CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201023

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES-TEAM LEADER'S MEMO

NDA/Serial Number:	NDA 201023/ SN 002
Drug Name:	Cabazitaxel (XRP6258)
Indication(s):	Treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing treatment regimen
Applicant:	Sanofi-Aventis U.S. Inc.
Date(s):	Submission date: 31 March 2010 PDUFA due date: 1 October 2010 Review completion date: 26 May 2010
Review Priority:	Priority
Biometrics Division:	Division of Biometrics 5 (HFD-711)
Primary Reviewer:	Chia-Wen Ko, Ph.D.
Secondary Reviewers:	Shenghui Tang, Ph.D., Team Leader
Concurring Reviewers:	Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Oncology Drug Products (HFD-150)
Clinical Team:	Amy McKee, M.D., Ian Waxman, M.D., John Johnson, M.D. & Amna Ibrahim, M.D.
Project Manager:	Christy Cottrell

Keywords: hormone refractory prostate cancer, overall survival, superiority

This is an original New Drug Application (NDA) submission seeking the indication of cabazitaxel in combination with prednisone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel (Taxotere®) containing regimen. The applicant has submitted results from one pivotal study, EFC6193, "A randomized, open-label multi-center study of XRP6258 at 25 mg/m^2 in combination with prednisone every 3 weeks compared to mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen". EFC6193 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 0.70 (95% confidence interval: 0.59-0.83, $p<0.0001$) for the experimental arm versus the control arm in overall survival. The median survival time was 15.1 months in the experimental arm compared to 12.7 months for patients in the control arm. Subgroup analyses showed consistent results in favor of cabazitaxel. There were no identified major statistical issues in efficacy analyses to prevent approval. For further details regarding the design, data analyses, and results of this phase 3 study, please refer to the statistical review by Dr. Chia-Wen Ko (May 26, 2010).

This team leader concurs with the recommendations and conclusions of the statistical reviewer (Dr. Chia-Wen Ko) of this application. The inference regarding favorable benefit-risk profile for the use of cabazitaxel in combination with prednisone in patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel (Taxotere®) containing regimen is deferred to the clinical review team.

(Pleased note that this is the updated version of the Team Leader's Memo.)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

SHENGHUI TANG
05/26/2010

RAJESHWARI SRIDHARA
05/26/2010

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

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Table of Contents

1. EXECUTIVE SUMMARY

This is an original New Drug Application (NDA) submission seeking the indication of cabazitaxel in combination with prednisone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel (Taxotere®) containing regimen. This NDA is comprised of one pivotal study, EFC6193, "A randomized, open-label multi-center study of XRP6258 at 25 mg/m^2 in combination with prednisone every 3 weeks compared to mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen". EFC6193 study protocol was reviewed and agreed by the Agency under a Special Protocol Assessment for demonstration of efficacy based on overall survival.

1.1 Conclusions and Recommendations

The pivotal trial met its study objective by showing a hazard ratio of 0.70 (95% confidence interval: 0.59-0.83, p<0.0001) for the experimental arm versus the control arm in overall survival. The median survival time was 15.1 months in the experimental arm compared to 12.7 months for patients in the control arm. Subgroup analyses showed consistent results in favor of cabazitaxel. There were no identified major statistical issues in efficacy analyses to prevent approval. The inference regarding favorable benefit-risk profile for the use of cabazitaxel in combination with prednisone in patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel (Taxotere®) containing regimen is deferred to the clinical review team.

1.2 Brief Overview of Clinical Studies

Table 1 Overview of pivotal study EFC6193

Study design	Efficacy endpoints	Treatment arms (number of randomized patients)	Study period Geographic region: n
Phase III, randomized, open-label, multi-center study of cabazitaxel+prednisone compared to mitoxantrone+prednisone in men with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen	Primary: • Overall survival Secondary: • Progression free survival • Overall response rate • Prostate specific antigen progression • Prostate specific antigen response • Pain progression • Pain response	cabazitaxel + Prednisone (n=378) mitoxantrone + Prednisone (n=377)	02 January 2007 – 25 September 2009 26 countries in: Europe: 402 North America: 235 (Canada: 32; United States: 203) Rest of world: 118

1.3 Statistical Issues and Findings

Major Statistical issues:

There are no major statistical issues identified for this application.

Primary findings:

Primary overall survival analyses from the pivotal study are summarized in Table 2 and Figure 1.

