CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201023

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
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Division / Office	DDOP / OODP
Reviewer Names	Amy McKee, M.D. Ian Waxman, M.D.
Review Completion Date	06/02/2010
Established Name	Cabazitaxel
Proposed Trade Name	Jevtana
Therapeutic Class	Taxane
Applicant	Sanofi-Aventis
Formulation	Intravenous
Dosing Regimen	25 mg/m^2 IV over 1 hour every 21 days
Indication	Hormone-refractory prostate cancer
Intended Population	Men with metastatic hormone-refractory prostate cancer who have previously received a docetaxel-containing regimen

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

We recommend approval of cabazitaxel for men with metastatic hormone-refractory prostate cancer after a docetaxel-containing regimen.

1.2 Risk Benefit Assessment

The recommendation for approval is based on the single, randomized clinical trial in which cabazitaxel in combination with prednisone showed a statistically significant survival advantage compared to the combination of mitoxantrone and prednisone in patients with metastatic, hormone-refractory prostate cancer (mHRPC).

The single clinical trial enrolled 755 men with mHRPC who had progressed on or after a docetaxel-containing regimen. The cabazitaxel arm had a median overall survival of 15.1 months compared to 12.7 months on the mitoxantrone arm. Although there were deaths due to toxicity on the cabazitaxel arm, an overall survival advantage was still demonstrated for cabazitaxel-treated patients. Furthermore, as some of the deaths were due to infectious complications during a period of neutropenia, infection-related deaths may be better prevented in the post-marketing setting with the use of prophylactic G-CSF in patients at high risk of neutropenic complications. The proposed patient population currently has no treatment options which offer a survival benefit, and the robust results in overall survival demonstrated by cabazitaxel would provide a new treatment option for these patients.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This drug will be prescribed by physicians familiar with the management of toxicity associated with chemotherapeutic agents. Severe toxicities that have led to death in the clinical trial will be described in the labeling. Standard post-marketing surveillance should be conducted by the applicant.

1.4 Recommendations for Postmarket Requirements and Commitments

Four clinical post-marketing requirements (PMRs) have been discussed with the applicant:

1. Conduct a Phase 3 randomized controlled trial in patients with hormone-refractory metastatic prostate cancer comparing first-line docetaxel/prednisone with cabazitaxel 20 mg/m^2/prednisone and cabazitaxel 25 mg/m^2/prednisone.

The primary endpoint should be overall survival. The trial should be powered to detect a realistic difference in overall survival. Submit the protocol for agency review prior to commencing the trial.

2. Conduct a Phase 3 randomized controlled trial in patients with hormone-refractory prostate cancer previously treated with docetaxel comparing cabazitaxel 20 mg/m^2/prednisone and cabazitaxel 25 mg/m^2/prednisone powered to preserve 50% of the treatment effect of cabazitaxel 25 mg/m^2. The primary endpoint should be overall survival. Submit the protocol for agency review prior to commencing the trial.
3. Organize a group of renal experts to review and analyze renal toxicity from all currently available cabazitaxel trials to identify etiologies and to provide recommendations for toxicity mitigation by patient selection or other measures. This group's findings and recommendations should be submitted within nine months of the cabazitaxel approval date.
4. Submit updates on renal toxicity from all active randomized trials every six months for three years after the cabazitaxel approval date.

Trial designs for the phase 3 randomized trials (PMRs #1 and #2 above) have not yet been finalized.

Refer to CMC and clinical pharmacology reviews for discipline-specific PMRs.

2 Introduction and Regulatory Background

2.1 Prostate Cancer

Prostate cancer is the most common cancer diagnosed in men, with an incidence in the United States of approximately 192,000 annually, and approximately 27,000 deaths are attributed annually to prostate cancer.[i] Prostate cancer is predominantly a disease of older men; the median age at diagnosis is 72 years. As the disease can be indolent in many, patients often do not have symptoms of their disease and die of causes other than prostate cancer.

More recently, the percentage of patients diagnosed with early-stage, low-risk disease has increased; 29.8% of newly- diagnosed patients in 1989-1992 compared to 45.3% in 1999-2001.[ii] This observation often is attributed to widespread screening of asymptomatic patients for the disease by serum prostate-specific antigen (PSA) levels, digital rectal examination and ultrasonography. However, there is controversy regarding screening of asymptomatic patients, as both false-positive rates with PSA screening and discovery of low-risk, indolent disease has led to invasive procedures and treatment that have significant morbidity and have not been shown to reduce overall mortality for the disease or to reduce it very modestly.[iii,iv]

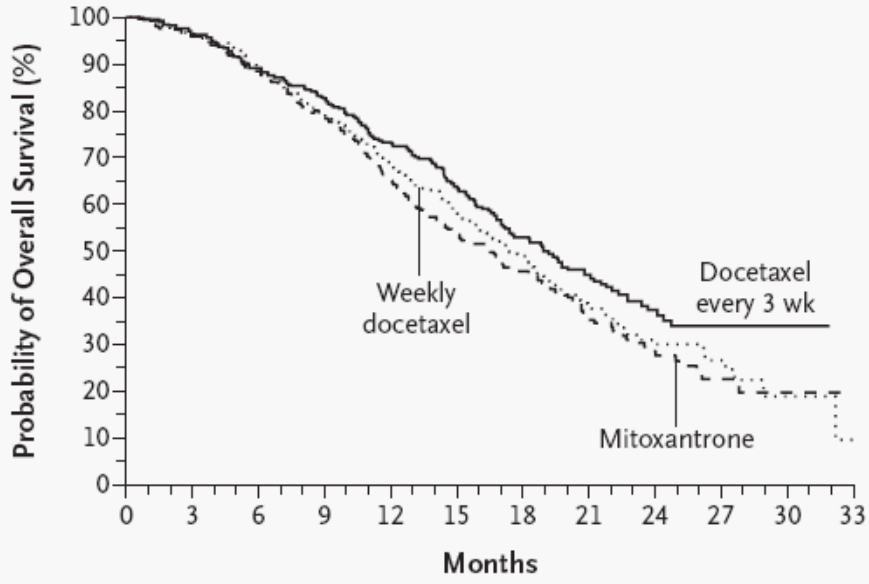
The value of PSA both for screening and measuring response is under question in the literature, though its measurement may be reliable for detecting relapse after surgery. Doubts have arisen as to whether PSA is sensitive or specific enough to warrant screening of asymptomatic men.[v,vi] Furthermore, the utility of PSA measurements as a marker for disease progression in advanced disease is under question. The Prostate Cancer Clinical Trials Working Group in its most recent consensus report (PCWG2) recommends that changes in PSA levels alone are not used to define progression in hormone-refractory disease,[vii] based on findings in the several recent studies.[viii,ix]

Patients with metastatic disease often have bone lesions that are not measurable by RECIST criteria, and the PCWG2 recognizes that there are no validated criteria for response based on radionuclide scans of the bone. For progression, the appearance of ≥ two new lesions is recommended by PCGW2 for progression based on radionuclide scans. Another measurement frequently used in prostate cancer both for response and progression is pain. A recent study on survival in men with metastatic hormone-refractory prostate cancer (mHRPC) who have progressed on or after first-line chemotherapy revealed that for men with isolated pain progression, continuing chemotherapy after documented pain progression was associated with improved OS compared with stopping chemotherapy; the authors concluded that if pain scales are to be used to define progression in men with CRPC, studies should additionally incorporate other measures of progressive disease before withdrawal of a patient from therapy.[x] This study points out the difficulties in using the subjective measurement of pain to define progression; the PCGW2 states that "the assessment of pain progression is more difficult because of the subjectivity as to what constitutes a 'clinically significant increase' from baseline or from the point of maximal response to an intervention."[7] Based on the difficulties noted above for measuring response and progression in the metastatic HRPC population, the recommended endpoint in a Phase 3 trial is overall survival.

2.2 Treatment of Patients with Prostate Cancer

First-line therapy for patients with metastatic prostate cancer is medical or surgical castration. Approximately 85% of patients will respond to this therapy, which includes gonadotropin-releasing hormone antagonists or surgery. However, approximately 15% of patients will not respond to hormonal intervention and responders will eventually become refractory to hormonal intervention.. For this metastatic HRPC population, recommended first-line therapy is the combination of docetaxel and prednisone, which showed a survival advantage compared to the combination of mitoxantrone and prednisone in the randomized, Phase 3 TAX327 trial.[xi]

Figure 1: Overall Survival for Patients with Metastatic HRPC in the TAX 327 Trial



No. at Risk						
Docetaxel every 3 wk	335	296	217	104	37	5
Weekly docetaxel	334	297	200	105	29	4
Mitoxantrone	337	297	192	95	29	3

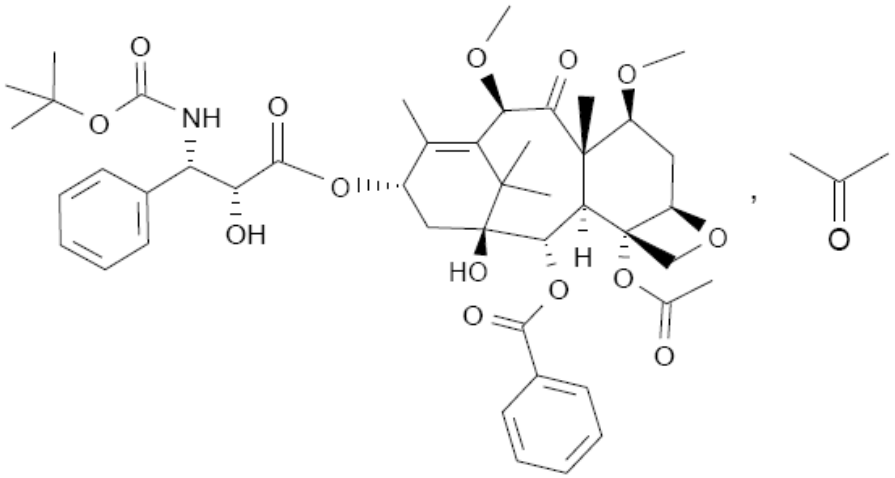
For patients who have progression on or after docetaxel-based therapy, there are no treatments that have shown a survival advantage. Mitoxantrone in combination with prednisone is labeled for pain palliation in this setting but has not demonstrated a survival advantage. Re-challenging patients who initially responded to docetaxel and progressed after completing treatment with a docetaxel-based regimen has brought some success with response rates,[xii] but survival has not been analyzed prospectively with this treatment option. Many single agents and combination regimens have been investigated in this setting but have shown either unacceptable toxicity or unpromising response rates, such as lenalidomide/paclitaxel,[xiii] the histone deacetylase inhibitor romidepsin,[xiv] pemetrexed,[xv] multi-kinase inhibitor sunitinib,[xvi] gefitinib, [xvii] microtubule inhibitor patupilone, [xviii] and bortezomib,[xix] among others.

Phase 3 studies are ongoing for the combination of docetaxel and atresentan and for the CYP17 inhibitor abiraterone, and promising Phase 2 results were seen with docetaxel in combination with bevacizumab and thalidomide.[xx] However, a recently reported large, double-blind, placebo-controlled Phase 3 trial in HRPC patients did not show a survival advantage with satraplatin compared to placebo.[xxi] Thus no treatment for metastatic HRPC patients after failure of the docetaxel/prednisone regimen has demonstrated a survival advantage.

2.3 Product Information

Cabazitaxel is a new molecular entity and is a novel taxane, similar to the taxanes docetaxel and paclitaxel. It is a semi-synthetic product derived from 10-deacetyl Baccatin III, which is extracted from European yew needles. The chemical name of cabazitaxel is (2α,5β,7β,10β,13α)-4-acetoxy-13-({(2R,3S)-3-[(tertbutoxycarbonyl) amino]-2-hydroxy-3-phenylpropanoyl}oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate – propan-2-one(1:1).

Figure 2: Structural Formula of Cabazitaxel



2.4 Tables of Currently Available Treatments for Proposed Indications

There are no currently available therapies specifically indicated for metastatic hormone-refractory prostate cancer patients who have previously received a docetaxel-containing regimen. Mitoxantrone in combination with prednisone is indicated for palliation of pain in this setting, but not for treatment of prostate cancer.

2.5 Availability of Proposed Active Ingredient in the United States

Please refer to CMC review.

2.6 Important Safety Issues With Consideration to Related Drugs

Both the Taxotere and Taxol labels carry black box warnings for severe hypersensitivity and neutropenia. The Taxotere label also carries black box warnings for hepatic impairment and severe fluid retention. See section 7.2.6.

2.7 Summary of Presubmission Regulatory Activity Related to Submission

April 14, 1999: IND 56,999 is activated to study malignant disease under the sponsorship of Sanofi-Aventis.

June 29, 2006: An End-of-Phase 2 meeting was held to discuss the indications of mHRPC (b) (4) At this meeting, FDA emphasized that a Phase 3 trial in mHRPC must win on its primary endpoint of overall survival before any analysis of secondary endpoints could be undertaken (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)

End-of-Phase 2 meeting minutes:
QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:
Sanofi-Aventis: We agree to have overall survival as the single, primary endpoint for both Phase 3 registration trials, for XRP9881 and for XRP6258. We seek clarification from FDA on the following issues:
1. We appreciate the FDA's detailed guidance on the pain intensity endpoint measurement in the XRP9881 response #3. (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)

2. We appreciate the FDA's comments on the pain endpoint in the XRP6258 response #5. (b) (4)

Discussion: See our response to question #1.

3 (b) (4) (b) (4)

4. We acknowledge the FDA comments on XRP6258 response #7 and propose to request a separate meeting with FDA to discuss the adequacy of the overall planned PK program and

address the questions raised by the FDA. However, at this time, we wish to obtain FDA agreement with our proposed pharmacokinetic strategy for our Phase III clinical protocol in HRPC patients. We propose to implement sparse sampling in as many patients as possible at cycle 1 in the Phase III protocol, EFC6193, in order to assess the PK profile in this population, assuming no effect of the first dose of prednisone on PK, of XRP6258 and to investigate PK/PD relationships for safety and efficacy. In addition, 25 patients will be sampled at cycle 2 in order to assess the effect of repeated administrations of prednisone on the PK of XRP6258. Does the FDA agree with this proposal for our Phase III HRPC protocol?
FDA Response: Yes

(b) (4)

Appendix I XRP9881 End-of-Phase I/II Meeting Questions (regarding HRPC only)
Questions
1. Does the FDA agree that the proposed patient population for study EFC6193 is adequately defined and suitable for a comparator-controlled Phase III study with marketing approval intent?
FDA Response: Yes. However, please clarify the following inclusion criteria found on page 2/11 of the briefing book "Previously irradiated lesions, primary prostate lesion and bone lesions are excluded".

2. Does the FDA agree that mitoxantrone in combination with prednisone is an appropriate comparator for this Phase III, randomized, comparator controlled trial?
FDA Response: Yes. However, M/P therapy can be administered for 12 cycles (cumulative dose ~ 140 mg/m2). The dose proposed for the pivotal study (6 cycles of 12 mg/m2, total 72 mg/m2) represents half the total dose permitted for mitoxantrone.

3. Does the FDA agree that one Phase III trial, EFC6193, is adequate to support a marketing application for full approval provided this trial demonstrates a clear benefit in survival for XRP6258 in combination with prednisone compared to mitoxantrone in combination with prednisone?
FDA Response: Possibly depending on the results. For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform. If an improvement in survival is demonstrated, a single

trial may be adequate. However, if the regulatory endpoint is pain improvement then a second controlled study would be required.

4. Does the FDA agree with the definition of the composite secondary endpoint, PFS, defined as meeting at least one of the criteria below?
• Tumor progression as defined by RECIST
• PSA Progression that is 25% increased over baseline or over nadir
• Death due to any cause

(b) (4)

5. Does the FDA agree that the protocol defined pain response provides supportive evidence of clinical benefit and supportive evidence for potential labeling?
FDA Response: No.
1. We recommend that you submit the final version of the PPI and the AS in the exact format it is administered in your protocol with instructions on how the instrument will be administered, directions explaining how scores will be derived, and how the statistical analyses will be applied.
2. Open-label data are only appropriate for labeling if results are convincing and conclusive.
3. Pain intensity should be assessed at screening, and then continued eligibility by pain score should be verified at baseline (i.e. before randomization/dosing).
4. Pain intensity should then be recorded daily, over the duration of the trial. There should also be evidence of efficacy over the entire duration of treatment.
5. (b) (4) **are not accepted efficacy endpoints in analgesic trials intended to support marketing of a product.**
6. Assessment of the "worst pain" will provide more reliable results than "average pain" over 24 hours.
7. Use of a known analgesic for rescue is acceptable (and recommended to reduce the number of placebo dropouts). The maximum amount of rescue should be prespecified. The statistical analysis plan should describe how the use of rescue medication will be incorporated into the primary analysis.

(b) (4)

6. If XRP6258 does not demonstrate a survival benefit but demonstrates superior clinical benefit in (b) (4) (b) (4)

(b) (4)

(b) (4) does the FDA agree that demonstration

(b) (4)

7. Does the FDA agree that the completed pharmacokinetics and the proposed population pharmacokinetic analysis are adequate to support a marketing application for the proposed indication: treatment of hormone refractory prostate cancer patients who have relapsed during or following Taxotere based therapy?

FDA Response: In order to maximize the ability to discern exposure-response relationships, we recommend that you perform pharmacokinetics sampling in all patients, rather than the planned subset of patients, in the efficacy and safety studies. We cannot comment on the overall adequacy of the planned program, as we lack answers to the numbered questions, below. These questions assume that FDA review of the preliminary data presented in the submission would agree with the conclusions of the Sponsor.

1. For pathways that contribute more than 25% of the clearance, we recommend that studies of the ability of inhibitors and inducers (if applicable) to alter the pharmacokinetics of the new drug be performed. Do you plan to perform *in vivo* drug interaction studies of the ability of a CYP3A4 inhibitor, a CYP3A4 inducer, and a CYP2C8 inhibitor to alter XPR6258 concentrations?

2. Based on *in vitro* data, are CYPs 1A2, 2C9, 2C19, and 2D6 likely each responsible for less than 25% of the *in vivo* elimination of XPR6258? If no, do you plan to perform *in vivo* drug interaction studies of the ability of inhibitors and inducers to alter XPR6258 concentrations? If yes, what are the designs of the planned studies?

3. Given that I/Ki for *in vitro* inhibition of CYP3A4 by XPR6258 exceeds 0.1, do you plan to perform an *in vivo* drug interaction study of the ability of XPR6258 to change concentrations of a reference CYP3A4 substrate? If yes, what is the design of the planned study?

4. Is I/Ki for *in vitro* inhibition of CYPs 1A2, 2C8 and 2C19 by XPR6258 less than 0.1? If no, do you plan to perform one or more *in vivo* studies of the ability of XPR6258 to alter concentrations of the relevant reference CYP substrates? If yes, what are the designs of the planned studies?

5. Does XPR6258 act as a CYP inducer *in vitro*? If yes, do you plan to perform one or more *in vivo* studies of the ability of XPR6258 to alter concentrations of reference CYP substrates? If yes, what are the designs of the planned studies?

6. Does XPR6258 act as a substrate or inhibitor of transporters *in vitro*? If yes, do you plan to perform *in vivo* studies with inhibitors or substrates? If yes, what are the designs of the planned studies?

7. If the results of the mass balance study show that 25% or more of elimination is renal, we recommend that a pharmacokinetic study in patients with renal impairment be performed. If the mass balance study shows that 25% or more of elimination is renal, do you plan to perform a pharmacokinetic study in patients with renal impairment? If yes, what will the design of the study be?
8. What is the design of the planned study in patients with hepatic impairment?
We recommend that you submit a summary that addresses the above questions and schedule a meeting to answer the question of the adequacy of the overall planned program.
Additional FDA comments:
1. Please provide information regarding the responses observed in patients with prostate cancer using this compound.
2. We remind you that you cannot claim efficacy based on the interim futility analysis. If you do conduct an efficacy overall survival interim analysis then you must adjust for alpha.
3. We recommend that you consider stratifying by measurable vs. non-measurable disease at randomization.
(End of meeting minutes)

September 11, 2006: Special Protocol Assessment request granted for pivotal study EFC6193. This is an open-label, randomized Phase 3 study in patients with metastatic hormone-resistant prostate cancer who have had progression during or after a docetaxel-based regimen comparing cabazitaxel/prednisone to mitoxantrone/prednisone. The primary endpoint is overall survival (b) (4)

September 11, 2008: Approval of an amendment to the statistical analysis plan for pivotal trial EFC6193 granted by FDA; the amendment states that an interim analysis for efficacy will be conducted at 307 events. Overall survival will be assessed based on the O'Brien-Fleming type I error spending function with a statistical significance level of p=0.0076.

2.8 Other Relevant Background Information

November 9, 2009: Fast track designation for mHRPC

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains all required components of the eCTD. The overall quality and integrity of the application appear reasonable.

3.2 Compliance with Good Clinical Practices

The protocol and its five amendments were submitted to Independent Ethics Committees (IEC) and/or Institutional Review Boards (IRB) for review, and the study was conducted after written approval.

The protocol and study conduct complied with recommendations of the 18th World Health Congress (Helsinki, 1964) and all applicable amendments approved by the World Medical Assemblies, and the International Conference for Harmonization (ICH) guidelines for Good Clinical Practice (GCP). The protocol also complied with the laws and regulations, as well as any applicable guidelines, of the countries where the studies were conducted.

