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Improvements in Radiographic Progression-Free Survival Stratified by *ERG* Gene Status in Castration-Resistant Prostate Cancer Patients Treated with Abiraterone

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Abstract

Purpose—Gene fusions leading to androgen receptor–modulated *ERG* overexpression occur in up to 70% of metastatic castration-resistant prostate cancers (mCRPC). We assessed the association between *ERG* rearrangement status and clinical benefit from abiraterone.

Experimental Design—COU-AA-302 is a phase III trial comparing abiraterone and prednisone versus prednisone in chemotherapy-naïve mCRPC. *ERG* status was evaluated by fluorescence *in situ* hybridization on archival tumors. End points included radiographic progression-free survival (rPFS), time to PSA progression (TTPP), rate of ≥50% PSA decline from baseline, and overall

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AUTHOR CONTRIBUTIONS

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Collection and assembly of data: Attard, de Bono, Logothetis, Fizazi, Mukherjee, Joshua, Schrijvers, van den Eertwegh, Li, Molina, Griffin, Kheoh, Ricci, Zelinsky, Rathkopf, Scher, Ryan
Data analysis and interpretation: Attard, de Bono, Li, Molina, Griffin, Ricci, Scher, Ryan
Manuscript writing: All authors
Final approval of manuscript: All authors

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Disclaimer: Abiraterone acetate was developed at The Institute of Cancer Research (ICR) and is licensed to Janssen Biotech. The ICR also has commercial interests in the development of PI3K, AKT, and HSP90 inhibitors. G.A. is included in the ICR co-inventors' reward scheme of abiraterone acetate.

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survival (OS). Cox regression was used to evaluate association with time-to-event measures and Cochran-Mantel-Haenszel for PSA response.

Results—*ERG* status was defined for 348 of 1,088 intention-to-treat patients. *ERG* was rearranged in 121 out of 348 patients with confirmed *ERG* status (35%). Cancers with an *ERG* fusion secondary to deletion of 21q22 and increased copy number of fusion sequences (class 2+ Edel) had a greater improvement in rPFS after abiraterone and prednisone (22 vs. 5.4 months; hazard ratio [95% confidence interval], 0.31 [0.15–0.68], $P = 0.0033$) than cancers with no *ERG* fusion (16.7 vs. 8.3 months; 0.53 [0.38–0.74], $P = 0.0002$) or other classes of *ERG* rearrangement. There was also greater benefit in this subgroup for TTPP.

Conclusions—Both *ERG* rearranged and wild-type cancers had a significant improvement in rPFS with abiraterone and prednisone in the COU-AA-302 trial. However, our data suggest that 2+ Edel cancers, accounting for 15% of all patients and previously associated with a worse outcome, derived the greatest benefit.

Keywords

ERG gene fusions; predictive biomarker; castration-resistant prostate cancer; abiraterone acetate

INTRODUCTION

Abiraterone acetate is a prodrug of abiraterone, a selective androgen biosynthesis inhibitor that blocks cytochrome P450 17A1 (CYP17A1) and suppresses androgen and estrogen synthesis (1, 2). Used in combination with prednisone, abiraterone acetate is now approved for use in men with metastatic castration resistant prostate cancer (mCRPC) in both the pre- and post-chemotherapy treated settings based on demonstrated survival benefit. A review of the outcomes in these populations shows that the response in individual patients ranged from prolonged and durable to none at all, suggesting the presence of molecular alterations in tumors that predict for response. This finding, coupled with the recent approval of several other effective treatments for mCRPC, has highlighted the urgent need for predictive biomarkers that enrich for patient subpopulations in which treatment has a significant effect on clinically meaningful benefits. These associations are best demonstrated in the setting of randomized clinical trials.

Overexpression of E26 transformation–specific (ETS) transcription factor family members has been implicated in prostate cancer progression (3). Recurrent *ETS* gene fusions have been shown to occur in 50–70% of treatment-naïve prostate cancers, resulting in androgen-driven overexpression of ETS family members, most commonly ERG on 21q22.2 (4, 5). We therefore hypothesized that *ERG*-rearranged prostate cancers represent a molecular subtype of prostate cancer that is more sensitive to endocrine manipulations targeting androgen-driven signaling. Examination of patient-matched archival therapy-naïve prostate cancer tissue, CRPC tumor biopsies, and circulating tumor cells obtained prior to starting abiraterone acetate revealed that genomic *ERG* rearrangement status did not change with the development of castration resistance (6). This supported the evaluation of *ERG* gene fusions in archival samples as a predictive biomarker for mCRPC patients receiving treatment with abiraterone acetate and prednisone.

