and Griffin are employees of Janssen Research & Development and hold stock options in Johnson & Johnson. Dr. Smith served as a consultant to Janssen Research & Development. Drs. Small and Protheroe have no disclosures or potential conflicts of interest to report. Dr. Mulders has served as a consultant and has received research support from Janssen Research & Development, Astellas, and Bayer. Dr. Fizazi has participated in advisory boards and served as a speaker for Janssen. Dr. Rathkopf has received research funding from Janssen Research & Development. Dr. Saad has served as a consultant and has received research funding from Janssen Research & Development. Dr. Scher has served as an uncompensated consultant to Janssen Research & Development and reports support to Memorial Sloan Kettering Cancer Center from Janssen Research & Development related to this work. He has also served as an uncompensated consultant to AstraZeneca, Bristol Myers Squibb, Celgene, Endocyte, Exelixis, Foundation Medicine, Genentech, Medivation, Novartis, Pfizer, Takeda-Millennium and Ventana – Member of Roche; a consultant to Astellas, BIND Pharmaceuticals, Chugai Academy for Advanced Oncology, Endo/Orion Pharmaceuticals, OncologySTAT, Palmetto GBA, LLC, Sanofi Aventis, and WCG Oncology; has received an honorarium from Chugai Academy for Advanced Science; and has received support for Memorial Sloan Kettering Cancer Center from BIND

Pharmaceuticals, Epic Sciences, Exelixis, and Medivation. Dr. Taplin has received institutional (Dana-Farber Cancer Institute) funding for clinical trials involving abiraterone. Dr. Davis has served as a consultant without remunerations from Janssen Research & Development, Medivation, BMS, Sanofi, Bayer, Astellas, and Ipsen. Dr. Schrijvers has participated in studies and served as a consultant and speaker boards for Janssen Research & Development and Sanofi. Dr. de Bono is a paid employee of The Institute of Cancer Research, which has a commercial interest in abiraterone, and has served as a paid consultant for Johnson & Johnson. Dr. Ryan has received honoraria from Janssen Research & Development. Dr. Oudard has received honoraria from Janssen Research & Development.

Funding/Support and role of the sponsor: This work was supported by Janssen Research & Development (formerly Ortho Biotech Research & Development, unit of Cougar Biotechnology). Employees of Janssen Research & Development participated in trial design and oversight, data monitoring and collection, data analysis, data interpretation, and writing of the report. The study sponsor was involved in trial design and provided grants to trial sites, but had no involvement in the conduct of the trial. Analyses done by Janssen for this report were funded by Janssen Global Services.

Acknowledgement statement: Writing assistance was provided by Ira Mills, PhD, of PAREXEL and was funded by Janssen Global Services.

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406 **Figure Legends**

407 **Fig.1 – Consolidated Standards of Reporting Trials diagram.**

408 **Fig. 2 – Radiographic progression-free survival Kaplan-Meier estimates in**
409 **COU-AA-301 patients with prior endocrine therapy exposure by duration in**
410 **quartiles. A. Gonadotropin-releasing hormone agonists; B. androgen receptor**
411 **antagonists. AA = abiraterone acetate; CI = confidence interval; HR = hazard**
412 **ratio; P = prednisone; rPFS = radiographic progression-free survival; Q =**
413 **quartile.**

414 **Fig. 3 – Radiographic progression-free survival Kaplan-Meier estimates in**
415 **COU-AA-302 patients with prior endocrine therapy exposure by duration in**
416 **quartiles. A. Gonadotropin-releasing hormone agonists; B. androgen receptor**
417 **antagonists. AA = abiraterone acetate; CI = confidence interval; HR = hazard**
418 **ratio; P = prednisone; rPFS = radiographic progression-free survival; Q =**
419 **quartile.**

420 **Fig. 4 – A. Prostate-specific antigen response in COU-AA-301 patients with**
421 **prior endocrine therapy exposure by duration in quartiles. B. Prostate-specific**
422 **antigen response in COU-AA-302 patients with prior endocrine therapy**
423 **exposure by duration in quartiles. AA = abiraterone acetate; GnRH =**
424 **gonadotropin-releasing hormone; P = prednisone; PSA = prostate-specific**
425 **antigen; Q = quartile.**

426 **Table 1 – Clinical outcomes in COU-AA-301 patients with prior endocrine therapy exposure by duration in quartiles**

	GnRH agonists							
	Q1 ≤28 mo		Q2 ≥29 to ≤45 mo		Q3 ≥46 to ≤71 mo		Q4 >71 mo	
Treatment	AA + P (*n* = 191)	P (*n* = 87)	AA + P (*n* = 174)	P (*n* = 109)	AA + P (*n* = 191)	P (*n* = 91)	AA + P (*n* = 195)	P (*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)	
p Value	0.9		0.001		0.05		0.03	
Median, mo	12.2	11.1	14.4	9.1	16.8	11.2	19.6	15.9
(95% CI)	(10.5–14.9)	(8.3–14.4)	(11.2–16.4)	(8.0–11.1)	(15.1–18.2)	(8.9–14.9)	(17.5–23.8)	(10.5–21.5)
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)	
p Value	0.3		0.002		0.0002		0.01	
Median, mo	5.2	2.9	5.6	3.3	5.7	3.4	9.1	5.6
(95% CI)	(3.0–5.6)	(2.8–5.6)	(5.5–6.5)	(2.9–5.6)	(5.6–8.3)	(2.8–5.6)	(6.5–11.1)	(2.9–8.7)

Treatment	Androgen receptor antagonists							
	Q1 ≤7 mo		Q2 ≥8 to ≤16 mo		Q3 ≥17 to ≤36 mo		Q4 >36 mo	
	AA + P (*n* = 155)	P (*n* = 95)	AA + P (*n* = 179)	P (*n* = 85)	AA + P (*n* = 167)	P (*n* = 82)	AA + P (*n* = 170)	P (*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)	
p Value	0.1		0.9		0.07		0.002	
Median, mo	11.9	10.7	14.9	13.5	16.2	10.7	19.2	11
(95% CI)	(10.0–16.0)	(8.8–13.6)	(12.8–16.8)	(10.0–18.7)	(14.2–18.2)	(8.9–16.6)	(16.7–23.3)	(8.8–15.3)
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)	
p Value	0.09		0.009		0.01		0.004	
Median, mo	5.2	3.2	6.4	5.4	5.9	4.2	8.3	4.7
(95% CI)	(2.9–5.7)	(2.8–5.6)	(5.6–8.3)	(2.8–6.6)	(5.6–8.3)	(2.9–6.8)	(5.6–11.0)	(2.9–6.3)

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

427

428 **Table 2 – Clinical outcomes in COU-AA-302 patients with prior endocrine therapy exposure by duration in quartiles**

