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RESEARCH**

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES-TEAM LEADER'S MEMO

NDA/BLA Serial Number: NDA 202379/N0000

Drug Name: ZYTIGA™

Indication(s): Metastatic (b) (4) (Castration-Resistant) Prostate Cancer
Previously Treated with (b) (4) - (b) (4) Chemotherapy

Applicant: Cougar Biotechnology, Inc.

Date(s): Submission Date: 20 December 2010
PDUFA Due Date: 20 June 2011
Review Completion Date: 14 April 2011

Review Priority: Priority

Biometrics Division: Division of Biometrics 5 (HFD-711)

Primary Reviewer: Lijun Zhang, Ph.D.

Secondary Reviewer: Shenghui Tang, Ph.D., Team Leader

Concurring Reviewer: Rajeshwari Sridhara, Ph.D., Division Director

Medical Division: Oncology Drug Products (HFD-150)

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Project Manager: Amy Tilley

Keywords:

Castration Resistant Prostate Cancer, Overall Survival, Double-Blind, Logrank Test, Interim Analysis

This is an original New Drug Application (NDA) submission seeking the approval of abiraterone acetate with prednisone for the treatment of metastatic castration-resistant prostate cancer (CRPC) in subjects who have received prior chemotherapy containing a (b) (4). The applicant has submitted results from one pivotal study, COU-AA-301, “A phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate plus prednisone in subjects with metastatic castration-resistant prostate cancer who have failed docetaxel-based chemotherapy”. COU-AA-301 study protocol was reviewed and agreed by the Agency under a Special Protocol Assessment for demonstration of efficacy based on overall survival.

The pivotal trial met its study objective by showing a hazard ratio of 0.646 (95% confidence interval: 0.543-0.768, $p < 0.0001$) for the experimental arm ($n=797$) versus the placebo control arm ($n=398$) in overall survival, at the interim analysis when 552 deaths (69% of the planned number of deaths for the final analysis) were observed. The median survival time was 14.8 months in the experimental arm compared to 10.9 months in the placebo control arm. The findings were confirmed in an updated overall survival analysis with 775 deaths (97% of the planned number of deaths for the final analysis). Furthermore, subgroup analyses showed consistent results in favor of abiraterone acetate treatment arm. No major statistical issues were identified in efficacy analyses. For further details regarding the design, data analyses, and results of this phase 3 study, please refer to the statistical review by Dr. Lijun Zhang (April 13, 2011).

This team leader concurs with the recommendations and conclusions of the statistical reviewer (Dr. Lijun Zhang) of this application. The inference regarding favorable benefit-risk profile for the use of abiraterone acetate with prednisone for the treatment of metastatic castration-resistant prostate cancer (CRPC) in subjects who have received prior chemotherapy containing a taxane is deferred to the clinical review team.

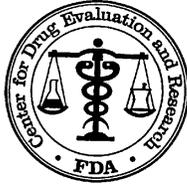
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/s/

SHENGHUI TANG
04/14/2011

RAJESHWARI SRIDHARA
04/14/2011

I concur with the primary reviewer and the team leader's recommendations



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STATISTICAL REVIEW AND EVALUATION

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Review Completion Date: 12 April 2011

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Biometrics Division: Division of Biometrics 5 (HFD-711)

Statistical Reviewer: Lijun Zhang, Ph.D.

Concurring Reviewers: Shenghui Tang, Ph.D., Team Leader
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1. EXECUTIVE SUMMARY

Abiraterone acetate, a steroidal inhibitor of 17-alpha-hydroxylase, is a new molecular entity (NME). In the current original New Drug Application (NDA) submission, the applicant seeks the approval of abiraterone acetate with prednisone for the treatment of metastatic castration-resistant prostate cancer (CRPC) in subjects who have received prior chemotherapy containing a

(b) (4)

This NDA was based on one pivotal trial, COU-AA-301, which is a Phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate plus prednisone versus prednisone alone in subjects with metastatic CRPC who have failed docetaxel-based chemotherapy. This study was agreed by the Agency under a Special Protocol Assessment.

The pivotal trial has met the primary objective with a hazard ratio of 0.646 (95% confidence interval: 0.543-0.768, $p < 0.0001$) for the experimental arm ($n=797$) versus the placebo control arm ($n=398$) in overall survival, at the interim analysis when 552 deaths (69% of the planned number of deaths for the final analysis) were observed. The median survival time was 14.8 months in the experimental arm compared to 10.9 months in the placebo control arm. The findings were confirmed in an updated overall survival analysis with 775 deaths (97% of the planned number of deaths for the final analysis). Furthermore, subgroup analyses showed consistent results in favor of abiraterone acetate treatment. No major statistical issues were identified in efficacy analyses. The final decision on the benefit-risk evaluation of abiraterone acetate treatment is deferred to the clinical review team.

2. INTRODUCTION

2.1 Overview

Docetaxel (plus prednisone) was approved in 2004 for a first-line therapy of androgen independent metastatic prostate cancer subjects based on a 2.4-month increase in median survival from 16.5 months to 18.9 months compared to mitoxantrone (plus prednisone) (Hazard Ratio (HR)= 0.761, 95% confidence interval (CI): 0.619-0.936). Cabazitaxel (plus prednisone) was approved in 2010 as a second-line therapy for hormone-refractory metastatic prostate cancer following a docetaxel-containing regimen. Cabazitaxel treatment improved survival by a median of 2.4 months compared to mitoxantrone (medians 15.1 vs. 12.7 months; HR =0.70; $p < 0.0001$).

Abiraterone acetate is a new molecular entity. *In vivo*, abiraterone acetate is converted to abiraterone, a steroidal irreversible inhibitor of CYP17 (17 α hydroxylase/C17, 20-lyase), which blocks two important enzymatic activities in the synthesis of testosterone. The proposed indication in the current NDA submission is for the treatment of metastatic CRPC in subjects who have received prior chemotherapy containing a (b) (4). A single pivotal trial, COU-AA-301, was conducted to support the proposed indication under IND 71,023.

