CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-449/S-035

Trade Name: Taxotere

Generic Name: docetaxel

Sponsor: Sanofi-Aventis U.S., Inc.

Approval Date: March 22, 2006

Changes: provides for the use of Taxotere® (docetaxel) Injection Concentrate in combination with cisplatin and fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-449/S-035

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-449/S-035

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-449/S-035

Sanofi-Aventis U.S., Inc
300 Sommerset Corporate Boulevard
Bridgewater, NJ 08807

Attention: Mark W. Moyer
Vice President
Drug Regulatory Affairs

Dear Mr. Moyer:

Please refer to your supplemental new drug application dated September 23, 2005, received September 26, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Taxotere® (docetaxel) Injection Concentrate, 20 mg and 80 mg.

We acknowledge receipt of your submissions dated October 31, 2005; January 20 and 30, 2006; February 6, 24 and March 9, 2006.

This supplemental new drug application provides for the use of Taxotere® (docetaxel) Injection Concentrate in combination with cisplatin and fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 20-449/S-035**." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Drug Oncology Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ann Staten, Regulatory Project Manager, at (301) 796-1468.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D.
Acting Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

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

/s/

Robert Justice

3/22/2006 03:36:46 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-449/S-035

LABELING

PATIENT INFORMATION LEAFLET
Detach and give to Patient

Rev. XXXX 200X

Patient Information Leaflet

Questions and Answers About Taxotere® Injection Concentrate
(generic name = docetaxel)
(pronounced as TAX-O-TEER)

What is Taxotere?

Taxotere is a medication to treat breast cancer, non-small cell lung cancer, prostate cancer and stomach cancer. It has severe side effects in some patients. This leaflet is designed to help you understand how to use Taxotere and avoid its side effects to the fullest extent possible. The more you understand your treatment, the better you will be able to participate in your care. If you have questions or concerns, be sure to ask your doctor or nurse. They are always your best source of information about your condition and treatment.

What is the most important information about Taxotere?

• Since this drug, like many other cancer drugs, affects your blood cells, your doctor will ask for routine blood tests. These will include regular checks of your white blood cell counts. People with low blood counts can develop life-threatening infections. The earliest sign of infection may be fever, so if you experience a fever, tell your doctor right away.

• Occasionally, serious allergic reactions have occurred with this medicine. If you have any allergies, tell your doctor before receiving this medicine.

• A small number of people who take Taxotere have severe fluid retention, which can be life-threatening. To help avoid this problem, you must take another medication such as dexamethasone (DECKS-A-METH-A-SONE) prior to each Taxotere treatment. You must follow the schedule and take the exact dose of dexamethasone prescribed (see schedule at end of brochure). If you forget to take a dose or do not take it on schedule you must tell the doctor or nurse prior to your Taxotere treatment.

• If you are using any other medicines, tell your doctor before receiving your infusions of Taxotere.

How does Taxotere work?

Taxotere works by attacking cancer cells in your body. Different cancer medications attack cancer cells in different ways.

Here's how Taxotere works: Every cell in your body contains a supporting structure (like a skeleton). Damage to this "skeleton" can stop cell growth or reproduction. Taxotere makes the "skeleton" in some cancer cells very stiff, so that the cells can no longer grow.

How will I receive Taxotere?

Taxotere is given by an infusion directly into your vein. Your treatment will take about 1 hour. Generally, people receive Taxotere every 3 weeks. The amount of Taxotere and the frequency of your infusions will be determined by your doctor.

As part of your treatment, to reduce side effects your doctor will prescribe another medicine called dexamethasone. Your doctor will tell you how and when to take this medicine. It is important that you take the dexamethasone on the schedule set by your doctor. If you forget to take your medication, or do not take it on schedule, make sure to tell your doctor or nurse **BEFORE** you receive your Taxotere treatment. **Included with this information leaflet is a chart to help you remember when to take your dexamethasone.**

What should be avoided while receiving Taxotere?