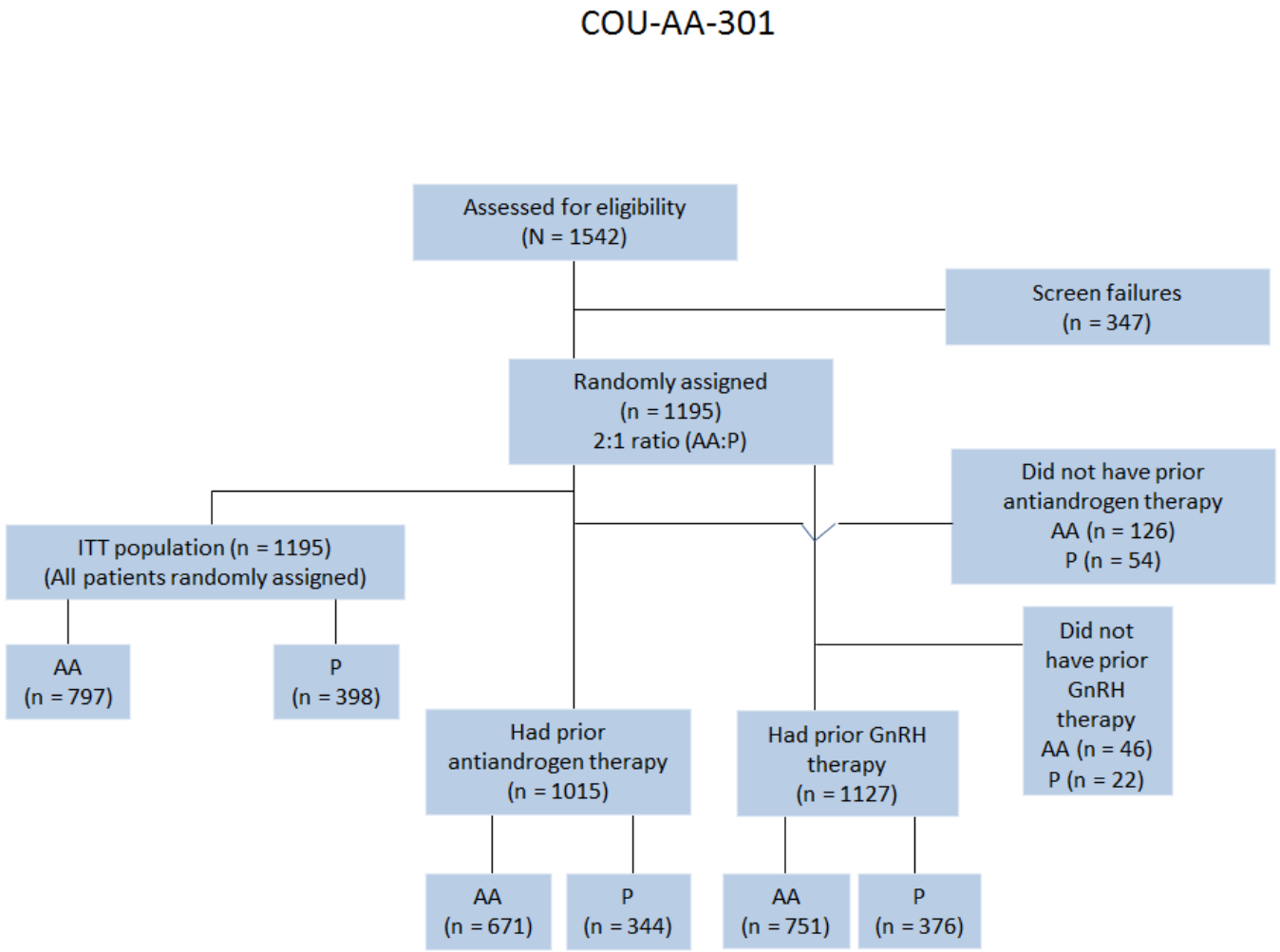
	GnRH agonists							
	Q1 ≤20 mo		Q2 ≥21 to ≤37 mo		Q3 ≥38 to ≤61 mo		Q4 >61 mo	
Treatment	AA + P (n = 119)	P (n = 133)	AA + P (n = 145)	P (n = 137)	AA + P (n = 127)	P (n = 127)	AA + P (n = 139)	P (n = 130)
Overall survival								
HR (95% CI)	0.79 (0.59–1.04)		0.69 (0.52–0.91)		1.05 (0.76–1.43)		0.78 (0.57–1.06)	
p Value	0.09		0.01		0.8		0.1	
Median, mo (95% CI)	26 (22.2–33.5)	21.8 (19.4–27.5)	33.2 (29.8–40.4)	30 (26.1–32.4)	34.5 (28.5–44.0)	38.5 (33.4–45.9)	43.5 (36.8–48.9)	34.9 (31.6–39.1)
Radiographic progression-free survival								
HR (95% CI)	0.52 (0.37–0.72)		0.46 (0.33–0.62)		0.67 (0.48–0.93)		0.46 (0.34–0.64)	
p Value	< 0.0001		< 0.0001		0.02		< 0.0001	
Median, mo (95% CI)	13.6 (10.4–16·6)	5.6 (5.4–8.5)	16.6 (13.6–22.0)	8.2 (5.4–8.4)	13.9 (11.2–19.3)	11 (8.2–13.8)	19.1 (16.4–27.8)	8.3 (5.6–13.5)

Treatment	Androgen receptor antagonists							
	Q1 ≤7 mo		Q2 ≥8 to ≤16 mo		Q3 ≥17 to ≤33 mo		Q4 >33 mo	
	AA + P (n = 138)	P (n = 134)	AA + P (n = 132)	P (n = 132)	AA + P (n = 138)	P (n = 131)	AA + P (n = 132)	P (n = 141)
Overall survival								
HR	0.62		0.83		0.97		0.88	
(95% CI)	(0.47–0.82)		(0.62–1.11)		(0.72–1.31)		(0.65–1.20)	
p Value	0.0008		0.2		0.8		0.4	
Median, mo	32.5	23.1	31.9	28.7	34.7	35.9	41.4	37.7
(95% CI)	(26.4–35.4)	(19.8–27.7)	(26.6–39.0)	(26.0–33.6)	(31.2–38.7)	(31.8–40.1)	(34.4–48.9)	(33.6–42.1)
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)	
p Value	< 0.0001		0.009		< 0.0001		< 0.0001	
Median, mo	13.7	5.5	13.7	8.3	17.2	9.7	19.1	10.8
(95% CI)	(10.9–16.8)	(3.8–8.2)	(11.0–16.5)	(8.0–10.9)	(13.9–27.6)	(7.9–11.4)	(13.8–27.6)	(8.1–13.6)