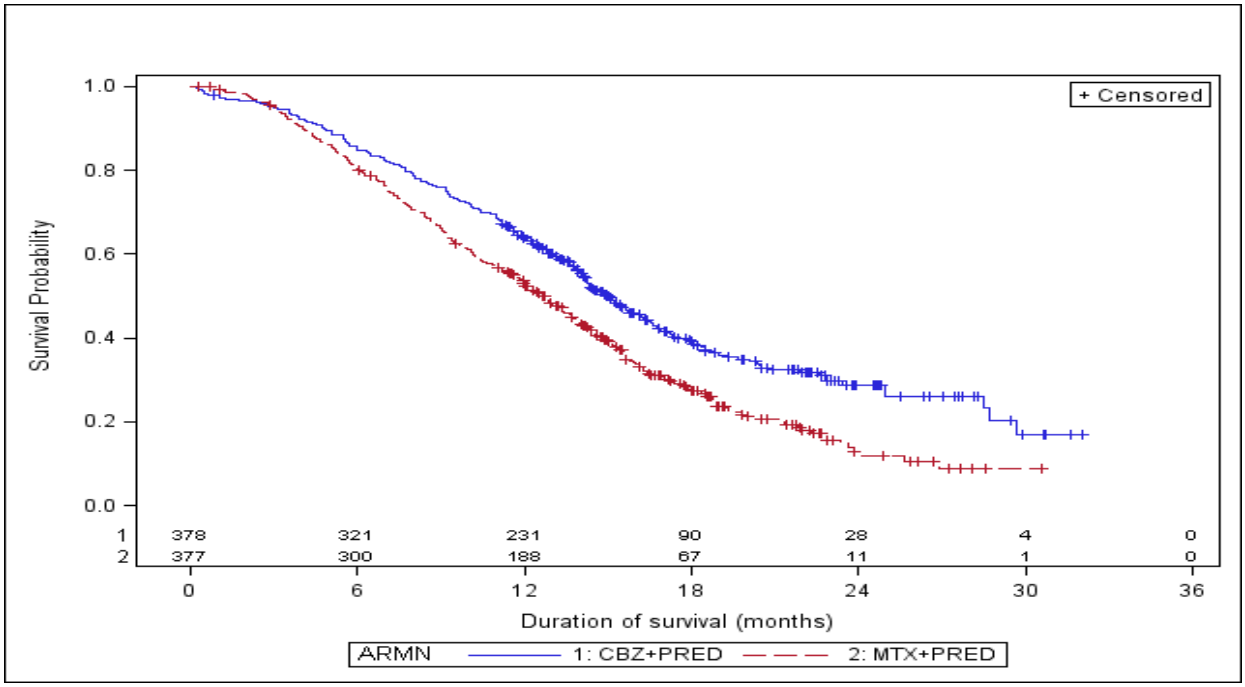
Table 2 Overall survival results - study EFC6193, ITT population

	Cabazitaxel+Prednisone n=378	Mitoxantrone+Prednisone n=377
Number of events (%)	234 (61.9%)	279 (74.0%)
Median survival (month) (95% CI)	15.1 (14.1-16.3)	12.7 (11.6-13.7)
Hazard ratio [1] (95% CI)	0.70 (0.59-0.83)	
p-value [2]	<0.0001	

[1] Hazard ratio estimated using a Cox proportional hazards model stratified by disease measurability and ECOG performance status at baseline

[2] p-value from log-rank test stratified by disease measurability and ECOG performance status at baseline

Figure 1 Kaplan-Meier overall survival curves - study EFC6193, ITT population



CBZ+PRED = cabazitaxel + prednisone; MTX+PRED = mitoxantrone + prednisone

2. INTRODUCTION

2.1 Overview

Docetaxel (Taxotere®) in combination with prednisone was approved in 2004 for the treatment of androgen independent metastatic prostate cancer patients based on an observed 2.4-month increase in median survival from 16.5 months to 18.9 months compared to mitoxantrone plus prednisone. The standard treatment for patients with metastatic hormone refractory prostate cancer following a docetaxel-based regimen in the first line setting is evolving, with no therapy currently approved for treatment of such patients.

The drug cabazitaxel (XRP6258) is a semisynthetic taxane derived from 10-deacetyl Baccatin III. This taxane was selected by the applicant for development based on its ability in stabilizing microtubules and its antitumor activity in tumor models. This drug was filed under investigational new drug (IND) number 56,999. Up to date of this application, cabazitaxel has no approved indications in the United States.

This new drug application (NDA) is based on a single pivotal trial, EFC6193, "A randomized, open-label multi-center study of XRP6258 at 25 mg/m^2 in combination with prednisone every 3 weeks compared to mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen". The primary study efficacy endpoint was overall survival. Secondary efficacy endpoints included: progression-free survival, overall response rate, prostate specific antigen (PSA) progression, PSA response, pain progression, and pain response. The study was conducted from 02 January 2007 for the first patient enrollment to the data cut-off date of 25 September 2009. A total of 755 patients from 26 countries were randomized into the study; 203 or 26.9% of them were studied in the United States.