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We previously demonstrated a significant association between *ERG* rearrangement identified by fluorescence *in situ* hybridization (FISH) and magnitude of prostate-specific antigen (PSA) decline in a cohort of pre- and post-chemotherapy CRPC patients treated with abiraterone acetate in phase I/II trials (6). *ERG* gene fusions can occur following either deletion or rearrangement of the region 5′ of *ERG*, and manifest using a break-apart FISH assay with probes to *ERG* and 5′ of *ERG* as either loss of the 5′ probe or a split signal (Supplementary Fig. S1). These two classes are hereafter referred to as Edel and Esplit, respectively. The Edel class can be further subdivided into 1 Edel and 2+ Edel, characterized in the latter case by more than one *ERG* gene fusion sequence. Cancers with 2+ Edel *ERG* rearrangements are associated with worse clinical outcomes independent of the effect of aneuploidy (7, 8). *ERG* gene fusions can also be identified using polymerase chain reaction–based assays, but no association was observed between the presence of *TMPRSS2:ERG* fusion transcripts and PSA decline following treatment with abiraterone acetate (9).

COU-AA-302 was a phase III randomized, double-blind, placebo-controlled study comparing the efficacy and safety of abiraterone acetate and prednisone versus prednisone alone in asymptomatic or mildly symptomatic chemotherapy-naïve patients with mCRPC. Abiraterone acetate and prednisone significantly improved radiographic progression-free survival (rPFS) and demonstrated a trend toward improved overall survival (OS), leading to extension of the regulatory approval for abiraterone acetate to include patients who had not received prior chemotherapy. Patients treated with abiraterone acetate and prednisone also showed a significant improvement in the prespecified secondary end points, including declines in PSA and time to PSA progression (TTPP) (10, 11).

This prospectively defined biomarker substudy of COU-AA-302 aimed to evaluate the association between *ERG* rearrangement subclasses defined by break-apart FISH and clinical outcome in chemotherapy-naïve mCRPC patients receiving abiraterone acetate and prednisone. We focused on *ERG* because it accounts for 90–95% of hormone-driven ETS family member prostate cancer gene rearrangements (4).

METHODS

Study Design and Treatment

The evaluation of association of *TMPRSS2:ERG* tumor status with clinical outcome after treatment with abiraterone acetate and prednisone was prospectively defined as an exploratory end point in the COU-AA-302 trial. A total of 1,088 patients were included in the trial as described previously (abiraterone acetate and prednisone, 546; prednisone alone, 542). Briefly, patients were required to have metastatic, histologically or cytologically confirmed prostate cancer, PSA progression according to Prostate Cancer Clinical Trials Working Group 2 criteria or radiographic progression in soft tissue or bone with or without PSA progression, and ongoing androgen deprivation with a serum testosterone level of less than 50 ng/d l (1.7 nmol/L) (11). Patients with visceral disease were excluded. Patients were stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1) and randomized 1:1 to abiraterone acetate 1 g daily and prednisone 5 mg twice daily, or placebo and prednisone 5 mg twice daily. The co-primary end points were rPFS by independent review and OS. rPFS was defined as the time from randomization to the first occurrence of

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either progression by bone scan, progression by computed tomography or magnetic resonance imaging as defined by modified Response Evaluation Criteria In Solid Tumors version 1.0 criteria, or death from any cause. rPFS by investigator review of bone scans was also conducted. Prespecified secondary end points included time to rPFS by investigator review, TTPP based on Prostate Cancer Working Group 2 criteria (12), and PSA response rate (≥50% PSA decline from baseline). Patients were offered the option to give informed consent to evaluation of *TMPRSS2:ERG* status in their tumor samples, and participating centers collected all available archival samples, which were then shipped to a central laboratory. Approval was obtained from the institutional review board of the participating centers.

ERG gene status was assessed in primary tumor samples by FISH as described previously (7); the assessment was conducted by ORIDIS Biomarkers (Graz, Austria). We used archived, paraffin-embedded, formalin-fixed pathology slides from (*a*) diagnostic tissue biopsy, (*b*) radical prostatectomy specimens, (*c*) transurethral resection of the prostate (TURP) specimens, or (*d*) tumor bone marrow, lymph nodes, or other metastatic sites. Characterization of *ERG* classes is shown in Supplementary Fig. S1. Classification of *ERG* gene status prioritized 2+ Edel over 1 Edel such that if regions of 2+ Edel were observed in combination with other classes, the patient was classified as 2+ Edel. Similarly, 1 Edel was prioritized over Esplit. A 1% cutoff was used for all *ERG* patterns, calculated based on analyses of normal epithelium as described previously (13). Clinical outcomes assessed for association with *ERG* status were rPFS, TTPP, and PSA response (≥50% decline from baseline).

