SYNOPSIS

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Name of Sponsor/Company	Cougar Biotechnology, Inc.
Name of Finished Product	Abiraterone acetate
Name of Active Ingredient	Abiraterone acetate (JNJ-212082)

Protocol No.: COU-AA-003 and COU-AA-003 EXT
Clinical Registry No.: NCT00474383

Title of Study:

COU-AA-003: A Phase II Open Label Study of CB7630 (Abiraterone Acetate) in Patients with Advanced Prostate Cancer Who Have Failed Androgen Deprivation and Docetaxel-Based Chemotherapy

COU-AA-003 EXT: An Extended Study of CB7630 (Abiraterone Acetate) in Patients with Advanced Prostate Cancer Who Have Failed Androgen Deprivation and Docetaxel-Based Chemotherapy and Completed Clinical Study COU-AA-003.

EudraCT Numbers: 2006-004571-36 (COU-AA-003) and 2008-002210-22 (COU-AA-003EXT)

Principal Investigators:

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COU-AA-003 EXT: Johann de Bono, M.D., Ph.D. – [redacted], U.K.

Publication (Reference): Reid AH (2010), Attard G, Danila DC, Oommen NB, Olmos D, Fong PC, et al. Significant and sustained antitumor activity in post-docetaxel, castration-resistant prostate cancer with the CYP17 inhibitor abiraterone acetate. J Clin Onc 2010;28(9):1489-95.

Study Period:
Study COU-AA-003: Study initiated 20 November 2006; Last subject enrolled 03 August 2007.
Study COU-AA-003EXT: Study initiated 18 December 2008; Last subject enrolled 07 January 2009.
Date of data cutoff: 22 January 2010

Phase of Development: 2

Objectives: The primary objective of Study COU-AA-003 was to evaluate the anti-tumor effects of abiraterone acetate in subjects with metastatic advanced prostate cancers who failed docetaxel-based chemotherapy, as measured by the proportion of subjects achieving a prostate specific antigen (PSA) decline of ≥50% (PSA response) according to Prostate Specific Antigen Working Group (PSAWG) criteria. The primary objective of Study COU-AA-003EXT was to provide additional abiraterone acetate treatment to subjects in the United Kingdom (UK) who completed 12 cycles of abiraterone acetate treatment and would receive clinical benefit from continued treatment.

Secondary objectives for Study COU-AA-003 were to assess the objective response rate (ORR) in subjects with measurable lesions by Response Evaluation Criteria in Solid Tumors (RECIST); to determine the duration of PSA decline and objective response (if applicable); to determine the duration of progression-free survival (PFS); to determine the safety and tolerability of abiraterone acetate; to assess clinical benefits as determined by disease stabilization and improvement of performance status; to evaluate the role of circulating tumor cell (CTC) enumeration and isolation in the assessment of prognosis; and treatment response in study population (optional assessment). Secondary objectives of Study COU-AA-003EXT were to continue to evaluate the safety and efficacy of abiraterone acetate.

Methods: Study COU-AA-003 was a Phase 2, multi-center, open-label, single-arm study that evaluated anti-tumor effects of abiraterone acetate in subjects with advanced prostate cancer who failed taxane-based chemotherapy,

including docetaxel. Eligible subjects received abiraterone acetate 1000 mg (four 250 mg capsules) orally once daily after an overnight fast. As of Amendment 2 of the study protocol, all ongoing subjects also received concurrent prednisone/prednisolone (5 mg twice daily) or dexamethasone (0.5 mg once daily). Each treatment cycle was 28 ± 2 days. Treatment continued through 12 cycles, or until documented disease progression, lack of disease response after 6 evaluable cycles of treatment, or unacceptable toxicity.

Study COU-AA-003EXT was an extension of Study COU-AA-003 which allowed responding subjects in the UK to continue receiving abiraterone acetate after 12 cycles. Subjects received the same dose and regimen of abiraterone acetate administered during Study COU-AA-003 along with concurrent prednisone/prednisolone 5 mg twice daily or dexamethasone 0.5 mg once daily. Treatment continued until subject's death, loss to follow-up, withdrawal of informed consent, sustained toxicity, disease progression, or the Sponsor's decision to terminate the study. Survival follow-up was performed every 12 weeks for up to 3 years after the subject's entry into the study.