Informed consent was obtained prior to the conduct of any study-related procedures. The written informed consent form (ICF) was signed, the names filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. The ICF used by the Investigator for obtaining the patient's informed consent was reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion. The patient informed consent form was modified according to the local regulations and requirements.

3.3 Financial Disclosures

Disclosure of financial interests of the investigators who conducted the clinical trials supporting this NDA was submitted in the FDA form 3454. The disclosure was certified by Mark Staudenmeier, Vice President-Finance and Didier Blondel, R&D Chief Financial Officer for the applicant. Eight investigators in the key study supporting this NDA were found to have financial conflict of interest, either a proprietary interest or significant payments from or equity interest in the applicant. These investigators received payments as honoraria for speaking events, professional fees and consulting fees ranging from totals of $29,550 to $94,000. Amount of honoraria was not provided for three investigators.

There were 142 sites where patients were enrolled on the pivotal, Phase 3 trial. The number of patients enrolled at each of the sites for the investigators with a financial disclosure was not found to drive the efficacy or safety data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to the CMC review.

4.2 Clinical Microbiology

Refer to clinical microbiology review.

4.3 Preclinical Pharmacology/Toxicology

Refer to the preclinical pharmacology/toxicology Review. No issues identified.

4.4 Clinical Pharmacology

Refer the Clinical Pharmacology review. The following PMRs were extracted from the Clinical Pharmacology review.

1. *Complete and submit the final report of trial TES10884, along with a thorough review of cardiac safety data, for the potential of cabazitaxel on QTc interval prolongation in patients.*
2. *Conduct and submit the final report of trial POP6972 to determine the pharmacokinetics and safety of cabazitaxel in patients with hepatic impairment.*
3. *Conduct a drug interaction trial to evaluate the effect of a strong CYP3A4 inducer (e.g., rifampin) on the pharmacokinetics of cabazitaxel in humans.*
4. *Conduct a drug interaction trial to evaluate the effect of a strong CYP3A4 inhibitor (e.g., ketoconazole) on the pharmacokinetics of cabazitaxel in humans.*

4.4.1 Mechanism of Action

Like the taxanes docetaxel and paclitaxel, cabazitaxel acts by targeting tubulin, the protein component of microtubules, to stabilize microtubules and prevent progression of mitosis in the cell cycle.

4.4.2 Pharmacodynamics

Refer to Clinical Pharmacology review for details. The following was extracted from the Clinical Pharmacology review. A conclusive exposure-response relationship could not be identified for overall survival possibly due to limited PK data (N=67) at one dose level (25 mg/m^2) collected in the pivotal trial. The shallow slope of the exposure – response

relationship for ≥ Grade 3 neutropenia suggested that dose reduction from 25 to 20 mg/m^2 will reduce the risk of having ≥ grade 3 neutropenia by 5% when no prophylactic G-CSF was used.

4.4.3 Pharmacokinetics

Two Phase 1 studies were conducted using the every-three-week schedule of administration of cabazitaxel. In one study (TED6188), the dose of 20 mg/m² administered every three weeks as a one-hour IV infusion was established as the recommended dose while in the second study (TED6190), 25 mg/m² administered every three weeks as a one-hour IV infusion was established as the recommended dose. Consequently, the dose of 20 mg/m² administered every three weeks as a one-hour IV infusion was selected initially for further clinical development. In a Phase 2 study with metastatic breast cancer patients (Study ARD6191), the safety and anti-tumor activity was assessed at the dose of 20 mg/m² every three weeks at the first cycle, with possible intra-patient escalation to 25 mg/m^2 at Cycle 2 allowed in the absence of any toxicity Grade >2 at Cycle 1. In 21 out of 71 patients, the dose of cabazitaxel could be escalated to 25 mg/m^2 IV after the first cycle.

The following was extracted from the Clinical Pharmacology review. *Following a 1-hour intravenous infusion, plasma concentrations of cabazitaxel can be described by a 3-compartment PK model with α-, β-, and γ- half-lives of 4 minutes, 2 hours, and 95 hours, respectively. Cabazitaxel demonstrates no major deviation from dose proportionality between 10 mg/m² and 30 mg/m². No accumulation or changes in the pharmacokinetics were observed for up to 3 treatment cycles. Mean human plasma protein binding was 92%. Based on the population pharmacokinetic analysis, steady-state volume of distribution and plasma clearance of cabazitaxel were 4,864 L and 48.5 L/h (i.e., 2,643 L/m² and 26.4 L/h/m² for a patient with a median BSA of 1.84 m²), respectively.*

Cabazitaxel was extensively metabolized by hepatic cytochrome P450 (CYP) 3A4/5 (80% to 90%) and to a lesser extent by CYP2C8. Cabazitaxel is primarily excreted into feces as metabolites (76% of the administered dose), with a low urinary excretion (3.7% of the administered dose, with 2.3% excreted as unchanged drug). At clinically relevant concentration in vitro, cabazitaxel does not inhibit CYPs or transporters including P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug-resistance protein (MRP). Based on in vitro studies, the potential for cabazitaxel to inhibit drugs that are substrates of major CYP isoenzymes is low. In addition, cabazitaxel did not induce CYP isozymes in vitro. Furthermore, cabazitaxel is a substrate of P-gp, but not a substrate of MRP1, MRP2, or BCRP.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1: Studies in NDA 201023

Study #	Population	Design	Dose[1] (mg/m^2)	# Any Cabazitaxel	# Cabazitaxel 25 mg/m^2 q 3 wks
TED6188	Solid Tumors	Dose Escalation	10-30 q 3 wks	21	6
TED6189	Solid Tumors	Dose Escalation	1.5-12 q 1 wk	31	0
		Oral Bioavailability	8.4 po c1d1 → 8.4 iv q wk	11	0
TED6190	Solid Tumors	Dose Escalation	10-25 q 3 wks	25	7
		Oral Biovailability	20 po c1d1 → 20 iv q 3 wks	11	0
BEX6702	Solid Tumors	PK Study	25 q 3 wks[2]	4	4
ARD6191	Metastatic Breast Cancer	Activity	10 q wk	13	0
			20-25 q 3 wks[3]	71	20
TCD6945	Metastatic Breast Cancer	Dose Escalation and Activity in Combination with Capecitabine	20-25 q 3 wks	33	6
EFC6193/ TROPIC	Metastatic Hormone-Refractory Prostate Cancer	Phase 3 Cabazitaxel + Prednisone vs. Mitoxantrone + Prednisone	25 q 3 wks	371	371
Total Exposed				**591**	**414**
ISS Total[4]				**558**	**408**
ISS Prostate[5]				**381**	**373**

[1]All doses were IV except for TED6189 and TED6190 oral bioavailability phase c1d1 po dose.
[2]First dose was radiolabeled [^{14}C]-cabazitaxel.
[3]All patients received 20 mg/m^2 at c1, with intra-patient escalation possible at c2.
[4]Excludes combination study TCD6945.
[5]Includes all patients from EFC6193 and 10 from Study TED6190 (8 in dose escalation phase, 2 in oral bioavailability phase). Among the 10 TED6190 prostate cancer patients, 2 received cabazitaxel 25 mg/m^2 q 3 wk dosing.

5.2 Review Strategy

The clinical review is based on the clinical study report for the EFC6193 trial, including the applicant's presentation slides, case report forms, primary data sets for efficacy and toxicity submitted by the applicant, study reports for other cabazitaxel clinical trials and literature review of HRPC.

5.3 Discussion of Individual Studies/Clinical Trials

This NDA is based primarily on overall survival from a single, randomized, open-label Phase 3 trial, EFC6193

Study Title: A Randomized, Open Label Multicenter Study of XRP6258 at 25 mg/m2 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 Taxotere®-Containing Regimen.

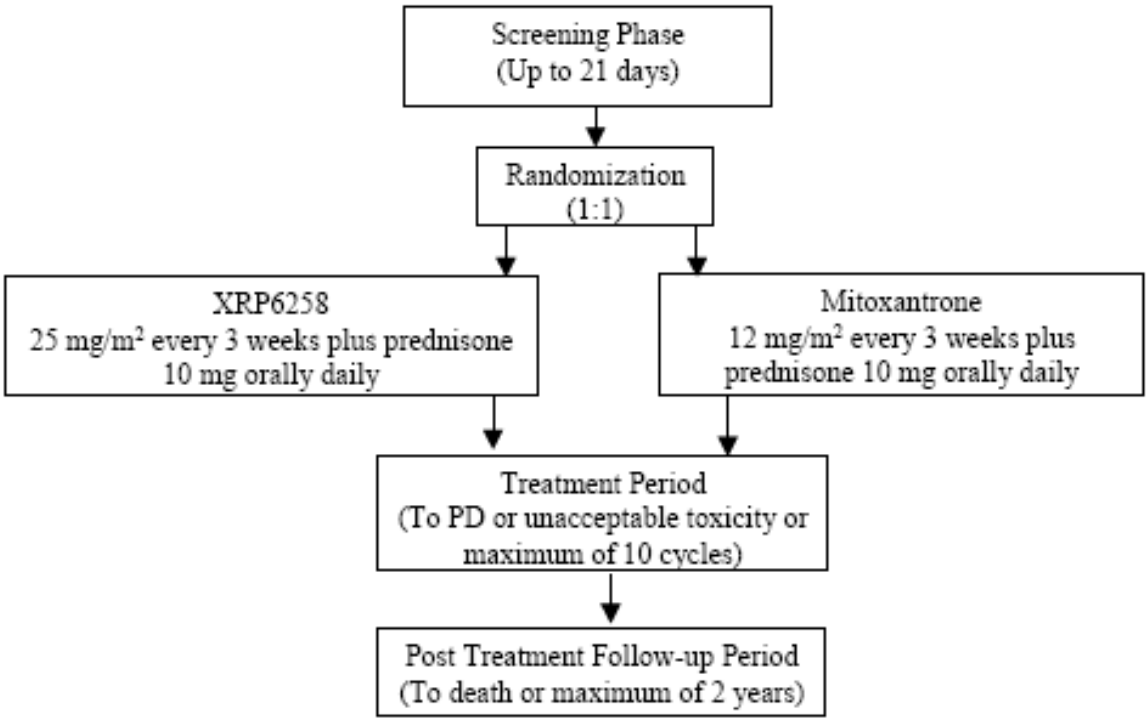
Objectives:

The primary objective of the trial was to determine whether cabazitaxel in combination with prednisone improves overall survival (OS) when compared to mitoxantrone in combination with prednisone.

5.3.1 Study design

EFC6193 was an open-label, randomized Phase 3 trial comparing cabazitaxel/prednisone (CBZ) versus mitoxantrone/prednisone (MTX) in patients with metastatic hormone-refractory prostate cancer who had previously received a docetaxel-containing regimen.

Figure 3: Study Design Schema



5.3.2 Study drug administration and schedule

The two treatment arms were as follows:

- Cabazitaxel 25 mg/m² intravenously (Day 1) over one hour every three weeks, and prednisone 10 mg orally given daily
- Mitoxantrone 12 mg/m² intravenously (Day 1) over 15 to 30 minutes every three weeks, and prednisone 10 mg orally given daily

Cycle length for both cabazitaxel and mitoxantrone was 3 weeks. New cycles of therapy started when absolute neutrophil counts (ANC) ≥1500/mm^3, platelet count ≥75,000/mm^3, and non-hematological toxicities (except alopecia) recovered to baseline. A maximum of two weeks delay was allowed between the two treatment cycles. Patients were removed from the study treatment if treatment was delayed for more than two weeks.

5.3.3 Study Endpoints

The primary efficacy endpoint was overall survival in the intent-to-treat population.

Secondary efficacy endpoints included

- To compare efficacy between the two treatment groups:
    - Progression free survival (defined as the first occurrence of any of the following events: tumor progression assessed by Response Evaluation Criteria in Solid Tumors [RECIST], PSA progression, pain progression, or death due to any cause)
    - Overall response rate (ORR)
    - PSA progression
    - PSA response
    - Pain progression
    - Pain response
- To assess the overall safety of cabazitaxel in combination with prednisone
- To assess the pharmacokinetics of cabazitaxel and its metabolite, RPR123142, in this patient population and effect of prednisone on the pharmacokinetics of cabazitaxel

Reviewer Comment: *The primary efficacy endpoint, OS, is the gold standard for this patient population.* (b) (4)

5.3.4 Eligibility Criteria

Inclusion criteria:

- Diagnosis of histologically or cytologically proven prostate adenocarcinoma, that was refractory to hormone therapy and previously treated with a Taxotere (or docetaxel)-containing regimen. Patients had documented progression of disease during or within six months after prior hormone therapy and disease progression during or after Taxotere (or docetaxel)-containing therapy.
- Either measurable or non-measurable disease.
    - Patients with measurable disease had to have documented progression of disease by RECIST criteria demonstrating at least one visceral or soft tissue metastatic lesion (including new lesion). The lesion was to measure at least 10 mm in the longest diameter (or two times the slice thickness) on spiral CT scan or MRI (chest, abdomen, pelvis) or 20 mm on conventional CT or chest X-ray for biopsy proven, clearly defined lung lesion surrounded by aerated lung. Previously irradiated lesions, primary prostate lesion, and bone lesions were considered non-measurable disease.
    - Patients with non-measurable disease had to have documented rising PSA levels or appearance of new lesion. Rising PSA was defined as at least two consecutive rises in PSA to be documented over a reference value [measure 1]

taken at least one week apart. The first rising PSA [measure 2] was to be taken at least seven days after the reference value. A third confirmatory PSA measure was required [second beyond the reference level] to be greater than the second measure and it was to be obtained at least 7 days after the second measure. Otherwise, a fourth PSA measure was required to be taken and the measure had to be greater than the second measure. The third [or the fourth] confirmatory PSA was taken within four weeks prior to randomization).

- Received prior castration by orchiectomy and/or LH-RH agonist with or without anti-androgen, anti-androgen withdrawal, monotherapy with estramustine, or other hormonal agents. A prior treatment by anti-androgen was not mandatory. However, if the patient had been treated with anti-androgens, and PSA was above 5 ng/mL at the last administration of antiandrogens, presence or absence of anti-androgen withdrawal syndrome was to be confirmed prior to the study entry. LH-RH agonist treatment should have continued during the study treatment period. Chlormadinone acetate or flutamide must have been stopped at least four weeks prior to, while bicalutamide must have been stopped at least six weeks prior to, the last PSA evaluation. The antiandrogen withdrawal syndrome is a decrease in PSA seen upon stopping an antiandrogen such as chlormadinone acetate, flutamide, or bicalutamide; this occurs because the antiandrogen has induced a mutation in the androgen receptor which is allowing the antiandrogen to stimulate prostate cancer growth rather than inhibit it.
- Life expectancy >2 months
- Eastern Cooperative Oncology Group performance status (PS) 0 to 2 (i.e., patient was to be ambulatory, capable of all self-care, and up and about more than 50% of waking hours).
- Age ≥18 years

Exclusion criteria:

- Previous treatment with mitoxantrone
- Previous treatment with <225 mg/m^2 cumulative dose of Taxotere or docetaxel
- Prior radiotherapy to ≥40% of bone marrow. Prior treatment with one dose of a bone-seeking radio-isotope (samarium-153, strontium-89, or P-32) was allowed, but eight weeks was to have elapsed after samarium-153 or P-32 and 12 weeks was to have elapsed after strontium-89 prior to first study drug administration.
- Prior surgery, radiation, chemotherapy, or other anti-cancer therapy within 4 weeks prior to enrollment in the study
- Active Grade ≥2 peripheral neuropathy
- Active Grade ≥2 stomatitis
- Active secondary cancer including prior malignancy from which the patient had been disease-free for ≤5 years (However, adequately treated superficial basal cell skin cancer before four weeks prior to entry was eligible for the study)
- Known brain or leptomeningeal involvement

- History of severe hypersensitivity reaction (≥Grade 3) to polysorbate 80 containing drugs
- History of severe hypersensitivity reaction (≥Grade 3) or intolerance to prednisone
- Other concurrent serious illness or medical conditions
- Inadequate organ function as evidenced by the following peripheral blood counts, and serum chemistries at enrollment:
    - Neutrophils ≤1.5 x 10^9/L
    - Hemoglobin ≤10 g/dL
    - Platelets ≤100 x 10^9/L
    - Total bilirubin ≥ upper limit of normal (ULN)
    - Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) ≥1.5 x ULN
    - Alanine aminotransferase/serum glutamate pyruvate transaminase (ALT/SGPT) ≥1.5 x ULN
    - Creatinine ≥1.5 x ULN
- Uncontrolled cardiac arrhythmias, angina pectoris, and/or hypertension. History of congestive heart failure, or myocardial infarction within last 6 months was also not allowed.
- Left ventricular ejection fraction ≤50% by multi-gated radionuclide angiography (MUGA) scan or echocardiogram
- Uncontrolled diabetes mellitus
- Active uncontrolled gastroesophageal reflux disease (GERD)
- Active infection requiring systemic antibiotic or anti-fungal medication
- Participation in another clinical trial with any investigational drug within 30 days prior to study enrollment.
- Concurrent or planned treatment with strong inhibitors of cytochrome P450 3A4/5. A one-week washout period was necessary for patients who were already on these treatments.
- For patients enrolled in the United Kingdom, the following exclusion criterion was applicable: Patient with reproductive potential not implementing accepted and effective method of contraception

5.3.5 Duration of Treatment

Patients continued to receive treatment until one of the following was met:
- Completion of the study treatment (i.e., 10 cycles of treatment)
- Disease progression (or death due to progressive disease [PD]): the date and evidence for disease progression were documented in the medical record (the patients were to be removed from the treatment for pain progression if the pain was cancer-related and supported by clinical evidence and/or radiological evidences of disease progression).

- Adverse event (including death), treatment-limiting toxicity, intercurrent medical problem, that contra-indicate continuation of anti-cancer chemotherapy
- Voluntary withdrawal
- Patient lost to follow-up
- Other reason (e.g., protocol violation, Investigator's decision)

Withdrawal from trial

Patients could be withdrawn from the trial for the following medical and/or administrative reasons:

- Completed follow-up period (two years)
- Death
- Poor compliance to protocol
- Voluntary withdrawal
- Patient lost to follow-up
- Other reason

Figure 4: Schedule of Evaluations

Evaluation	Screening (-21 days)	Prior to each infusion (Day 1) (a)	Cycle 1 through Cycle 10	End of Study Treatment**	Post-treatment Follow-up***
Informed Consent Form	X*				
Contraceptive Counseling	X				
Previous Medical/Surgical History (b)	X*				
Physical Examination including vital signs/Height/Weight/BSA/ECOG PS (c)	X*	X		X	
Randomization (g)	X				
XRP6258 + Prednisone or Mitoxantrone + Prednisone Administration (h)			X		
Concomitant Medication (k)	X*	X		X	X
Hematology (d)	X*	X		X	
Biochemistry (e)	X*	X		X	
Testosterone	X*			X	
ECG (f)	X			X	
LVEF (n)	X	X		X	
Pharmacokinetic Sampling			X (o)		
PSA (l)	X*	X		X	X
Bone Scan (l)	X	X		X	X (m)
CT Scan or MRI (l)	X	X		X	X (m)
Pain Assessment (i)(l)	X	X		X	X
Analgesic Diary (i)(l)	X	X		X	
AE/SAE Recording (if any) (j)	X	X		X	X

* Assessment must be performed prior to registration (rather than prior to initial dose) for eligibility determination.