Statistical Analyses

Distributions of time-to-event variables with two-sided 95% confidence intervals (CIs) were estimated using the Kaplan-Meier product limit method. The stratified log-rank test was used for comparisons of time-to-event outcomes for abiraterone acetate and prednisone and prednisone alone subgroups according to *ERG* rearrangement status. Cox regression was used to evaluate association of *ERG* status through hazard ratio (HR) with time-to-event end points, and through odds ratio (OR) with Cochran-Mantel-Haenszel for PSA response in each treatment group separately and in the overall population. Analysis was performed at 43% or 56% OS events as specified in the text. Subjects with missing data for *ERG* status were excluded from the association analysis. If a subject had missing data for a clinically defined end point, that subject was excluded from that particular association analysis. All statistical analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Sample Collection and Patient Characteristics

Of the 1,088 total patients in the intention-to-treat population of the COU-AA-302 trial, 826 consented to participate in this biomarker substudy and samples from 501 patients were collected, including two samples from 14 patients and three or more samples from four patients (Fig. 1). The trial was conducted at 151 sites, of which 119 contributed at least one sample. The majority of patient tissue samples were from trans-rectal biopsies of the

prostate (*n* = 357), with other tissue samples obtained from radical prostatectomy (*n* = 113), TURP (*n* = 44), bone marrow (*n* = 3), lymph nodes (*n* = 6), and other metastatic sites (*n* = 7). *ERG* rearrangement class was defined for 348 of 501 (69%) patients (abiraterone acetate and prednisone, *n* = 178; prednisone alone, *n* = 170). Unevaluable samples (*n* = 171) resulted from various technical issues, including missing sample (*n* = 35), tissue lost in processing (*n* = 36), lack of a hybridization signal (*n* = 69), background binding of probe (*n* = 3), and autofluorescence (*n* = 28).

Demographics and baseline characteristics of the 348 patients with confirmed *ERG* status were similar to those of the intention-to-treat population, with the following exceptions: median time from initial diagnosis and time from start of luteinizing hormone–releasing hormone analog to first dose of abiraterone acetate and prednisone were shorter and more patients were treated by surgery in the biomarker population (Table 1). These differences may be reflective of a higher success rate for obtaining tumor samples from more recently diagnosed patients and those treated by surgery.

Distribution of *ERG* Rearrangement Classes

ERG was rearranged in 121 of 348 patients (35%) (abiraterone acetate and prednisone, *n* = 112; prednisone alone, *n* = 115). Of the 348 patients with confirmed *ERG* status, six patients with an *ERG* rearrangement had solely an Esplit (2%) and 115 patients (33%) had an Edel-type rearrangement. Sixty-four patients with an Edel-type rearrangement were of the 1 Edel class (18%) and 51 (15%) were of the 2+ Edel class (Table 2). Fourteen 1 Edel cancers had areas with Esplit, and 45 2+ Edel cancers had areas with 1 Edel and were prioritized as 1 Edel or 2+ Edel cancers, respectively. Since there were too few Esplit cancers, this class was not included in the analyses of association with clinical outcome. Demographic and baseline characteristics were well-balanced between the rearranged and non-rearranged classes (Supplementary Table S1).

Improvements in rPFS Stratified by *ERG* Class

A significant improvement in rPFS, as measured by independent radiographic review, with abiraterone acetate and prednisone versus prednisone alone was observed in the biomarker population, as described previously in the intention-to-treat population (10) (Fig. 2). Treatment with abiraterone acetate plus prednisone resulted in an improvement in rPFS relative to prednisone alone for all classes of *ERG* rearrangement. By category, the differences were 22.0 months versus 5.4 months for 2+ Edel cancers (HR [95% CI], 0.31 [0.15–0.68], *P* = 0.0033) (Fig. 3A), 13.8 months versus 10.9 months for 1 Edel class (HR [95% CI], 0.56 [0.29–1.08], *P* = 0.0852) (Fig. 3B), and 16.4 months versus 8.3 months nonrearranged class (HR [95% CI], 0.53 [0.38–0.74], *P* = 0.0002) (Fig. 3C). These data suggest that the improvement in rPFS with abiraterone acetate and prednisone for 2+ Edel versus nonrearranged cancers (HR [95% CI], 0.58 [0.30–1.09], *P* = 0.09) is greater than the difference in improvement between other *ERG* classes (HR [95% CI], 0.96 [0.58–1.61], *P* = 0.89) (Fig. 3D). There was no difference in rPFS as assessed by investigator review or OS and different *ERG* classes (Supplementary Table S2).