Number of Subjects (planned and analyzed): The total number of subjects planned for Study COU-AA-003 was 33 subjects. An additional 12 subjects were to be enrolled during Study COU-AA-003 EXT. Forty-seven subjects were enrolled in the study; all 47 were included in the intent-to-treat (ITT) and safety populations.

Diagnosis and Main Criteria for Inclusion: Castrated male subjects with metastatic advanced prostate cancer who failed taxane-based chemotherapy, including docetaxel, were eligible for Study COU-AA-003. Subjects must have had histologically or cytologically confirmed adenocarcinoma of the prostate consistent with the diagnosis and an ongoing deprivation with serum testosterone. Eastern Cooperative Oncology Group (ECOG) performance status must have been ≥2 (or Karnofsky Performance Status of at least 50%). Subjects with adrenal insufficiency, hyperaldosteronism, or New York Heart Association classification of III or IV were ineligible. Subjects must have had no other uncontrolled medical condition or comorbidity that could have interfered with their participation in the study. Subjects in the UK who had completed Study COU-AA-003 (12 cycles of treatment) were eligible for Study COU-AA-003EXT.

Test Product, Dose and Mode of Administration, Batch No.: Abiraterone acetate 1000 mg (provided as four 250 mg capsules) administered orally once daily after an overnight fast. Concurrent prednisone/prednisolone 5 mg twice daily or dexamethasone 0.5 mg once daily was administered to all ongoing subjects following Amendment 2 of the study protocol. The batch numbers of abiraterone acetate used in Study COU-AA-003 were: 0244A, 0356B, 0063B, 0321B, 0272B, 0321B, 0357B, 0043C, 9407.001, 0079C, 0095C, 0118C, 0133C, 0166C, 0180C, 0252C, 0299C, 0329C, 0355C, and 0388C. The batch numbers of abiraterone acetate used in Study COU-AA-003 EXT were: 0355C, 0417C, and 0443C.

Reference Therapy, Dose and Mode of Administration, Batch No.: None.

Duration of Treatment: For Study COU-AA-003, treatment continued through 12 cycles, or until documented disease progression, lack of disease response after 6 evaluable cycles of treatment, or unacceptable toxicity. For Study COU-AA-003EXT, treatment continued until subject's death, loss to follow-up, withdrawal of informed consent, sustained toxicity, disease progression, or the Sponsor's decision to terminate the study.

Criteria for Evaluation: The efficacy endpoints for Studies COU-AA-003 and COU-AA-003EXT included the following: serum PSA decline evaluation according to PSAWG criteria; tumor measurements and response evaluation using RECIST criteria; overall survival (OS); and, ECOG performance status evaluations

Safety variables included monitoring of adverse events, clinical laboratory test results, vital signs measurements, physical examination findings, and chest x-rays.

Statistical Methods: The analysis sets included the ITT population (all enrolled subjects) and the safety population (all subjects who received at least 1 dose of study medication). The evaluable population was defined as all subjects who had tumor assessments/PSA assessments at baseline and at least 1 post-baseline assessment, and had received a minimum of 3 evaluable cycles of study treatment. In the event of tumor progression or unacceptable toxicity including death, subjects who received less than 3 evaluable cycles were considered evaluable for efficacy.

Sample size determination: The attained 2-stage design was to allow for the possibility of stopping subject accrual after the first stage. To test a null hypothesis that the PSA response rate is ≤10% versus the alternative that it is

≥30%, an interim analysis occurred after the first 20 subjects in Stage 1 received 3 cycles of abiraterone acetate. The study was to be stopped if fewer than 3 PSA responders were observed after the first stage; otherwise 13 additional subjects were to be enrolled for the study to proceed to the second stage. The null hypothesis of the PSA response rate of less ≤10% was to be rejected with a power of 91% and an alpha of 4% if there were more than 7 responders out of 33 subjects at the end of the second stage. To account for subjects dropouts, more than 33 subjects were enrolled to achieve the required sample size.