** End of the study treatment performed at least 30 days after the last study drug infusion

*** Performed every 6 weeks for first 6 months and then every 3 months for rest of the period (a total of 2 years)

a **Day 1:** Cycle 1 Day 1 (Day 1 of the study) refers to the day the patient receives the initial dose of study medication. The Cycle 1 Day 1 Assessments noted in the Study Schedule are not required if acceptable screening for the assessment is performed within 5 days prior to the start of treatment with study drug. However, all of these assessments must be performed for subsequent cycles (e.g., Cycle 2 Day 1, Cycle 3 Day 1, etc.). Day 1 of each subsequent cycle is defined by the date that study drug administration is started within that cycle. Patients must be seen by the responsible physician on Day 1 of each cycle

b **Medical & Oncologic History:** including: diagnosis; prior surgery, radiotherapy, systemic therapy, hormonal therapy, concurrent illness; history of allergy.

c **Physical Examination:** Examination of major body systems including vital signs (temperature, blood pressure, heart rate), height (Screening only), body weight, and ECOG PS. Results will be recorded on appropriate CRFs (e.g., medical/tumor history, adverse events).

d **Hematology:** CBC, Diff., Platelets

e **Biochemistry:** Total bilirubin, SGOT (AST), SGPT (ALT), alkaline phosphatase, creatinine, BUN, glucose, sodium, potassium, chloride and bicarbonate

f **ECG:** To be performed at baseline and end of study. Additional tests should be performed if clinically indicated.

g **Randomization:** Patient study number and treatment arm will be assigned by an IVRS after investigator confirmation of eligibility

h **BSA, Study Drug Administration, Dispensing, and Accountability**: At the start of each treatment cycle, the patient's BSA will be determined using the current weight and screening height. Study drug will be administered in the clinic.

i **Pain Assessment and analgesic diary**: Pain will be assessed using a composite score of pain severity assessed by McGill-Melzack and analgesic consumption as morphine equivalents.

j **Adverse Event Assessment**: The period of observation for collection of adverse events extends from the time of the first dose of the study drug until 30 days after the final dose of study drugs. Serious adverse events should be followed as described in the protocol.

k **Assessment of Concomitant Medications and Treatments:** Concomitant medications and treatments will be recorded from 30 days prior to the initial dose of study drugs until 30 days after the final dose of study drugs.

l **Tumor Assessment**:

- **CT or MRI** of the chest, abdomen, and pelvis to be performed at baseline (screening). Repeat at the end of every other cycle (2, 4, 6, and 8), whenever disease progression is suspected, and at the end of treatment/withdrawal visit, using the same method for each assessment.
- **Bone Scan** will be performed in all patients at baseline. If initially positive, repeat at the end of every other cycle (2,4, 6, and 8), whenever disease progression is suspected, and at the end of treatment/withdrawal visit. If initially negative, repeat when clinically indicated.
- **PSA** will be performed at baseline and every cycle. PSA response will be evaluated at the end of every other cycle (2, 4, 6, and 8), whenever disease progression is suspected, and at the end of treatment/withdrawal visit.
- **Pain** will be assessed at baseline and every cycle. Pain response will be evaluated only in those patients with median PPI ≥2 on McGill-Melzack scale and/or mean Analgesic Score ≥10 points at baseline. Pain response will be evaluated at the end of every cycle, whenever disease progression is suspected, and at the end of treatment/withdrawal visit.

m **Post-Study Therapy and Survival Status:** During the first 6 months of the follow-up period, patients who went off study treatment prior to documented disease progression will be evaluated by CT/MRI for tumor progression every 6 weeks from End of Study Treatment until disease progression or start of other anticancer therapy. For rest of the follow-up period, patient will be evaluated every 3 months. Bone scan will be performed during the follow-up period when clinically indicated. In addition, during the first 6 months of the follow-up period, patients will be evaluated every 6 weeks for PSA and/or pain progression until documented progression or start of other anticancer therapy. For the rest of the follow-up period patients will be evaluated every 3 months.

n **LVEF:** To be performed at baseline and prior to every other treatment cycle (2, 4, 6, and 8), and at the end of treatment/withdrawal visit in the mitoxantrone arm only. For XRP6258 treatment arm, LVEF should be performed at baseline and then only if clinically indicated. Additional tests should be performed if clinically indicated.

o **Pharmacokinetic sampling:** In the XRP6258 treatment arm, blood samples will be collected using sparse sampling strategy in as many patients as possible in Cycle 1 and in 25 of these patients in Cycle 2.

5.3.6 Primary Endpoint Evaluation

The primary efficacy assessment was OS defined as the time interval from the date of randomization to the date of death due to any cause. In the absence of confirmation of death, the survival time was censored at the last date patient was known to be alive or at the cut-off date, whichever had come first.

5.3.7 Secondary Endpoint(s) Evaluation

5.3.7.1 PSA

PSA Response

Response requires a PSA decline of ≥50% confirmed at least three weeks later. The duration of PSA response will be measured from the first to the last assessment at which the above criteria are satisfied.

PSA Progression

In PSA non-responders: progression will be defined as a 25% increase over the nadir value (provided that the rise is a minimum of 5ng/ml) and confirmed by a second value at least 3 week later.

In PSA responders and in patients not evaluable for PSA response at baseline: progression will be defined as a 50% increase over the nadir value (provided that the rise is a minimum of 5ng/ml) and confirmed by a second value at least three weeks later.

5.3.7.2 Tumor Lesion-Measurable Disease

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions.
Partial Response (PR): At least a 30% decrease in the sum of LD of target lesions taking as reference baseline sum LD
Progression (PD): At least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum LD since the treatment started.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.
Incomplete Response/Stable Disease: Persistence of one or more non-target lesion(s).
Progression (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Evaluation of Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. The overall assessment of response will involve all parameters as depicted below.

Figure 5: Overall Assessment of Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete Response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Confirmation

To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than four weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate. In the present study, any interval of longer than four weeks is appropriate, but it is recommended to use a six-week interval. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval defined in the protocol. In the present study, this interval is 35 days.

5.3.7.3 Progression-Free Survival

Progression-Free Survival will be evaluated in all randomized patients. PFS is defined as the time between randomization and the date of progression or date of death (due to any cause) where a progression is either a PSA progression, or a tumor progression, or a pain progression.

5.3.7.4 Pain

Pain will be assessed prior to registration, every three weeks, at end of study treatment. In addition, during the first six months of the follow-up period, patients will be evaluated every six weeks for pain progression until documented progression or start of other anticancer therapy, for the rest of the follow-up period patients will be evaluated every three months with the Present Pain Intensity scale (PPI) from the McGill-Melzack questionnaire. It will be averaged over the prior week. The patient will be asked to complete the PPI every day for the one week period prior to each evaluation.

Pain Response (applies only to patients with median PPI ≥2 on McGill-Melzack scale and/or mean Analgesic score(AS) ≥10 points at baseline)

A two-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. Either criterion must be maintained for two consecutive evaluations at least three weeks apart. The duration of pain response will be measured from the first to the last assessment at which the above pain response criteria are satisfied.

Pain Progression (applies to all patients)

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.

Median PPI and mean AS will be calculated only if five of the seven expected values are actually available in the Patient Pain Diary. Otherwise, the patient will be considered as not evaluable for pain efficacy criteria at the corresponding cycle:
• Pain response is not evaluable if >2 AS are missing and/or >2 PPI values are missing (over the same week)
• Pain progression is not evaluable if >2 AS are missing and/or >2 PPI values are missing (over the same week) unless a complete evaluation (i.e. at least five values) of AS or PPI shows a pain progression.

5.3.8 Major Protocol Amendments

Table 2: Major Protocol Amendments

Number	Date	Amendment
1	10/16/2006	• Allow for the use of prednisolone (10 mg orally daily) in combination with XRP6258 or mitoxantrone in those countries where prednisone is not commercially available. • Allow for the inclusion of patients who have had prior brachytherapy. • Allow for the administration of a single fraction of palliative radiotherapy to non-target bone lesions during the study treatment period. • Clarify that bone scans are required at baseline for all patients and need only be repeated when clinically indicated. • Add hematology assessments at Day 8 and Day 15 of every treatment cycle for safety monitoring. • Revise dose modifications for hypersensitivity reactions to correct recommendations for resuming the infusion as well as for rate reduction of subsequent infusions. • Allow a ± 3-day window around the treatment cycles. • Allow a – 3-day window around the Day 1 hematology and chemistry assessments. • Allow a ± 1-day window around the Day 8 and Day 15 hematology assessments. • Clarify reporting of laboratory adverse events to require only those that are serious or result in treatment discontinuation or dose modification. • Incorporate use of (b) (4) as a central laboratory to provide PK sample collection and shipping materials and to receive PK samples from study sites and forward to sanofi-aventis GMPK Department in France.
2	12/19/2006	Delete the administration of a single fraction of palliative radiotherapy to non-target bone lesions during the study treatment period per FDA recommendation.
3	6/19/2007	Further to MHRA requirements, an exclusion criterion (double barrier contraceptive measures) has been added and will apply for United Kingdom only.
4	7/27/2007	• Allow prior treatment with all docetaxel commercially available • Add an exclusion criterion to exclude patients that have not received at least 3 cycles or <225 mg/m^2 cumulative dose of prior docetaxel therapy • Add exclusion criteria to exclude patients with grade ≥2 peripheral neuropathy or stomatitis • Modify requirement for beginning new cycles of therapy, such that toxicities should recover to their baseline status, rather than requiring recovery to grade ≤1 • Modify definition of pain progression such that pain must be cancer-related and pain progression must be supported by clinical and/or radiological evidence of disease progression. Accordingly, patients should only be removed from study treatment for cancer-related pain progression. • Modify the PK sampling schedules times to allow a broader window for later collection times.
5	7/21/2008	Add one interim analysis at the time of 307 deaths (the 60% of the 511 deaths in the final analysis of the protocol) to assess the primary efficacy endpoint of overall survival based on the O'Brien-Fleming type I error spending function. The purpose of this interim analysis is to test for overwhelming efficacy.

6 Review of Efficacy

Efficacy Summary

This application is based on the primary endpoint of overall survival (OS) in a single, randomized, open-label study comparing cabazitaxel with prednisone to mitoxantrone with prednisone in 755 patients. The analysis for overall survival was performed in the intent-to-treat population.

- The applicant reports a median OS of 15.1 months in the cabazitaxel arm compared to 12.7 months in the mitoxantrone arm, with a hazard ratio of 0.70 (95% CI 0.59, 0.83).
- There were 10 patients censored prior to the end of the study, with seven in the mitoxantrone arm and three in the cabazitaxel arm. The ten patients were lost to follow-up for multiple reasons, including withdrawal from the study at the patient's request and referral for subsequent therapy. In a worst-case analysis in which the seven mitoxantrone patients were assigned a censored date of the study cut-off date and the cabazitaxel patients were assigned an OS event one day after their censored date, the OS analysis remains statistically significant in favor of the cabazitaxel arm, with a HR of 0.73.
- There were few major protocol violations that could have affected the primary endpoint analysis. The most major protocol violations concerned missing pain assessments for the secondary pain endpoints and inadequate organ function at study entry

(b) (4)

6.1 Indication

The proposed indication is for cabazitaxel in combination with prednisone for treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.

6.1.1 Methods

Clinical review is based primarily on the CSR for the EFC6193 trial, the applicant's presentation slides, case report forms, primary data sets for efficacy and toxicity submitted by the applicant and literature review of mHRPC.

6.1.2 Demographics

The demographics of the pivotal study EFC6193 are presented in Table 3. The median age was 67 years in the MTX arm and 68 years in the CBZ arm. (range 46-92). The majority of patients were Caucasian/White in both arms (83.3% in MTX, 83.9% in CBZ). Three hundred thirty-nine patients (89.9%) entered with an ECOG performance status of 0 or 1 in the MTX arm compared to 345 patients (91.3%) in the CBX arm. Slightly over half of the patients in both arms had measurable disease at baseline (204 patients in MTX, 201 patients in CBZ).

Table 3: Patient Characteristics

Category		**MTX+PRED (N=377)**	**CBZ+PRED (N=378)**
Age (years)	Median (Min, Max)	67.0 (47, 89)	68.0 (46, 92)
Race	Caucasian/White Black Asian/Oriental Other	314 (83.3%) 20 (5.3%) 32 (8.5%) 11 (2.9%)	317 (83.9%) 20 (5.3%) 26 (6.9%) 15 (4.0%)
ECOG	0,1 2 Missing	339 (89.9%) 32 (8.5%) 6 (1.6%)	345 (91.3%) 27 (7.1%) 6 (1.6%)
PSA (ng/mL)	Median Min, Max	127.5 2, 11220	143.9 2, 7842
Measurable Disease	Yes No	204 (54.1%) 173 (45.9%)	201 (53.2%) 177 (46.8%)

Reviewer Comment: *African-American patients, who represent a significant portion of the target population in the United States, were under-represented in this trial.*

As shown in table 4, the vast majority of patients (99.3%) had prior hormonal therapy. Additionally, slightly over half the patients in both arms had received surgery prior to entering this trial. Docetaxel was the first chemotherapy regimen received in 87.5% of the patients and also was the second most commonly received regimen at 30% of patients.

Table 4: Prior Treatment

Treatment type	MTX+PRED (N=377)	CBZ+PRED (N=378)
Biologic modifiers	36 (9.5%)	26 (6.9%)
Hormonal Therapy	375 (99.5%)	375 (99.2%)
Surgery	205 (54.4%)	198 (52.4%)
Radiation		
Curative	112 (29.7%)	98 (25.9%)
Palliative	110 (29.2%)	134 (35.4%)
Chemotherapy		
1 regimen	268 (71.1%)	260 (68.8%)
2 regimens	79 (21.0%)	94 (24.9%)
≥3 regimens	30 (8.0%)	24 (6.3%)

Applicant's Analysis

Until protocol amendment #4 in July 2007, patients were allowed to enter the protocol having received less than 225 mg/m^2 of docetaxel. However, as 225 mg/m^2 of docetaxel would represent three cycles according to the labeled dose of 75 mg/m^2 for mHRPC, the applicant chose to exclude patients who did not complete at least three cycles of docetaxel as the proposed indication is for patients who have progressed after receiving a docetaxel-containing regimen. As shown in Table 5, 66.7% of patients in the CBZ arm received ≥450 mg/m^2 of docetaxel, as did 61.0% of patients in the MTX arm. These doses indicate that the majority of patients received the equivalent of at least 6 cycles of docetaxel at a dose of 75 mg/m^2.

Reviewer Comment: *The trial initially allowed enrollment of patients who had received less than 225 mg/m^2 of docetaxel; however, the applicant amended to the trial to exclude these patients. This reviewer agrees with this strategy, as these patients may not be considered refractory or resistant to docetaxel and could potentially be re-treated with docetaxel. The number of patients on both arms in this subgroup is small (30 on MTX arm and 29 on CBZ arm) and balanced between the two arms thus is unlikely to bias the OS results towards a favorable finding for the CBZ arm.*

Table 5: Prior Docetaxel Exposure

	MTX+PRED (N=377)	CBZ+PRED (N=378)
<225 mg/m^2	30 (8.0%)	29 (7.7%)
≥225 to 450 mg/m^2	112 (29.7%)	94 (24.9%)
≥450 to 675 mg/m^2	105 (27.9%)	112 (29.6%)
≥675 to 900 mg/m^2	57 (15.1%)	74 (19.6%)
≥900 mg/m^2	68 (18.0%)	66 (17.5%)
Missing	5 (1.3%)	3 (0.8%)

Applicant's Analysis

6.1.3 Subject Disposition

Patient disposition in trial EFC6193 is shown in table 6.. Overall, more than twice as many patients completed study treatment in the CBZ arm (N=105) compared to the MTX arm (N=46). Most patients discontinued due to disease progression, with 267 (70.8%) in the MTX arm compared to 180 (47.6%) in the CBZ arm. However, patients who discontinued due to an adverse event were higher in the CBZ arm (N=76) compared to the MTX arm (N=32). Two patients total were lost to follow-up, and 25 patients discontinued at their request. The "other" category in table 6 represents patients who were removed due to eligibility criteria that were not met but who were initially treated; other major protocol violations; at the investigator's discretion; patient refusal to follow protocol procedures; and suspected progression that did not meet protocol criteria for progression.

Table 6: Patient Disposition

	MTX+PRED (N=377)	**CBZ+PRED (N=378)**
Completed study treatment	46 (12.2%)	105 (27.8%)
Disease Progression	267 (70.8%)	180 (47.6%)
Adverse Event	32 (8.5%)	67 (17.7%)
Poor Compliance To Protocol	0	1 (0.3%)
Lost To Follow-Up	2 (0.5%)	0
Other	7 (1.9%)	10 (2.6%)
Subject's Request	17 (4.5%)	8 (2.1%)
Not Treated	6 (1.6%)	7 (1.9%)

Applicant's Analysis

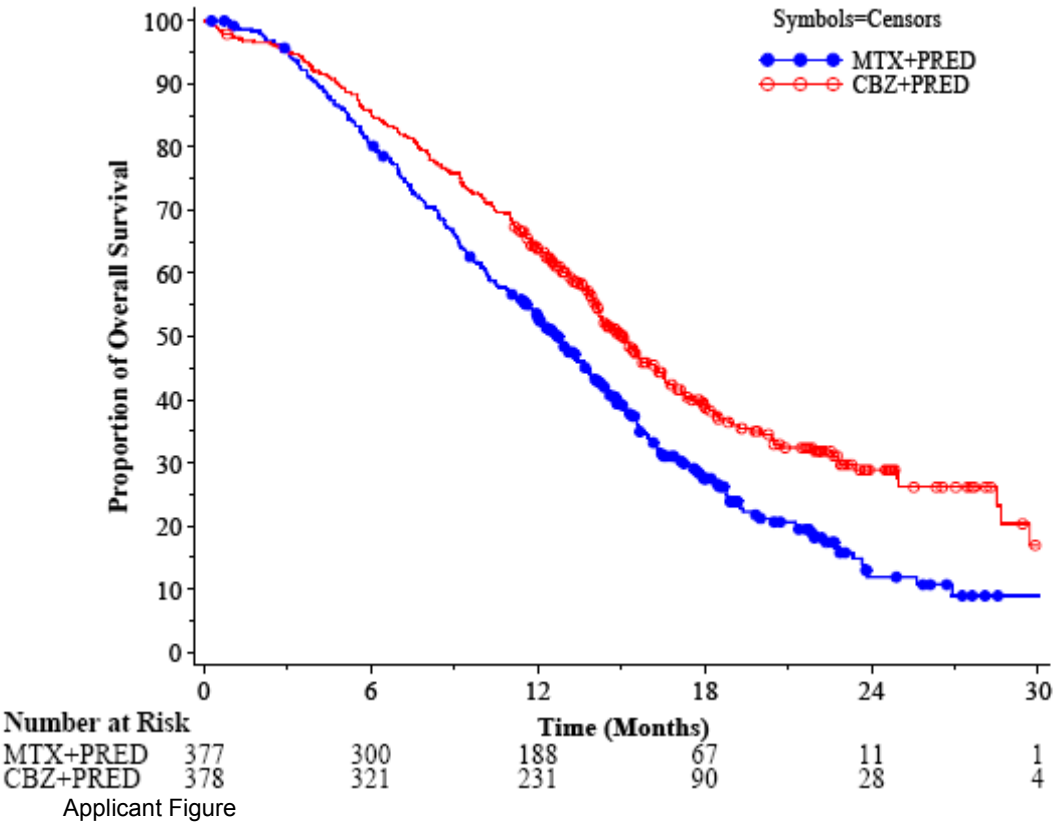
6.1.4 Analysis of Primary Endpoint

Table 7: Overall Survival per Applicant

	MTX+PRED (N=377)	**CBZ+PRED (N=378)**
Number of patients with deaths (%)	279 (74.0%)	234 (61.9%)
Median survival in months (95% CI)	12.7 (11.6 - 13.7)	15.1 (14.1 - 16.3)
Hazard ratio (95% CI)	0.70 (0.59-0.83)	
P-value	<0.0001	

Applicant's Analysis

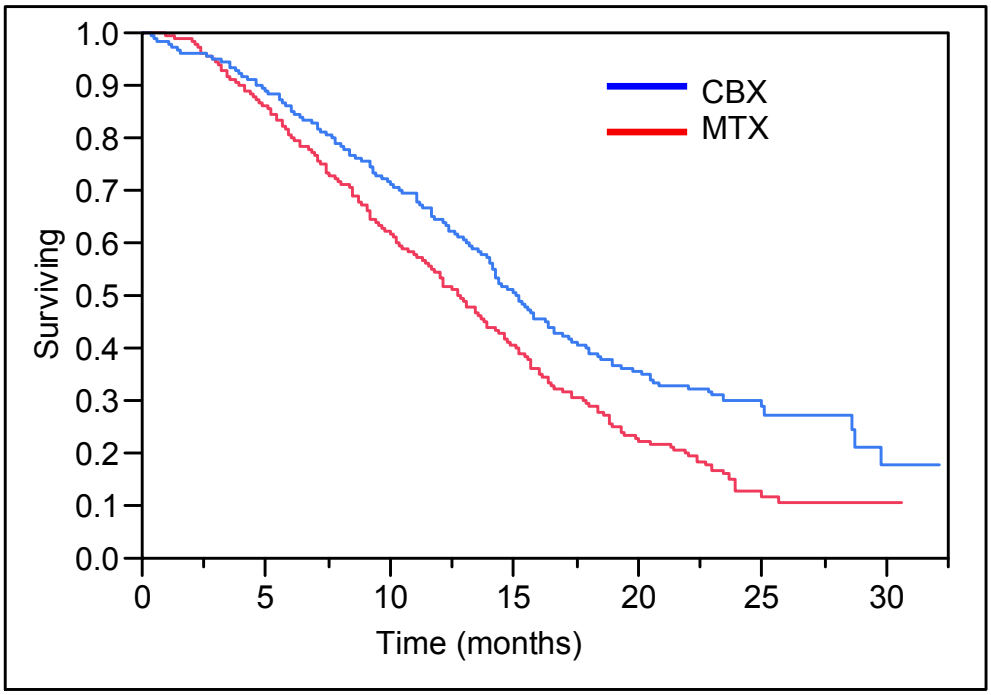
Figure 6: Kaplan-Meier Plot of Overall Survival per Applicant



Applicant Figure

The applicant's OS results have been confirmed by FDA review. There were 10 patients who were censored prior to the study cut-off date for reasons other than an OS event. Seven of these patients were on the MTX arm, and three were on the CBZ arm. Among the reasons that these patients were censored included lost to follow-up, at subject's request, and referral for alternative treatment. A worst-case sensitivity analysis was performed in which the MTX arm patients all were assigned an end-of-study date of the trial cut-off date, and all the CBZ patients were assigned a date of death one day after they were censored. The results for OS remain in favor of the CBZ arm (see Figure 7), with a HR of 0.73 (95% CI 0.61, 0.87).