Study EFC6193 received a special protocol assessment (SPA) agreement in 2006. (b) (4)

Protocol EFC6193 was amended in 2008 under protocol amendment #5 for performing an additional interim overall survival analysis for efficacy at the time of 307 deaths (60% of total required events for the final analysis) based on the O'Brien-Fleming type I error spending function. This amendment was accepted by the Agency.

2.2 Data Sources

Data used for this review are located on network with network path:
\\cdsesub1\evsprod\NDA201023\0002\m5\datasets\efc6193\analysis

Additional data requested for verification purpose are located in:
\\cdsesub1\evsprob\NDA201023\0011\m5\datasets\efc6193\analysis

3. STATISTICAL EVALUATION

Data from the pivotal study EFC6193 will be the basis of this statistical evaluation.

3.1 Evaluation of Efficacy

3.1.1 Study EFC6193 – Overall Design Description

The pivotal trial EFC6193 was a randomized, open-label, multi-national study for testing superiority of cabazitaxel in combination with prednisone over mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.

This study included patients over 18 years of age with hormone refractory metastatic prostate cancer either measurable by RECIST criteria or non-measurable disease with rising PSA levels or appearance of new lesions, and ECOG (Eastern Cooperative Oncology Group) performance status 0-2. Patients had to have neutrophils ≥1,500 cells/mm3, platelets ≥100,000 cells/mm3, hemoglobin ≥10 g/dL, creatinine ≤1.5 x upper limit of normal (ULN), total bilirubin ≤ 1xULN, AST ≤1.5 x ULN, and ALT ≤1.5 x ULN. Patients with a history of congestive heart failure, or myocardial infarction within last 6 months, or patients with uncontrolled cardiac arrhythmias, angina pectoris, and/or hypertension were not included in the study.

Patients were randomized at 1:1 ratio to either cabazitaxel 25 mg/m^2 intraveneously every 3 weeks with prednisone 10 mg orally daily (CBZ+PRED), or to mitoxantrone 12 mg/m^2 intraveneously every 3 weeks with prednisone 10 mg orally daily (MTX+PRED). Each patient was treated until the disease progression, death, unacceptable toxicity or for a maximum of up to 10 cycles. Randomization was based on two stratification factors: measurability of disease (measurable vs. non-measurable) and ECOG performance status (0 or 1 vs. 2).

3.1.2 Study EFC6193 – Planned Statistical Analyses

3.1.2.1 Sample Size Determination

Assuming the median survival time in the MTX+PRED group was 8 months, a sample size of 720 patients was calculated for the study to have 511 death events needed to detect a 25% reduction in hazard rate (a hazard ratio of 0.75; or equivalent, a 2.7-month increase in median survival) in the CBZ+PRED group relative to the MTX+PRED group with a power of 90% at a 2-sided 5% alpha level. A 24-month accrual period was anticipated in the sample size calculation.

3.1.2.2 Efficacy Endpoints and Analysis Methods

Primary Endpoint

The primary efficacy endpoint was overall survival (OS), defined as the time form 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 patient was known to be alive or at the data cut-off date, whichever had come first.

Overall survival was compared between the two treatment groups by the log-rank test stratified by the stratification factors at randomization: measurability of disease per RECIST criteria (measurable versus non-measurable disease) and ECOG performance status (0 or 1 versus 2) in the intent-to-treat (ITT) population with all randomized patients. Estimation of hazard ratio and corresponding 95% confidence interval (CI) were performed 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 by treatment group.

Secondary Endpoints

Secondary efficacy endpoints included:

- PSA response (evaluated in patients with baseline PSA >= 20 ng/mL), as a decline of ≥ 50% from baseline PSA value confirmed by a second PSA value at least three weeks later.
- PSA progression (evaluated in all patients), defined as a ≥ 25% increase over the nadir (provided that the increase in the absolute value PSA level is at least 5 ng/mL) in PSA non-responders; as a ≥ 50% increase over the nadir (provided that the increase in the absolute value PSA level is at least 5 ng/mL) in PSA responders and patients not evaluable for a PSA response.
- Pain Response (evaluate in patients with median PPI ≥2 on McGill-Melzack scale and/or mean Analgesic Score ≥10 points at baseline), defined as a 2-point or greater reduction from baseline median PPI with no concomitant increase in analgesic score, or a reduction of at least 50% in analgesic use from baseline mean AS (only in patients with baseline mean AS ≥10) with no concomitant increase in pain.
- Pain Progression (evaluated in all patients), defined as an increase of ≥1 point in the median PPI from its nadir noted on two consecutive three-week-apart visits or ≥25% increase in the mean analgesic score compared with the baseline score and noted on two consecutive three-week-apart visits or requirement for local palliative radiotherapy.
- Overall response rate (evaluated in patients with measurable disease), defined as the rate of complete or partial responses as assessed by investigators according to RECIST criteria.
- Progression-free survival (evaluated in all patients), defined as the time from randomization to the first occurrence of any of the following events: tumor progression, PSA progression, pain progression, or death due to any cause, whichever occurred first.