Primary efficacy analyses: The primary efficacy endpoint was the evaluation of PSA response according to PSAWG criteria. For COU-AA-003, the first 20 subjects who had 3 evaluable cycles (12 weeks) of study treatment were summarized and analyzed for the Stage 1 assessment of PSA decline by ≥50% according to the PSAWG criteria. The Week 12 response for all subjects was summarized similarly. There were no adjustment and no inferential statistics for the hypothesis testing for the 2-stage design. The exact (Clopper-Pearson) 95% confidence interval (CI) was calculated. The waterfall graphs were produced for the Week 12 and maximal PSA decline.

Secondary efficacy analyses: The key secondary efficacy analyses included PSA response rate, ORR as assessed by the investigator, time to PSA progression, duration of PSA response, progression-free survival as assessed by the investigator, and overall survival. Median time-to-event endpoints were estimated using the Kaplan-Meier method. Response rate was presented using RECIST criteria.

RESULTS:

Study Population:

Forty-seven subjects were enrolled in the study; 34 in the UK and 13 in the United States. All 47 were included in the ITT and safety populations. As of the data cutoff date, 6 subjects had completed Study COU-AA-003, and 6 were receiving treatment in COU-AA-003EXT. Forty-one (87%) subjects discontinued from the study, most frequently due to disease progression (49%) and adverse events (23%). As of the data cutoff, 36 (77%) subjects had died during follow up and 2 (4%) subjects were alive.

The median age of all subjects was 67 years (range: 48 to 87 years). Forty percent of subjects were <65 years of age. Median baseline PSA was 403.0 ng/mL (range: 9.9 to 10325.0 ng/mL). Gleason score was >7 for 38% of subjects, 7 for 32% of subjects, and <7 for 19% of subjects (score missing for 5 subjects). Fifty-seven percent of subjects had an ECOG performance score of 1. Seventy percent of subjects had bone and soft tissue as sites of metastatic disease. All subjects had received prior hormonal, immunological, and/or biological therapy as treatment for prostate cancer and 70% received prior radiotherapy.

Efficacy:

For the primary efficacy endpoint, PSA response, 6 (30%) of the first 20 subjects in Stage 1, had a confirmed PSA decrease from baseline of ≥50%, allowing the study to proceed to Stage 2. At the end of Stage 2, 36% of the total population of 47 subjects had a confirmed PSA decrease from baseline of ≥50%. For all 47 subjects, 45% achieved a confirmed PSA decrease from baseline of ≥50%; 15% had a confirmed decrease in PSA from baseline of ≥90%.

For 23 subjects with measurable disease at baseline, confirmed ORR (complete response [CR] or partial response [PR]) was achieved by 26% of subjects. For the 40 subjects who were considered evaluable for response, 30% subjects were assessed as having a PR.

The median time to PSA progression was 5.6 months for all 47 subjects. For the 21 subjects who were considered responders, the median duration of PSA response was also 5.6 months. The median OS was 12.5 months and the median PFS was 15.0 months. ECOG performance status score changed negligibly with abiraterone acetate therapy.

Safety:

All subjects experienced at least 1 adverse event. Forty-seven percent and 6% of subjects, respectively, experienced Grade 3 and Grade 4 events. The system organ classes with the highest incidences of adverse events were Metabolism and Nutrition Disorders (75%) and General Disorders and Administration Site Conditions (72%). The most frequently reported adverse events were hypokalemia (62%) and fatigue (47%).

Treatment-related adverse events were experienced by 94% of subjects; 23% experienced Grade 3 or 4 treatment-related adverse events. The system organ classes with the highest incidences of treatment-related adverse events were Metabolism and Nutrition Disorders (72%) and General Disorders and Administration Site Conditions (47%). The most frequently reported treatment-emergent adverse events were hypokalemia (57%) and fatigue (32%). Adverse events leading to discontinuation were reported for 19% of subjects; 11% of subjects discontinued due to treatment-related adverse events.

