Efficacy and Safety of Abiraterone Acetate in Elderly (75 Years or Older) Chemotherapy Naïve Patients with Metastatic Castration Resistant Prostate Cancer

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Purpose: Metastatic castration resistant prostate cancer primarily affects elderly men. In this post hoc analysis we investigated the safety and efficacy of abiraterone acetate in elderly (age 75 years or greater) and younger (less than 75 years) patient subgroups at the prespecified interim analysis (55% of total overall survival events) for the COU-AA-302 (Abiraterone Acetate in Asymptomatic or Mildly Symptomatic Patients with Metastatic Castration-Resistant Prostate Cancer) trial.

Materials and Methods: Patients were stratified and randomized 1:1 to abiraterone acetate 1,000 mg plus prednisone/prednisolone 5 mg twice daily (abiraterone-prednisone) vs placebo plus prednisone/prednisolone 5 mg twice daily (prednisone alone). Co-primary end points were radiographic progression-free and overall survival. Median time to event and HR were estimated using the Kaplan-Meier method and a Cox model, respectively.

Results: A total of 350 elderly patients treated with abiraterone-prednisone had significant improvements in overall and radiographic progression-free survival vs those with prednisone alone (HR 0.71, 95% CI 0.53–0.96 vs HR 0.63, 95% CI 0.48–0.83), similar to 738 younger patients (HR 0.81, 95% CI 0.63–1.03 vs HR 0.49, 95% CI 0.40–0.59). All secondary end points favored the abiraterone-prednisone arm for both age subgroups. Specific adverse events with abiraterone-prednisone were similar between the age subgroups. Elderly patients in both treatment arms had higher rates of fluid retention and cardiac disorders than younger patients, although rates of dose reduction or treatment interruptions due to adverse events were low in both age subgroups.

Conclusions: Abiraterone acetate demonstrated clinical benefit and was well tolerated in elderly and younger men with chemotherapy naïve, metastatic castration resistant prostate cancer. Thus, findings support it as a treatment option for elderly patients who may not tolerate other therapies with greater toxicity.

Key Words: prostatic neoplasms; aged; 17-(3-pyridyl)-5, 16-androstadien-3beta-acetate; drug tolerance; treatment outcome

Abbreviations and Acronyms

AE = adverse event

ECOG PS = Eastern Cooperative Oncology Group performance status

mCRPC = metastatic castration resistant prostate cancer

OS = overall survival

PSA = prostate specific antigen

rPFS = radiographic progression-free survival

TTPP = time to PSA progression

Accepted for publication June 9, 2015.

Study received review board approval at all participating institutions.

Supported by Janssen Research & Development (formerly Ortho Biotech Oncology Research & Development) unit of Cougar Biotechnology.

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† Financial interest and/or other relationship with Janssen.

‡ Financial interest and/or other relationship with Johnson & Johnson.

0022-5347/15/1945-1277/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2015.07.004
Vol. 194, 1277-1284, November 2015
Printed in U.S.A.

Prostate cancer is a leading cause of cancer death in older men.[1] Compared with younger patients (age less than 75 years) elderly men are more likely to present with advanced disease.[2] Analysis of the SEER (Surveillance, Epidemiology and End Results) database showed that almost half (48%) of all metastatic prostate cancer cases and more than half of all prostate cancer deaths were in patients 75 years old or older.[3] Age alone should not prevent patients from deriving benefit from novel therapies.[2] Treatment decisions should be based on patient health status, including consideration of the severity of comorbid conditions.[4] Optimizing therapy for elderly patients who are more likely to experience other medical comorbidities, physical frailty and serious toxicities from certain kinds of treatment (eg chemotherapies) remains a considerable challenge.[2,4–6]

Abiraterone acetate is converted in vivo to abiraterone, an androgen biosynthesis inhibitor, which targets 17 α-hydroxylase/C17,20-lyase. In patients with mCRPC who had received prior docetaxel chemotherapy, treatment with abiraterone acetate (hereafter termed abiraterone) plus low dose prednisone improved OS by 4.6 months (HR 0.74, 95% CI 0.64–0.86, p <0.0001) vs treatment with prednisone alone.[7,8] In a recent post hoc analysis Mulders et al found that in elderly (age 75 years or greater) patients with mCRPC progression after docetaxel chemotherapy, treatment with abiraterone-prednisone vs prednisone alone was well tolerated.[9] It led to improved OS (p = 0.0022, HR 0.64, 95% CI 0.478–0.853), TTPP (p = 0.1995, HR 0.76, 95% CI 0.503–1.155) and rPFS (p = 0.0019, HR 0.66, 95% CI 0.506–0.859).