Study COU-AA-301 was entitled “A phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate plus prednisone in subjects with metastatic castration-resistant prostate cancer who have failed docetaxel-based chemotherapy”. The primary study efficacy

endpoint was overall survival. The secondary efficacy endpoints included time-to-PSA progression, radiographic progression-free survival, and PSA response rate. A total of 1,195 subjects from 147 sites in North America, Europe, and Australia were enrolled and randomized into the study from 08 May 2008 to 28 July 2009, with 498 (41.7%) subjects studied in the United States. As of the study cut-off date (22 January 2010), 276 subjects were still on study treatment.

The original COU-AA-301 protocol was dated 07 February 2008. This study received a special protocol assessment (SPA) agreement in 2008. In the Amendment #3 (dated August 2010), the study was un-blinded per recommendations from the Independent Data Monitoring Committee (IDMC), as the pre-specified interim efficacy analysis boundary of overall survival (552 deaths) was crossed. All subjects in the placebo group were offered the option of abiraterone acetate treatment.

There are no major statistical issues identified for this application.

Table 1: Overview of Pivotal Study COU-AA-301

Study design	Treatment period	Follow-Up period	Treatment arms (number of randomized subjects)	Enrollment period Geographic region: n
Phase III, randomized (2:1), double-blind, placebo-controlled study of abiraterone acetate plus prednisone in patients with metastatic castration-resistant prostate cancer who have failed docetaxel-based chemotherapy	Treated until PD or unacceptable toxicity	Follow-up for survival every 3 months up to 5 years	Abiraterone Acetate + Prednisone (n=797) Placebo + Prednisone (n=398)	08 May 2008 – 28 July 2009 147 sites in: North America: 652 (Canada: 154; United States: 498) Europe: 439 Australia: 104

Throughout this review, subjects who were randomized to receive abiraterone acetate and prednisone are referred as the “abiraterone acetate group” in the text and as “AA” in the tables/figures, whereas subjects who were randomized to receive matching placebo and prednisone are referred as the “placebo group” in the text and as “Placebo” in the tables/figures.

2.2 Data Sources

Analysis datasets and SDTM tabulations are located on network with network path: <\\CDSESUB1\EVSPROD\NDA202379\0000>.

3. STATISTICAL EVALUATION

This statistical evaluation is based on data from the pivotal study COU-AA-301.

3.1 Data and Analysis Quality

The overall survival time and censoring status were derived and saved in an analysis dataset, “ATRISK”. This NDA submission has provided all source data for the death dates as well as the maximal follow-up dates. This reviewer checked and verified that the derived overall survival analysis data could be reproduced from the NDA source datasets.

3.2 Evaluation of Efficacy

3.2.1 Study Design, Endpoints, and Statistical Analysis Plan

3.2.1.1 Overall Study Design

The pivotal trial, COU-AA-301, is a Phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate plus prednisone in subjects with metastatic CRPC who have failed docetaxel-based chemotherapy.

A total of 1,195 subjects were randomized at a 2:1 ratio to receive 4 X 250-mg tablets of abiraterone acetate or matching placebo for treatment arm and placebo arm, respectively. Prednisone 5 mg orally twice daily was co-administered in both arms. Subjects were treated until the disease progression, unacceptable toxicity, initiation of new anticancer treatment, or administration of prohibited medications. The randomization was conducted using a centralized Interactive Web Response System (IWRS) based on four stratification factors:

- baseline ECOG performance status (0-1 versus 2)
- baseline pain (presence versus absence)
- number of prior cytotoxic chemotherapy regimens (1 versus 2)
- documented type of prostate cancer progression at entry (PSA progression only versus radiographic progression in bone or soft tissue with or without PSA progression).

3.2.1.2 Sample Size Determination

Assuming the median survival time in the placebo group was 12 months, a sample size of 1,158 subjects was calculated for the study to have 797 death events needed to detect a 20% reduction in hazard rate (a HR of 0.80; or equivalent, a 3-month increase in median survival) in the abiraterone acetate group relative to the placebo group with a power of 85% at a 2-sided 5% alpha level. A 13-month accrual period was anticipated in the sample size calculation.

3.2.1.3 Efficacy Endpoints

Primary Endpoint

The primary efficacy endpoint was overall survival (OS), defined as the time from date of randomization to the date of death due to any cause. In the absence of a confirmed death, the survival time was censored at the last date subject was known to be alive or at the data cut-off date, whichever had come first.

Secondary Efficacy Endpoints

Secondary efficacy endpoints included:

- Time to PSA progression based on the protocol-specific PSAWG criteria
- Radiographic progression-free survival (PFS) based on imaging studies
- Proportion of subjects achieving a PSA decline $\geq 50\%$ according to the protocol-specific PSAWG criteria

Other Efficacy Endpoints

- Objective response rate according to modified RECIST criteria (baseline lymph node size ≥ 2 cm were considered targeted lesion)
- Proportion of subjects experiencing pain palliation which is defined as a reduction of $\geq 30\%$ in the BSI-SF worst pain intensity score over the last 24 hrs observed at 2 consecutive evaluations 4 weeks apart without any increase in analgesic usage score
- Time to pain progression based on BPS-SF and analgesic usage score
- Time to first skeletal-related event
- Modified PFS based on criteria for discontinuation of study treatment
- Proportion of subjects achieving a decline in circulating tumor cells (CTCs/7.5mL) to <5 with a baseline CTC ≥ 5
- Function status as assessed using FACT-P

3.2.1.4 Efficacy Analysis Population

The Intention-to-Treat (ITT) population was defined as the population of all randomized subjects. Subjects were analyzed in the treatment group as they were assigned to at randomization. The ITT population was the primary analysis population for all efficacy analyses, as well as for analyses of disposition, demographic, and baseline disease characteristics.

3.2.1.5 Analysis Methods

OS was compared between the two treatment groups in the ITT population using the stratified log-rank test with stratification factors at randomization from IWRS: baseline ECOG performance status, baseline pain, number of prior cytotoxic chemotherapy regimens, and documented type of prostate cancer progression at entry. The hazard ratio and corresponding 95% confidence interval were estimated using the Cox proportional hazards model stratified by the same stratification factors as those used for the log-rank test. Survival curves were generated using Kaplan-Meier estimates. The following sensitivity analyses were conducted by the applicant to evaluate the robustness of the primary analysis: a stratified log-rank test using stratification factors based on eCRF data, a non-stratified log-rank test, and an analysis excluding subjects with major protocol deviations. The reviewer also performed a worst-case analysis to further evaluate the OS benefit of abiraterone acetate.