Progression-free survival (PFS), PSA progression, and pain progression were compared between the two treatment groups by the log-rank test procedure stratified by randomization factors.

Hazard ratios and 95% confidence intervals were calculated using a Cox proportional hazards model adjusted for stratification variables. Tumor, PSA, and pain response were compared between groups using chi-square tests.

3.1.2.3 Efficacy Analysis Populations

The primary analysis of overall survival was performed in the intent-to-treat (ITT) population with all randomized patients. The applicant also defined a per-protocol population to include patients who received at least one dose of study treatment for supportive analyses purpose only.

Some secondary endpoints were analyzed only in evaluable patients: PSA response was analyzed among patients with baseline PSA ≥ 20 ng/mL; overall response rate was analyzed among patients with measurable disease; pain response was analyzed among patients with median PPI ≥ 2 on McGill-Melzack scale and/or mean Analgesic score ≥ 10 points at baseline.

3.1.2.4 Interim Analyses

Study EFC6193 had a pre-planned interim futility analysis of PFS performed after occurrence of 225 PFS events. This interim analysis was assessed by a data monitoring committee (DMC) for probability of rejecting the null hypothesis of no treatment differences upon completion of the trial to be less than 10% based on the conditional power calculation

Protocol amendment #5, dated 21 July 2008, added one interim analysis of OS for efficacy at the time of 307 deaths (the 60% of 511 deaths needed for the final OS analysis) with the O'Brien-Fleming type I error spending function for alpha adjustment. This amendment was agreed by the Agency.

The PFS interim analysis for futility was performed after 225 PFS events were collected. The stopping criteria were not met, and no adverse safety issues were identified and therefore, the IDMC recommended that the study continue under close observation and the study team to remain blinded to study treatment allocation and outcome of patients on treatment.

The IDMC reviewed the OS interim analysis of 365 deaths in June 2009, did not express any concerns regarding the safety on the 2 study treatment arms, and recommended that the trial should continue to the final analysis. The study team remained blinded to the treatment allocation and outcome throughout the trial.

Reviewer's comment:

The DMC reviewed the interim OS analysis with 365 deaths, instead of 307 deaths as planned. The applicant did not provide a reason for such delay. However, it is unlikely that the DMC would have a different recommendation with an analysis of 307 deaths, which had less information than what was provided from the analysis based on 365 events.

3.1.2.5 Multiplicity Adjustment

Per Statistical Analysis Plan, the statistical significance level for stratified log-rank test at the final OS analysis was calculated to be 0.0476 to adjust for the type I error of 0.0076 spent at the interim analysis with 307 deaths.

The statistical testing of secondary endpoints was conducted at the two-sided 0.05 level in a step-down procedure. The testing was in the order of progression free survival, overall response rate, PSA progression, PSA response, pain progression, pain response.

Reviewer's comments:

- Since the interim OS analysis was conducted with 365 deaths instead of the planned 307 deaths, the statistical significance level for the final OS analysis was re-calculated to become 0.0452 to adjust for the type I error of 0.0160 already spent at the interim analysis per O'Brien-Fleming alpha spending function.
- Although a hierarchical testing procedure was applied to control for overall false positive rate at the level of 0.05, secondary endpoints which have PSA as a component (including PFS, PSA response, and PSA progression) as well as pain and analgesic endpoints (such as pain progression and pain response) (b) (4)
- Some of these analyses were conducted in a subgroup of patients instead of ITT population.

3.1.3 Study EFC6193 – Efficacy Results

Disposition of patients

A total of 755 patients from 26 countries were randomized; 378 patients randomized to the CBZ+PRED group, and 377 patients randomized to the MTX+PRED group. The median age of randomized patients was 67 years (minimum-maximum: 46-92 years). Majority of randomized patients were Caucasian (n=631, 83.6%); followed by Asians (n=58, 7.7%), blacks (n=40, 5.3%), and others (n=26, 3.4%). Three hundred and seventy one (371) patients in each treatment group were treated.

The two treatment groups were compared for demographics, medical history, prior anticancer therapy exposure, and disease or other characteristics at baseline. No major differences were found between the treatment groups.