TTPP Stratified by *ERG* Class

The TTPP in 2+ Edel cancers treated with abiraterone acetate and prednisone was 14 months compared with 8.3 months in 1 Edel and 8.4 months in nonrearranged cancers (Fig. 4A). As with rPFS, the improvement in TTPP in the abiraterone acetate and prednisone arm in 2+ Edel compared with nonrearranged cancers (HR [95% CI], 0.63 [0.38–1.05], $P = 0.0784$) was greater than in 1 Edel versus nonrearranged cancers. Similarly, there was no difference in TTPP between different *ERG* classes in the prednisone alone arm (Fig. 4B). There was no difference in magnitude of PSA decline, which is a less clinically relevant end point, between different *ERG* classes (Supplementary Table S3).

DISCUSSION

Patients with chemotherapy-naïve mCRPC derive greater clinical benefit from abiraterone acetate and prednisone compared with prednisone alone, independent of *ERG* status. The improvement in rPFS and TTPP was greatest in patients with 2+ Edel cancers but did not reach statistical significance, likely due to the small sample size. This interim analysis of the COU-AA-302 trial did not reach significance for OS, and therefore, it was not surprising that we did not observe a significant association between *ERG* status and OS. However, we previously demonstrated a robust association between rPFS and OS (14), which provided support for the use of rPFS as a primary/co-primary endpoint in phase 3 mCRPC studies. In this biomarker population, investigator-defined rPFS was sufficiently different and overall less accurate than centrally reviewed rPFS to explain the absence of the association observed for central rPFS. Noteworthy was that 2+ Edel cancers are associated with a significantly worse outcome in patients who never received abiraterone acetate (7, 8). The 15% frequency of 2+ Edel cancers among patients in the COU-AA-302 population with confirmed *ERG* status is higher than observed previously at the time of diagnosis (7%) (7). Nonetheless, the small overall number of cases (51 in total) limited our ability to confirm a statistically significant difference in HR for the different *ERG* classes.

The biological explanation for these observations is unclear. It is possible that 2+ Edel cancers have significantly higher levels of expression of androgen-driven ERG protein as a result of fusion sequence copy number gain and are therefore more sensitive to downregulation of ERG following inhibition of androgen receptor activation by abiraterone acetate. Alternatively, 2+ Edel cancers could represent a molecularly distinct subclass with structural differences additional to duplication of *ERG* gene fusion sequences. Ongoing molecular studies could explain the differential outcome of *ERG* fusion subclasses. Although studies on metastases obtained at rapid autopsy or by biopsy or capture of circulating tumor cells reported consistent 21q deletion in all CRPC metastases (6, 15), emerging evidence from circulating tumor DNA studies suggests the presence in CRPC of distinct clones with different *ERG* status from the primary tumor (16) This could suggest that strategies for tracking *ERG* status in multiple heterogeneous CRPC clones at initiation of abiraterone acetate could more accurately confirm an association between class 2+ Edel and outcome.

Baseline serum androgens (17), circulating tumor cell count (CellSearch) (Scher HI, et al., unpublished observations, 2014) and neutrophil/lymphocyte ratio (18) have been shown to

provide prognostic information in patients receiving treatment with abiraterone acetate and prednisone. Also required are biomarkers that identify subgroups of patients who are most likely to respond in order to guide treatment decisions and improve the prostate cancer management paradigm. The COU-AA-302 phase III study succeeded in collecting tumor samples from close to half of all accrued patients. This confirms the enthusiasm in the prostate cancer community to support molecular characterization analyses, and we trust this will encourage tissue collection to be similarly integrated into future phase III CRPC trials.