Furthermore, the secondary endpoints such as radiographic progression-free survival, and time-to-PSA progression were compared between the two treatment groups by stratified log-rank test. Hazard ratios and 95% confidence intervals were calculated using the stratified Cox proportional

hazards model. PSA response rate was compared using chi-square test. The type I error rate for these three secondary efficacy endpoints was controlled using Hochberg test procedure.

No type I error adjustments for other exploratory efficacy endpoints were planned.

Reviewer's comments:

- Though the Hochberg test procedure was used to control the overall type I error rate, the secondary endpoints will not be included in labeling due to concerns on the validity and clinical interpretation of their assessment.

3.2.1.6 Interim Analysis

Study COU-AA-301 had a pre-planned interim superiority analysis of OS after occurrence of 534 deaths (67% information) with the O'Brien-Fleming type I error spending function for alpha adjustment (alpha for the interim analysis = 0.0124; alpha for the final analysis = 0.0462).

The IDMC reviewed the OS interim analysis of 552 deaths in August 2010. The nominal significance level for the interim analysis with 552 deaths was 0.0141 (two-sided) using the O'Brien-Fleming spending function. Given an observed p-value of <0.0001, the IDMC concluded that the prespecified efficacy boundary had been crossed and there was a significant OS improvement in favor of abiraterone acetate treatment. The IDMC recommended that the blinded portion of the study be terminated. The study COU-AA-301 was then amended (Amendment #3) to allow subjects in the placebo group to receive abiraterone acetate treatment.

Reviewer's comments:

- The interim analysis with 552 deaths was submitted to support the efficacy in the current NDA submission, with a nominal significance level of 0.0141 (two-sided) per the O'Brien-Fleming spending function.

3.2.2. Efficacy Results

3.2.2.1 Subject Disposition, Demographic and Baseline Characteristics

Subjects Enrollment and Treatment Discontinuation

A total of 1,195 subjects were randomized, with 797 subjects to abiraterone acetate group and 398 subjects to the placebo group, at 147 sites in the U.S., Europe, Australia, and Canada. Of the 1,195 subjects (the ITT population), 10 subjects (6 from abiraterone acetate and 4 from placebo) did not receive study treatment (Table 2).

At the time of study cut-off, the proportions of subjects who discontinued treatment were 72% in the abiraterone acetate group and 86% in the placebo group. The most common reason for discontinuation in both groups was disease progression (39% and 33% in the abiraterone acetate and placebo groups, respectively), as shown in Table 2.

Table 2. Subject Disposition, ITT Population

	AA	Placebo
All Randomized	797 (100.0%)	398 (100.0%)
Never Treated	6 (0.8%)	4 (1.0%)
Treated	791 (99.2%)	394 (99.0%)
Treatment Ongoing	222 (28.1%)	54 (13.7%)
Treatment Discontinued	569 (71.9%)	340 (86.3%)
Reasons for Discontinuation		
Disease Progression	219 (38.5%)	112 (32.9%)
Initiation of new anticancer therapy	107 (18.8%)	64 (18.8%)
Adverse event	98 (17.2%)	70 (20.6%)
Withdrawal of consent to treatment	70 (12.3%)	40 (11.8%)
Investigator discretion	36 (6.3%)	27 (7.9%)
Death	21 (3.7%)	9 (2.6%)
Subject choice	5 (0.9%)	4 (1.2%)
Administration of prohibited medication	3 (0.5%)	1 (0.3%)
Dosing noncompliance	3 (0.5%)	3 (0.9%)
Other	7 (1.2%)	10 (2.9%)

AA=abiraterone acetate

[Source: Study Report COU-AA-301 Table 9]

Demographic and Baseline Characteristics

Demographics and baseline characteristics were balanced between the two groups, as shown in Tables 3 and 4.

Table 3. Demographics, ITT Population

	AA (n=797)	Placebo (n=398)	Total (n=1195)
Age (years)			
Mean (SD)	69.1 (8.40)	68.9 (8.61)	69.0 (8.46)
Median	69.0	69.0	69.0
Range	(42, 95)	(39, 90)	(39, 95)
Ethnicity			
Hispanic or Latino	39 (4.9%)	7 (1.8%)	46 (3.9%)
Not Hispanic or Latino	757 (95.1%)	390 (98.2%)	1147 (96.1%)
Race			
White	743 (93.3%)	368 (92.7%)	1111 (93.1%)
Black	28 (3.5%)	15 (3.8%)	43 (3.6%)
Asian	11 (1.4%)	9 (2.3%)	20 (1.7%)
American Indian or Alaska Native	3 (0.4%)	0	3 (0.3%)
Native Hawaiian or other Pacific Islander	0	0	0
Other	11 (1.4%)	5 (1.3%)	16 (1.3%)

AA=abiraterone acetate

Note: The information of age was not missing for one subject in the placebo arm; the information of ethnicity and race were missing for two subjects, one from each arm.

[Source: Study Report COU-AA-301 Table 10]