Study COU-AA-302 compared the efficacy and safety of abiraterone plus low dose prednisone vs prednisone alone in asymptomatic or mildly symptomatic men with chemotherapy naïve mCRPC.[10] Abiraterone-prednisone doubled time to rPFS vs prednisone alone (median 16.5 vs 8.3 months). All secondary end points significantly favored abiraterone-prednisone vs prednisone alone.[10] We present results from a post hoc analysis to assess the efficacy and safety of abiraterone-prednisone vs prednisone alone in elderly (75 years or greater) and younger (less than 75 years) patient subgroups at the prespecified interim analysis for study COU-AA-302.

MATERIALS AND METHODS

Patients and Study Design

Study COU-AA-302 (ClinicalTrials.gov NCT00887198) is a phase III, multinational, randomized, double-blind, placebo controlled study performed at 151 sites in a total of 12 countries.[10] Patients were enrolled from April 2009 to June 2010. Screening procedures to evaluate patient eligibility for study were done within 14 days prior to cycle 1, day 1. Eligible patients were randomized and returned to the site for the cycle 1, day 1 visit and dosing. Randomization took place at all study sites using a centralized interactive web/voice response system. All study personnel were blinded to patient treatment assignments. At the time of disease progression patient treatment assignments remained blinded.

Patients were stratified by ECOG PS score (0 vs 1) and randomized 1:1 to abiraterone acetate 1 gm daily plus prednisone or prednisolone 5 mg twice daily (hereafter termed abiraterone-prednisone) vs placebo plus prednisone/

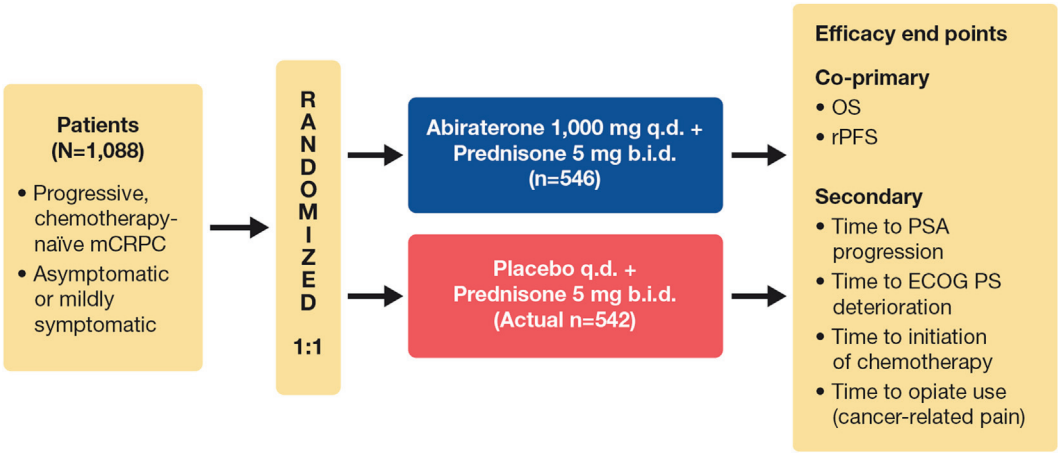

Figure 1. Study COU-AA-302 design. OS was defined as time from randomization to death from any cause. rPFS was determined by independent radiologist unaware of study group assignments, and dates of death were confirmed. rPFS was defined as freedom from death from any cause; freedom from progression in soft tissue lesions as measured with computerized tomography or magnetic resonance imaging, defined as "progressive disease" according to modified Response Evaluation Criteria in Solid Tumors criteria; or progression on bone scan according to criteria adapted from Prostate Cancer Working Group 2.[11] Changes in PSA level were not included in definition of rPFS. *q.d.*, daily. *b.i.d.*, twice daily.