Serious adverse events were experienced by 51% of subjects; 30% experienced treatment-related serious adverse events. Grade 3 and 4 serious adverse events were experienced by 30% and 6% of subjects, respectively. Grade 3 and Grade 4 treatment-related serious adverse events were experienced by 13% and 4% of subjects, respectively. The most commonly reported serious adverse events of all toxicity grades were anemia (11%), nausea (9%), vomiting, and anorexia (6% each). The only Grade 3 serious adverse event reported by more than 2 subjects was vomiting (3 subjects, 6%). The only Grade 4 serious adverse events were anemia (2 subjects, 4%) and transaminases increased (1 subject, 2%).

The most frequently reported adverse event of interest was hypokalemia (62%). All of these events were Grade 1, with the exception of 1 Grade 3 event. Other adverse events of interest were peripheral edema (28%) and hypertension (21%). All other events were experienced by only 1 or 2 subjects. The only Grade 4 adverse event of interest was experienced by 1 (2%) subject who had increased transaminases.

Three subjects died during treatment, all due to events considered by the investigators to be unrelated or unlikely to be related to abiraterone acetate.

No subject experienced a Grade 4 hematology laboratory abnormality during the study, and only 3 subjects experienced a Grade 3 hematology laboratory abnormality Three subjects experienced a Grade 4 chemistry laboratory abnormality during the study: 1 subject each for ALT, AST, and hypophosphatemia. For ALP, Grade 2 and 3 test results were reported for 12 and 14 subjects, respectively, during the study. Ten subjects experienced Grade 3 chemistry laboratory abnormalities during the study for all other chemistry analytes.

CONCLUSION:

Study COU-AA-003 was a Phase 2 study conducted to evaluate the antitumor effects and safety of abiraterone acetate with metastatic advanced prostate cancer who failed androgen deprivation and chemotherapy, including docetaxel. Study COU-AA-003EXT was an extension of Study COU-AA-003 which allowed responding subjects in the UK to continue receiving abiraterone acetate after 12 cycles. In anticipation of Phase 3 study development, this study was designed to confirm the antitumor activity of abiraterone acetate using the proposed registration regimen of abiraterone acetate at 1000 mg daily.

A ≥50% decline in PSA was confirmed in 36% of subjects. This response rate is consistent with Study COU-AA-004, which evaluated abiraterone acetate in 58 patients with advanced prostate cancer who failed docetaxel-based chemotherapy (38%). The median time to PSA progression in this study was 5.6 months, which is identical to that observed in Study COU-AA-004. In Study COU-AA-003, confirmed tumor responses (CR or PR) were observed in 26% of subjects with measurable disease at baseline. For best overall response per RECIST criteria, PR was observed in 30%, SD was reported for 48%, and PD was reported in 22% of subjects with measurable disease at baseline. The median duration of PSA response was 5.6 months, the median OS was 12.5 months, and the median PFS was 15.0 months.

While the duration of treatment was approximately 23 weeks, the longest treatment duration at the clinical cutoff was 148 weeks (2.8 years), and more than 25% of subjects remained on treatment for at least 48 weeks. Treatment compliance was also high (85% of subjects with compliance of 95% to 100%). These extended durations of treatment indicate that abiraterone acetate was well tolerated in this heavily pretreated patient population.

The incidences of mineralocorticoid-related toxicities were concerning (hypokalemia 62%; hypertension 21%), but this may be due to most subjects beginning the study with abiraterone acetate as monotherapy. Although corticosteroids were not mandated at the initiation of the study, the incidence of adverse events related to mineralocorticoid excess with abiraterone acetate monotherapy was of sufficient frequency to support the routine use of glucocorticosteroids. At the discretion of the investigator(s) the majority of subjects (57%) received eplerenone to treat hypokalemia or hypertension. These events were addressed by the addition of low-dose prednisone/prednisolone or dexamethasone via protocol addenda in early 2009. Furthermore, only 1 subject had a dose reduction of abiraterone acetate due to hypertension, and treatment compliance was high, indicating that it was very well tolerated.

The results of Study COU-AA-003 demonstrate that abiraterone acetate is well tolerated, with encouraging antitumor activity in this patient population with advanced prostate cancer as assessed by PSA response by PSAWG criteria; objective response by RECIST criteria; and duration of response. These results also support the use of the 1000 mg daily dose of abiraterone acetate in the treatment of metastatic advanced prostate cancer, in view of the antitumor activity and safety profile observed at this dose.

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