Table 4. Baseline Disease Characteristics, ITT Population

	AA (n=797)	Placebo (n=398)	Total (n=1195)
Time since initial diagnosis to first dose (days)*			
Mean (SD)	69.1 (8.40)	68.9 (8.61)	69.0 (8.46)
Median	69.0	69.0	69.0
Range	(42, 95)	(39, 90)	(39, 95)
Baseline PSA (ng/mL)*			
Mean (SD)	439.2 (888.5)	400.6 (810.5)	426.3 (863.2)
Median	128.8	137.7	131.4
Range	(0.4, 9253.0)	(0.6, 10114.0)	(0.4, 10114.0)
Gleason Score at initial diagnosis*			
<7	104 (14.9%)	37 (10.6%)	141 (13.5%)
3+4=7	140 (20.1%)	61 (17.4%)	201 (19.2)
4+3=7	97 (13.9%)	63 (18.0%)	160 (15.3%)
>=8	356 (51.1%)	189 (54.0%)	545 (52.1%)
Evidence of disease progression			
PSA only	238 (29.9%)	125 (31.4%)	363 (30.4%)
Radiographic progression with or without PSA progression	559 (70.1%)	273 (68.6%)	832 (69.6%)
ECOG performance score			
0 or 1	715 (89.7%)	353 (88.7%)	1068 (89.4%)
2	82 (10.3%)	45 (11.3%)	127 (10.6%)
Pain			
Present	357 (44.8%)	179 (45.0%)	536 (44.9%)
Absent	440 (55.2%)	219 (55.0%)	659 (55.1%)
Number of prior cytotoxic chemotherapy			
1	558 (70.0%)	275 (69.1%)	833 (69.7%)
2	239 (30.0%)	123 (30.9%)	362 (30.3%)
Extent of Disease			
Bone	709 (89.2%)	357 (90.4%)	1066 (89.6%)
Soft tissue, not otherwise specified	0 (0%)	0 (0%)	0 (0%)
Node	361 (45.4%)	164 (41.5%)	525 (44.1%)
Viscera, not otherwise specified	1 (0.1%)	0 (0.0%)	1 (0.1%)
Liver	90 (11.3%)	30 (7.6%)	120 (10.1%)
Lung	103 (13.0%)	45 (11.4%)	148 (12.4%)
Prostate mass	60 (7.5%)	23 (5.8%)	83 (7.0%)
Other viscera	46 (5.8%)	21 (5.3%)	67 (5.6%)
Other tissue	40 (5.0%)	20 (5.1%)	60 (5.0%)

AA=abiraterone acetate

* Not available in some subjects

[Source: Study Report COU-AA-301 Table 11]

It is noted that there were 203 subjects with inconsistent stratification factor data between IWRS system and eCRF (Table 5). However, the distribution of randomized subjects was balanced between the two treatment arms by stratification factors either IWRS- based or eCRF-based.

Table 5. Discrepancies on Stratification Factors between CRF and IWRS data, ITT Population

	AA (N=797)	Placebo (N=398)
Total number of subjects with discrepancies	145 (18.2%)	58 (14.6%)
For each stratification factor		
Number of Prior Cytotoxic Chemotherapy Regimens	54 (6.8%)	24 (6.0%)
Evidence of Disease Progression	49 (6.1%)	21 (5.3%)
Pain	47 (5.9%)	18 (4.5%)
ECOG Performance Status	12 (1.5%)	1 (0.3%)

AA=abiraterone acetate

[Source: Study Report COU-AA-301 Attachment 1.1.2]

Reviewer's comments:

- Racial minorities were under-represented in this study. The incidence rates for prostate cancer are significantly higher in African Americans than in whites (232 per 100,000 vs. 146 per 100,000); however, African Americans comprised only 4% of the subject population of this study.
- The primary analysis of OS used stratification variables as recorded in the IWRS system. Given the discrepancies on the stratification factor data between eCRF and IWRS, a sensitivity analysis of OS was performed using stratification variables from eCRF (see Section 3.2.2.3 for more details).

Protocol Deviations

Fifteen percent of subjects in both groups had major protocol deviations, as summarized in Table 6. Enrollment and entry criteria deviations were the most common, accounting for 8% of subjects in the abiraterone acetate group and 9% of subjects in the placebo group. The most frequently violated criterion was the use of prior ketoconazole (2% of subjects in both groups).

The most common major protocol deviation after enrollment and entry criteria deviations was the use of prohibited concurrent medications (5% and 4% of subjects in the abiraterone acetate and placebo groups, respectively), such as 5-alpha reductase inhibitors, non-steroidal antiandrogens, spironolactone, and radioisotopes.

Table 6. Summary of Major Protocol Deviations, ITT Population

	AA (N=797)	Placebo (N=398)	Total (N=1195)
Total no. subjects with a major deviation	122 (15.3%)	60 (15.1%)	182 (15.2%)
Enrollment and entry criteria	65 (8.2%)	34 (8.5%)	99 (8.3%)
Prohibited concurrent medication(s)	41 (5.1%)	16 (4.0%)	57 (4.8%)
Investigational product ^a	11 (1.4%)	4 (1.0%)	15 (1.3%)
Tests/assessments/exams/procedures	8 (1.0%)	5 (1.3%)	13 (1.1%)
Treatment discontinuation not followed per protocol sect. 6.8	1 (0.1%)	6 (1.5%)	7 (0.6%)

AA=abiraterone acetate;

^a This category is comprised of the following deviations: subject missed >14 days per 28-day cycle of study medication in the absence of toxicity, dosing error during treatment, and drug dispensing error.

[Source: Study Report COU-AA-301 Table 15]

Reviewer's comments:

- The major protocol deviations were comparable between the two treatment groups. A sensitivity analysis of the primary endpoint, OS, has been performed with the dataset excluding subjects who had major protocol deviations (see Section 3.2.2.3 for more details).

3.2.2.3 Results and Conclusions

Primary Endpoint Overall Survival Results

Primary Findings Based on Interim Analysis

The interim analysis of overall survival was based on when 552 deaths were observed at the study cut-off date of 22 January 2010 (534 deaths targeted per sample size determination). The results are summarized in Table 7 and Figure 1.

There was an improvement in overall survival for subjects in the abiraterone acetate arm compared to subjects in the placebo arm, with a 3.9-month longer median survival and a statistically significant hazard ratio of 0.646 (95% CI: 0.543-0.768, p-value < 0.0001). The median follow-up time for all subjects was 12.8 months at the cut-off date.