Taxotere can interact with other medicines. Use only medicines that are prescribed for you by your doctor and **be sure** to tell your doctor all the medicines that you use, including nonprescription drugs.

What are the possible side effects of Taxotere?

Low Blood Cell Count – Many cancer medications, including Taxotere, cause a temporary drop in the number of white blood cells. These cells help protect your body from infection. Your doctor will routinely check your blood count and tell you if it is too low. Although most people receiving Taxotere do not have an infection even if they have a low white blood cell count, the risk of infection is increased.

Fever is often one of the most common and earliest signs of infection. Your doctor will recommend that you take your temperature frequently, especially during the days after treatment with Taxotere. If you have a fever, tell your doctor or nurse immediately.

Allergic Reactions – This type of reaction, which occurs during the infusion of Taxotere, is infrequent. If you feel a warm sensation, a tightness in your chest, or itching during or shortly after your treatment, tell your doctor or nurse immediately.

Fluid Retention – This means that your body is holding extra water. If this fluid retention is in the chest or around the heart it can be life-threatening. If you notice swelling in the feet and legs or a slight weight gain, this may be the first warning sign. Fluid retention usually does not start immediately; but, if it occurs, it may start around your 5th treatment. Generally, fluid retention will go away within weeks or months after your treatments are completed.

Dexamethasone tablets may protect patients from significant fluid retention. It is important that you take this medicine on schedule. If you have not taken dexamethasone on schedule, you must tell your doctor or nurse before receiving your next Taxotere treatment.

Gastrointestinal – Diarrhea has been associated with TAXOTERE use and can be severe in some patients. Nausea and/or vomiting are common in patients receiving TAXOTERE. Severe inflammation of the bowel can also occur in some patients and may be life threatening.

Hair Loss – Loss of hair occurs in most patients taking Taxotere (including the hair on your head, underarm hair, pubic hair, eyebrows, and eyelashes). Hair loss will begin after the first few treatments and varies from patient to patient. Once you have completed all your treatments, hair generally grows back.

Your doctor or nurse can refer you to a store that carries wigs, hairpieces, and turbans for patients with cancer.

Fatigue – A number of patients (about 10%) receiving Taxotere feel very tired following their treatments. If you feel tired or weak, allow yourself extra rest before your next treatment. If it is bothersome or lasts for longer than 1 week, inform your doctor or nurse.

Muscle Pain – This happens about 20% of the time, but is rarely severe. You may feel pain in your muscles or joints. Tell your doctor or nurse if this happens. They may suggest ways to make you more comfortable.

Rash – This side effect occurs commonly but is severe in about 5%. You may develop a rash that looks like a blotchy, hive-like reaction. This usually occurs on the hands and feet but may also appear on the arms, face, or body. Generally, it will appear between treatments and will go away before the next treatment. Inform your doctor or nurse if you experience a rash. They can help you avoid discomfort.

Odd Sensations – About half of patients getting Taxotere will feel numbness, tingling, or burning sensations in their hands and feet. If you do experience this, tell your doctor or nurse. Generally, these go away within a few weeks or months after your treatments are completed. About 14% of patients may also develop weakness in their hands and feet.

Nail Changes – Color changes to your fingernails or toenails may occur while taking Taxotere. In extreme, but rare, cases nails may fall off. After you have finished Taxotere treatments, your nails will generally grow back.

Eye Changes – Excessive tearing, which can be related to conjunctivitis or blockage of the tear ducts, may occur.

If you are interested in learning more about this drug, ask your doctor for a copy of the package insert.

Aventis Pharmaceuticals Inc.
Bridgewater, NJ 08807 USA
www.aventis-us.com

Rev. XXXX 200X

Every three-week injection of TAXOTERE for breast, non-small cell lung and stomach cancers
Take dexamethasone tablets, 8 mg twice daily.

