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Prostate Cancer

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.

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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.

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 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 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 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 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%];