Table 7. Overall Survival Results, ITT Population

	AA (N=797)	Placebo (N=398)
Subjects randomized	797	398
Death	333 (41.8%)	219 (55.0%)
Censored	464 (58.2%)	179 (45.0%)
Overall survival (months) ^a		
Median (95% CI)	14.8 (14.1, 15.4)	10.9 (10.2, 12.0)
p value ^b	< 0.0001	
Hazard ratio (95% CI) ^c	0.646 (0.543, 0.768)	

AA=abiraterone acetate

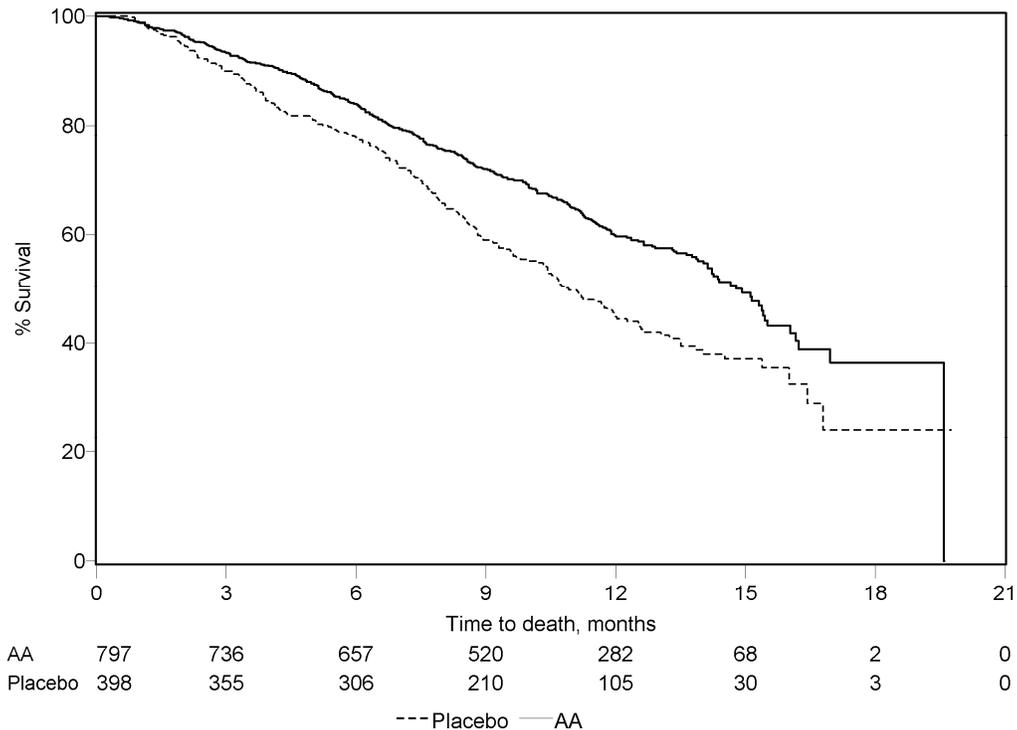
^a Survival time is calculated as months from date of randomization to date of death from any cause. Subjects who are not deceased at time of analysis are censored on the last date subject was known to be alive or lost to follow-up.

^b p value is from a log-rank test stratified by ECOG performance status score (0-1, 2), pain score (absent, present), number of prior chemotherapy regimens (1, 2), and type of progression (PSA only, radiographic).

^c Hazard Ratio is from a stratified proportional hazards model. Hazard ratio <1 favors AA.

[Source: Study Report COU-AA-301 Table 21]

Figure 1 Kaplan-Meier Overall Survival Curves, ITT Population



AA=abiraterone acetate

[Adapted from Study Report COU-AA-301 Figure 4]

Reviewer's comment:

- Per the O'Brien-Fleming boundary, the significance level for the interim OS analysis with 552 deaths was a two-sided alpha of 0.0141. The p-value from the interim OS analysis was <0.0001, which indicated a statistically significant improvement of OS for the abiraterone acetate treatment in the overall study population.

Updated Overall Survival Analysis

An updated overall survival analysis was conducted with 775 deaths observed (97% of the planned number of deaths for final analysis) as of 20 September 2010. The results are shown in Table 8 and Figure 7.

A HR of 0.740 was observed (95% CI: 0.638, 0.859; $p < 0.0001$). The median survival was improved by 41% (15.8 months in the abiraterone acetate group and 11.2 months for the placebo group). The median follow-up was 20.1 months for the study.

Table 8. Updated Overall Survival Results, ITT Population

	AA (N=797)	Placebo (N=398)
Subjects randomized	797	398
Death	501 (62.9%)	274 (68.8%)
Censored	296 (37.1%)	124 (31.2%)
Overall survival (months) ^a		
Median (95% CI)	15.8 (14.8, 17.0)	11.2 (10.4, 13.1)
Hazard ratio (95% CI) ^b	0.740 (0.638, 0.859)	