Overall survival results

Primary findings

Primary overall survival analyses from the pivotal study are summarized below (the same Table 2 and Figure 1 as in section 1.3). At the study cut-off date of 25 September 2009, there were 513 death occurrences (511 deaths targeted per sample size determination). There was an improvement in overall survival for patients in the CBZ+PRED group compared to patients in the MTX+PRED group, with a 2.4-month longer median survival and a statistically significant hazard ratio of 0.70 (95% CI: 0.59 – 0.83, p-value < 0.0001).

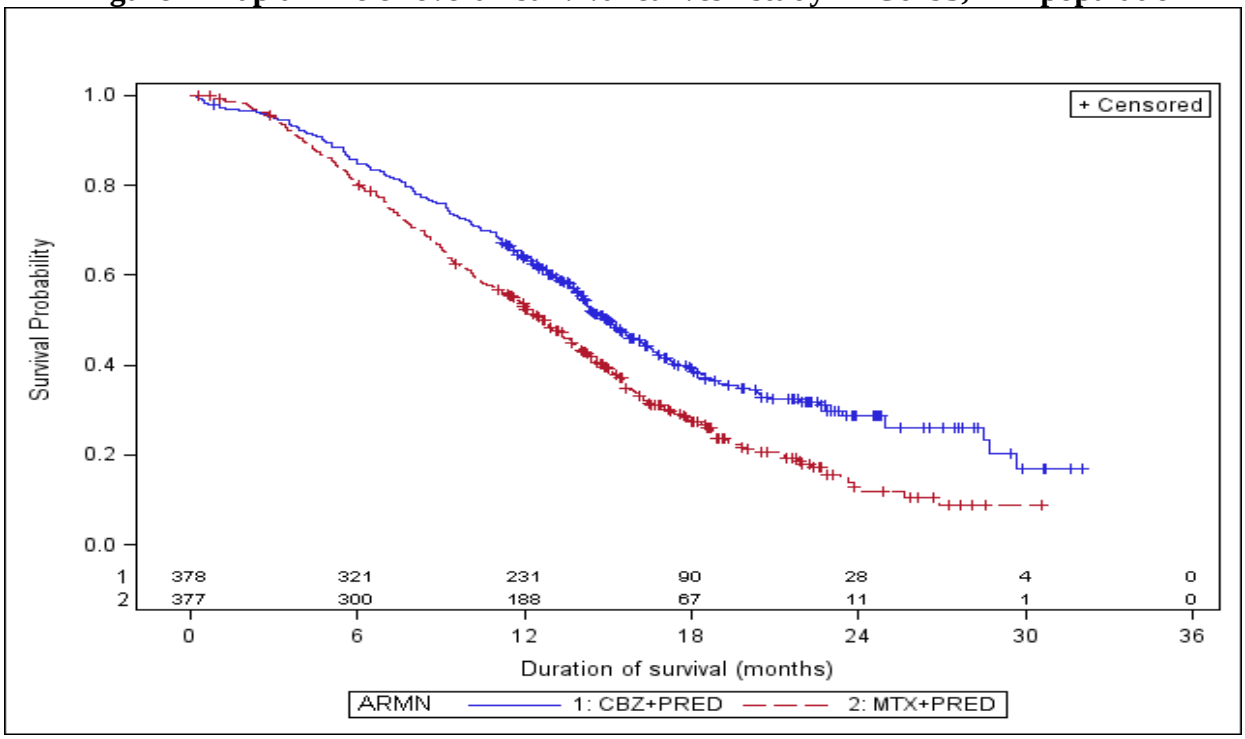
Table 2 Overall survival results - study EFC6193, ITT population

	Cabazitaxel+Prednisone n=378	Mitoxantrone+Prednisone n=377
Number of events (%)	234 (61.9%)	279 (74.0%)
Median survival (month) (95% CI)	15.1 (14.1-16.3)	12.7 (11.6-13.7)
Hazard ratio [1] (95% CI)	0.70 (0.59-0.83)	
p-value [2]	<0.0001	

[1] Hazard ratio estimated using a Cox proportional hazards model stratified by disease measurability and ECOG performance status at baseline

[2] p-value from log-rank test stratified by disease measurability and ECOG performance status at baseline

Figure 1 Kaplan-Meier overall survival curves - study EFC6193, ITT population



CBZ+PRED = cabazitaxel + prednisone; MTX+PRED = mitoxantrone + prednisone

Sensitivity analyses

There were 3 patients in the CBZ+PRED group and 7 patients in the MTX+PRED group who were lost to follow up before the study cut-off date 25 September 2009. The applicant performed a worst-case sensitivity analysis assuming that the 3 cabazitaxel patients died on the last visit and those 7 mitoxantrone patients survived up to the study cut off date. The result remained similar to the primary analysis, with a hazard ratio of 0.71 (95% CI: 0.59 – 0.84) and p-value=0.0001.