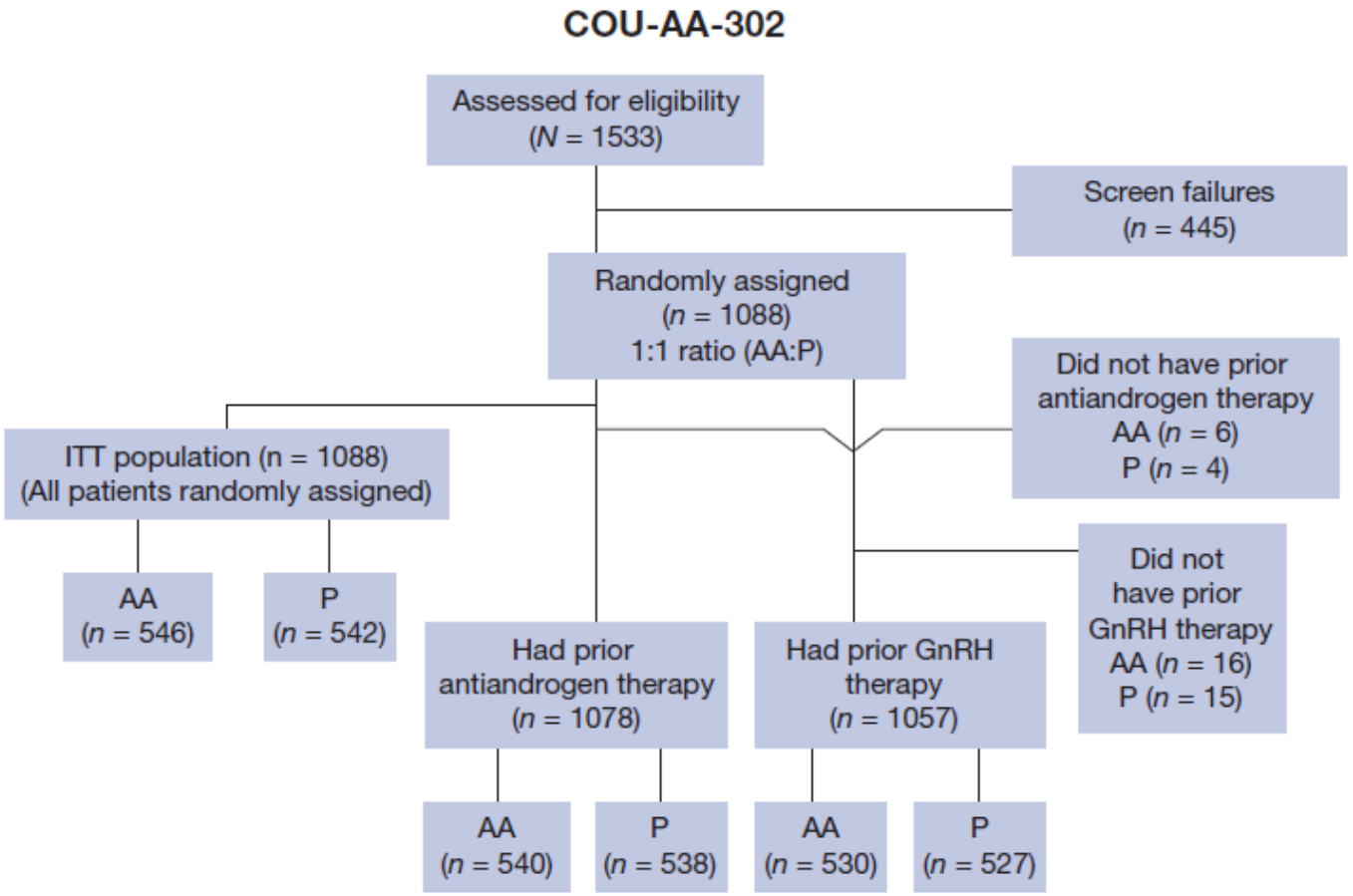
AA = abiraterone acetate; CI = confidence interval; GnRH = gonadotropin-releasing hormone; HR = hazard ratio; P = prednisone; Q = quartile.

429

Figure 1A.

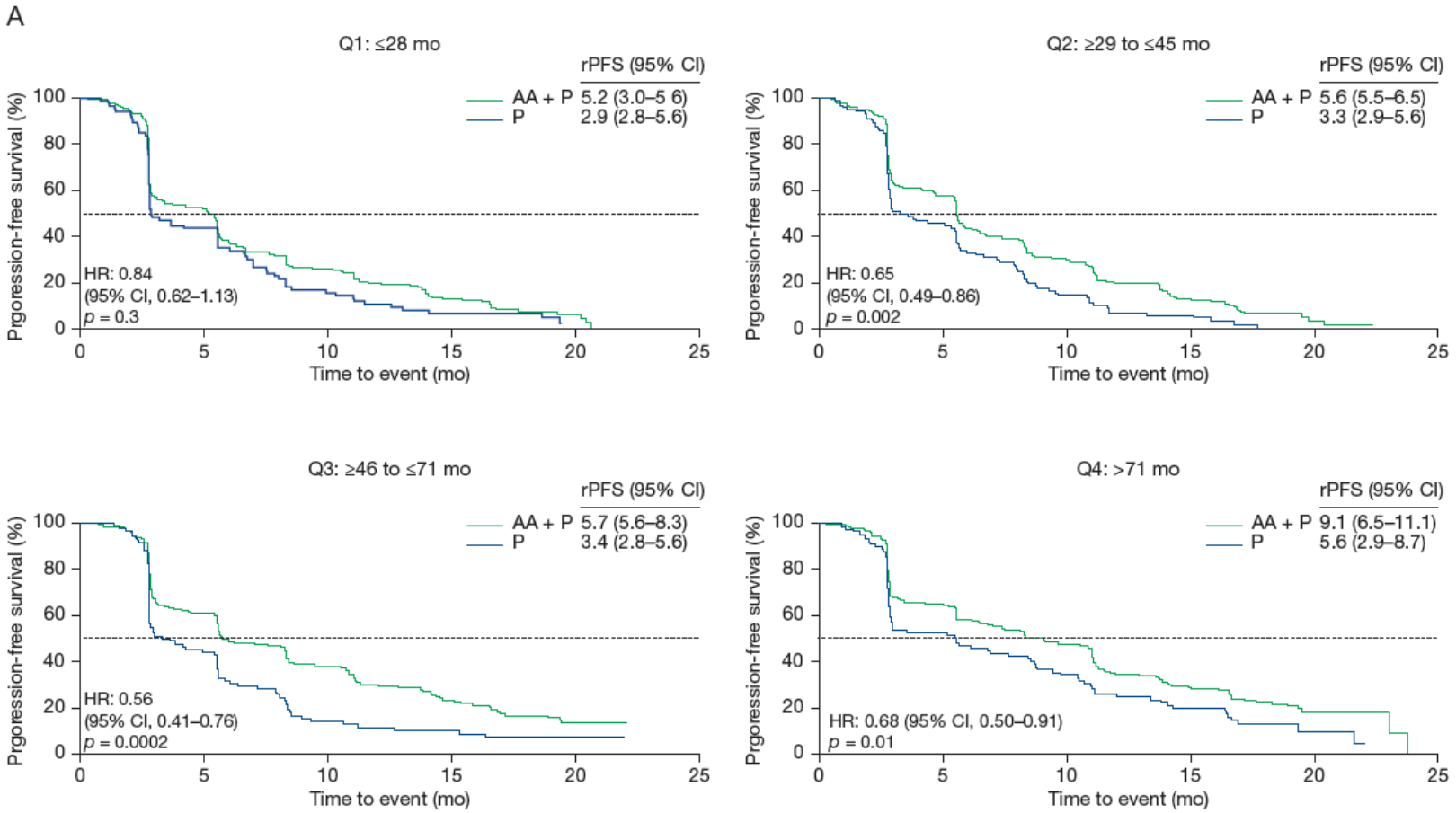

COU-AA-301
Assessed for eligibility
(N = 1542)
Screen failures
(n = 347)
Randomly assigned
(n = 1195)
2:1 ratio (AA:P)
Did not have prior antiandrogen therapy
AA (n = 126)
P (n = 54)
ITT population (n = 1195)
(All patients randomly assigned)
AA
(n = 797)
P
(n = 398)
Did not have prior GnRH therapy
AA (n = 46)
P (n = 22)
Had prior antiandrogen therapy
(n = 1015)
Had prior GnRH therapy
(n = 1127)
AA
(n = 671)
P
(n = 344)
AA
(n = 751)
P
(n = 376)