Figure 7: Overall Survival-Worst-Case Analysis



Reviewer Comment: *The overall survival results are robust. There were very few patients lost to follow-up or censored for other reasons prior to the end of the study. Dates of death have been confirmed for a number of patients in the case report forms submitted with the NDA.*

6.1.5 Analysis of Secondary Endpoints

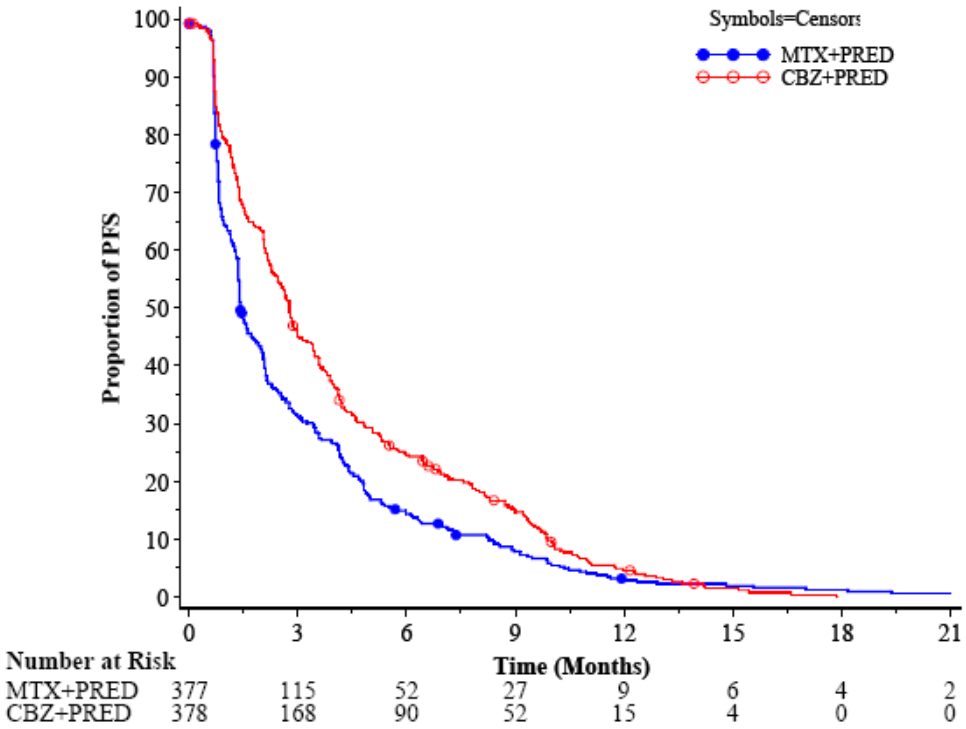
6.1.5.1 Progression-Free Survival

Table 8: Progression-Free Survival per Applicant

	MTX+PRED (N=377)	CBZ+PRED (N=378)
PFS events	367 (97.3%)	364 (96.3%)
Death	29 (7.7%)	38 (10.1%)
Tumor progression	68 (18.0%)	67 (17.7%)
PSA progression	186 (49.3%)	163 (43.1%)
Pain progression	70 (18.6%)	86 (22.8%)
Symptom deterioration	14 (3.7%)	10 (2.6%)
Censored	10 (2.7%)	14 (3.7%)
Median PFS (months) 95% CI	1.4 1.4 - 1.7	2.8 2.4 - 3.0

Applicant's Analysis

Figure 8: Kaplan-Meier Plot of Progression-Free Survival per Applicant



(b) (4)

6.1.5.2 Overall Response Rate (ORR)

There were 204 patients (54.1%) in the MTX arm and 201 patients (53.2%) in the CBX who were eligible for assessment of ORR based on presence of measurable disease at study entry. ORR was assessed by the investigator, and there was no independent review of the data. THE ORR was 4.4% in the MTX arm and 14.4% in the CBZ arm (see Table 9). There were no complete responders, thus all the responses were partial response. For the MTX arm, 37 patients (18.1%) had missing data or were not evaluable, compared to 28 patients (13.9%) in the CBZ arm.

Table 9: Overall Response Rate per Applicant

	MTX+PRED (N=204)	**CBZ+PRED (N=201)**
Number with CR or PR (%)	9 (4.4%)	29 (14.4%)
95% CI	1.6-7.2%	9.6-19.3%
P-value	0.0005	

Applicant's Analysis

Reviewer Comment: *ORR was assessed by the investigator in this unblinded trial, and there was no independent confirmation of the response results. Additionally, there was missing data assessments for a substantial number of patients resulting in a total of 65 patients out of 405 who were not evaluable. The number of patients for whom there was missing data could potentially affect the results, as the total number of responses was 38. However, all the patients who were deemed to have a response had confirmatory scans, as confirmed by this reviewer. Therefore, this information could be included in the labeling with the notation that these results were assessed by the investigator.*

6.1.5.3 PSA Progression or Response

There were 325 patients (86.2%) in the MTX arm and 329 patients (87.0%) in the CBX arm who were eligible for assessment of PSA response based on PSA levels ≥20 ng/mL measured at study entry. The PSA response rate was 17/8% in the MTX arm and 39.2% in the CBX arm. The applicant reports median time to PSA progression of 3.1 months in the MTX arm and 6.4 months in the CBZ, with a HR of 0.75 (0.63-0.90).

(b) (4)

6.1.5.4 Pain Progression or Response

There were 168 patients (44.6%) in the MTX arm and 174 patients (46.0%) in the CBZ arm who were eligible for pain response based on a median Present Pain Intensity (PPI) Score of ≥2 on McGill-Melzack scale and/or mean analgesic score (AS) ≥10 points at study entry. The applicant reports a pain response rate of 7.7% in the MTTX arm and 9,2% in the CBZ arm. The median time to pain progression was 11.1 months in the CBZ arm and was not reached in the MTX arm.

(b) (4)

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

The sponsor conducted multiple subpopulation analyses, including the prognostic factors of ECOG performance status, disease measurability, number of prior chemotherapy regimens, age, country, pain at baseline, PSA status, time from last docetaxel to randomization, docetaxel dose, and time of progression from last docetaxel. Overall survival showed a consistent trend towards favoring the cabazitaxel arm, except for country and docetaxel dose <225 mg/m^2. However, the applicant did not correct for multiplicity in these calculations and did not pre-specify these analyses in the statistical analysis plan, they are considered exploratory and will not be included in the labeling.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose of 25 mg/m^2 in this clinical trial is associated with serious toxicity and some deaths; however, the survival benefit is confirmed despite these toxicities. As the efficacy cannot be guaranteed with a lower dose, the recommended dose will remain 25 mg/m^2; however, the applicant will be given a post-marketing requirement to study both 25 mg/m^2 and 20 mg/m^2 in a first-line metastatic, hormone-refractory population to determine whether the efficacy of cabazitaxel is retained with a lower dose that presumably will be less toxic.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

There were 453 major protocol violations in 228 patients (see table 10). Among these violations, 93 were due to inclusion or exclusion criteria not being met at study entry, 340 were treatment deviations from the protocol, and 20 were due to patients taking medications either during or prior to the trial that were prohibited. The largest number of violations concerned missing pain assessments or analgesic scores. The second largest number of violations was associated with inadequate organ function at study entry.

There were 83 patients who did not meet all the entry criteria for this trial. The majority had inadequate organ function (48 violations among 46 patients), with decreased hemoglobin and increased bilirubin or increased liver enzymes as the most common reasons cited. Seventeen patients had received other therapy within four weeks of their first study dose. There was one patient who had not received hormonal therapy prior to study entry on the MTX arm, and two patients had received prior treatment with mitoxantrone. Two patients had not received receive prior castration by orchiectomy or Luteinizing Hormone-Releasing Hormone (LH-RH).

There were 340 treatment deviations in 162 patients. As noted above, the largest number was 216 missing pain assessments in 106 patients. There were 76 instances in which a patient received the incorrect dose of mitoxantrone or cabazitaxel (14 patients on MTX arm, 16 patients on CBZ arm). Five patients with measurable disease did not have a tumor assessment during the trial, and nine patients were missing a PSA value.

Table 10: Major Protocol Violations

	MTX+PRED (N=377)	CBZ+PRED (N=378)
Missing at least 5 pain intensity and analgesic scores	57 (15.4%)	49 (13.2%)
Inadequate organ function	22 (5.8%)	24 (6.3%)
Actual dose is less than or greater than intended dose	14 (3.8%)	16 (4.3%)
Prior surgery, radiation, chemotherapy, or other anti-cancer therapy within 4 weeks prior to first dose	10 (2.7%)	7 (1.9%)
Missing a PSA value	6 (1.6%)	3 (0.8%)
Previous treatment with less than 3 cycles or < 225 mg/m^2 cumulative dose of docetaxel	3 (0.8%)	2 (0.5%)
Missing a tumor measurement	3 (0.8%)	2 (0.5%)
Previous treatment with mitoxantrone.	1 (0.3%)	1 (0.3%)
Did not have docetaxel or hormone-containing regimen and/or did not progress during or after docetaxel/hormone containing regimen	1 (0.3%)	0
Did not receive prior castration (surgical or medical)	0	2 (0.5%)

Reviewer Comment: *Though there were 83 patients who did not meet all the entry criteria for this trial, many of the patients with inadequate organ function had very mildly decreased hemoglobin or platelets or mildly elevated liver enzymes or bilirubin. Patients who had other entry criteria violations included many who had received prior therapy within four weeks of study entry. This reviewer does not believe that these violations affected the survival benefit shown for cabazitaxel.*

7 Review of Safety

Safety Summary

The safety of cabazitaxel was evaluated in 371 patients with hormone-refractory prostate cancer in the phase 3 trial EFC6193, in which patients were randomized to receive either cabazitaxel 25 mg/m^2 with prednisone every three weeks or mitoxantrone 12 mg/m^2 with prednisone every three weeks for up to 10 cycles. A summary of important safety results is included below.

- Deaths not directly attributed to disease progression and occurring within 30 days of the last dose of study drug were reported in 18 (5%) cabazitaxel-treated patients and three (<1%) mitoxantrone-treated patients. The most common fatal adverse reactions in cabazitaxel-treated patients were infections (n=5) and renal failure (n=4). The majority (80%) of fatal infection-related adverse reactions occurred after a single dose of cabazitaxel. Other fatal adverse reactions in cabazitaxel-treated patients included electrolyte imbalance in a patient with diarrhea, ventricular fibrillation, cerebral hemorrhage, and dyspnea.

- The most common (≥ 10%) grade 1-4 adverse reactions in cabazitaxel-treated patients were neutropenia, anemia, leukopenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia.
- The most common (≥ 5%) grade 3-4 adverse reactions in cabazitaxel-treated patients were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia.
- Adverse reactions of interest in cabazitaxel-treated patients included neutropenic complications (febrile neutropenia and infection), renal failure, hematuria, and cardiac toxicity.
- Treatment discontinuations due to adverse drug reactions occurred in 18% of patients who received cabazitaxel and 8% of patients who received mitoxantrone. The most common adverse reactions leading to treatment discontinuation on the cabazitaxel arm were neutropenia and renal failure.
- Dose reductions were reported in 12% of cabazitaxel-treated patients and 4% of mitoxantrone-treated patients. Dose delays were reported in 28% of cabazitaxel-treated patients and 15% of mitoxantrone-treated patients.

7.1 Methods

The phase 3 trial EFC6193 included safety assessments at baseline, prior to each infusion, and at the end of treatment (within 30 ± 3 days of last dose). Serious adverse events that had not recovered completely by the end of treatment were to be followed until resolution.

At baseline, safety assessments included medical, oncologic, and surgical history, physical exam, laboratories (hematology, chemistries, liver function), assessment of ECOG PS, ECG, and LVEF by echocardiogram. Pre-infusion safety assessments were the same as at baseline, except ECGs were not required prior to each infusion and echocardiograms were required for the mitoxantrone arm only (every other cycle). At the end of treatment, all patients received an ECG and mitoxantrone arm patients received an additional echocardiogram. Post-treatment follow-up was to occur every three months for up to two years and included adverse event recording.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Seven trials for which the applicant included safety data are summarized in section 5.1 table 1. Six trials (TED6188, TED 6189, TED 6190, BEX6702, ARD6191, and EFC6193) were included in the integrated summary of safety (ISS), while data from TCD6945, a study of cabazitaxel in combination with capecitabine, was presented

separately. The ISS included a total of 558 patients treated with single-agent cabazitaxel or cabazitaxel + steroid. Among these 558 patients, 408 (73.1%) received the same dose and schedule as used in the phase 3 trial EFC6193.

Reviewer Comment: *The vast majority of patients with prostate cancer who received any cabazitaxel (97.4%) or who received the 25 mg/m^2 q 3 weekly dosing schedule (99.5%) were treated on the phase 3 trial EFC6193. For this reason, the safety analyses, other than those provided in section 7.1.3 below, will focus primarily on data from this trial.*

7.1.2 Categorization of Adverse Events

MedDRA terminology (version 12.0) was used to characterize all adverse events in the phase 3 trial EFC6193. Adverse event grading was done according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse event data from 6 trials was included in the integrated safety database (see Section 7.1.1, table 11 above). The rates of the most common (>15% of patients) treatment-emergent adverse events in cabazitaxel-treated patients on EFC6193 were compared to event rates in the entire ISS database. This analysis is presented in table 11 below.

Table 11: Incidence of Most Common (>15%) Treatment-Emergent Adverse Events in ISS Database

	EFC6193 N = 371		ISS Database N = 558	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Anemia[1]	361 (97.8%)	39 (10.6%)	535 (96.2%)	54 (9.7%)
Leukopenia[1]	355 (96.2%)	253 (68.6%)	508 (91.4%)	321 (57.7%)
Neutropenia[1]	347 (94.0%)	303 (82.1%)	478 (86.0%)	397 (71.4%)
Thrombocytopenia[1]	176 (47.7%)	15 (4.1%)	217 (39.0%)	20 (3.6%)
Diarrhea	173 (46.6%)	23 (6.2%)	262 (50.0%)	38 (6.8%)
Fatigue	136 (36.7%)	18 (4.9%)	228 (40.9%)	29 (5.2%)
Nausea	127 (34.2%)	7 (1.9%)	219 (39.2%)	9 (1.6%)
Vomiting	83 (22.4%)	6 (1.6%)	142 (25.4%)	9 (1.6%)
Asthenia	76 (20.5%)	17 (4.6%)	112 (20.1%)	26 (4.7%)
Constipation	76 (20.5%)	4 (1.1%)	114 (20.4%)	4 (<1%)
Abdominal Pain[2]	64 (17.3%)	7 (1.9%)	107 (19.2%)	7 (1.3%)
Hematuria	62 (16.7%)	7 (1.9%)	72 (12.9%)	8 (1.4%)
Back Pain	60 (16.2%)	14 (3.8%)	76 (13.6%)	14 (2.5%)
Anorexia	59 (15.9%)	3 (<1%)	113 (20.3%)	4 (<1%)

[1]Calculated using the ADLB (Laboratory Tests) dataset rather than ADAE (Adverse Events) dataset. Denominators for anemia, leukopenia, neutropenia, and thrombocytopenia include only patients who had at least 1 post-baseline lab value (cabazitaxel: N = 369; ISS: N = 556).
[2]Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.
The above information was verified using the ISS ADAE (Adverse Events) dataset.

The incidences of the most common treatment-emergent adverse events occurring in cabazitaxel-treated patients on study EFC6193 were similar to the incidences in the integrated safety database. Of note, less grade 3-4 neutropenia was reported for the integrated safety population than for cabazitaxel-treated patients on EFC6193.

Reviewer Comment: *The lower rate of grade 3-4 neutropenia in patients in the ISS database vs. patients in the phase 3 trial could be at least partially accounted for by the inclusion of patients who received cabazitaxel doses <25 mg/m^2 in the ISS database. The association between doses ≥25 mg/m^2 and higher rates of grade 3-4 neutropenia is further discussed in section 7.5.1 below.*

Febrile neutropenia and renal failure are not included in the above table because they each occurred in <15% of cabazitaxel-treated patients treated on trial EFC6193. Both of these adverse events occurred more frequently in EFC6193 than in the ISS database. Grade 3-4 febrile neutropenia occurred in 27 (7.3%) EFC6193 patients and 31 (5.6%) ISS patients. Grade 1-4 renal failure occurred in 11 (3.0%) EFC6193 patients and 12 (2.2%) ISS patients. Grade 3-4 renal failure occurred in 8 (2.2%) EFC6193 patients and 9 (1.6%) ISS patients. Only one patient treated on a trial other than EFC6193 developed renal failure. This patient, 840-594-019, was a 58 year-old female with NSCLC treated on TED6190 whose course was complicated by several concurrent adverse events. On the same day she developed grade 4 renal failure, grade 3 intestinal obstruction and grade 5 intra-abdominal sepsis were also reported. She died nine days later from grade 5 respiratory distress syndrome.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure to cabazitaxel and comparator therapy in the phase 3 trial EFC6193 is summarized in table 12 below.

Table 12: Exposure

	Cabazitaxel N = 371	Mitoxantrone N = 371
Number of Cycles Median	6.0	4.0
Total Cumulative Dose (mg/m^2) Median	148.5	46.4
Dose Per Cycle (mg/m^2) Median	Planned: 25	Planned: 12
Cycle 1	24.7	11.8
Cycle 2	24.7	11.8
Cycle 3	24.7	11.8
Cycle 4	24.7	11.8
Cycle 5	24.6	11.8
Cycle 6	24.6	11.8
Cycle 7	24.6	11.7
Cycle 8	24.6	11.7
Cycle 9	24.5	11.7
Cycle 10	24.6	11.6
Relative Dose Intensity (%) Median	96.1	97.3

The above information was verified using the ADEX (Exposure) dataset.

Cabazitaxel arm patients received more cycles of treatment than did comparator arm patients. The median cabazitaxel dose per cycle remained fairly stable through the duration of treatment. The relative dose intensity was close to 100% on both arms.

Dose delays, interruptions, and reductions are summarized in the table below.

Table 13: Dose Modifications

	Cabazitaxel N = 371	Mitoxantrone N =371
Any Modification	138 (37.2%)	68 (18.3%)
Delay[1]	103 (27.8%)	56 (15.1%)
Reduction[2]	45 (12.1%)	13 (3.5%)
Interruption	18 (4.9%)	4 (1.1%)

[1]Includes dose delays alone and dose delays with reduction.
[2]Includes dose reductions alone and dose delays with reduction.
The above information was verified using the ADAE (Adverse Events) dataset.

Twice as many patients on the cabazitaxel arm required a dose modification. Nearly twice as many cabazitaxel-treated patients underwent dose delay. More than three times as many cabazitaxel-treated patients underwent dose reduction.

Adverse events leading to dose modification in ≥3 patients on either arm are summarized in table 14 below. In addition, discontinuations due to adverse events occurred in 18.3% of cabazitaxel arm patients and 8.4% of mitoxantrone arm patients (see section 7.3.3, table 21).

Table 14: Adverse Events Leading to Dose Modification (≥3 Patients, Either Arm)

	Cabazitaxel N = 371		Mitoxantrone N = 371	
	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4
Neutropenia	36 (9.7%)	36 (9.7%)	22 (5.9%)	16 (4.3%)
Anemia[1]	15 (3.8%)	6 (1.6%)	3 (<1%)	1 (<1%)
Diarrhea	11 (3.0%)	5 (1.3%)	0	0
Asthenia	7 (1.9%)	5 (1.3%)	2 (<1%)	0
Liver Enzymes Increased[2]	7 (1.9%)	2 (<1%)	3 (<1%)	1 (<1%)
Peripheral Neuropathy[3]	7 (1.9%)	0	1 (<1%)	1 (<1%)
Dehydration	5 (1.3%)	3 (<1%)	0	0
Fatigue	5 (1.3%)	2 (<1%)	2 (<1%)	1 (<1%)
Febrile Neutropenia	5 (1.3%)	5 (1.3%)	2 (<1%)	2 (<1%)
Thrombocytopenia	5 (1.3%)	3 (<1%)	5 (1.3%)	0
Abdominal Pain[4]	4 (1.1%)	0	0	0
Back Pain	4 (1.1%)	1 (<1%)	1 (<1%)	1 (<1%)
Hematuria	4 (1.1%)	1 (<1%)	1 (<1%)	0
Leukopenia	4 (1.1%)	2 (<1%)	3 (<1%)	1 (<1%)
Nausea	4 (1.1%)	0	0	0
Pulmonary Infection[5]	4 (1.1%)	1 (<1%)	0	0
Cellulitis	3 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Dysuria	3 (<1%)	0	0	0
Flushing	3 (<1%)	0	0	0
Hypersensitivity	3 (<1%)	0	0	0
Urinary Tract Infection	3 (<1%)	0	2 (<1%)	2 (<1%)

[1]Includes hemoglobin decreased.
[2]Includes ALT increased, AST increased, GGT increased, and transaminases increased.
[3]Includes peripheral motor neuropathy and peripheral sensory neuropathy.
[4]Includes abdominal pain upper.
[5]Includes lower respiratory tract infection, lung infection, pneumonia, and pneumonia klebsiella.
The above information was verified using the ADAE (Adverse Events) dataset.

Grade 3-4 neutropenia accounted for the majority of dose modifications on both arms, but was a more frequent cause on the cabazitaxel arm. Diarrhea, dehydration, abdominal pain, nausea, dysuria, flushing, and hypersensitivity each accounted for dose modification in at least three patients on the cabazitaxel arm but none on the comparator arm.