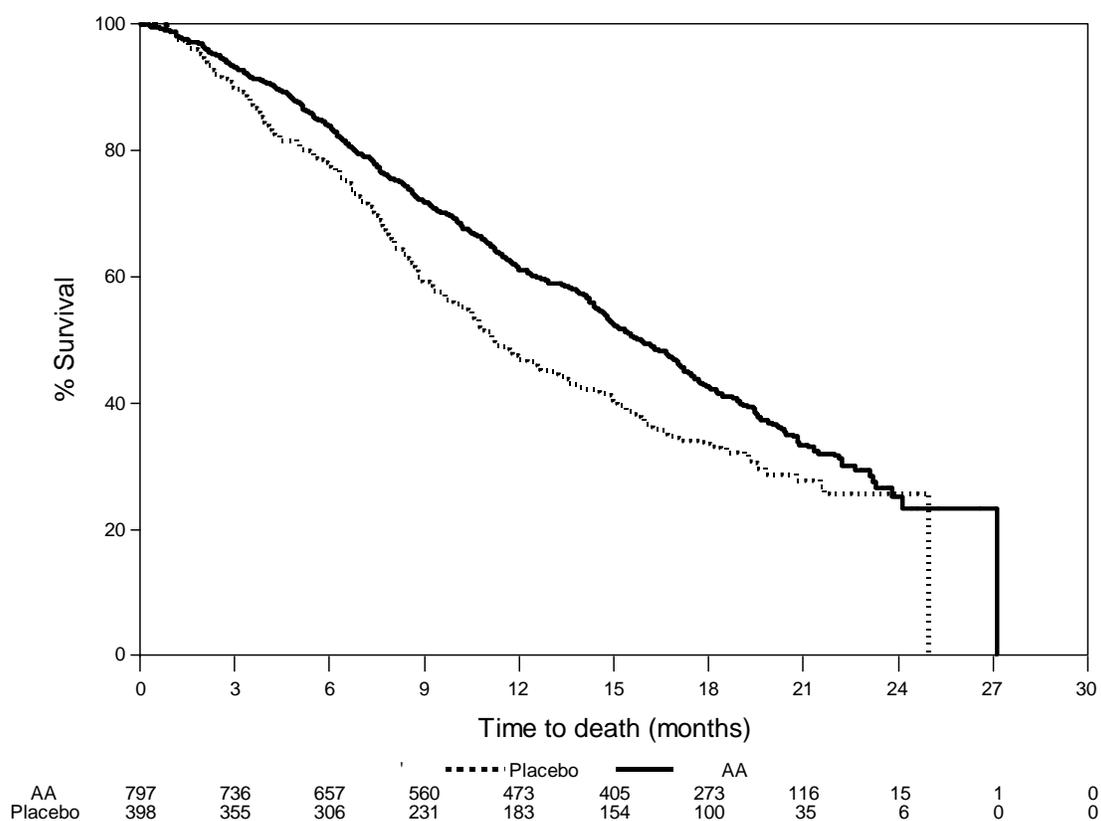
AA=abiraterone acetate

^a Survival time is calculated as months from date of randomization to date of death from any cause. Subjects who are not deceased at time of analysis are censored on the last date subject was known to be alive or lost to follow-up.

^b Hazard Ratio is from a stratified proportional hazards model. Hazard ratio <1 favors AA.

[Source: Study Report COU-AA-301-OS-update Table 1]

Figure 2 Updated Kaplan-Meier Overall Survival Curves, ITT Population



AA=abiraterone acetate

[Adapted from Study Report COU-AA-301-OS-update Figure 1]

Reviewer's comment:

- The updated OS analysis was conducted per the Agency's request to confirm the OS estimates. The cut-off date for the updated OS analysis was before the first subject crossing over. No cross-over data was included in this NDA submission. The reviewer verified that the updated OS analysis was consistent with the interim analysis on the primary findings.

Sensitivity Analyses

Sensitivity analyses on OS conducted by the applicant evaluated the robustness of the OS benefit of abiraterone acetate treatment, as summarized in Table 9.

Table 9. Sensitivity Analyses on Overall Survival

Sensitivity Analysis Description	HR (95% CI) ^a	P-value ^b
1. Using a un-stratified log-rank test	0.664 (0.560-0.788)	<0.0001
2. Based on stratification factor data from eCRF	0.653 (0.549-0.776)	<0.0001
3. Excluding subjects with major protocol deviations (463 death events included: 277 in the abiraterone acetate group and 186 in the placebo group)	0.636 (0.527, 0.769)	<0.0001

^a Hazard ratio is from Cox proportional hazards model. Hazard ratio <1 favors abiraterone acetate.

^b P-value is from logrank test

Reviewer's comments:

- Twelve and four subjects on abiraterone acetate arm and placebo arm, respectively, received docetaxel during the study. To evaluate the impact of these violations on the overall survival, the reviewer did a sensitivity analysis by excluding these sixteen subjects as well as other subjects with major protocol deviations. The hazard ratio was 0.644 (95% CI: 0.533-0.779) with a p-value <0.0001.
- This reviewer performed an exploratory worst case analysis.

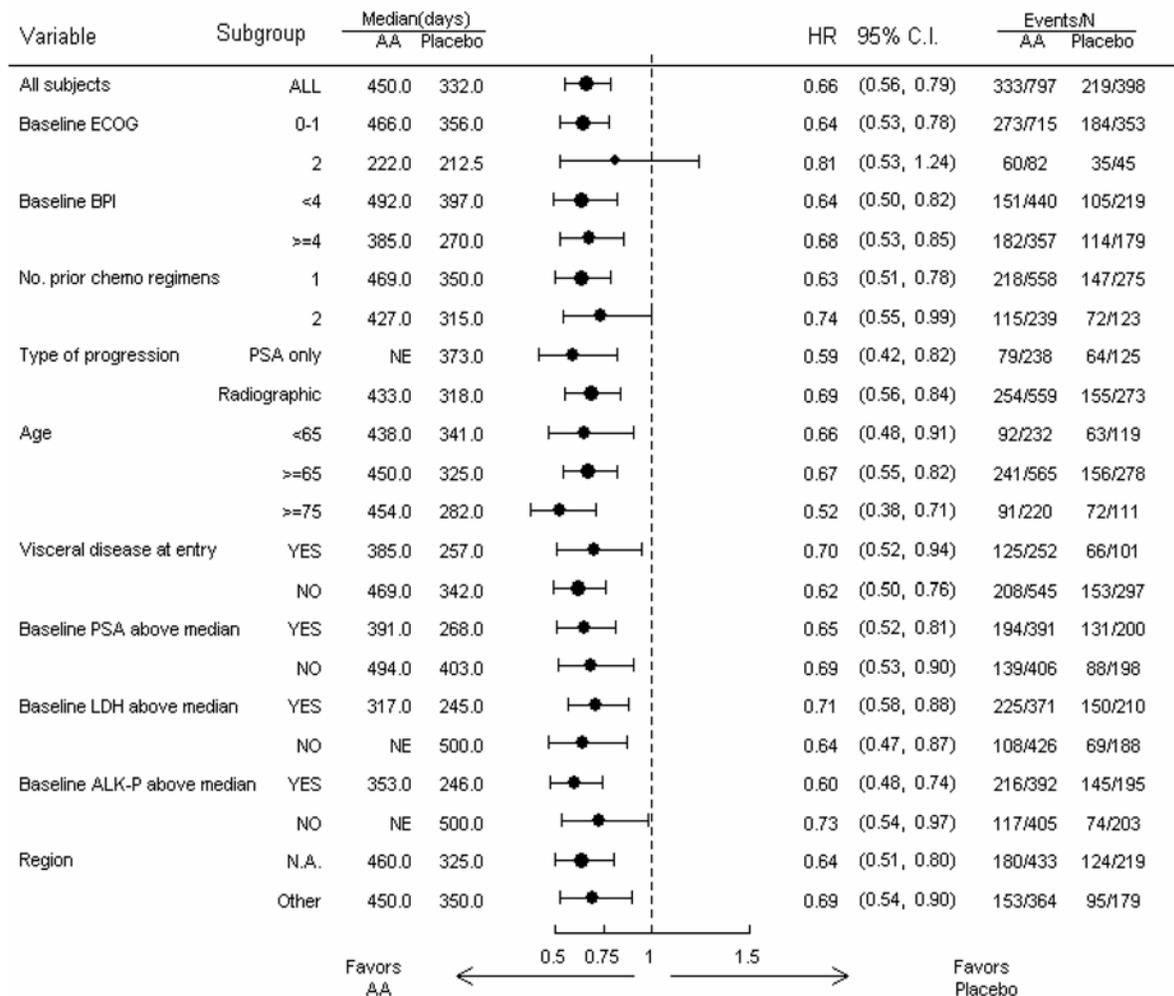
There were 29 subjects (21 in the abiraterone acetate group and 8 subjects in the placebo group) who were either lost to follow up or withdrew consent from study before the study cut-off date. The reviewer performed a worst-case sensitivity analysis assuming that the 21 abiraterone acetate subjects died on the last visit and the 8 placebo subjects survived up to the study cut-off date. The result was in favor of abiraterone acetate too, with a hazard ratio of 0.707 (95% CI: 0.596 – 0.839) and a p-value <0.0001.