433 **Figure 1B.**

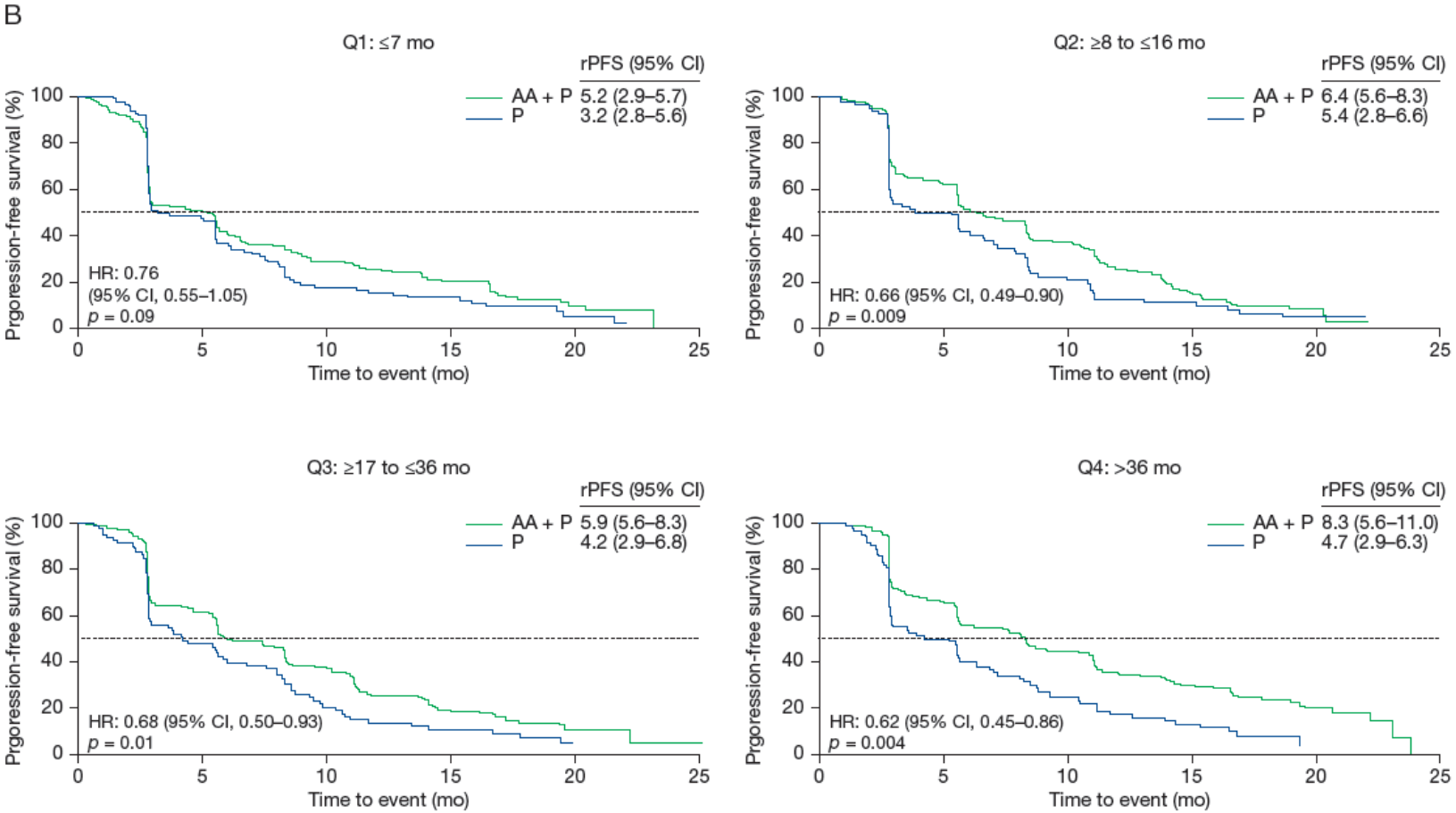


434

435 **Figure 2**

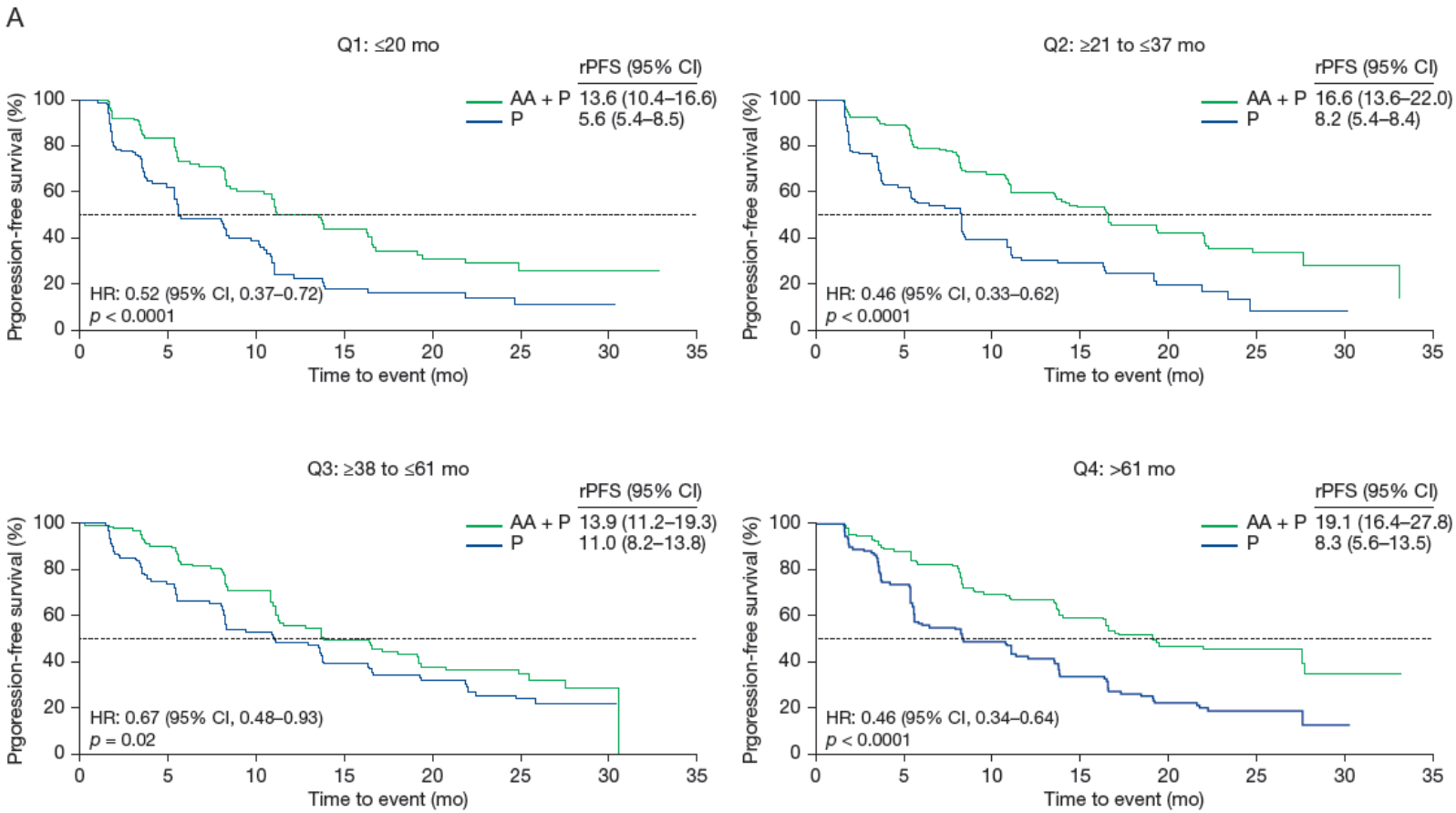


436


B
Q1: ≤7 mo
rPFS (95% CI)
AA + P 5.2 (2.9–5.7)
P 3.2 (2.8–5.6)
HR: 0.76
(95% CI, 0.55–1.05)
p = 0.09
Prgoression-free survival (%)
Time to event (mo)
Q2: ≥8 to ≤16 mo
rPFS (95% CI)
AA + P 6.4 (5.6–8.3)
P 5.4 (2.8–6.6)
HR: 0.66 (95% CI, 0.49–0.90)
p = 0.009
Prgoression-free survival (%)
Time to event (mo)
Q3: ≥17 to ≤36 mo
rPFS (95% CI)
AA + P 5.9 (5.6–8.3)
P 4.2 (2.9–6.8)
HR: 0.68 (95% CI, 0.50–0.93)
p = 0.01
Prgoression-free survival (%)
Time to event (mo)
Q4: >36 mo
rPFS (95% CI)
AA + P 8.3 (5.6–11.0)
P 4.7 (2.9–6.3)
HR: 0.62 (95% CI, 0.45–0.86)
p = 0.004
Prgoression-free survival (%)
Time to event (mo)