7.2.2 Explorations for Dose Response

There is evidence of an exposure-response for grade ≥3 neutropenia. See section 2.2.4.2 of the Clinical Pharmacology review.

7.2.3 Special Animal and/or In Vitro Testing

See the pharmacology/toxicology review for details.

7.2.4 Routine Clinical Testing

See sections 7.4.2-7.4.4.

7.2.5 Metabolic, Clearance, and Interaction Workup

See the summary of the clinical pharmacology review in section 4.4.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Taxotere (docetaxel) and Taxol (paclitaxel) are other drugs that belong to the taxane family.

The Taxotere and Taxol labels include warnings and precautions for hypersensitivity reactions, hematologic effects, hepatic impairment, acute myeloid leukemia (Taxotere label only), cutaneous reactions (Taxotere label only), fluid retention (Taxotere label only), neurologic symptoms, asthenia (Taxotere label only), cardiovascular events (Taxol label only), and injection site reactions (Taxol label only). Hepatic impairment, AML, cutaneous reactions, fluid retention, and injection site reactions are discussed in this section, whereas hypersensitivity reactions are discussed in Section 7.4.6, cardiovascular events are discussed in Sections 7.3.4 and 7.4.1, and neurologic symptoms (peripheral neuropathy) and asthenia are included in Section 7.4.1.

<u>Hepatic Impairment</u>

A hepatic impairment warning is included in the black-box of the Taxotere label and a precaution is included in the Taxol label. Additionally, elevations in transaminases and alkaline phosphatase have been reported in some breast cancer trial patients who received Taxotere and rare cases of hepatitis have been reported during the post-

marketing period, and this information is included in the Taxotere label. The Taxol label includes hepatic adverse events (hyperbilirubinemia, alkaline phosphatase elevations, and AST elevations) in a summary table.

Taxanes, including cabazitaxel, are metabolized and excreted via the hepatic route. No hepatic impairment study has been conducted for cabazitaxel, although the applicant has submitted a protocol for such a trial. Cabazitaxel itself does not appear to be hepatotoxic, with ≤1% of patients on EFC6193 experiencing bilirubin elevation or transaminase elevation (see section 7.4.2, table 34). Drug-induced liver injury (DILI) based on Hy's law did not occur in any patients in the ISS database. Four patients in the ISS database (TED6188: 250-881-002; TED6189: 250-194-001, 724-150-012; TED6191:840-016-001) experienced total bilirubin elevation ≥2 times the upper limit of normal (ULN) and transaminase elevation >3 x ULN. However, three of these patients also had alkaline phosphatase elevations >2x ULN. Only 1 patient (TED6189: 250-194-001) met the laboratory criteria for Hy's Law, with ALT >3x ULN, bilirubin ≥2x ULN, and alkaline phosphatase <2x ULN. This patient was a 67 year-old male with carcinoid tumor of the small intestine who received weekly cabazitaxel 1.5 mg/m^2 x 4 doses, with the last dose given on study day 22. He experienced ALT 3.1x ULN on study day 28, and total bilirubin 3.2x ULN on study day 32. Bilirubin rose to 3.8x ULN on study day 34. The patient was found to have grade 4 ileus and grade 3 septicemia which both began on study day 30. Blood cultures were positive for E. coli and Candida albicans. An abdominal ultrasound revealed a dilatation of the intra- and extra-hepatic biliary tract without obstruction. The patient recovered from septicemia on study day 41. Elevated ALT completely resolved by study day 37, while total bilirubin was improving (1.5x ULN). As other explanations for this patient's liver injury exist (tumor location, septicemia), this case does not meet the definition of a Hy's Law case. Note that no cabazitaxel-treated patients on the phase 3 trial EFC6193 met the laboratory criteria for Hy's Law.

Acute Myeloid Leukemia

Acute myeloid leukemia is included under warnings and precautions in the Taxotere label. According to the post-marketing experience section of the Taxotere label, treatment-related AML or myelodysplasia has occurred in patients who received taxotere in combination with anthracyclines and/or cyclophosphamide, but not in patients who received single-agent therapy. There are no adverse events of leukemia or myelodysplasia reported in the cabazitaxel ISS database.

Cutaneous Reactions

Localized erythema of the extremities with edema followed by desquamation has been observed following taxotere administration and is reported in the Taxotere label. Thirteen (2.3%) patients in the cabazitaxel integrated safety database experienced adverse events with preferred terms erythema, rash, and rash erythematous. Note that

this search was not limited to events involving the extremities. All AEs were grade 1 (N=12) or grade 2 (N=1) and all occurred in patients treated on the phase 3 trial EFC6193. There were no patients in the entire ISS database who discontinued therapy due to skin toxicity.

Fluid Retention

According to the Taxotere label, severe fluid retention has been reported following Taxotere therapy. Grade 1-4 fluid retention, edema, peripheral edema, or weight gain occurred in 87 (16.6%) patients in the cabazitaxel ISS database and 44 (11.9%) patients on the phase 3 trial EFC6193. Four (<1%) patients experienced grade 3 edema or peripheral edema and none experienced a grade 4 event. One patient (250-194-017, TED6189) who received weekly cabazitaxel dosing permanently discontinued study therapy due to grade 2 peripheral edema and subsequently recovered.

Injection Site Reactions

According to the Taxol label, injection site reactions secondary to extravasation have been reported, including rare serious events of phlebitis, cellulitis, induration, skin exfoliation, necrosis and fibrosis. Ten (2.7%) cabazitaxel-treated patients on the phase 3 trial EFC6193 experienced adverse events of catheter site infection, cellulitis (excluding one patient with oral cellulitis), extravasation, phlebitis, or skin atrophy. Note that not all events included in this analysis necessarily occurred at the injection site, as such information was not provided in the application. However, all events were grade 1-2, except for two events of grade 3 cellulitis (hand and supra-axillary).

7.3 Major Safety Results

7.3.1 Deaths

More deaths not directly attributed to disease progression and occurring within 30 days of the last dose of study drug were reported on the cabazitaxel arm (4.9% on the cabazitaxel arm vs. <1% on the mitoxantrone arm). However, more total deaths occurred on the mitoxantrone arm. All-cause deaths within 30 days of last drug dose were 4.9% on the cabazitaxel arm and 2.4% on the mitoxantrone arm. All deaths occurring in the safety population are included in table 15 below.

Table 15: Safety Population Deaths

	Cabazitaxel N = 371	Mitoxantrone N = 371
Total Deaths	227 (61.2%)	275 (74.1%)
TEAEs[1]	19 (5.1%)	5 (1.3%)
Progression[2]	198 (53.4%)	256 (69.0%)
Other[3]	10 (2.7%)	14 (3.8%)
Unknown	6	7
Other Events	4	7
Deaths within 30 Days of Last Dose	18 (4.9%)	9 (2.4%)
TEAEs[4]	18 (4.9%)	3 (<1%)
Progression[5]	0	6 (1.6%)
Other	0	0
Unknown	0	0
Other Events	0	0
Deaths within 60 Days of Last Dose	24 (6.5%)	25 (6.7%)
TEAEs[1]	19 (5.1%)	4 (1.1%)
Progression[6]	5 (1.3%)	18 (4.9%)
Other	0	3 (<1%)
Unknown	0	2
Other Events	0	1

[1]Includes 840-041-003 on the cabazitaxel arm, coded as unknown cause of death, but with adverse event-related death, excludes 250-004-018 and 840-014-006 on the mitoxantrone arm, whose deaths were due to disease progression rather than adverse events.
[2]On the cabazitaxel arm, includes 840-041-001, coded as adverse event, but with grade 5 "disease progression" and 840-071-004, coded as other event but with death reported to be due to end-stage hormone-refractory prostate cancer. On the mitoxantrone arm, includes 2 patients with progressive disease who were coded as adverse events (250-004-018 and 840-014-006) and 1 patient with progressive disease who was coded as an other event (250-001-042), and excludes 380-005-003 who died due to dyspnea and is included as a TEAE.
[3]On the cabazitaxel arm, excludes 840-041-003, coded as unknown cause of death but with adverse event-related death and 840-071-004, coded as other event but with death reported to be due to end-stage hormone-refractory prostate cancer. On the mitoxantrone arm, excludes 250-001-042 whose death was due to progressive disease.
[4]Excludes 250-004-018 and 840-014-006 on the mitoxantrone arm, whose deaths were due to disease progression rather than adverse events.
[5]Includes 250-004-018 and 840-014-006 on the mitoxantrone arm, whose deaths were due to disease progression rather than adverse events.
[6]On the cabazitaxel arm, includes 380-003-004, 710-001-004, 840-011-004, 840-041-001, and 840-047-001. On the mitoxantrone arm, includes 032-001-004, 208-003-009, 208-003-017, 250-004-018, 380-005-003, 484-001-002, 710-001-001, 752-002-001, 752-002-002, 752-002-006, 792-001-027, 840-001-003, 840-014-006, 840-039-009, 840-043-003, 840-050-005, 840-060-003, 840-083-002.
The above information was verified using the ADAE (Adverse Events) and ADDS (Disposition) datasets.

More information regarding the 18 (4.9%) cabazitaxel-treated patients who experienced grade 5 TEAEs other than disease progression within 30 days of the last dose of study drug is provided in the table below.

Table 16: Grade 5 Treatment-Emergent Adverse Events Excluding Disease Progression and Occurring Within 30 Days of Last Dose on the Cabazitaxel Arm

Patient ID	Grade 5 AE Preferred Term	Last Dose (Day)	Grade 5 AE (Day)	Death (Day)	Days from Last Dose to Death	Cycle #
056-003-001	Ventricular Fibrillation	64	73	73	9	4
158-003-003	Fungal Sepsis	1	13	15	14	1
208-001-014	Cardiac Arrest	1	8	8	7	1
208-003-005	Sepsis	1	9	16	15	1
250-001-023	Cardiac Failure	192	210	210	18	10
276-008-003	Cerebral Hemorrhage	22	36	39	17	2
356-001-004	Anemia, Neutropenia, Thrombocytopenia	161	168	174	13	8
356-001-007	Dyspnea	23	33	33	10	2
356-001-010	Aspiration, Vomiting	1	9	9	8	1
356-007-003	Cardiac Arrest	22	30	30	8	2
484-001-006	Electrolyte Imbalance	1	8	8	7	1
528-001-002	Neutropenic Sepsis	142	149	150	8	7
710-005-005	Renal Failure	106	125	135	29	6
724-003-002	Abdominal Pain, Enterocolitis, Febrile Neutropenia, Renal Failure, Septic Shock	1	13	15	14	1

Patient ID	Grade 5 AE Preferred Term	Last Dose (Day)	Grade 5 AE (Day)	Death (Day)	Days from Last Dose to Death	Cycle #
752-001-008	Renal Failure	106	124	125	19	6
792-001-006	Acute Renal Failure, Respiratory Failure	92	101, 103	105	13	5
826-007-003	Neutropenic Sepsis	1	12	13	12	1
840-073-001	Sudden Death	116	118	118	2	6

The above information was verified using the ADAE (Adverse Events) and ADEX (Exposure) datasets.

One additional cabazitaxel-treated patient died secondary to treatment-emergent adverse events, though his death did not occur within 30 days of the last dose of study drug. Patient 840-041-003 was a 77 year-old male with a history of COPD, sinus tachycardia, and right bundle branch block who developed grade 3 neutropenic sepsis nine days after his first dose of cabazitaxel. Blood culture was positive for Pseudomonas aeruginosa. Four days after the onset of neutropenic sepsis, the patient developed hypotension and wheezing and was found to have a right middle lobe pneumonia. Eighteen days after the administration of cabazitaxel, the patient developed grade 3 acute renal failure, followed two days later by grade 4 respiratory failure. The patient discontinued study therapy due to acute renal failure, which required hemodialysis. He died 43 days after his first dose of cabazitaxel. The investigator attributed his death to unknown causes rather than an adverse event.

Seven of the above deaths occurred in conjunction with or as a result of neutropenia: neutropenic sepsis (two cases), fungal sepsis, sepsis, septic shock, pancytopenia, and vomiting with aspiration in the setting of neutropenia. Five-neutropenia associated deaths occurred during cycle 1. Four deaths during cycle 1 were due to infection.

Reviewer Comment: Due to the occurrence of four infection-related deaths during cycle 1 of cabazitaxel therapy, primary prophylaxis with G-CSF should be considered in patients at high risk for neutropenia complications (age >65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities).

Five mitoxantrone-treated patients had a grade 5 TEAE other than disease progression (also excluding the preferred terms metastases to meninges and prostate cancer metastatic. Among mitoxantrone-treated patients with grade 5 TEAEs not directly attributed to disease progression, only three (250-001-027, 380-003-014, and 724-004-005) occurred within 30 days of the last dose of drug.

Table 17: Grade 5 Treatment-Emergent Adverse Events Excluding Disease Progression and Occurring Within 30 Days of Last Dose on the Mitoxantrone Arm

Patient ID	Grade 5 AE Preferred Term	Last Dose (Day)	Grade 5 AE (Day)	Death (Day)	Days from Last Dose to Death	Cycle #
250-001-027	Pneumococcal Sepsis	22	30	37	15	2
380-003-014	Multiple Fractures	91	93	93	2	5
724-004-005	Pleural Effusion	1	15	23	22	1

The above information was verified using the ADAE (Adverse Events) and ADEX (Exposure) datasets.

Grade 5 TEAEs not attributed to disease progression and leading to death within 30 days of the last dose are summarized in the table below.

Table 18: Summary of Grade 5 Treatment-Emergent Adverse Events Excluding Disease Progression and Leading to Death Within 30 Days of Last Dose

Grade 5 AE	Cabazitaxel N = 18	Mitoxantrone N = 3
Infection[1]	5	1
Cardiac Disorders[2]	4	0
Renal Failure[3]	4	0
Respiratory Disorders[4]	2	1
Other Neutropenia-Associated[5]	2	0
Other Not Neutropenia-Associated[6]	3	1

[1]Includes 158-003-003/fungal sepsis, 208-003-005/sepsis, 528-001-002/neutropenic sepsis, 724-003-002/septic shock (also renal failure), and 826-007-003/neutropenic sepsis on the cabazitaxel arm, and 250-001-027/pneumococcal sepsis on the mitoxantrone arm.
[2]Includes 056-003-001/ventricular fibrillation, 208-001-014/cardiac arrest, 250-001-023/cardiac failure, and 356-007-003/cardiac arrest on the cabazitaxel arm.
[3]Includes 710-005-005/renal failure, 724-003-002/renal failure, 752-001-008/renal failure, and 792-001-006/acute renal failure on the cabazitaxel arm. Note that 724-003-002 is also included under infections (septic shock) and 792-001-006 is also included under respiratory disorders (respiratory failure).
[4]Includes 356-001-007/dyspnea and 792-001-006/respiratory failure (also with acute renal failure) on the cabazitaxel arm, and 724-004-005/pleural effusion on the mitoxantrone arm.
[5]Includes 356-001-004/pancytopenia and 356-001-010/aspiration.
[6]Includes 276-008-003/cerebral hemorrhage, 484-001-006/electrolyte imbalance, and 840-073-001/sudden death on the cabazitaxel arm, and 380-003-014/multiple fracture on the mitoxantrone arm.
This above information was verified using the ADAE (Adverse Events) dataset.

Grade 5 infections, cardiac disorders and renal failure were reported more frequently on the cabazitaxel arm. These events are discussed in more detail in section 7.3.4.

7.3.2 Nonfatal Serious Adverse Events

Nonfatal serious adverse events occurred in 36.1% of patients on the cabazitaxel arm and 18.1% on the mitoxantrone arm. SAEs are summarized in the table below.

Table 19: Nonfatal Serious Adverse Events (≥1% on Either Arm)

	Cabazitaxel N = 371		Mitoxantrone N = 371	
	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4
Any SAE	134 (36.1%)	121 (32.6%)	67 (18.1%)	57 (15.4%)
Blood & Lymphatic Disorders				
Febrile Neutropenia	24 (6.5%)	24 (6.5%)	4 (1.1%)	4 (1.1%)
Neutropenia	17 (4.6%)	17 (4.6%)	3 (<1%)	1 (<1%)
Gastrointestinal Disorders				
Diarrhea	9 (2.4%)	7 (1.9%)	0	0
Abdominal Pain[1]	6 (1.6%)	4 (1.1%)	0	0
Vomiting	5 (1.3%)	2 (<1%)	2 (<1%)	0
General Disorders & Admin Site Conditions				
Pyrexia	6 (1.6%)	2 (<1%)	1 (<1%)	0
Infections & Infestations				
Pneumonia[2]	9 (2.4%)	8 (2.2%)	1 (<1%)	1 (<1%)
Urinary Tract Infection[3]	6 (1.6%)	3 (<1%)	3 (<1%)	3 (<1%)
Metabolism & Nutrition Disorders				
Dehydration	4 (1.1%)	4 (1.1%)	1 (<1%)	0
Musculoskeletal & Connective Tissue Disorders				
Back Pain	3 (<1%)	2 (<1%)	4 (1.1%)	4 (1.1%)
Nervous System Disorders				
Spinal Cord Compression	4 (1.1%)	4 (1.1%)	3 (<1%)	3 (<1%)
Renal & Urinary Disorders				
Hematuria	10 (2.7%)	6 (1.6%)	2 (<1%)	1 (<1%)
Renal Failure[4]	7 (1.9%)	5 (1.3%)	0	0
Ureteric Obstruction	4 (1.1%)	4 (1.1%)	0	0
Hydronephrosis	4 (1.1%)	3 (<1%)	1 (<1%)	(<1%)
Respiratory, Thoracic & Mediastinal Disorders				
Pulmonary Embolism	5 (1.3%)	5 (1.3%)	6 (1.6%)	5 (1.3%)

[1]Includes abdominal pain lower.
[2]Includes bronchopneumonia, lobar pneumonia, and pneumonia klebsiella.
[3]Includes urinary tract infection enterococcal and urinary tract infection fungal.
[4]Includes acute renal failure.
The above information was verified using the ADAE (Adverse Events) dataset.

Febrile neutropenia and neutropenia were the most common serious adverse event among cabazitaxel-treated patients. Hematuria, pneumonia, diarrhea, and renal failure were the next most common serious adverse events on the cabazitaxel arm, occurring in at least seven patients each.

7.3.3 Dropouts and/or Discontinuations

Reasons for treatment discontinuation are summarized in the table below. Disease progression was the most common reason for treatment discontinuation on both arms. More patients discontinued treatment due to adverse events on the cabazitaxel arm than on the comparator arm (18.3% vs. 8.4%, respectively).

Table 20: Reasons for Treatment Discontinuation

	Cabazitaxel N = 371	Mitoxantrone N = 371
Disease Progression	179 (48.2%)	268 (72.2%)
Completed Study Treatment Period	105 (28.3%)	46 (12.4%)
Adverse Event	68 (18.3%)	31 (8.4%)
Other Reason[1]	10 (2.7%)	7 (1.9%)
Subject's Request	8 (2.2%)	17 (4.6%)
Poor Compliance to Protocol	1 (<1%)	0
Subject Lost to Follow-Up	0	2 (<1%)

[1]Other reasons on the cabazitaxel arm were: PI decision for lack of benefit (076-001-004), subject's family request (158-002-004), incorrect enrollment (203-001-010), PI discretion (250-002-006), medical decision not safety related (380-004-003), patient met exclusion criteria for prior radiotherapy (484-001-004), PI discretion in view of fever, antibiotics, and increased WBC (702-001-008), PI discretion, no definitive PD (724-003-001), abnormal LFTs (826-005-014), unable to travel to clinic (840-003-001). Other reasons on the mitoxantrone arm were: suspected disease progression (032-001-007), clinical deterioration (032-002-003), ineligible due to elevated transaminases at baseline (208-002-006), protocol violation/radiotherapy within 4 weeks of randomization (752-002-004), decreased EF at baseline (840-016-001), protocol violation/on prohibited concomitant medication (840-024-002), PI discretion (840-063-004).
The above information was verified using the ADDS (Disposition) dataset.

Specific adverse events leading to treatment discontinuation are summarized in the table below.

Table 21: Discontinuations due to Adverse Events (≥2 Patients on Either Arm)

	Cabazitaxel N = 371	Mitoxantrone N = 371
Any Adverse Event	68 (18.3%)	31 (8.4%)
Neutropenia	9	0
Renal Failure[1]	7	0
Infection[2]	6	1
Hematuria	5	1
Sepsis[3]	5	1
Fatigue	4	1
Diarrhea	4	1
Abdominal Pain	3	0
Febrile Neutropenia	3	0
Anemia	2	1
Asthenia	2	2
Back Pain	2	2
Cardiac Arrest	2	0
Deep Vein Thrombosis	2	0
Hepatic Enzyme Increased[4]	2	0
Leukopenia	2	1
Thrombocytopenia	2	1
Cardiotoxicity[5]	2	2
Ejection Fraction Decreased	0	2
Pulmonary Embolism	1	2

[1]Includes acute renal failure.
[2]ncludes cellulitis, pneumonia, salmonellosis, campylobacter infection, and urinary tract infection fungal.
[3]Includes neutropenic sepsis, pneumococcal sepsis, and septic shock.
[4]Includes transaminases increased.
[5]Includes cardiac failure and ventricular fibrillation.
The above information was verified using the ADAE (Adverse Events) dataset.