There is currently no prospectively collected set of samples that could allow further evaluation of the observations in this study. Overall, our data suggest that identification of 2+ Edel cancers could have a role in a predictive biomarker panel for identifying mCRPC patients who may be more likely to respond to abiraterone acetate and prednisone. Strategies that recognize the potential emergence of CRPC clones with a different *ERG* status and additional factors that could refine the prediction further are under evaluation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosure of potential conflicts of interest

Dr. Attard is an employee of the ICR, which has a commercial interest in the development of abiraterone acetate; has served as a paid consultant/advisor to Abbott Laboratories, Astellas, Janssen-Cilag, Millennium Pharmaceuticals, Novartis, Roche-Ventana, and Veridex; has received research support from Astra Zeneca, Genentech, and Janssen; has patents/licences/royalties from ICR as part of the inventors' rewards scheme; and has received other renumeration from Abbott Laboratories, Astellas, Janssen-Cilag, Millennium Pharmaceuticals, Novartis, Roche-Ventana, and Veridex and has served on a speakers' bureau for Janssen, Sanofi-Aventis and Astellas. Dr. de Bono is an employee of the ICR, which has a commercial interest in the development of abiraterone acetate; has received honoraria from Johnson & Johnson; has served as a paid consultant/advisor to Johnson & Johnson; and has served on a speakers' bureau for Janssen, Sanofi-Aventis and Astellas. Dr. Logothetis has received honoraria from, served as a paid consultant/advisor to, and received research funding from Astellas, Bristol Myers-Squibb, Johnson & Johnson, Pfizer, and

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Exelixis. Dr. Fizazi has served on a speakers' bureau for Janssen. Dr. Mukherjee has received honoraria from and served as a paid consultant/advisor to Janssen and Astellas, and has received paid travel/accommodations/expenses from Amgen. Dr. Joshua has received research funding from Janssen. Dr. Schrijvers has held a leadership role at Janssen Pharmaceutical companies; and has received honoraria from, served as a paid consultant/advisor to, served on a speakers' bureau for, and received research funding from Janssen Pharmaceutical companies and Sanofi. Dr. van den Eertwegh has nothing to disclose. Dr. Rathkopf has received research funding from Janssen. Dr. Scher has served as an unpaid consultant for Aragon Pharmaceuticals, Bristol-Myers Squibb, Celgene, Endo/Orion Pharmaceuticals, Johnson & Johnson Pharmaceutical Development, Medivation, and Millennium; has served as a paid consultant for Millennium, Novartis, and Ortho Biotech Oncology Research and Development; and has received institutional research funding from Aragon Pharmaceuticals, Exelixis, Janssen Research & Development, and Medivation. Dr. Ryan has received honoraria from Janssen. Drs. Li, Molina, Griffin, Kheoh, and Ricci are employees of Janssen and own stock in Johnson & Johnson. Kathy Zelinsky is an employee of Janssen.

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TRANSLATIONAL RELEVANCE

Abiraterone acetate improves survival in CRPC but not all patients respond. With the recent approval of several effective treatments for CRPC, there is an urgent need to develop biomarker strategies that identify patient sub-groups enriched for sensitivity to a specific treatment. Here we demonstrate that although all *ERG* classes demonstrated an improvement in radiographic progression-free survival with abiraterone acetate and prednisone compared with prednisone alone in the COU-AA-302 Phase III trial, the molecular sub-class 2+ Edel, which was previously shown to be associated with worse survival, appeared to derive the greatest benefit. Although the biological explanation for this observation remains unclear, our data introduce the possibility that specific biological subtypes of CRPC are more sensitive to AR targeting with abiraterone acetate. This supports the further evaluation of multiplex biomarker panels that include 2+Edel *ERG* rearrangement status defined by FISH studies.