437

438 **Figure 3**



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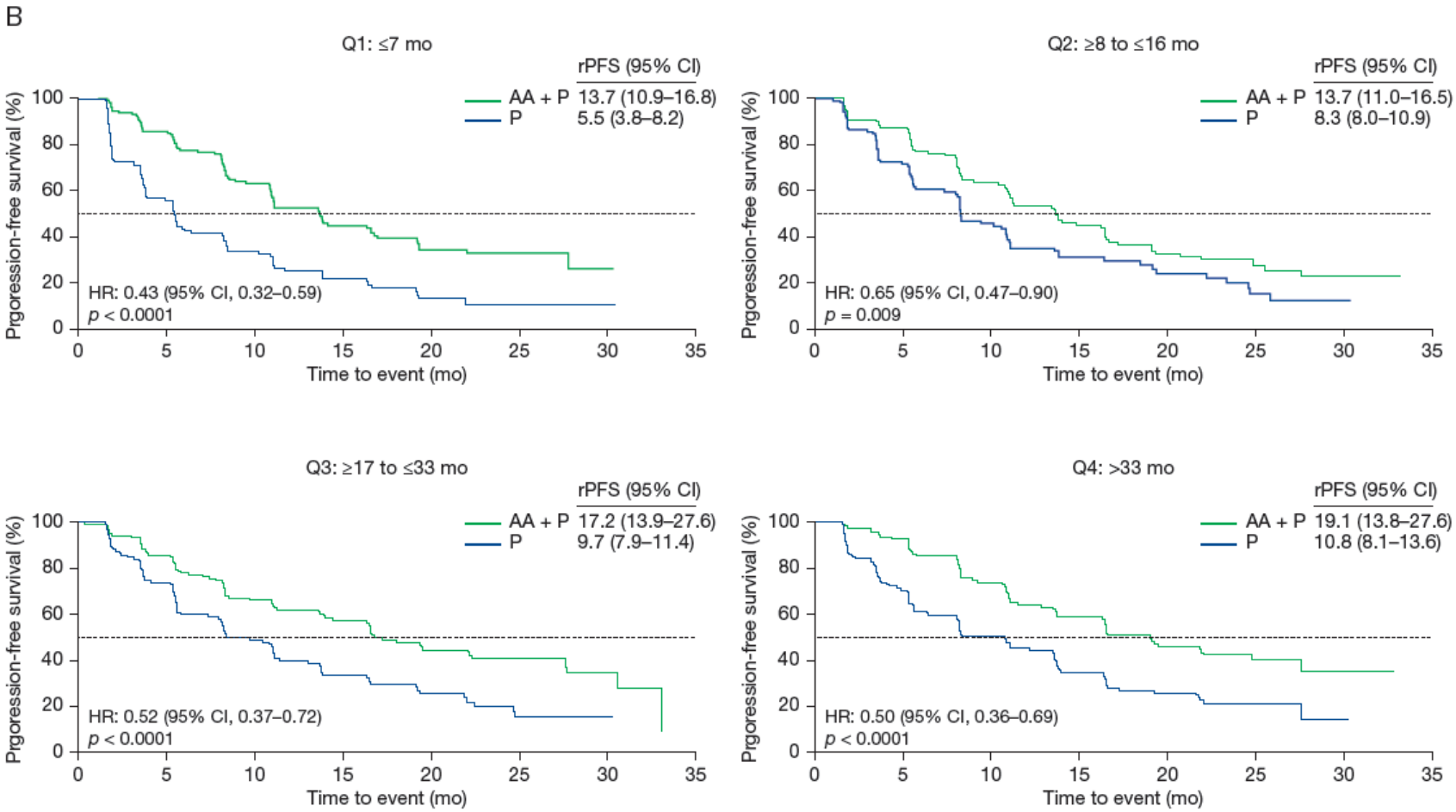
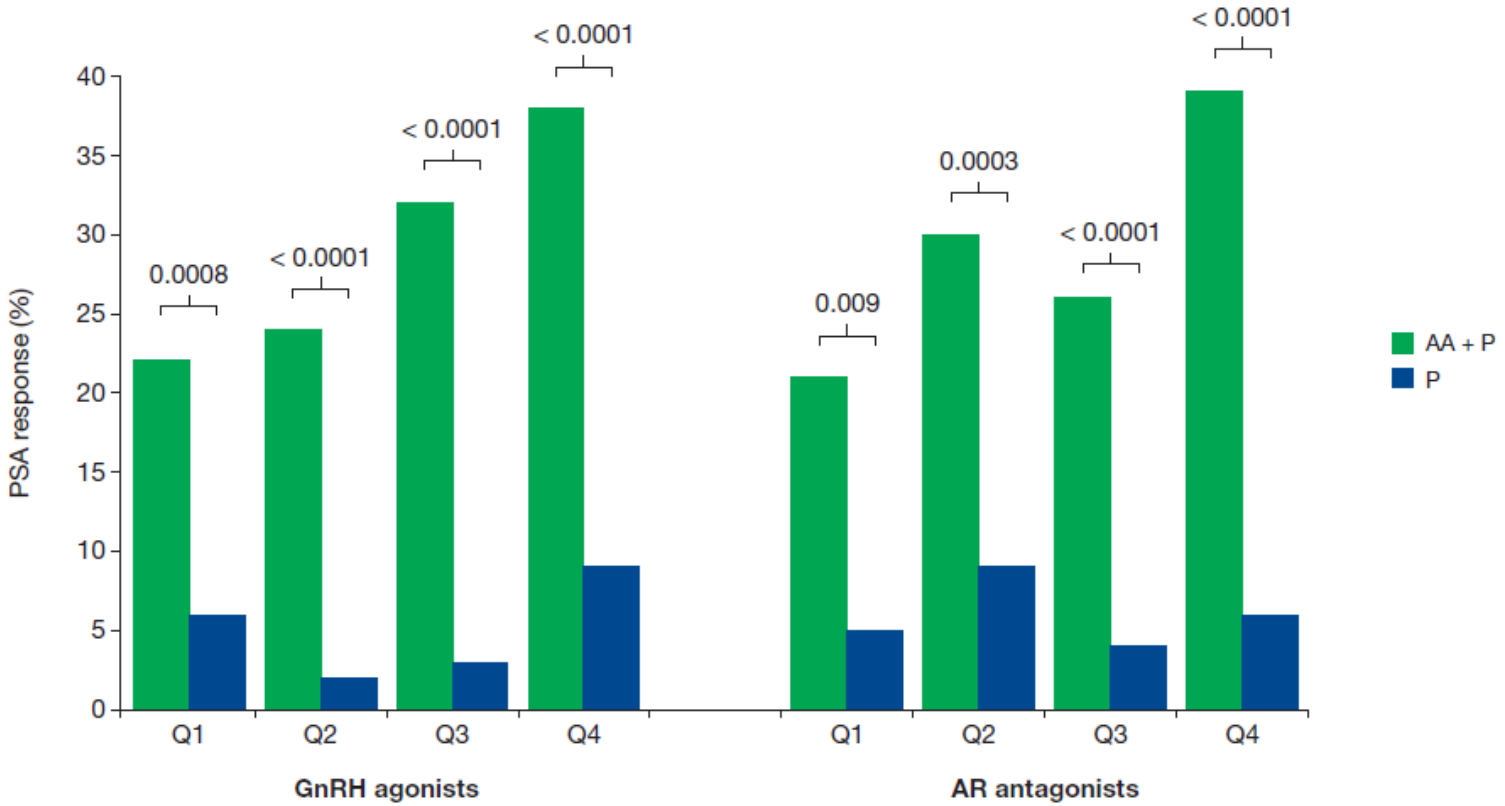