Twenty-two (6%) patients discontinued JEVTANA treatment due to neutropenia, febrile neutropenia, sepsis, or infection (including preferred terms campylobacter infection, pneumonia, salmonellosis, and UTI fungal). Neutropenia led to more treatment discontinuations than any other adverse event on the cabazitaxel arm. Note that no discontinuations due to neutropenia occurred on the comparator arm.

7.3.4 Significant Adverse Events

Neutropenia and Infection

There were five infection-related grade 5 adverse events on the cabazitaxel arm and one on the mitoxantrone arm. Details for these six patients are provided in the table below.

Table 22: Infection-Related Deaths on EFC6193

Arm/Patient ID	Grade 5 AE	Cycle #	Treatment with G-CSF?
Cabazitaxel			
158-003-003	Fungal Sepsis	1	Y
208-003-005	Sepsis	1	
528-001-002	Neutropenic Sepsis	7	
724-003-002	Septic Shock	1	
826-007-003	Neutropenic Sepsis	1	Y
Mitoxantrone			
250-001-027	Pneumococcal Sepsis	2	

Four of five infection-related deaths on the cabazitaxel arm occurred during cycle 1. Two patients received treatment G-CSF. None of these patients received prophylactic G-CSF.

Reviewer Comment: *There was a clear relationship between neutropenia and grade 5 infection. Among the five infection-related deaths on the cabazitaxel arm, all had concurrent grade 4 neutropenia. Among the five patients with infection-related deaths, two received G-CSF after development of neutropenia, but none were given G-CSF prophylactically. In addition, patient 356-001-004 on the cabazitaxel arm had febrile neutropenia at the time of death, but no documented infection. This patient developed grade 4 neutropenia despite the use of prophylactic G-CSF.*

Reviewer Comment: *The applicant states that after the IDMC recommendation to review and follow ASCO guidelines concerning the use of G-CSF (Dear Investigator letter dated July 30, 2008), no more infection-related deaths occurred. However, most infection-related deaths (80.0%) occurred during the first cycle. By July 30, 2008, only 51 (13.7%) patients had not yet received their first dose of cabazitaxel and 280 of 340 (82.1%) patients who received a second cycle had already begun cycle 2. Hence, the absence of infection-related deaths after the IDMC recommendation more likely reflects the timing of the recommendation rather than any changes in clinical practice.*

As displayed in table 23 below, there was more grade 3-4 neutropenia and febrile neutropenia on the cabazitaxel arm. Additionally, more cabazitaxel-treated patients discontinued study treatment secondary to infection-related causes.

Table 23: Neutropenia Adverse Events and Related Discontinuations on EFC6193

	Cabazitaxel N = 371	Mitoxantrone N = 371
Grade 3-4 Neutropenia[1]	303 (81.7%)	215 (58.0%)
Grade 3-4 Febrile Neutropenia	27 (7.3%)	5 (1.3%)
Discontinuations		
Any of the below	22 (5.9%)	2 (<1%)
Neutropenia	9	0
Infection[2]	6	1
Sepsis	5	1
Febrile Neutropenia	3	0

[1]Includes all laboratory-based grade 3-4 neutropenia: cabazitaxel N = 369, mitoxantrone N = 370.
[2]Includes cellulitis, pneumonia, salmonellosis, campylobacter infection, and UTI fungal.
The above information was verified using the ADAE (Adverse Events) dataset.

166 (44.7%) of cabazitaxel-treated patients received at least one dose of colony stimulating factor (filgrastim, G-CSF, lenograstim, pegfilgrastim, and sargramostim) during cycles 1 through 10.

The applicant analyzed neutrophil nadirs in patients before and after receiving G-CSF. The results are shown in table 24 below.

Table 24: Neutrophil Count Nadirs (10^9/L) in Cabazitaxel-Treated Patients Before and After First Use of G-CSF

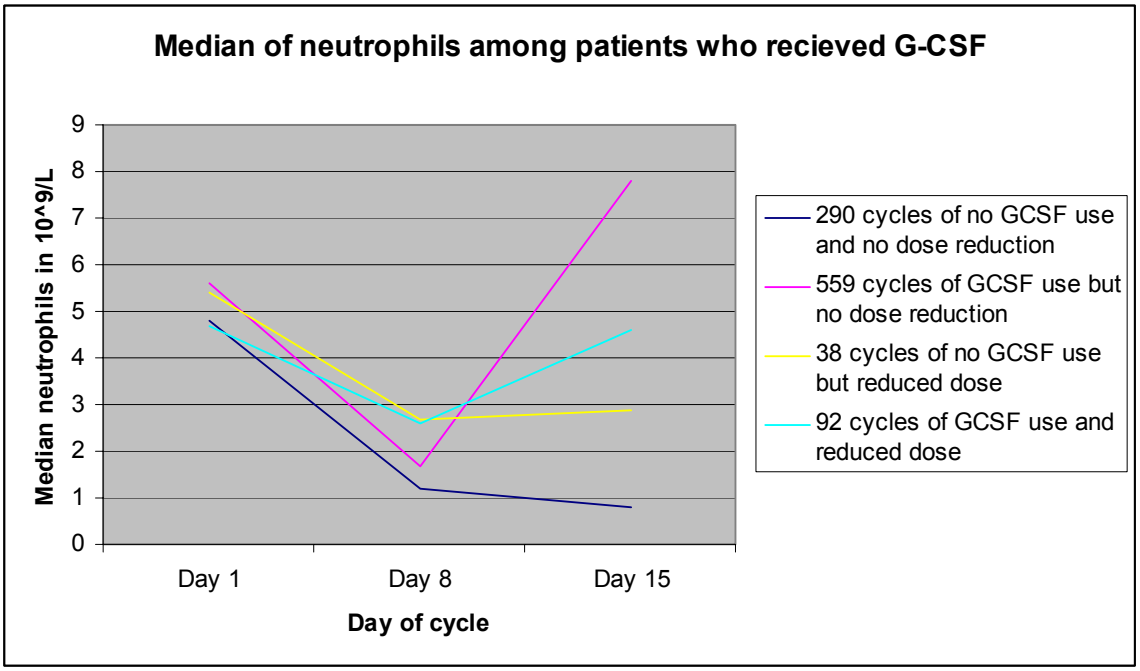
Nadir neutrophil count: quartiles before G-CSF	Nadir neutrophil count: Quartiles after G-CSF	Number of patients
Minimum-<0.250	Minimum-<0.250	18
	0.250-<0.500	9
	0.500-<0.750	6
	0.750 -<1.000	3
	≥1.000	15
0.250-<0.500	Minimum-<0.250	9
	0.250-<0.500	11
	0.500-<0.750	5
	0.750 -<1.000	6
	≥1.000	14
0.500-<0.750	Minimum-<0.250	0
	0.250-<0.500	4
	0.500-<0.750	3
	0.750 -<1.000	2
	≥1.000	19
0.750-<1.000	Minimum-<0.250	3
	0.250-<0.500	2
	0.500-<0.750	2
	0.750 -<1.000	1
	≥1.000	3
≥1.000	Minimum-<0.250	1
	0.250-<0.500	3
	0.500-<0.750	1
	0.750 -<1.000	0
	≥1.000	5

Applicant's Analysis

Reviewer Comment: *Thirty-three (64.7%) patients with median pre-G-CSF neutrophil nadirs below 0.25 x 10^9/L experienced an improvement in nadirs after G-CSF use. Twenty-five (55.6%) patients with median pre-G-CSF neutrophil count nadirs in the 0.25 - <0.5 x 10^9/L range experienced an improvement in counts after G-CSF use. In summary, more than half of patients treated with G-CSF with initial median neutrophil count nadirs less than 0.5 x 10^9/L had some improvement in median neutrophil count nadir after exposure to G-CSF.*

The applicant also provided an analysis of the effect of dose reduction alone on neutrophil nadirs, as well as the effect of combined G-CSF and dose reduction on neutrophil nadirs. These analyses are illustrated in figures 9 and 10 below.

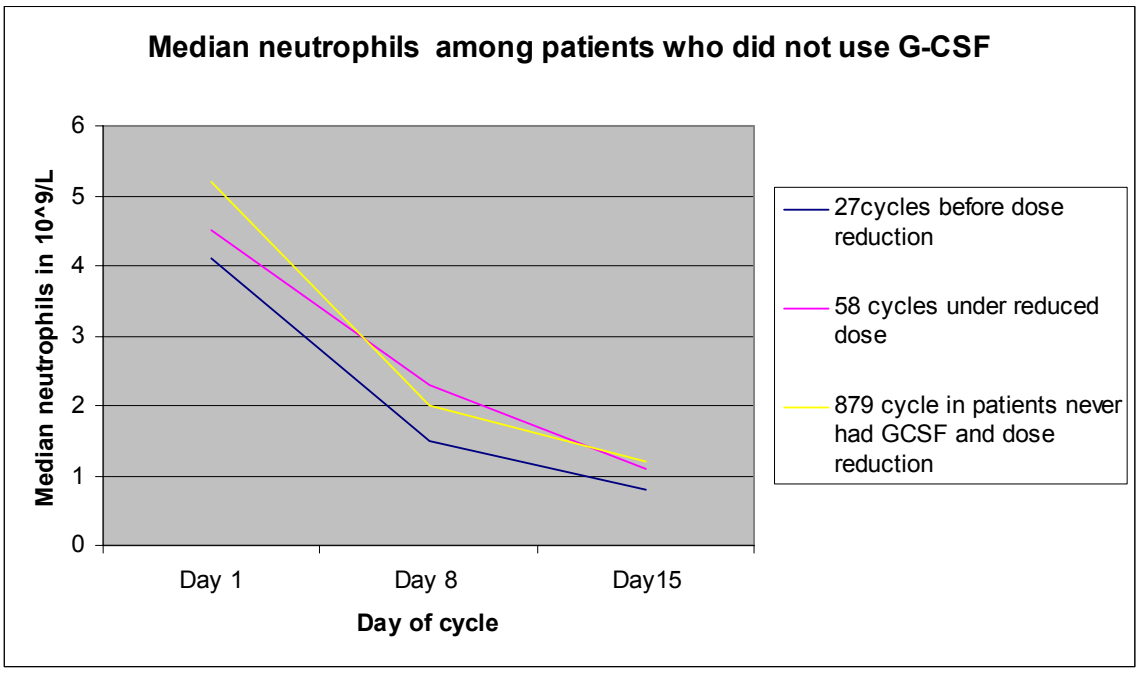
Figure 9: Effect of G-CSF Use, Dose Reduction, or Combination of Both on Median Neutrophil Count Nadirs in Patients Who Received At Least One Dose of G-CSF



Applicant's Analysis

Reviewer Comment: *G-CSF use, dose reduction and the combination of both all resulted in improved neutrophil nadirs in the subset of patients who received at least one dose of G-CSF. However, this analysis does not take into account duration of severe neutropenia, which is considered to be more clinically important when evaluating infection risks.*

Figure 10: Effect of Dose Reduction on Median Neutrophil Counts in Patients Who Did Not Receive Any G-CSF



Applicant's Analysis

Reviewer Comment: Among cabazitaxel-treated patients who did not receive any G-CSF and underwent a dose reduction during the trial, higher median neutrophil nadirs were attained during cycles after dose reduction. However, as noted in the preceding reviewer comment, this analysis does not take into account duration of severe neutropenia, which is considered to be more clinically important when evaluating infection risks.

Renal Failure

Fifteen cabazitaxel-treated patients and no mitoxantrone-treated patients treated in the phase 3 trial EFC6193 experienced renal failure of any grade. Clinical details for the 15 cabazitaxel-treated patients with renal failure are provided in the table below.

Table 25: Renal Failure Adverse Events in Cabazitaxel-Treated Patients

Subject ID	Grade	Renal Failure Onset (day)	Creatinine Grade (Day of Onset)[1]	Action Taken	Confounder?	Resolved?
056-001-007	2	88	2 (88)	None	Dilated calyx and ureter	Y
076-003-001	3	133	3 (134)	None	IV contrast, nausea, vomiting	Y
152-005-004	3	163	3 (162)	None	No obvious confounder	N
158-003-003	3	11		None	Pleural effusion, pneumonia, fungal sepsis	N
710-005-005	5	125	1 (128)	None	No obvious confounder	Fatal
724-003-002	5	13	1 (14)	Discontinued	Septic shock	Fatal
752-001-008	5	124	3 (125)	Discontinued	No obvious confounder except elevated WBC	Fatal
792-001-006	5	101	2 (13)	Discontinued	Diarrhea, dehydration	Fatal
826-001-005	2	106/216		Delayed/None	Dehydration	Y
826-002-001	3	45	2 (47)	None	Bladder neck obstruction	Y
826-004-009	3	8		Discontinued	Hydronephrosis	Y/sequelae
840-014-002	4	16		Discontinued	Urosepsis	Y
840-022-005	1	123	1 (123)	None	Ureteric obstruction, hydronephrosis	Y
840-039-006	3	23		Discontinued	Dehydration	Y/sequelae
840-041-003	3	19		Discontinued	Sepsis, pneumonia	N

[1]Creatinine grade nearest to onset of renal failure is reported.
The above information was verified using the ADAE (Adverse Events) and ADLB (Laboratory Tests) datasets, as well as narratives and CRFs.

Among the 15 patients with an adverse event of renal failure, nine had at least one elevated creatinine laboratory value. All three patients with grade 1-2 renal failure recovered. However, among 12 patients with grade ≥3 renal failure, seven (58.3%) did not recover. While the majority of these events were possibly attributed by the FDA clinical reviewer to other conditions such as infection, dehydration, and structural abnormalities, three of the 12 grade ≥3 renal failure events could not be readily attributed to other conditions. Event details for the three patients with no clear etiology for renal failure are described below.

Patient 152-005-004 was a 62 year-old male with a history of hypertension and thromboembolic disease who received 8 cycles of cabazitaxel. Baseline BUN and creatinine were within normal limits at 18 mg/dL and 1.1 mg/dL, respectively. Grade 1 hematuria began during cycle 6 (day 134). Of note, grade 2 diarrhea was reported five days prior to onset of hematuria, but resolved at the time hematuria began. An increase in serum creatinine was reported during cycle 7 (grade 2: 2.3 mg/dL). Hematuria progressed to grade 2 during cycle 8. Grade 3 renal failure was reported on day 163 (cycle 8); serum creatinine of 4.5 mg/dL (grade 3) was reported one day prior. Treatment discontinuation occurred secondary to disease progression. Renal impairment was assessed by the investigator as due to progressive disease based on a rising PSA. However, there was no reported kidney involvement. Renal function began to recover after cabazitaxel was discontinued, with a serum creatinine of 3.4 mg/dL reported 18 days after the last dose. Aside from discontinuation of study medication, no other intervention was reported. Death on day 577, 414 days after the last dose, was attributed to disease progression.

Patient 710-005-005 was a 74 year-old male with a history of CVA, hypertension, and diabetes mellitus who received six cycles of cabazitaxel. Baseline BUN and creatinine were 7.9 µmol/L (WNL) and 154 µmol/L (Grade 1, ULN: 124 µmol/L), respectively. The patient experienced recurrent events of neutropenia and anemia (cycles 4, 5, and 6). The final episode of neutropenia and anemia resolved during cycle 6 (day 120). Grade 5 renal failure began on day 125, one day after onset of grade 3 urinary retention. Serum creatinine remained a grade 1 toxicity from baseline until cycle 6, but increased to grade 3 (601 µmol/L) on day 128. The patient collapsed secondary to grade 3 hypoxia on day 134 and died of renal failure on day 135. The patient had measurable kidney involvement at baseline, but not at final assessment.

Patient 752-001-008 was a 60 year-old male with no past medical history. Baseline BUN and creatinine were within normal limits at 3.2 mmol/L and 45 µmol/L, respectively. The patient's course was complicated by grade 3 diarrhea during cycle 1 and grade 2 vomiting during cycles 1, 2, 3 and 4, all of which resolved within six days of onset. Grade 3 abdominal pain with hematuria began on day 96 (cycle 5). An abdominal CT scan 7 days later was normal and the patient recovered from abdominal pain on day 105. Grade 5 renal failure was reported on day 124 (cycle 6). The patient also experienced nausea, confusion, and auditory hallucinations on this day. Serum

creatinine, which had been within normal limits throughout therapy, increased to 528 µmol/L (grade 3) on day 125. WBC was elevated to 54.9 x 10^9/L with low-grade fever. No blood gases, radiology or blood pressure were measured. The patient died one day after onset of renal failure. No autopsy was performed.

The applicant reports that 15 patients had grade ≥3 renal failure. The applicant has included patients 203-001-020, 840-006-003, and 840-077-011 in the group of grade ≥3 renal failure patients, though none of these patients had an investigator-reported adverse event of renal failure and only 840-077-011 had an elevated creatinine (grade 1).

Reviewer Comment: *It remains unclear whether cabazitaxel exposure contributes directly to renal toxicity. The occurrence of two renal failure deaths and one unresolved grade 3 event in patients without clear confounders suggest that direct drug toxicity may have contributed to these events. Although patient 752-001-008 did have an elevated WBC and low-grade fever at time of death, there is no documentation of sepsis or infection.*

Hematuria

Hematuria of all grades was increased on the cabazitaxel arm, as shown in the table below. Note that total numbers of hematuria events in this section differ slightly from those presented in other sections, as the following analyses include all hematuria-associated events (blood urine present, urinary tract hemorrhage, and urinary bladder hemorrhage), rather than strictly events with the preferred term hematuria.

Table 26: Hematuria Adverse Events[1]

Adverse Event	Cabazitaxel N = 371	Mitoxantrone N = 371
All Grades	67 (18.1%)	15 (4.0%)
Grade ≥2	24 (6.5%)	9 (2.4%)
Grade 1	43 (11.6%)	6 (1.6%)
Grade 2	16 (4.3%)	6 (1.6%)
Grade 3	7 (1.9%)	2 (<1%)
Grade 4	1 (<1%)	0
Grade 5	0	1 (<1%)

[1]Includes blood urine present, urinary tract hemorrhage, and urinary bladder hemorrhage.
The above information was verified using the ADAE (Adverse Events) dataset.

There were more hematuria adverse events on the cabazitaxel arm. Of note, a similar rate of hematuria adverse events occurred among the 558 cabazitaxel-treated patients in the ISS database, with 78 (14.0%) and 32 (5.7%) of patients experiencing treatment-emergent hematuria adverse events of any grade and grade ≥2, respectively.

Reviewer Comment: *Analyses of clinically relevant hematuria include all events grade ≥2. The occurrence of grade ≥2 hematuria is of clinical importance because grade 2 hematuria is characterized by gross bleeding, medical intervention, or urinary tract irrigation.*

The number of patients in the entire safety population with confounding factors for hematuria was similar between arms, as shown in the table below.

Table 27: Confounding Factors for Hematuria in Safety Population

Confounder	Cabazitaxel N = 371	Mitoxantrone N = 371
No Confounder	210 (56.6%)	219 (59.0%)
Any Confounder	161 (43.4%)	152 (41.0%)
Aspirin/Anti-Thrombotic Agent Use	124	132
Urinary Tract Infection	29	12
Cystitis	11	5
Ureteric Stenosis/Obstruction	11	2
Hydronephrosis	9	6
Tumor Involvement of Kidney	7	8
Pyelonephritis/Urosepsis	2	3

The above information was verified using the ADAE (Adverse Events), ADCM (Concomitant Medications), and ADLS (Tumor Measurements) datasets.

The number of patients with grade ≥2 hematuria and confounding factors was also similar between arms, as shown in table 28 below.

Table 28: Confounding Factors in Patients with Grade ≥2 Hematuria[1]

Confounder	Cabazitaxel N = 24	Mitoxantrone N = 9
No Confounder	8 (33.3%)	3 (33.3%)
Any Confounder	16 (66.7%)	6 (66.7%)
Aspirin/Anti-Thrombotic Agent Use	9	6
Urinary Tract Infection[2]	2	1
Cystitis[2]	1	0
Ureteric Stenosis/Obstruction	2	1
Hydronephrosis	4	0
Tumor Involvement of Kidney	2	0
Pyelonephritis/Urosepsis	0	0
Traumatic Catheterization	1	0

[1]Includes 2 patients with adverse event of urinary tract hemorrhage rather than hematuria: 840-023-001/cabazitaxel and 840-026-004/mitoxantrone.
[2]If recovered, within 30 days of developing hematuria
This data was verified using the ADAE (Adverse Events), ADCM (Concomitant Medications), and ADLS (Tumor Measurements) datasets, as well as CRFs and narratives.

Reviewer Comment: *Patients who developed grade ≥2 hematuria were more likely to have at least 1 confounding factor for hematuria than were patients in the entire safety population. However, the percentage of patients with at least one confounding factor was similar between arms for the entire safety population as well as for patients with grade ≥2 hematuria. This balance in the presence of confounding factors between arms at the entire population level and at the grade ≥2 hematuria population level suggests that cabazitaxel exposure itself is at least partly responsible for increased grade ≥2 hematuria on the study drug arm.*

The effect of dose delay or discontinuation on hematuria was analyzed and is presented in table 29 below.