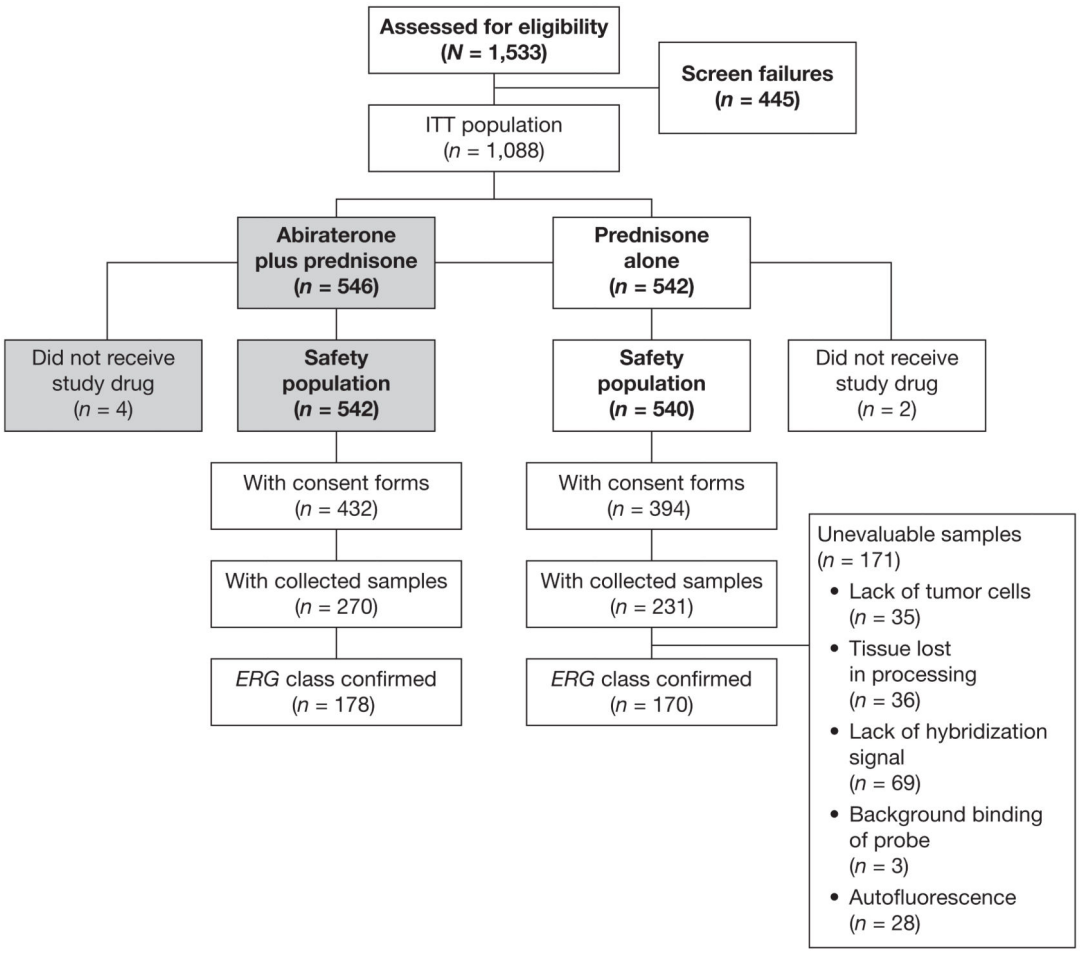

Figure 1.
CONSORT diagram. ITT, intention to treat.

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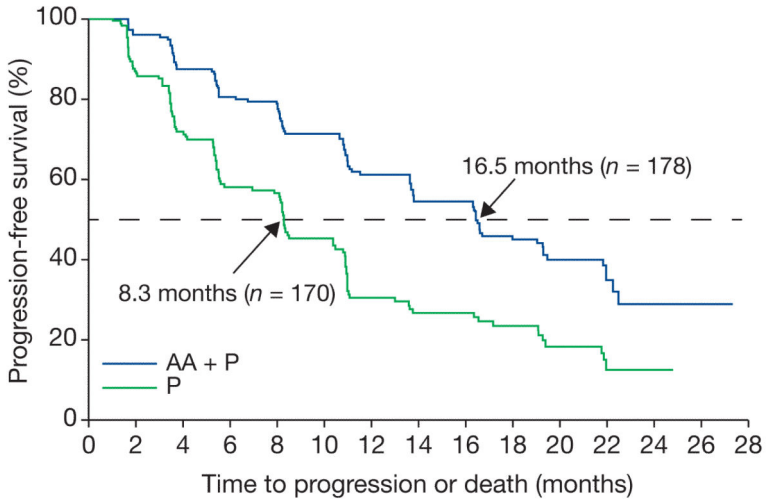

Figure 2.

Radiographic progression-free survival (independent radiographic review)[a] as assessed in the intention-to-treat (A) and biomarker COU-AA-302 (B) populations. [a]Analysis at 56% overall survival events. AA, abiraterone acetate; P, prednisone.