On 26 April 2010, information request was sent to the applicant for missing baseline ECOG performance status data in 6 patients. In response, the applicant indicated data from visit 1 Day 1 was used in those 6 patients for analyses assuming no change in performance status between baseline and visit 1. Data from the Interactive Voice Response System (IVRS) at the time of randomization were submitted by the applicant for verification. The no change in performance status assumption was verified, but discrepancies between IVRS and CRF data in disease measurability classification were found in 100 patients by the reviewer. A sensitivity analysis using the stratification variables from IVRS was performed. Results remained similar compared to the primary analysis, with a hazard ratio of 0.67 (95% CI: 0.57 – 0.80) and p-value<0.0001.

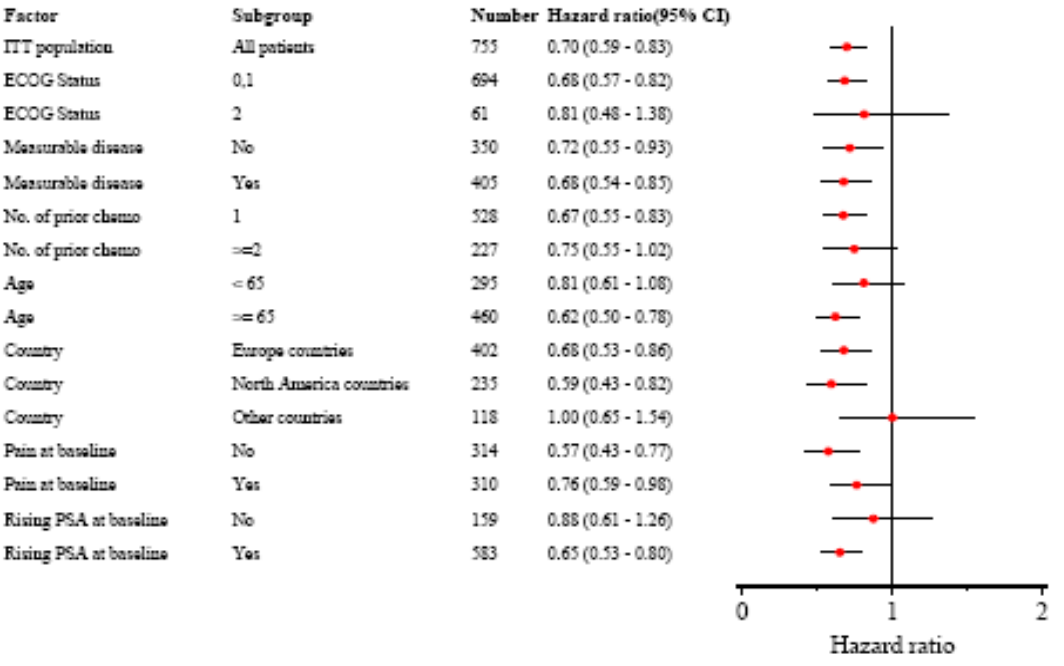
Reviewer's comment:

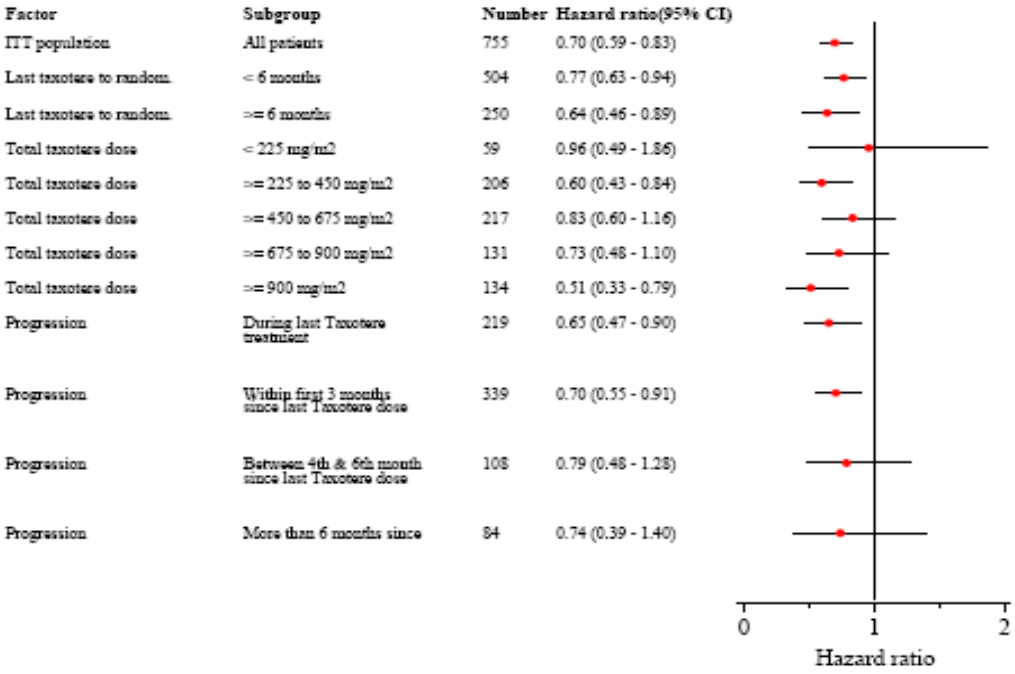
The primary analysis for overall survival, as submitted, used stratification variables as recorded in the CRF. This is acceptable, since CRF data are usually more accurate and results are very similar between the IVRS- and CRF-based analyses.