- All sensitivity analysis results were consistent with the primary analysis results.

Subgroup Analyses

The treatment effect of abiraterone acetate on OS was consistently favorable across all subgroups. In the subgroup of subjects with baseline ECOG performance status score of 2, the 95% CI was wider and cross the no-treatment-effect reference of HR=1.0, potentially due to small sample size. Results of applicant's subgroup analyses are displayed below.

Figure 3 Subgroup Analyses for Overall Survival



AA=abiraterone acetate; ALK-P=alkaline phosphatase; BPI=Brief Pain Inventory; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; LDH=lactic dehydrogenase; N.A.=North America; NE=not evaluable; PSA=prostate-specific antigen

Note: Hazard ratio is based on a non-stratified proportional hazards model.

[Source: Study Report COU-AA-301 Figure 5]

Secondary Endpoint Results

The results of secondary endpoints are summarized as below:

- The median time to PSA progression was 10.2 months in the abiraterone acetate group and 6.6 months in the placebo group. Treatment with abiraterone acetate decreased the risk of PSA progression by 42% compared with placebo (HR=0.580; 95% CI: 0.462 - 0.728; p<0.0001).
- The median radiographic PFS was 5.6 months in the abiraterone acetate group and 3.6 months in the placebo group. The hazard ratio was 0.673 (95% CI: 0.585 - 0.776) in favor of abiraterone acetate, with a p-value <0.0001.

- The confirmed PSA response was 29% in the abiraterone acetate group, compared to 6% for the placebo group. The p-value was less than 0.0001. Total response (confirmed and unconfirmed) was also greater in the abiraterone acetate group than in the placebo group (38% vs. 10%; p<0.0001).

Reviewer's comments:

- The secondary endpoints were positive in favor of the abiraterone acetate treatment. However, these secondary endpoints will not be included in the label due to concerns on the validity and clinical interpretation.

Results of Other Exploratory Efficacy Endpoints

This pivotal trial had more exploratory efficacy endpoints as listed in Section 3.2.1.3 and no adjustments for multiple testing were planned. The reviewer reported ORR and CTC response rate, as follows:

- Objective Response Rate

Overall response rate (ORR) by RECIST criteria was evaluated in 573 subjects who had measurable disease (392 from the abiraterone acetate group and 181 from the placebo group). The ORR was 14.0% (95% CI: 10.8 - 17.9) in the abiraterone acetate group compared to 2.8% (95% CI: 0.9 - 6.3) in the placebo group.

- CTC Response Rate

As of the clinical cut-off date, only data from sites in North America were available in the clinical database. A total of 293 subjects (188 and 105 in the abiraterone acetate group and the placebo group, respectively) with a baseline CTC count ≥ 5 and at least 1 post-baseline CTC count have been included in this analysis. The proportion of subjects who had a CTC response was 51% in the abiraterone acetate group and 22% in the placebo group.

Reviewer's comments:

- In response to an Information Request by FDA (SN 0004, dated 01 February 2011), the applicant clarified that additional CTC data from the European sites are currently undergoing data reconciliation and are not available for analyses; a separate report will summarize the analysis results based on all CTC data after the NDA review.

Conclusions for Efficacy

The pivotal trial COU-AA-301 met the study objective by showing a hazard ratio of 0.646 (95% CI: 0.543 – 0.768, p-value < 0.0001) for the abiraterone acetate arm versus the placebo arm in overall survival at the interim analysis with 69% information (552 deaths). The median survival time was 14.8 months in the abiraterone acetate arm compared to 10.9 months in the placebo arm. The finding was confirmed by the updated overall survival analysis with 775 deaths (97% of the planned number of deaths for final analysis), with a HR of 0.740 (95% CI: 0.638-0.859;

p<0.0001) and a median survival of 15.8 months versus 11.2 months for the abiraterone acetate arm and the placebo arm, respectively. Furthermore, subgroup analyses showed consistent results in favor of abiraterone acetate. Sensitivity analyses confirmed the findings of the primary analysis. There are no major statistical issues in the efficacy analyses.

3.3 Evaluation of Safety

Please refer to Clinical Evaluations of this application for safety results and conclusions for safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 10 summarized Study COU-AA-301 overall survival subgroup analyses by age, race and geographic region. Subgroup analysis by gender for this male-only study is not applicable.

Table 10. Hazard Ratios for Overall Survival by Age, Race, and Region, ITT Population

	AA # event / n (%)	Placebo # event / n (%)	Hazard ratio* (95% CI)
Age, < 65 yrs	92 / 232 (39.7%)	63 / 119 (52.9%)	0.66 (0.48 – 0.91)
Age, ≥65 yrs	241 / 565 (42.7%)	156 / 278 (56.1%)	0.67 (0.55 – 0.82)
Age, ≥75 yrs	91 / 220 (41.4%)	72 / 111 (64.9%)	0.52 (0.38 – 0.71)
Race, Black	9 / 28 (32.1%)	5 / 15 (33.3%)	1.01 (0.34 – 3.01)
Race, Caucasian/White	311 / 743 (41.9%)	204 / 368 (55.4%)	0.66 (0.55 – 0.79)
Country, USA	142 / 336 (42.3%)	87 / 162 (53.7%)	0.72 (0.55 – 0.93)
Country, non-USA	191 / 461 (41.4%)	132 / 236 (55.9%)	0.63 (0.50 – 0.79)

AA=Abiraterone Acetate

* Hazard ratio for Abiraterone Acetate versus Placebo

Reviewer's comments:

The subgroup analyses by age, race, and geographic region showed that the effect of abiraterone acetate on OS was consistent cross the subgroups, except for black subjects. However, the HR for black subjects was not robust due to a small sample size (n=40).