B
Q1: ≤7 mo
rPFS (95% CI)
AA + P 13.7 (10.9–16.8)
P 5.5 (3.8–8.2)
HR: 0.43 (95% CI, 0.32–0.59)
p < 0.0001
Q2: ≥8 to ≤16 mo
rPFS (95% CI)
AA + P 13.7 (11.0–16.5)
P 8.3 (8.0–10.9)
HR: 0.65 (95% CI, 0.47–0.90)
p = 0.009
Q3: ≥17 to ≤33 mo
rPFS (95% CI)
AA + P 17.2 (13.9–27.6)
P 9.7 (7.9–11.4)
HR: 0.52 (95% CI, 0.37–0.72)
p < 0.0001
Q4: >33 mo
rPFS (95% CI)
AA + P 19.1 (13.8–27.6)
P 10.8 (8.1–13.6)
HR: 0.50 (95% CI, 0.36–0.69)
p < 0.0001
Prgoression-free survival (%)
Time to event (mo)

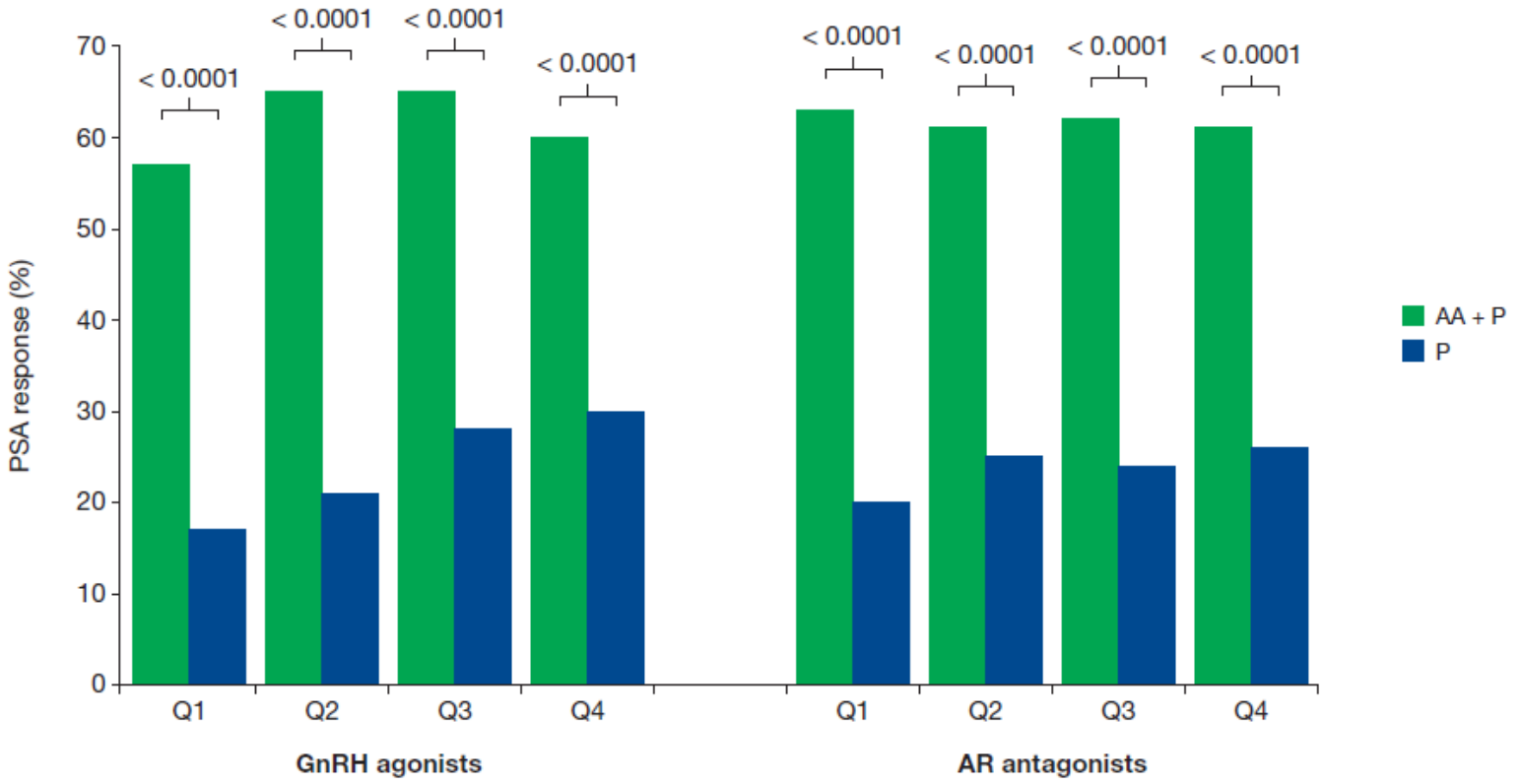
440

441 **Figure 4A**



442

443 **Figure 4B**



444

Supporting Table 1 – Prior endocrine therapies

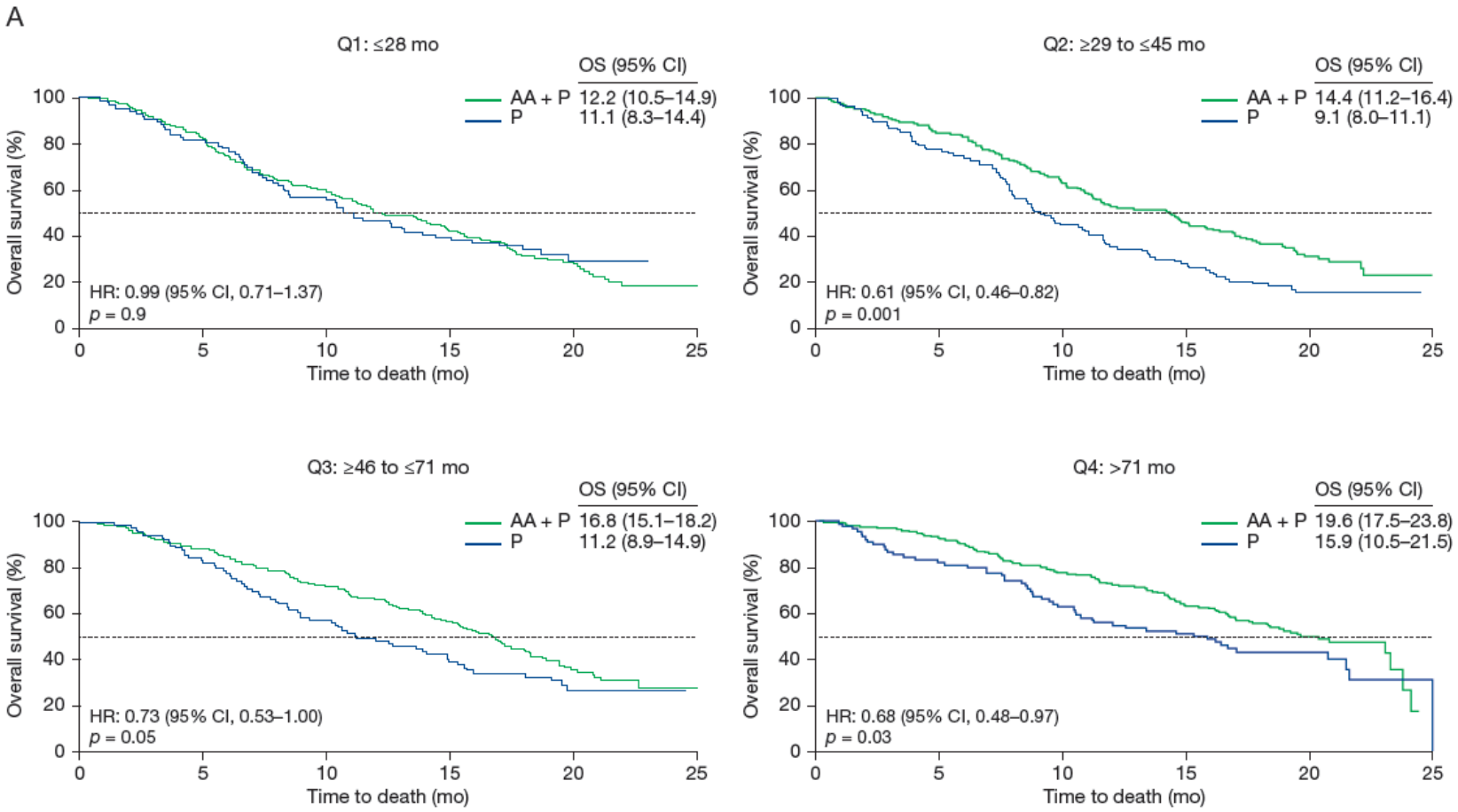
Method of castration	Androgen receptor antagonists