Subgroup analyses

The applicant performed subgroup analyses for overall survival by the following prognostic factors: ECOG performance status, disease measurability, number of prior chemotherapy regimens, age, country, pain at baseline, PSA status, time from last Taxotere to randomization, Taxotere dose, and time of progression from last Taxotere. The hazard ratios were 1 or less than 1 for all subgroups. A hazard ratio close to 1.00 was estimated for countries outside of Europe or North America, and for patients with a prior docetaxel dose <225 mg/m^2. No explanation was provided, except for relatively small number of patients in the sub-groups. Results of applicant's subgroup analyses are displayed below.

Figure 2 Applicant's subgroup analyses for overall survival





Source: Clinical study report Figure 4

Summary results of secondary endpoints

Summary results of secondary endpoints from applicant's analyses:

- Median PFS was 2.8 months in the cabazitaxel group and 1.4 months in the mitoxantrone group. The hazard ratio was 0.74 (95% CI: 0.64 - 0.86) in favor of cabazitaxel.
- Overall response rate (ORR) was evaluated in 405 patients who had measurable disease (201 cabazitaxel patients [53.2%], 204 mitoxantrone patients [54.1%]). The ORR was 14.4% (95% CI: 9.6 - 19.3) in the cabazitaxel group compared to 4.4% (95% CI: 1.6 - 7.2) in the mitoxantrone group.
- The PSA response was 39.2% with a median PSA progression of 6.4 months in the cabazitaxel group, compared to 17.8% with a median PSA progression of 3.1 months for the mitoxantrone group.
- The pain response was 9.2% in the cabazitaxel group, compared to 7.7% for the mitoxantrone group. The hazard ratio of pain progression was 0.91 (95% CI: 0.69 – 1.19).

Reviewer's comment:

PFS and PSA secondary endpoints were positive in the cabazitaxel group. (b) (4) [redacted]

3.1.4 Conclusions for Efficacy

The pivotal trial EFC6193 met its study objective by showing a hazard ratio of 0.70 (95% CI: 0.59 – 0.83, p-value<0.0001) for the experimental arm versus the control arm in overall survival. The median survival time was 15.1 months in the experimental arm compared to 12.7 months for patients in the control arm. Subgroup analyses showed consistent results in favor of cabazitaxel. There are no major statistical issues in the efficacy analyses.

3.2 Evaluation of Safety

A total of 558 patients were treated with cabazitaxel in 6 studies. In the pivotal study EFC6193, there were 371 patients in each of the cabazitaxel and mitoxantrone groups; in the Phase 1/Phase 2 studies there were 89 patients in the <25 mg/m2 cabazitaxel group, 43 patients in the ≥25 mg/m2 cabazitaxel group, and 55 patients in the weekly cabazitaxel group. Since these studies did not have formal hypotheses for safety evaluations, no statistical evaluation of safety is presented here. 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 and Age

The table below summaries Study EFC6193 overall survival subgroup analyses by age and race (subgroup analysis by gender for this male-only study is not applicable). The hazard ratios were less than 1 for all age and race subgroups, except for the black racial group (n=40) which had a hazard ratio of 1.30 but with a 95% confidence interval ranged from 0.62 to 2.70.