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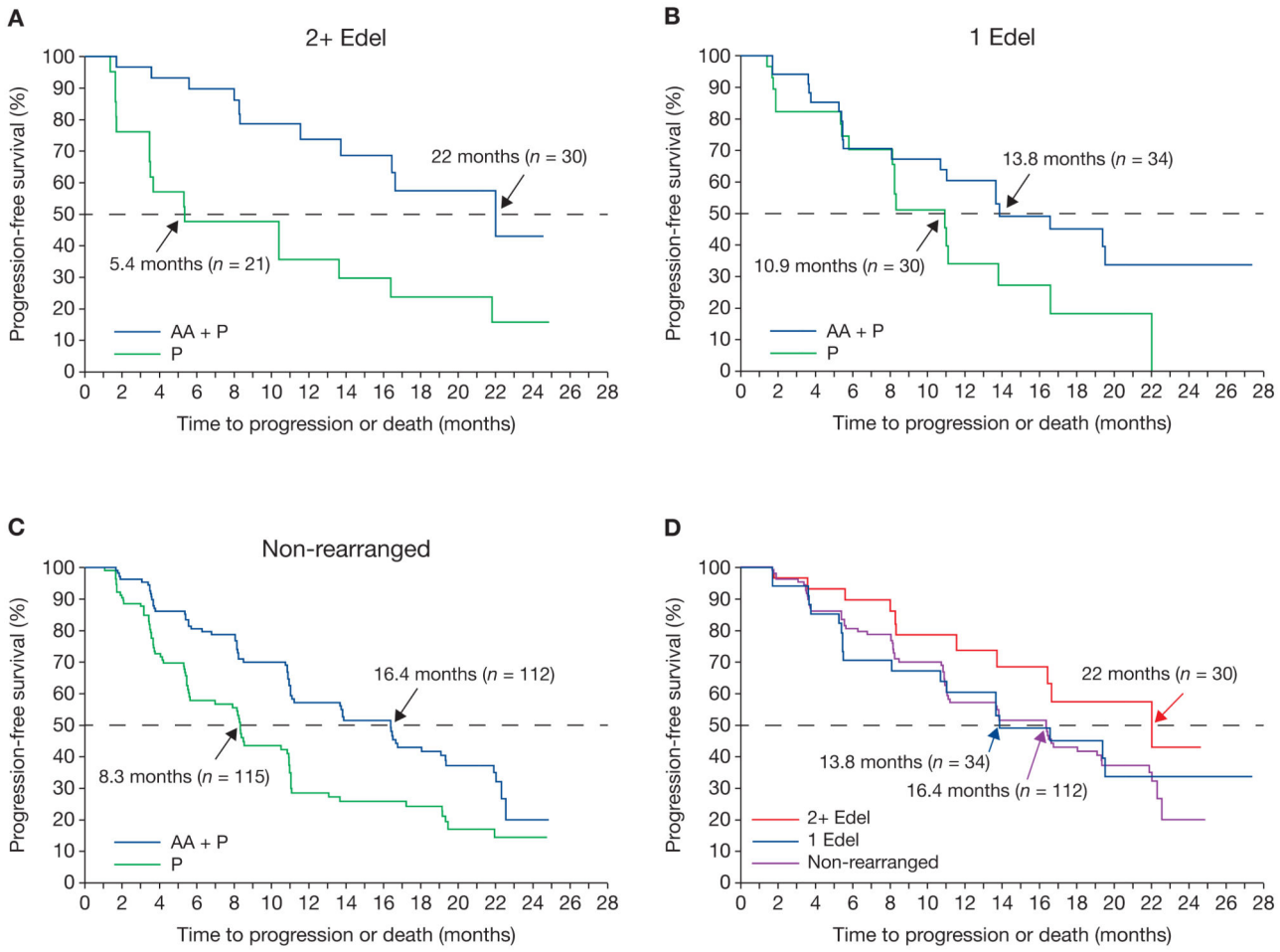

Figure 3.

Treatment effect on radiographic progression-free survival (rPFS) (independent review)[a] in the 2+ Edel, 1 Edel, and nonrearranged *ERG* classes (A, B, C) and rPFS (independent review)[a] by *ERG* class (D). [a]Analysis at 43% overall survival events. AA, abiraterone acetate; P, prednisone.