Table 29: Hematuria Dose Delays and Discontinuations[1]

	Cabazitaxel N = 371			Mitoxantrone N = 371		
	No Action/ Recovered	Delayed/ Recovered	Discontinued/ Recovered	No Action/ Recovered	Delayed/ Recovered	Discontinued/ Recovered
Grade						
≥2	18/14	2/2	4/4	8/6	0	1/0
2	14/11	1/1	1/1	6/5	0	0
3	4/3	1/1	2/2	2/1	0	0
4	0	0	1/1	0	0	0
5	0	0	0	0	0	1/0

[1]Includes blood urine present, urinary tract hemorrhage, and urinary bladder hemorrhage.
The above information was verified using the ADAE (Adverse Events) dataset. Each patient with a hematuria event is included only once, using highest toxicity grade and final outcome.

All cabazitaxel-treated patients with grade ≥2 hematuria had eventual recovery if treatment was delayed or discontinued. Additionally, 14 of 18 patients with grade ≥2 hematuria who did not undergo dose delay or discontinuation also eventually recovered.

Three cases of renal failure occurred among cabazitaxel-treated patients with grade ≥2 hematuria. Two of these patients (076-003-001/grade 3, 840-022-005/grade 1) recovered completely, while one (152-005-004/grade 3) did not recover by the end of follow-up. Twelve other cases of renal failure cases on the cabazitaxel arm all occurred in patients without hematuria of any grade.

Reviewer Comment: *As all cabazitaxel-treated patients with grade ≥2 hematuria who delayed or discontinued therapy eventually recovered and only one case of irreversible renal failure occurred among all cabazitaxel-treated patients with hematuria, the occurrence of hematuria appears to be manageable and not closely correlated with irreversible renal failure.*

Cardiac Toxicity

Four grade 5 cardiac-related adverse events occurred in patients who received cabazitaxel, while none occurred in mitoxantrone-treated patients. Details of these events are provided in the table and summaries below.

Table 30: Cardiac Deaths on the Cabazitaxel Arm (EFC6193)

Patient ID	Grade 5 AE
056-003-001	Ventricular Fibrillation
208-001-014	Cardiac Arrest
250-001-023	Cardiac Failure
356-007-003	Cardiac Arrest

Patient 056-003-001 was a 71 year-old male with a history of diabetes and pulmonary embolism one year prior to therapy on aspirin therapy. The patient developed ventricular fibrillation on day 73 (9 days after the administration of the cycle 4 dose), progressing to cardiac shock with acidosis. Troponin T was elevated (1.9 ng/ml, ULN 0.030 ng/ml), as was troponin I (8.5 ng/ml, ULN <0.040 ng/ml). An ECG showed complete left bundle branch block, atrial fibrillation and prolonged QT interval. Despite treatment with heparin and dopamine, the patient's condition continued to worsen. The patient died the same day. No autopsy was performed.

Patient 208-001-014 was a 65 year-old male with a history of hypertension, diabetes, and atrial fibrillation who developed severe respiratory distress at home on study day 8 (7 days after the administration of the cycle 1 dose). He was hypotensive and bradycardic with a respiratory rate of 10 breaths/minute. Pupils were dilated and heart rhythm was irregular. The patient became progressively hypotensive and bradycardic and suffered grade 5 cardiac arrest while in the ambulance en route to the hospital. No autopsy was performed.

Patient 250-001-023 was an 83 year-old male with a history of hypertension. He received warfarin during the course of the trial. The patient's course was complicated by grade 4 neutropenia and febrile neutropenia during cycles 2 and 4, respectively. On study day 210 (18 days after the administration of the cycle 10 dose), the patient experienced grade 5 cardiac failure followed by sudden death. When the ambulance arrived, he had a Glasgow Coma Score of 3, was asystolic and had non-reactive dilated pupils. Despite the administration of amiodarone and electric shocks, the patient died. No autopsy was performed.

Patient 356-007-003 was an 83 year-old male with no relevant past history who developed chest pain on study day 30 (eight days after the administration of the cycle 2 dose), followed by grade 5 cardiac arrest. Death occurred before the patient was brought to the hospital. No autopsy was performed.

Reviewer Comment: *Although there were more grade 5 cardiac adverse events on the cabazitaxel arm, three of the four patients had confounding factors including diabetes, hypertension, atrial fibrillation, prior warfarin use, and history of pulmonary embolism. The only patient without a past cardiac history was an 83 year-old male whose death appears to have been secondary to myocardial infarction. Hence, there is no clear relationship between cabazitaxel exposure and fatal cardiotoxicity.*

Table 31 includes all grade 1-4 cardiac adverse events on either treatment arm in EFC6193. Although total numbers of grade 1-4 cardiac adverse events were similar between arms, there were more arrhythmia-related events on the cabazitaxel arm.

Table 31: Cardiac Adverse Events on EFC6193

	Cabazitaxel N = 371		Mitoxantrone N = 371	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Any Cardiac AE	31 (8.4%)	7 (1.9%)	31 (8.4%)	5 (1.3%)
Arrhythmia[1]	18 (4.9%)	4 (1.1%)	6 (1.6%)	1 (<1%)
Cardiac Failure	1 (<1%)	1 (<1%)	0	0
Cardiotoxicity	0	0	2 (<1%)	0
Chest Pain[2]	12 (3.2%)	2 (<1%)	8 (2.2%)	1 (<1%)
Ejection Fraction Decreased[3]	1 (<1%)	0	9 (2.4%)	1 (<1%)
Electrocardiogram QT Prolonged	1 (<1%)	1 (<1%)	0	0
Left Ventricular Dysfunction	1 (<1%)	0	6 (1.6%)	1 (<1%)
Myocardial Infarction	0	0	1 (<1%)	1 (<1%)
Palpitations	3 (<1%)	0	2 (<1%)	0
Tachycardia NOS	6 (1.6%)	0	0	0
Troponin Increased	0	0	1 (<1%)	1 (<1%)

[1]Includes atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block complete, bradycardia, palpitations, supraventricular tachycardia, tachyarrhythmia, and tachycardia.
[2]Includes angina pectoris.
[3]Includes EF abnormal.
The above information was verified using the ADAE (Adverse Events) dataset.

Grade 3-4 cardiac events on the cabazitaxel arm included: AV block complete (056-003-001), atrial fibrillation (208-003-005, 840-041-003), cardiac failure (208-003-005), chest pain (250-001-034, 356-0070003), ECG QT prolonged (840-022-022), and atrial flutter (840-041-003).

Grade 3-4 cardiac events on the mitoxantrone arm included: atrial fibrillation (076-003-004), EF abnormal (152-005-008), LV dysfunction (208-001-001), and chest pain (250-001-003).

Four syncopal adverse events were reported on each treatment arm. Three patients (patients 208-001-006, 208-002-013, and 840-039-004) experienced grade 3 events on the cabazitaxel arm, while two experienced grade 3 events on the mitoxantrone arm. One of the syncopal events on the cabazitaxel arm occurred in association with UTI and dehydration. All events were followed by recovery (with sequelae in one comparator arm patient) and none led to dose modification or treatment discontinuation.

Reviewer Comment: *More arrhythmia-related adverse events occurred on the cabazitaxel arm. When adverse events of palpitations and tachycardia NOS are excluded, there were 10 cabazitaxel-treated patients with arrhythmia-related events vs. five mitoxantrone-treated patients with such events. The numbers of grade 3-4 arrhythmia events remain unchanged when palpitations and tachycardia NOS are excluded. As expected, more events of LV dysfunction and EF decreased occurred on the mitoxantrone arm.*

7.3.5 Submission Specific Primary Safety Concerns

Submission-specific safety concerns of neutropenia and infection, renal failure, hematuria, and cardiac toxicity are addressed in section 7.3.4 above. In summary, neutropenia, febrile neutropenia, renal failure, hematuria, and arrhythmias all occurred more commonly on the cabazitaxel arm. Grade 4 neutropenia was associated with infection leading to fatal outcome in five cabazitaxel-treated patients and one mitoxantrone-treated patient. Neutropenia-related adverse events (neutropenia, infection, sepsis, and febrile neutropenia) led to 22 treatment discontinuations on the cabazitaxel arm and two discontinuations on the mitoxantrone arm. Post-submission analyses suggest that a proportion of patients who experience neutropenia benefited from G-CSF use or dose reduction. Grade ≥3 renal failure occurred in 12 patients on the cabazitaxel arm and no patients on the mitoxantrone arm. Four grade 5 renal failure events were reported on the cabazitaxel arm. Although the majority of renal failure adverse events were confounded by other factors, two fatal cases were not readily attributable to other causes. Along with this increased rate of renal failure on the cabazitaxel arm, an increased rate of hematuria were also noted. Increased rates of grade ≥2 hematuria were not accounted for by a disproportionate number of confounding factors on the cabazitaxel arm; the two arms had similar percentages of patients with confounding factors for hematuria at baseline and in the subset of patients with grade ≥2 hematuria. Finally, an increased arrhythmia rate was noted on the cabazitaxel arm (4.9%) compared to the mitoxantrone arm (1.6%). This included 4 grade 3-4 adverse events and one fatal grade 5 ventricular fibrillation on the cabazitaxel arm. One grade ≥3 arrhythmia event occurred on the mitoxantrone arm.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

More patients on the cabazitaxel arm experienced grade 1-4 and grade 3-4 adverse events. The most common grade 1-4 treatment-emergent adverse events are included in the table below. The most common grade 1-4 treatment-emergent adverse events in cabazitaxel-treated patients on EFC6193 were: anemia (97.8%), leukopenia (96.2%) neutropenia (94.0%), thrombocytopenia (47.7%), diarrhea (46.6%), fatigue (36.7%),

nausea (34.2%), vomiting (22.4%), asthenia (20.5%), constipation (20.5%), abdominal pain (17.3%), hematuria (16.7%), back pain (16.2%) and anorexia (15.9%).

Table 32: Grade 1-4 Adverse Events (≥5% Patients, Either Arm)

	Cabazitaxel N = 371		Mitoxantrone N = 371	
	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4
Any Adverse Event	353 (95.1%)	208 (56.1%)	327 (88.1%)	139 (37.5%)
Blood & Lymphatic Disorders[1]				
Anemia	361 (97.8%)	39 (10.6%)	302 (81.6%)	18 (4.9%)
Leukopenia	355 (96.2%)	253 (68.6%)	343 (92.7%)	157 (42.4%)
Neutropenia	347 (94.0%)	303 (82.1%)	325 (87.8%)	215 (58.1%)
Thrombocytopenia	176 (47.7%)	15 (4.1%)	160 (43.2%)	6 (1.6%)
Febrile Neutropenia	27 (7.3%)	27 (7.3%)	5 (1.3%)	5 (1.3%)
Cardiac Disorders				
Arrhythmia[2]	18 (4.9%)	4 (1.1%)	6 (1.6%)	1 (<1%)
Gastrointestinal Disorders				
Diarrhea	173 (46.6%)	23 (6.2%)	39 (10.5%)	1 (<1%)
Nausea	127 (34.2%)	7 (1.9%)	85 (22.9%)	1 (<1%)
Vomiting	83 (22.4%)	6 (1.6%)	38 (10.2%)	0
Constipation	76 (20.5%)	4 (1.1%)	57 (15.4%)	2 (<1%)
Abdominal Pain[3]	64 (17.3%)	7 (1.9%)	23 (6.2%)	0
Dyspepsia[4]	36 (9.7%)	0	9 (2.4%)	0
General Disorders & Admin Site Conditions				
Fatigue	136 (36.7%)	18 (4.9%)	102 (27.5%)	11 (3.0%)
Asthenia	76 (20.5%)	17 (4.6%)	46 (12.4%)	9 (2.4%)
Pyrexia	45 (12.1%)	4 (1.1%)	23 (6.2%)	1 (<1%)
Peripheral Edema	34 (9.2%)	2 (<1%)	34 (9.2%)	1 (<1%)
Mucosal Inflammation	22 (5.9%)	1 (<1%)	10 (2.7%)	1 (<1%)
Pain	20 (5.4%)	4 (1.1%)	18 (4.9%)	7 (1.9%)
Infections & Infestations				
Urinary Tract Infection[5]	29 (7.8%)	6 (1.6%)	12 (3.2%)	4 (1.1%)
Pneumonia[6]	12 (3.2%)	9 (2.4%)	4 (1.1%)	3 (<1%)
Investigations				
Weight Decreased	32 (8.6%)	0	28 (7.5%)	1 (<1%)
Metabolism & Nutrition Disorders				
Anorexia	59 (15.9%)	3 (<1%)	39 (10.5%)	3 (<1%)

	Cabazitaxel N = 371		Mitoxantrone N = 371	
	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4
Musculoskeletal & Connective Tissue Disorders				
Back Pain	60 (16.2%)	14 (3.8%)	45 (12.1%)	11 (3.0%)
Arthralgia	39 (10.5%)	4 (1.1%)	31 (8.4%)	4 (1.1%)
Pain in Extremity	30 (8.1%)	6 (1.6%)	27 (7.3%)	4 (1.1%)
Muscle Spasms	27 (7.3%)	0	10 (2.7%)	0
Bone Pain	19 (5.1%)	3 (<1%)	19 (5.1%)	9 (2.4%)
Musculoskeletal Pain	18 (4.9%)	2 (<1%)	20 (5.4%)	3 (<1%)
Nervous System Disorders				
Peripheral Neuropathy[7]	50 (13.5%)	3 (<1%)	12 (3.2%)	3 (<1%)
Dysgeusia	41 (11.1%)	0	15 (4.0%)	0
Dizziness	30 (8.1%)	0	21 (5.7%)	2 (<1%)
Headache	28 (7.5%)	0	19 (5.1%)	0
Renal & Urinary Disorders				
Hematuria	62 (16.7%)	7 (1.9%)	13 (3.5%)	1 (<1%)
Dysuria	25 (6.7%)	0	5 (1.3%)	0
Respiratory, Thoracic & Mediastinal Disorders				
Dyspnea	43 (11.6%)	4 (1.1%)	16 (4.3%)	2 (<1%)
Cough	40 (10.8%)	0	22 (5.9%)	0
Skin & Subcutaneous Tissue Disorders				
Alopecia	37 (10.0%)	0	18 (4.9%)	0
Vascular Disorders				
Hypotension	20 (5.4%)	2 (<1%)	9 (2.4%)	1 (<1%)

[1]Calculated using the ADLB (Laboratory Tests) dataset rather than the ADAE (Adverse Events) dataset, except for febrile neutropenia. Denominators for anemia, leukopenia, neutropenia, and thrombocytopenia include only patients who had at least one post-baseline lab value (cabazitaxel: N=369; mitoxantrone: N=370).
[2]Includes atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block complete, bradycardia, palpitations, supraventricular tachycardia, tachyarrhythmia, and tachycardia.
[3]Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.
[4]Includes gastroesophageal reflux disease and reflux gastritis.
[5]Includes urinary tract infection enterococcal and urinary tract infection fungal.
[6]Includes bronchopneumonia, lobar pneumonia, and pneumonia klebsiella.
[7]Includes peripheral motor neuropathy and peripheral sensory neuropathy.

Hemorrhoids and urinary incontinence each occurred more commonly in cabazitaxel-treated patients (≥2% difference between arms), but are not included in the table above because they occurred in <5% of patients on either arm.

Bone pain, pain in extremity, and musculoskeletal pain, although included in the adverse event tables, are known to be associated with metastatic prostate cancer and occurred in similar numbers of patients on each arm.

The most common grade 3-4 treatment-emergent adverse events are included in the table below. The most common grade 3-4 treatment-emergent adverse events in cabazitaxel-treated patients on EFC6193 were: neutropenia (81.7%), leukopenia (68.2%), anemia (10.6%), febrile neutropenia (7.3%), diarrhea (6.2%), fatigue (4.9%), asthenia (4.6%), thrombocytopenia (4.0%), back pain (3.8%), pneumonia (2.4%), dehydration (2.2%), and renal failure (2.2%).

Table 33: Grade 3-4 Adverse Events (≥1% Patients, Either Arm)

	Cabazitaxel N = 371	Mitoxantrone N = 371
Any Adverse Event	208 (56.1%)	139 (37.5%)
Blood & Lymphatic Disorders[1]		
Neutropenia	303 (81.7%)	215 (58.0%)
Leukopenia	253 (68.2%)	157 (42.3%)
Anemia	39 (10.6%)	18 (4.9%)
Thrombocytopenia	15 (4.0%)	6 (1.6%)
Febrile Neutropenia	27 (7.3%)	5 (1.3%)
Cardiac Disorders		
Arrhythmia[2]	4 (1.1%)	1 (<1%)
Gastrointestinal Disorders		
Diarrhea	23 (6.2%)	1 (<1%
Nausea	7 (1.9%)	1 (<1%)
Vomiting	6 (1.6%)	0
Abdominal Pain[3]	7 (1.9%)	0
Constipation	4 (1.1%)	2 (<1%)
General Disorders & Admin Site Conditions		
Fatigue	18 (4.9%)	11 (3.0%)
Asthenia	17 (4.6%)	9 (2.4%)
Pain	4 (1.1%)	7 (1.9%)
Pyrexia	4 (1.1%)	1 (<1%)
Infections & Infestations		
Pneumonia[4]	9 (2.4%)	3 (<1%)
Metabolism & Nutrition Disorders		
Dehydration	8 (2.2%)	3 (<1%)

	Cabazitaxel N = 371	Mitoxantrone N = 371
Musculoskeletal & Connective Tissue Disorders		
Back Pain	14 (3.8%)	11 (3.0%)
Pain in Extremity	6 (1.6%)	4 (1.1%)
Arthralgia	4 (1.1%)	4 (1.1%)
Bone Pain	3 (<1%)	9 (2.4%)
Nervous System Disorders		
Spinal Cord Compression	4 (1.1%)	3 (<1%)
Renal & Urinary Disorders		
Renal Failure[5]	8 (2.2%)	0
Hematuria	7 (1.9%)	1 (<1%)
Ureteric Obstruction	5 (1.3%)	0
Urinary Tract Infection[6]	6 (1.6%)	4 (1.1%)
Respiratory, Thoracic & Mediastinal Disorders		
Pulmonary Embolism	7 (1.9%)	8 (2.2%)
Dyspnea	4 (1.1%)	2 (<1%)
Vascular Disorders		
Deep Vein Thrombosis	7 (1.9%)	3 (<1%)

[1]Calculated using the ADLB (Laboratory Tests) dataset rather than the ADAE (Adverse Events) dataset, except for febrile neutropenia. Denominators for anemia, leukopenia, neutropenia, and thrombocytopenia include only patients who had at least one post-baseline lab value (cabazitaxel: N=369; mitoxantrone: N=370).
[2]Includes atrial fibrillation, atrial flutter, and atrioventricular block complete on the cabazitaxel arm and
[3]Includes abdominal pain lower.
[4]Includes bronchopneumonia, lobar pneumonia, and pneumonia klebsiella.
[5]Includes acute renal failure.
[6]Includes urinary tract infection enterococcal and urinary tract infection fungal.

Grade 3-4 hypertension and hypotension were reported infrequently. Only one cabazitaxel-treated patient developed grade 3 hypertension and two developed grade 3-4 hypotension.

7.4.2 Laboratory Findings

Laboratory adverse events are summarized in the table below. Note that hematology laboratories are included under the “blood & lymphatic disorders” subheading of the adverse events tables above and are not repeated here.

Table 34: Laboratory Adverse Events

	Cabazitaxel N = 371		Mitoxantrone N = 371	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Chemistries				
Sodium				
Hyponatremia	59/356 (16.6%)	11/356 (3.1%)	52/363 (14.3%)	7/363 (1.9%)
Hypernatremia	33/356 (9.3%)	1/356 (<1%)	35/363 (9.6%)	0/363
Potassium				
Hypokalemia	59/356 (16.6%)	3/356 (<1%)	55/363 (15.2%)	2/363 (<1%)
Hyperkalemia	61/356 (17.1%)	12/356 (3.4%)	55/363 (15.2%)	9/363 (2.5%)
Bicarbonate (low)	78/320 (24.4%)	2/320 (<1%)	65/338 (19.2%)	2/338 (<1%)
Glucose				
Hypoglycemia	30/351 (8.5%)	0/351	17/353 (4.8%)	0/353
Hyperglycemia	227/351 (64.7%)	8/351 (2.3%)	236/353 (66.9%)	16/353 (4.5%)
Hepatic Function				
AST	103/351 (29.3%)	3/351 (<1%)	104/359 (29.0%)	2/359 (<1%)
ALT	96/352 (27.3%)	4/352 (1.1%)	70/363 (19.3%)	1/363 (<1%)
Total Bilirubin	14/349 (4.0%)	2/349 (<1%)	17/362 (4.7%)	3/362 (<1%)
Alkaline Phos	199/350 (56.9%)	27/350 (7.7%)	214/357 (59.9%)	36/357 (10.1%)
Renal				
Creatinine	58/355 (16.3%)	5/355 (1.4%)	43/363 (11.8%)	2/363 (<1%)

The above information was verified using the ADLB (Laboratory Tests) dataset. Denominators include all patients who had a lab test done after baseline.

7.4.3 Vital Signs

Vital signs recorded during the active treatment period were examined for extreme abnormalities. Among 371 cabazitaxel-treated patients in the safety population, only one had a recorded temperature >39°C. Tachycardia was commonly reported, with heart rate >100 bpm and heart rate >120 bpm reported for 60 (16.2%) and 7 (1.9%) patients, respectively. Elevated systolic blood pressures were commonly reported, with systolic BP ≥150 mm Hg and systolic BP ≥170 reported for 138 (37.2%) and 39 (10.5%) patients, respectively. Elevated diastolic blood pressures were also commonly reported, with diastolic BP ≥90 mm Hg and diastolic BP ≥100 mm Hg reported for 124 (33.4%) and 24 (6.5%) patients, respectively.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were performed at baseline and end of treatment. However, QTc data was not collected.