Table 3 Hazard ratios for overall survival by age and race

- Study EFC6193, ITT Population

	CBZ+PRED # event / n (%)	MXT+PRED # event / n (%)	Hazard ratio* (95% CI)
Age, < 65 yrs	87 / 133 (65.4%)	114 / 162 (70.4%)	0.81 (0.61 – 1.08)
Age, >=65 yrs	147 / 245 (60.0%)	165 / 215 (76.7%)	0.62 (0.50 – 0.78)
Race, Asian/Oriental	17 / 26 (65.4%)	23 / 32 (71.9%)	0.73 (0.39 – 1.39)
Race, Black	15 / 20 (75.0%)	15 / 20 (75.0%)	1.30 (0.62 – 2.70)
Race, Caucasian/White	194 / 317 (61.2%)	231 / 314 (73.6%)	0.67 (0.55 – 0.81)
Race, Other	8 / 15 (53.3%)	10 / 11 (90.9%)	0.51 (0.19 – 1.35)
Country, USA	60 / 97 (61.9%)	83 / 106 (78.3%)	0.67 (0.48 – 0.94)
Country, non-USA	174 / 281 (61.9%)	196 / 271 (72.3%)	0.70 (0.57 – 0.86)

CBZ+PRED = cabazitaxel + prednisone; MXT+PRED = mitoxantrone + prednisone
* Hazard ratio for CBZ+PRED versus MXT+PRED

4.2 Other Special/Subgroup Populations

In addition to age and race subgroup analyses, this reviewer conducted a subgroup analysis by country (USA or non-USA) for overall survival. Results in Table 3 showed the hazard ratios were less than 1 for both country subgroups.

The applicant performed subgroup analyses for overall survival by the following prognostic factors: ECOG performance status, disease measurability, number of prior chemotherapy regimens, age, country, pain at baseline PSA status, time from last Taxotere to randomization, Taxotere dose and time of progression from last Taxotere. The hazard ratios were 1 or less than 1 for all subgroups. Results of applicant's subgroup analyses for overall survival are displayed in section 3.1.3 Figure 2.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There are no major statistical issues identified in this application.

5.2 Conclusions and Recommendations

The pivotal trial met its study objective by showing a hazard ratio of 0.70 (95% confidence interval: 0.59-0.83, $p<0.0001$) for the experimental arm versus the control arm in overall survival. The median survival time was 15.1 months in the experimental arm compared to 12.7 months for patients in the control arm. Subgroup analyses showed consistent results in favor of cabazitaxel. There were no identified major statistical issues in efficacy analyses to prevent approval. The inference regarding favorable benefit-risk profile for the use of cabazitaxel in combination with prednisone in patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel (Taxotere®) containing regimen is deferred to the clinical review team.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Chia-Wen Ko, Ph.D.
Date: May 26, 2010

Concurring Reviewers: Shenghui Tang, Ph.D.
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HFD-700/Ms. Lillian Patrician

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHIA-WEN KO
05/26/2010

SHENGHUI TANG
05/26/2010

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05/26/2010

NDA # / SN # Indication	Drug Name	Applicant	Submission Date	NDA Type
201023 / 0002 Metastatic prostate cancer which has progressed during or after a docetaxel-based therapy	Cabazitaxel (XRP6258)	sanofi aventis	31 March 2010	Original NDA

On **initial** overview of the NDA application for fileability: There are no filling issues - all necessary documents are available to allow statistical review to begin.

	Content Parameter	Yes	No	N/A	Comments
1	Is Index sufficient to locate necessary reports, tables, data, etc.?	X			
2	Are study reports including original protocols, subsequent amendments, etc. complete and available?	X			
3	Were safety and efficacy for gender, racial, and geriatric subgroups investigated (if applicable)?	X			• Only men were enrolled in the pivotal study • Age, race are reported as baseline patient characteristics • Safety analyses by race and subgroup analyses of OS by age were performed
4	Are data sets in EDR accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets)?	X			
5	Were ISS and ISE submitted?	X			ISS submitted. ISE is not required because the treatment efficacy will be evaluated based on a single study.
6	Designs utilized appropriate for the indications requested	X			
7	Endpoints and methods of analysis spelled out in the protocols	X			
8	Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	X			An interim (futility) analysis of PFS was planned to be performed after 225 PFS events had occurred. The second interim analysis was added after a protocol amendment to be performed at the time of the 307 deaths (the 60% of the 511 deaths in the final analysis of the protocol) to assess the primary efficacy endpoint of OS based on the O'Brien-Fleming type I error spending function. The actual number of deaths at the second interim analysis was 365 instead of 307. Therefore, the type I error of the second and final analyses were adjusted according to the O'Brien-Fleming type I error spending function. The corresponding statistical significance levels for the interim analysis and the final analysis of OS were 0.0160 and 0.0452, respectively.
9	Appropriate references included for novel statistical methodology (if present)	X			
10	Sufficient data listings and intermediate analysis tables to permit a statistical review	X			
11	Intent-to-treat analyses	X			
12	Effects of dropouts on primary analyses investigated	X			Efficacy analyses repeated in PP population Censoring rule applied for time-to-event endpoints

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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

/s/

CHIA-WEN KO
04/14/2010

SHENGHUI TANG
04/15/2010