• Buserelin • Buserelin acetate • Gonadotropin-releasing hormone analogues (undefined) • Goserelin • Goserelin acetate • Leuprorelin • Leuprorelin acetate • Orchiectomy • Triptorelin • Triptorelin acetate • Triptorelin embonate	• Androgen receptor antagonists (undefined) • Bicalutamide • Cyproterone • Cyproterone acetate • Flutamide • Nilutamide

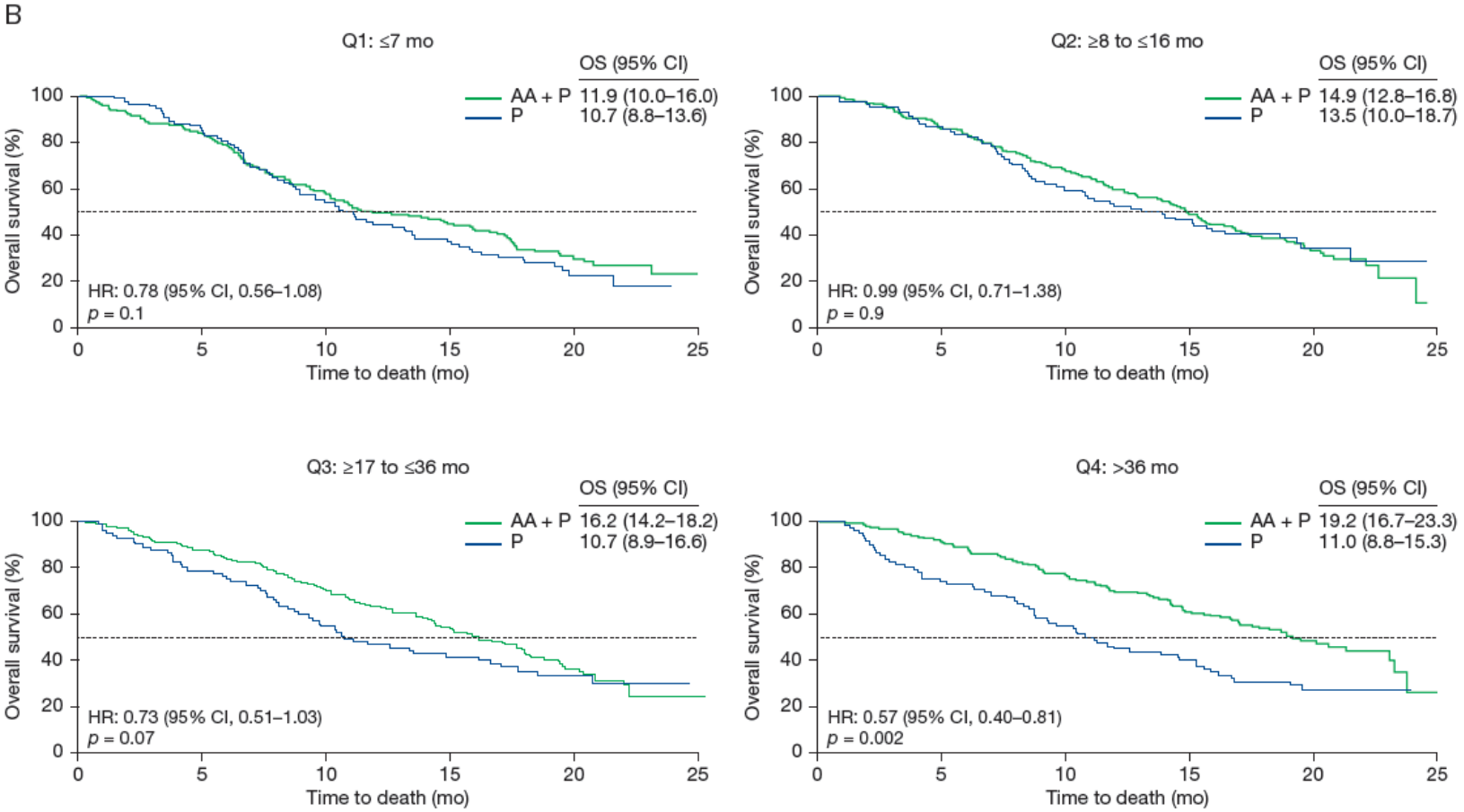
448 Supporting Table 2 – Interaction analysis

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

449

Supporting Fig. 1 – Overall survival Kaplan-Meier estimates in COU-AA-301 patients with prior endocrine therapy exposure by duration in quartiles. A. Gonadotropin-releasing hormone agonists; B. androgen receptor antagonists.