4.2 Other Special/Subgroup Populations

The applicant performed subgroup analyses for overall survival by the following prognostic factors: ECOG performance status, BPI at baseline, number of prior chemotherapy regimens, documented type of prostate cancer progression at entry, age, visceral disease at entry, baseline PFS level, baseline LDH level, baseline ALK-P level, and region. The hazard ratios were 1 or less than 1 for all subgroups except for subjects with ECOG performance score of 2 which might be due to small sample size. Results of applicant's subgroup analyses for OS are displayed in section 3.1.3 Figure 3.

5. SUMMARY AND CONCLUSIONS

The current NDA application seeks the indication of abiraterone acetate with prednisone for the treatment of metastatic CRPC in subjects who have received prior chemotherapy containing a

^{(b) (4)} The pivotal trial COU-AA-301 study is double-blind, randomized, multicenter, multinational, randomized phase 3 trial compared abiraterone acetate with placebo, in combination with prednisone, for metastatic CRPC subjects who have failed docetaxel-based chemotherapy. This study enrolled a total of 1,195 subjects from 147 sites. The primary efficacy endpoint was overall survival. The abiraterone acetate group showed statistically significant improvement over placebo group with respect to overall survival at the interim analysis (HR: 0.646; 95% CI: 0.543 – 0.768; p-value < 0.0001).

5.1 Statistical Issues and Collective Evidence

There are no major statistical issues identified in this application.

5.2 Conclusions and Recommendations

This NDA submission was based on a multicenter phase 3 randomized trial (COU-AA-301) comparing abiraterone acetate plus prednisone vs. placebo plus prednisone in subjects with metastatic CRPC who have failed docetaxel-based chemotherapy. The trial showed overall survival benefit of abiraterone acetate treatment over placebo. The statistical results support the efficacy claims in the primary endpoint overall survival. The final decision on the benefit-risk evaluation of abiraterone acetate treatment is deferred to the clinical review team.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Lijun Zhang, Ph.D.
Date:

Concurring Reviewer(s)

Statistical Team Leader: Shenghui Tang, Ph.D.

Biometrics Division Director: Rajeshwari Sridhara, Ph.D.

cc:

Project Manager: Amy Tilley

Medical Officer: Yangmin (Max) Ning, M.D; Paul Kleutz, M.D.

Medical Team Leader: Ke Liu, M.D.

Primary Statistical Reviewer: Lijun Zhang, Ph.D.

Statistical Team Leader: Shenghui Tang, Ph.D.

Biometrics Division Director: Rajeshwari Sridhara, Ph.D.

Lillian Patrician

CHECK LIST

Number of Pivotal Studies: 1

Trial Specification

Specify for each trial:

Protocol Number (s): COU-AA-301

Protocol Title (optional): A phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate plus prednisone in patients with metastatic castration-resistant prostate cancer who have failed docetaxel-based chemotherapy

Phase: 3

Control: Placebo Control

Blinding: Double-Blind

Number of Centers: 147

Region(s) (Country): US, Europe, Australia, and Canada

Treatment Arms: abiraterone acetate + prednisone versus placebo + prednisone

Treatment Schedule: (e.g., 40 mg administered orally twice daily (b.i.d.))

Randomization: Yes

Ratio: 2:1

Method of Randomization: stratified, permuted block

Central via an IWRS

If stratified, then the Stratification Factors:

ECOG PS (0 or 1 vs. 2)

Pain (Present vs. Absent)

Number of prior cytotoxic chemotherapy regimens (1 vs. 2)

Evidence of disease progression (PSA only vs. Radiographic progression with or without PSA progression)

Primary Endpoint: overall survival

Primary Analysis Population: ITT

Statistical Design: Superiority

Adaptive Design: No

Primary Statistical Methodology: stratified logrank test

Interim Analysis: Yes

If yes:

No. of Times: 1

Method: stratified logrank test

α Adjustment: Yes

α Spending Function: O'Brien-Fleming Spending Function

DSMB: Yes

Sample Size: 1195

Sample Size Determination: based on primary endpoint OS

Statistic = logrank test statistic

Power= 85%

HR=0.80 (15 months versus 12 months in medians of OS for abiraterone acetate and placebo groups, respectively)

α = 0.05 (2-sided)

- Was there an **Alternative Analysis** in case of violation of assumption; e.g., Lack of normality, Proportional Hazards Assumption violation. No.
- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No.
- Were the **Covariates** pre-specified in the protocol? No.
- Did the Applicant perform **Sensitivity Analyses**? Yes
- How were the **Missing Data** handled? Censored
- Was there a **Multiplicity** involved? No.
If yes,
Multiple Arms (Yes/No)?
Multiple Endpoints (Yes/No)?
Which method was used to control for type I error?
- **Multiple Secondary Endpoints:** Not included in the label

Were Subgroup Analyses Performed? Yes

- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report? No.
- Overall, was the study positive (Yes/No)? Yes

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/s/

LIJUN ZHANG
04/13/2011

SHENGHUI TANG
04/13/2011

RAJESHWARI SRIDHARA
04/13/2011

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 202379 **Applicant: Cougar Biotechnology Inc.** **Stamp Date: 12/20/2010**

Drug Name: Abiraterone Acetate (Zytiga) **NDA Type: NME**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			ISE is not required because the treatment efficacy will be evaluated based on a single study.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			1. Only men were enrolled in the pivotal study 2. Age, race are reported as baseline patient characteristics. 93% are white and 3.6% are black. 3. Subgroup analyses of OS by age were performed
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.			X	

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Lijun Zhang 01/14/2011
Reviewing Statistician Date

Shenghui Tang 01/14/2011
Supervisor/Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LIJUN ZHANG
01/17/2011

SHENGHUI TANG
01/20/2011