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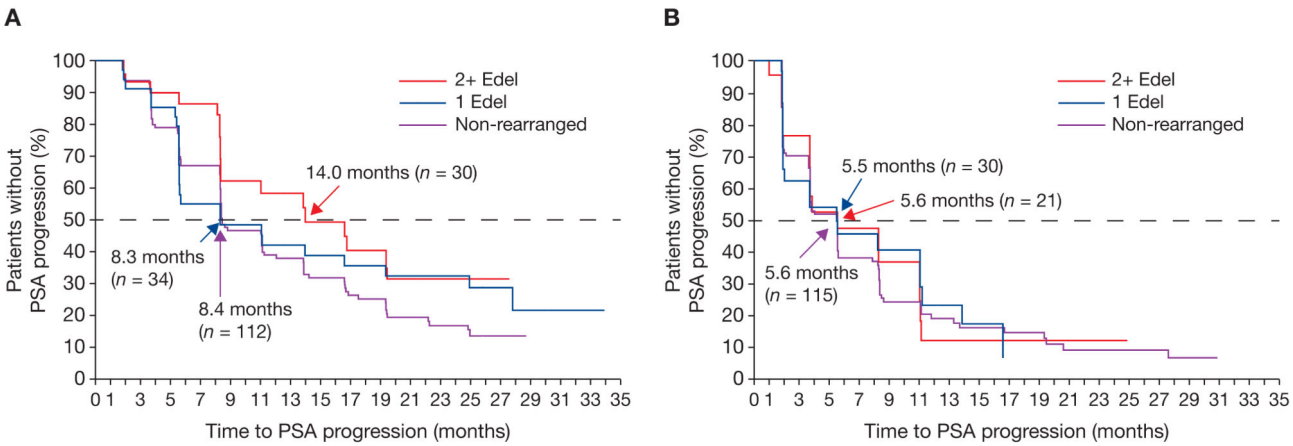

Figure 4.

Time to prostate-specific antigen progression[a] by *ERG* class in the abiraterone acetate and prednisone arm (A) or prednisone alone arm (B). [a]Analysis at 56% overall survival events. PSA, prostate-specific antigen.

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Table 1

Demographics and baseline characteristics

	Biomarker		ITT	
	AA + P (*n* = 178)	**P (*n* =170)**	**AA + P (*n* = 546)**	**P (*n* = 542)**
Median age, years (range)	70 (49–90)	69 (50–89)	71 (44–95)	70 (44–90)
ECOG PS 1	21%	19%	25%	25%
Gleason ≥8	56%	51%	54%	50%
Median testosterone (ng/mL) (range)	0.4(0.1-2.2)	0.4(0.1-3.9)	0.4 (0-2.2)	0.4(0.1-3.9)
Median LDH (IU/L) (range)	181 (60-871)	188 (87-349)	187 (60-871)	184 (87-781)
Median ALP (IU/L) (range)	92 (32-1,927)	90 (21-1,236)	93 (32-1,927)	90 (21-3,056)
Median Hb (g/dL) (range)	13.2 (10-15.5)	13.2 (9.9-16.6)	13.0 (7.2-16.6)	13.1 (7.0-15.7)
Median PSA (ng/mL) (range)	38 (2–1,716)	37 (1–6,606)	42 (0–3,927)	38 (1–6,606)
Median time from initial diagnosis to first dose, years	4.3	4.2	5.5	5.1
Median time from LHRHa to treatment start, years	3.1	3.2	3.4	3.4
Previous cancer treatment				
Surgery	51%	53%	47%	45%
Radiotherapy	51%	52%	52%	56%
Extent of disease				
Bone	80%	81%	83%	80%
Soft tissue	47%	52%	49%	50%
Other	1%	0%	1%	1%

Abbreviations: AA, abiraterone acetate; ALP, alkaline phosphatase; ECOG PS 1, Eastern Cooperative Oncology Group performance status 1; Hg, hemoglobin; ITT, intention to treat; LDH, lactate dehydrogenase; LHRHa; luteinizing hormone–releasing hormone analog; P, prednisone; PSA, prostate-specific antigen; y, years

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Table 2

Frequencies of *ERG* rearrangement patterns in COU-AA-302 compared with previously reported data

Study	*ERG* nonrearranged	*ERG* rearranged	Esplit	Edel Total	1 Edel	2+ Edel
COU-AA-302						
Total population (*N* = 348)	227 (65.2%)	121 (34.8%)	20 (5.7%)	115 (33.0%)	64 (18.4%)	51 (14.7%)
AA + P (*n* = 178)	112 (62.9%)	66 (37.1%)	10 (5.6%)	64 (36.0%)	34 (19.1%)	30 (16.9%)
P (*n* = 170)	115 (67.6%)	55 (32.4%)	10 (5.9%)	51 (30.0%)	30 (17.6%)	21 (12.4%)
TURPs (7) *N* = 445	311 (69.9%)	134 (30.1%)	41 (9.2%)	93 (20.9%)	65 (14.6%)	28 (6.3%)

Abbreviations: AA, abiraterone acetate; P, prednisone; TURP, transurethral resection of the prostate.