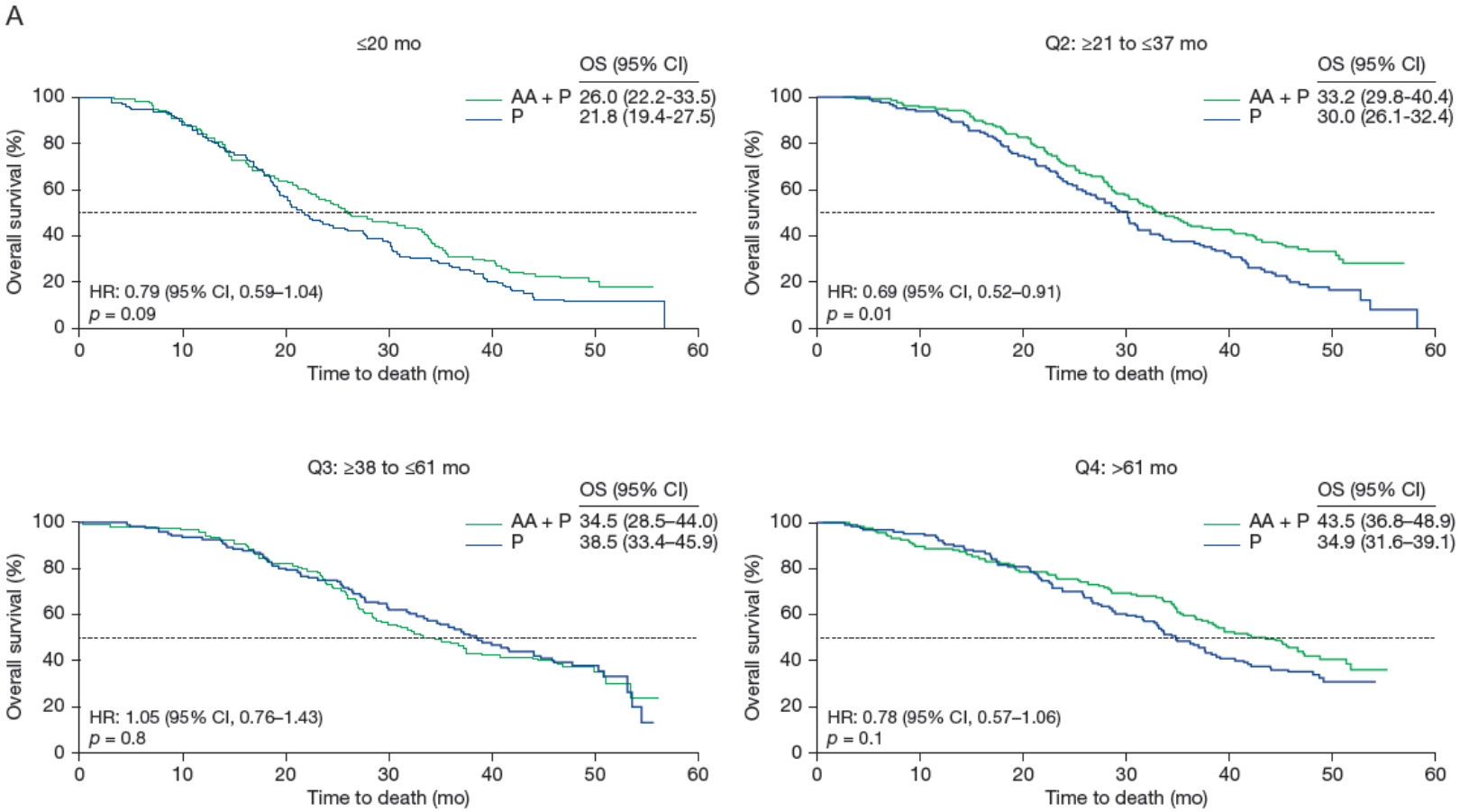




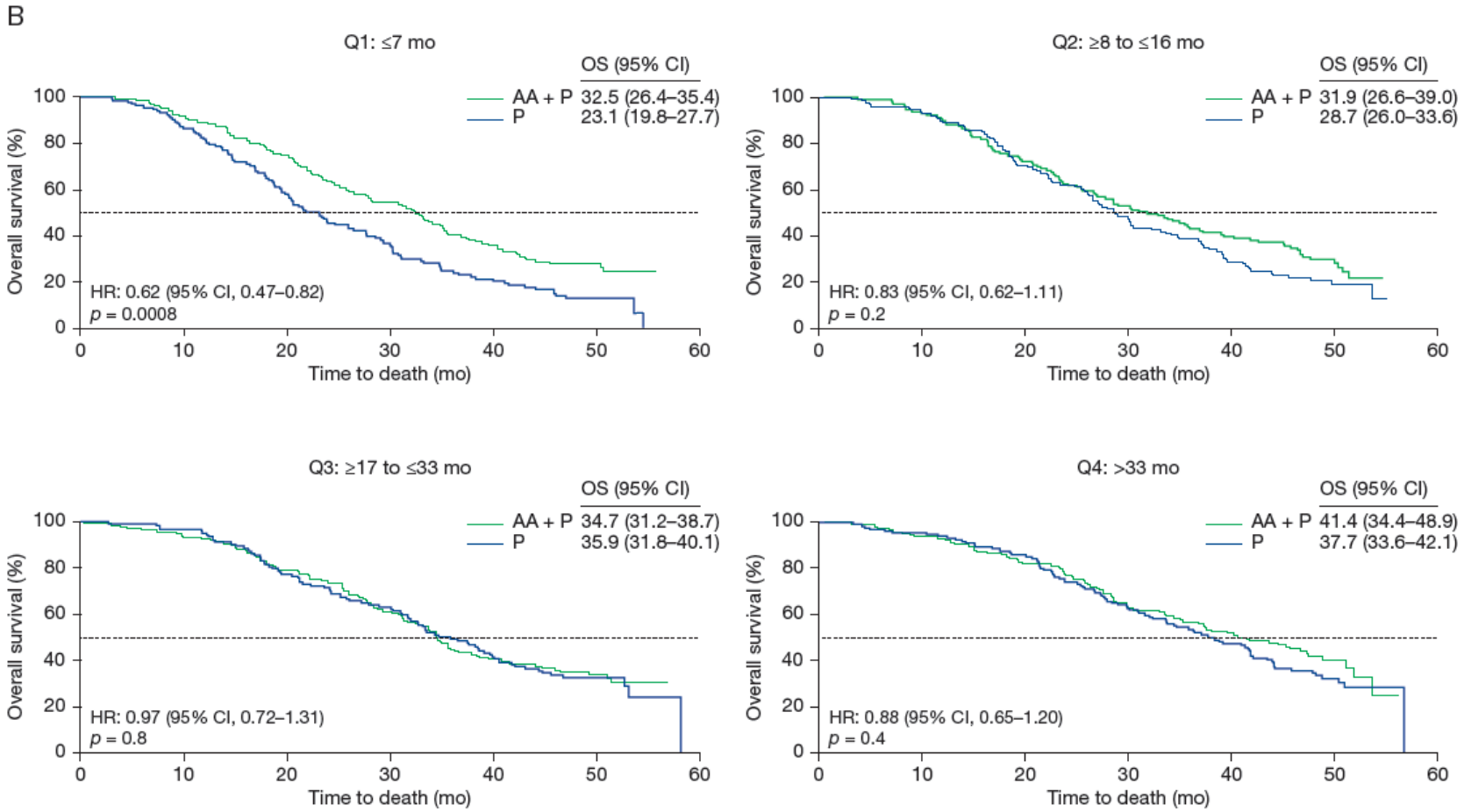
AA = abiraterone acetate; CI = confidence interval; HR, hazard ratio; P = prednisone; OS = overall survival; rPFS = radiographic progression-free survival; Q = quartile.

456 **Supporting Fig. 2 – Overall survival Kaplan-Meier estimates in COU-AA-302 patients with prior endocrine therapy**

457 **exposure by duration in quartiles A. GnRH agonists; B. androgen receptor antagonists.**



458



459
460 AA = abiraterone acetate; CI = confidence interval; HR, hazard ratio; P = prednisone; OS = overall survival; rPFS = radiographic
461 progression-free survival; Q = quartile.