358 patients in the cabazitaxel arm safety population had at least one ECG, while 202 (54.5%) had a baseline ECG and at least one subsequent ECG.

349 (94.1%) patients in the safety population had a baseline ECG, 85 (24.4%) of which were reported as abnormal. 204 (55.0%) patients had an end-of-treatment ECG, 57 (27.9%) of which were reported as abnormal. Among 15 (4.0%) patients with unscheduled ECGS, 8 (53.3%) were reported as abnormal.

Twenty-eight (13.8%) patients with at least two ECGs had normal ECGs at baseline, but abnormalities reported subsequently, either during an unscheduled assessment or at end of treatment.

7.4.5 Special Safety Studies/Clinical Trials

No organ dysfunction studies have been conducted to date. Patients were required to have total bilirubin <1x ULN, AST/ALT <1.5x ULN, and creatinine <1.5x ULN in order to enroll. Of 358 cabazitaxel arm patients with total bilirubin levels reported between study day -7 to study day 1, none had a total bilirubin value ≥1.5x ULN.

Of 358 cabazitaxel arm patients with AST or ALT reported between study day -7 to study day 1, three (patients 208-003-005, 484-001-006, and 840-086-001) had a reported AST or ALT value ≥2.5x ULN. Two of these patients (208-003-005 and 484-001-006) had no subsequent values reported, as they both died during cycle 1. Patient 208-003-005 died from sepsis while patient 484-001-006 died secondary to a diarrhea-induced electrolyte imbalance. 840-086-001 had no subsequent values ≥2.5x ULN.

Reviewer Comment: *No conclusions regarding the use of cabazitaxel in patients with hepatic impairment can be drawn the phase 3 trial EFC6193, as the trial included no patients with bilirubin elevations ≥1.5x ULN within 7 days of the start of study treatment and only 3 patients with AST or ALT elevations ≥2.5x ULN within seven days of the start of study treatment, only one of which had on-therapy follow-up labs.*

Of 358 cabazitaxel arm patients with creatinine reported between study day -7 to study day 1, one (patient 484-001-006) had a reported creatinine value ≥1.5x ULN. This patient also had AST ≥2.5x ULN. There are no subsequent creatinine values reported, as the patient died during cycle 1 secondary to diarrhea-induced electrolyte imbalance.

7.4.6 Immunogenicity

The following adverse event preferred terms were considered possibly related to immunogenicity: chills, drug hypersensitivity, hypersensitivity, hypotension, pruritis, rash, rash erythematous, respiratory failure, swelling face, and wheezing. For each of these preferred terms, events that occurred within three days of cabazitaxel administration were reviewed. Sixteen patients experienced events within three days of study drug administration, as detailed in the table below.

Table 35: Adverse Events Possibly Related to Immunogenicity

Patient ID	AE Preferred Term	Grade	Last Dose (Day)	AE Start (Day)	Time from Dose to AE (Days)	Action with Study Drug
056-001-004	Hypersensitivity	2	1	1	0	Interrupted
056-001-018	Chills	1	29	29	0	None
056-001-020	Hypersensitivity	1	42	42	0	Interrupted
124-002-005	Hypersensitivity Hypersensitivity	1 1	22 42	22 42	0 0	None Interrupted
208-003-006	Hypersensitivity Hypersensitivity	1 1	22 148	23 149	1 1	None None
250-001-010	Rash Rash	2 1	43 64	43 66	0 2	None None
276-005-003	Hypersensitivity	2	22	22	0	None
276-008-010	Rash	1	148	150	2	None
410-002-006	Swelling Face	1	134	135	1	None
792-001-003	Hypotension	2	1	4	3	None
840-005-003	Rash	1	1	4	3	None
840-011-005	Hypotension	2	1	1	0	None
840-022-002	Hypotension	2	98	101	3	None
840-047-001	Rash	1	43	43	0	None
840-060-001	Rash Hypotension	1 2	43 192	46 192	3 0	None Interrupted
840-077-012	Hypotension	2	43	43	0	None

The above information was verified using the ADAE (Adverse Events) and ADEX (Exposure) datasets.

Of 371 patients who received at least one dose of cabazitaxel, 16 (4.3%) developed at least one possible immunogenicity-related adverse event. All patients recovered, except for 840-060-001, with ongoing rash. No patients discontinued permanently due to immunogenicity.

Of note, patient 250-001-017 was also coded as having a drug hypersensitivity reaction, which began seven days after cabazitaxel administration and was attributed to

levofloxacin given on the same day as the event. No action was taken with the study drug.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Grade 1-4 neutropenia and grade 3-4 neutropenia occurred more frequently in ISS database patients who received ≥25 mg/m^2 q3 weekly cabazitaxel dosing than in patients who received lower doses.

Table 36: Neutropenia in Cabazitaxel-Treated Patients Receiving <25 mg/m^2 q3 Weekly Dosing vs. ≥25 mg/m^2 q3 Weekly Dosing in ISS Database

	<25 mg/m^2 q3 week N = 89	≥25 mg/m^2 q3 week N = 412
Grade 1-4 Neutropenia	72 (80.9%)	387 (93.9%)
Grade 3-4 Neutropenia	54 (60.7%)	335 (81.3%)

The above information was verified using the ISS ADAE (Adverse Events) dataset.

The applicant performed an analysis of the rates of grade 1-4 and grade 3-4 neutropenia in patients who received 20 mg/m^2 q3 weekly dosing in supportive studies, including a total of 77 patients. A comparison of neutropenia rates in these 77 patients is compared to cabazitaxel-treated patients on EFC6193 in table 38 below.

Table 37: Neutropenia in Cabazitaxel-Treated Patients Receiving 20 mg/m^2 q3 Weekly Dosing in ISS Database

	EFC6193 25 mg/m^2 Dosing N = 369	TED6188, TED6190, ARD6191 20 mg/m^2 Dosing N = 77
Neutropenia		
All Grades	347 (94.0%)	62 (80.5%)
Grade 3-4	303 (82.1%)	44 (57.1%)

Applicant's Analysis

Reviewer Comment: The rate of grade 3-4 neutropenia was lower among patients who received 20 mg/m^2 dosing. Of note, fifty of the 77 patients who received 20 mg/m^2 dosing were breast cancer patients treated on ARD6191. Despite the lower rate of grade 3-4 neutropenia, patients on ARD6191 were found to have a higher overall exposure to cabazitaxel.

7.5.2 Time Dependency for Adverse Events

Time-dependency of neutropenia was examined. The table below displays time to first onset of grade 3-4 neutropenia for patients on the cabazitaxel arm.

Table 38: Time to First Onset of Grade 3-4 Neutropenia

Cycle	Grade 3-4 Neutropenia (1st event)
Any Cycle	303
1	245
2	29
3	15
4	6
5	1
6	3
7	2
8	0
9	1
10	1

The above information was verified using the ADLB (laboratory tests) dataset.

The majority (80.9%) of cabazitaxel-treated patients who developed grade 3-4 neutropenia did so during cycle 1.

Time-dependency of hematuria was examined. The table below displays time to first onset of grade ≥2 hematuria.

Table 39: Time to First Onset of Grade ≥2 Hematuria

Cycle	Hematuria (1st event)
Any Cycle	23
1	2
2	1
3	3
4	2
5	4
6	3
7	2
8	4
9	2
10	0

The above information was verified using the ADAE (adverse events) dataset.

New onset grade ≥2 hematuria events occurred at a low frequency from cycle 1 through cycle 9. The majority of events did not occur during the first cycle.

7.5.3 Drug-Demographic Interactions

Rates of common (>15%) grade 1-4 adverse events were examined by age (<65 years of age vs. ≥65 years of age) and race (white vs. non-white) and are presented in table 40 below.

Overall, grade 1-4 adverse event rates were similar in patients <65 years old and ≥65 years old. However, among the most common (>15%) grade 1-4 adverse events, several occurred more frequently (≥5% difference) in older patients. The common grade 1-4 events that occurred more frequently in patients ≥65 years old were: neutropenia (89.2% in <65 yrs vs. 96.7% in ≥65 yrs), thrombocytopenia (39.2% in <65 yrs vs. 52.3% in ≥65 yrs), fatigue (29.8% in <65 yrs vs. 40.4% in ≥65 yrs), and asthenia (14.5% in <65 yrs vs. 23.8% in ≥65 yrs).

Several less common grade 1-4 adverse events also occurred more commonly in older patients, including pyrexia in 7.6% <65 yrs vs. 14.6% ≥65 yrs, dizziness 4.6% <65 yrs vs. 10.0% ≥65 yrs, urinary tract infection in 3.1% <65 yrs vs. 10.4% ≥65 yrs, and dehydration in 1.5% <65 yrs vs. 6.7% ≥65 yrs.

Overall, grade 1-4 adverse event rates were similar in white and non-white patients. Comparisons of rates of adverse events between white and non-white patients are not reliable, as few non-white patients were treated. Among the most common (>15%) grade 1-4 adverse events, several occurred more frequently (≥5% difference) in white patients. The common grade 1-4 events that occurred more frequently in white patients were: fatigue (39.2% in white patients vs. 23.3% in non-white patients), nausea (37.3% in white patients vs. 18.3% in non-white patients), vomiting (23.5% in white patients vs. 16.7% in non-white patients), constipation (22.2% in white patients vs. 11.7% in non-white patients), abdominal pain (18.3% in white patients vs. 10.0% in non-white patients), and anorexia (16.7% in white patients vs. 11.7% in non-white patients).

Table 40: Grade 1-4 Adverse Events by Age and Race

	Age		Race	
	<65 yrs N = 131	≥65 yrs N = 240	White N = 311	Non-White N = 60
Any Grade 1-4[1]	126 (96.2%)	227 (94.6%)	296 (95.2%)	57 (95.0%)
Anemia[2]	124 (95.4%)	237 (99.2%)	303 (97.7%)	58 (98.3%)
Leukopenia[2]	122 (93.8%)	233 (97.5%)	297 (95.8%)	58 (98.3%)
Neutropenia[2]	116 (89.2%)	231 (96.7%)	292 (94.2%)	55 (93.2%)
Thrombocytopenia[2]	51 (39.2%)	125 (52.3%)	146 (47.1%)	30 (50.8%)
Diarrhea	63 (48.1%)	110 (45.8%)	145 (46.6%)	28 (46.7%)
Fatigue	39 (29.8%)	97 (40.4%)	122 (39.2%)	14 (23.3%)
Nausea	48 (36.6%)	79 (32.9%)	116 (37.3%)	11 (18.3%)
Vomiting	30 (22.9%)	53 (22.1%)	73 (23.5%)	10 (16.7%)
Asthenia	19 (14.5%)	57 (23.8%)	66 (21.2%)	10 (16.7%)
Constipation	24 (18.3%)	52 (21.7%)	69 (22.2%)	7 (11.7%)
Abdominal Pain[3]	23 (17.6%)	40 (16.7%)	57 (18.3%)	6 (10.0%)
Hematuria	21 (16.0%)	41 (17.1%)	52 (16.7%)	10 (16.7%)
Back Pain	21 (16.0%)	39 (16.3%)	52 (16.7%)	8 (13.3%)
Anorexia	23 (17.6%)	36 (15.0%)	52 (16.7%)	7 (11.7%)

[1]Does not include adverse events captured only in ADLB (laboratory tests) dataset.
[2]Derived from the ADLB (laboratory tests) dataset. Denominator includes only patients with at least 1 post-baseline lab value; <65 yrs: N=130, ≥65 yrs: N=239, White: N=310, Non-White: N=59.
[3]Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.
The above information was verified using the ADDM (demographics), ADAE (adverse events), and ADLB (laboratory tests) datasets.

Rates of common (>2%) grade 3-4 adverse events were also examined by age (<65 years vs. ≥65 years) and race (white vs. non-white) and are presented in table 41 below.

Overall, grade 3-4 adverse event rates were higher in patients ≥65 years old. Among the most common (>2%) grade 3-4 adverse events, several occurred more frequently (≥5% difference) in older patients. The common grade 3-4 events that occurred more frequently in patients ≥65 years old were: neutropenia (73.8% in <65 yrs vs. 86.6% in ≥65 yrs) and leukopenia (57.7% in <65 yrs vs. 74.5% in ≥65 yrs). Grade 3-4 febrile neutropenia, anemia, asthenia, thrombocytopenia, pneumonia, and dehydration were also more common in older patients.

Overall, grade 3-4 adverse event rates were similar in white and non-white patients. As mentioned above, comparisons of rates of adverse events between white and non-white patients are not reliable, as few non-white patients were treated. Among the most common (>2%) grade 3-4 adverse events, none occurred more frequently (≥5% difference) in white or non-white patients.

Table 41: Grade 3-4 Adverse Events by Age and Race

	Age		Race	
	<65 yrs N = 131	≥65 yrs N = 240	White N = 311	Non-White N = 60
Any Grade 3-4[1]	64 (48.9%)	144 (60.0%)	172 (55.3%)	36 (60.0%)
Neutropenia[2]	96 (73.8%)	207 (86.6%)	252 (81.3%)	51 (86.4%)
Leukopenia[2]	75 (57.7%)	178 (74.5%)	211 (68.1%)	42 (71.2%)
Anemia[2]	10 (7.7%)	29 (12.1%)	34 (11.0%)	5 (8.5%)
Febrile Neutropenia	8 (6.1%)	19 (7.9%)	22 (7.1%)	5 (8.3%)
Diarrhea	8 (6.1%)	15 (6.3%)	18 (5.8%)	5 (8.3%)
Fatigue	8 (6.1%)	10 (4.2%)	17 (5.5%)	1 (1.7%)
Asthenia	4 (3.1%)	13 (5.4%)	15 (4.8%)	2 (3.3%)
Thrombocytopenia[2]	2 (1.5%)	13 (5.4%)	13 (4.2%)	2 (3.4%)
Back Pain	7 (5.3%)	7 (2.9%)	12 (3.9%)	2 (3.3%)
Pneumonia[3]	2 (1.5%)	7 (2.9%)	8 (2.6%)	1 (1.7%)
Dehydration	2 (1.5%)	6 (2.5%)	6 (1.9%)	2 (3.3%)
Renal Failure[4]	4 (3.1%)	4 (1.7%)	5 (1.6%)	3 (5.0%)

[1]Does not include adverse events captured only in ADLB (laboratory tests) dataset.
[2]Derived from the ADLB (Laboratory Tests) dataset. Denominator includes only patients with at least 1 post-baseline lab value; <65 yrs: N=130, ≥65 yrs: N=239, White: N=310, Non-White: N=59.
[3]Includes bronchopneumonia, lobar pneumonia, and pneumonia klebsiella.
[4]Includes acute renal failure.
The above information was verified using the ADDM (demographics), ADAE (adverse events), and ADLB (laboratory tests) datasets.

Three of 131 (2%) patients <65 years of age and 15 of 240 (6%) ≥65 years of age died of causes other than disease progression within 30 days of the last cabazitaxel dose.

Grade 5 adverse events in the three patients <65 years of age included electrolyte imbalance (patient 484-001-006), renal failure (patient 752-001-008), and neutropenic sepsis (patient 826-007-003). The remainder of grade 5 adverse events occurred in patients ≥65 years of age. Four of 5 infection-related grade 5 events occurred in patients ≥65 years of age (ages 67 years, 73 years [2 patients], and 80 years). In addition, three of four grade 5 renal failure adverse events occurred in patients ≥65 years of age, and all four grade 5 cardiac events occurred in patients ≥65 years of age.

Reviewer Comment: Four of five infection-related grade 5 events occurred in patients >65 years of age. These patients are considered to be at high risk for neutropenia complications based on age >65 years. Only one patient who developed a fatal infection was younger than age 65. Of note, this patient did not have any other reported high-risk features, such as poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities. Based on the occurrence of fatal infections in patients >65 years of age,

primary prophylaxis with G-CSF appears to be appropriate in this high-risk patient population.

7.5.4 Drug-Disease Interactions

The phase 3 trial EFC6193 included only prostate cancer patients, so drug-disease interactions are not relevant for this trial. However, the population PK analysis identified tumor type as a significant covariate, with a 60% decrease in plasma CL in patients with breast cancer. See section 2.3.2.3 of the clinical pharmacology review.

7.5.5 Drug-Drug Interactions

Although no *in vivo* drug-drug interaction studies were conducted, *in* vitro data suggests that drug-drug interactions can occur. See section 2.4.2.2 of the clinical pharmacology review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No cabazitaxel-treated patients developed acute myeloid leukemia or myelodysplastic syndrome. See pharmacology-toxicology review.

7.6.2 Human Reproduction and Pregnancy Data

See pharmacology-toxicology review.

7.6.3 Pediatrics and Assessment of Effects on Growth

Cabazitaxel has not been studied in a pediatric population. A pediatric waiver was granted by the Pediatric Review Committee.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose, drug abuse potential, withdrawal, and rebound are not relevant to this application.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

As this application is for a new molecular entity with no prior approval history, there is no postmarket experience.

9 Appendices

9.1 Literature Review/References

See below.

9.2 Labeling Recommendations

See the final version of the label revised by all of the FDA scientific disciplines..

9.3 Advisory Committee Meeting

This application was not presented to or discussed by the Oncologic Drugs Advisory Committee.

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[i] American Cancer Society: Cancer Facts and Figures 2009. Atlanta, Ga: American Cancer Society, 2009. Last accessed March 30, 2010.

[ii] Cooperberg MR, Lubeck DP, Meng MV, Mehta SS, Carroll PR. The changing face of low-risk prostate cancer: trends in clinical presentation and primary management. *J Clin Oncol* 2004;22(11):2141-9.

[iii] Andriole GL, Grubb RL 3rd, Buys SS, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009; 360(13): 1310-9.

[iv] Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360:1320-1328.

[v] Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. *N Engl J Med* 2004;350 (22): 2239-46.

[vi] Lilja H, Ulmert D, Vickers AJ. Prostate-specific antigen and prostate cancer: prediction, detection and monitoring. *Nat Rev Cancer* 2008;8:268-278.

[vii] H.I. Scher, S. Halabi and I. Tannock *et al.* Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group, *J Clin Oncol* 2008; 26:1148–1159.

[viii] Smaletz O, Scher HI, Small EJ et al. Nomogram for overall survival of patients with progressive metastatic prostate cancer after castration. I 2002;20(19): 3972-82.

[ix] Halabi S, Small EJ, Kantoff PW, et al: Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. *J Clin Oncol* 2003; 21:1232-1237.

[x] Armstrong AJ, Garrett-Mayer E, de Wit R et al. Prediction of survival following first-line chemotherapy in men with castration-resistant metastatic prostate cancer. *Clin Cancer Res* 2010;16(1):203-11.

[xi] Tannock IF, de Wit R, Berry WR, et al: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004; 351:1502-1512.

[xii] Eymard JC, Oudard S, Gravis G. Docetaxel reintroduction in patients with metastatic castration-resistant docetaxel-sensitive prostate cancer: a retrospective multicentre study. *BJU Int* 2010 Mar 9. [Epub ahead of print]

[xiii] Mathew P, Tannir N, Tu SM et al. A modular Phase I study of lenalidomide and paclitaxel in metastatic castration-resistant prostate cancer following prior taxane therapy. *Cancer Chemother Pharmacol* 2010; 65(4):811-5.

[xiv] Molife LR, Attard G, Fong PC et al. Phase II, two-stage, single-arm trial of the histone deacetylase inhibitor (HDACi) romidepsin in metastatic castration-resistant prostate cancer (CRPC). *Ann Oncol* 2010;21(1):109-13.

[xv] Hahn NM, Zon RT, Yu M et al. A phase II study of pemetrexed as second-line chemotherapy for the treatment of metastatic castrate-resistant prostate cancer (CRPC); Hoosier Oncology Group GU03-67. *Ann Oncol* 2009;20(12):1971-6.

[xvi] Dror Michaelson M, Regan MM, Oh WK et al. Phase II study of sunitinib in men with advanced prostate cancer. *Ann Oncol* 2009;20(5):913-20.

[xvii] Pezaro C, Rosenthal MA, Gurney H et al. An open-label, single-arm phase two trial of gefitinib in patients with advanced or metastatic castration-resistant prostate cancer. *Am J Clin Oncol* 2009;32(4):338-41.

[xviii] Hussain A, DiPaola RS, Baron AD et al. Phase II trial of weekly patupilone in patients with castration-resistant prostate cancer. *Ann Oncol* 2009;20(3):492-7. Epub 2008 Dec 15.

[xix] Morris MJ, Kelly WK, Slovin S et al. A phase II trial of bortezomib and prednisone for castration resistant metastatic prostate cancer. *J Urol* 2007;178(6):2378-83; discussion 2383-4. Epub 2007 Oct 22.

[xx] Ning YM, Gulley JL, Arlen PM et al. Phase II trial of bevacizumab, thalidomide, docetaxel, and prednisone in patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 2010; 28(12):2070-6.

[xxi] Sternberg CN, Petrylak DP, Sartor O et al. Multinational, double-blind, phase III study of prednisone and either satraplatin or placebo in patients with castrate-refractory prostate cancer progressing after prior chemotherapy: the SPARC trial. *J Clin Oncol* 2009;27(32):5431-8.

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

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