Dexamethasone dosing:

Day 1 Date:_____ Time:_____AM _____PM

Day 2 Date:_____ Time:_____AM _____PM
(Taxotere Treatment Day)

Day 3 Date:_____ Time:_____AM _____PM

Every three-week injection of TAXOTERE for prostate cancer
Take dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before TAXOTERE infusion.

Dexamethasone dosing:

Date:_____ Time:_____

Date:_____ Time:_____
(Taxotere Treatment Day)
Time:_____

Prescribing Information as of XXXX 200X

℞ only

TAXOTERE®
(docetaxel)

Injection Concentrate

WARNING

TAXOTERE® (docetaxel) Injection Concentrate should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

The incidence of treatment-related mortality associated with TAXOTERE therapy is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who receive TAXOTERE as a single agent at a dose of 100 mg/m^2 (see **WARNINGS**).

TAXOTERE should generally not be given to patients with bilirubin > upper limit of normal (ULN), or to patients with SGOT and/or SGPT >1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase > 1.5 x ULN also had a higher rate of febrile neutropenia grade 4 but did not have an increased incidence of toxic death. Bilirubin, SGOT or SGPT, and alkaline phosphatase values should be obtained prior to each cycle of TAXOTERE therapy and reviewed by the treating physician.

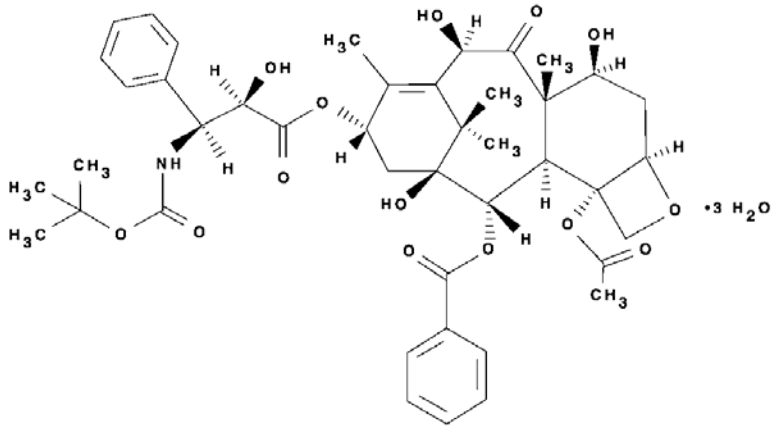
TAXOTERE therapy should not be given to patients with neutrophil counts of < 1500 cells/mm^3. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving TAXOTERE.

Severe hypersensitivity reactions characterized by hypotension and/or bronchospasm, or generalized rash/erythema occurred in 2.2% (2/92) of patients who received the recommended 3-day dexamethasone premedication. Hypersensitivity reactions requiring discontinuation of the TAXOTERE infusion were reported in five patients who did not receive premedication. These reactions resolved after discontinuation of the infusion and the administration of appropriate therapy. TAXOTERE must not be given to patients who have a history of severe hypersensitivity reactions to TAXOTERE or to other drugs formulated with polysorbate 80 (see **WARNINGS**).

Severe fluid retention occurred in 6.5% (6/92) of patients despite use of a 3-day dexamethasone premedication regimen. It was characterized by one or more of the following events: poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention (due to ascites) (see **PRECAUTIONS**).

DESCRIPTION

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. Docetaxel has the following structural formula:



Docetaxel is a white to almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14}\bullet 3H_2O$, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water. TAXOTERE (docetaxel) Injection Concentrate is a clear yellow to brownish-yellow viscous solution. TAXOTERE is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg (0.5 mL) or 80 mg (2 mL) docetaxel (anhydrous). Each mL contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80.

TAXOTERE Injection Concentrate requires dilution prior to use. A sterile, non-pyrogenic, single-dose diluent is supplied for that purpose. The diluent for TAXOTERE contains 13% ethanol in water for injection, and is supplied in vials.

CLINICAL PHARMACOLOGY

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

HUMAN PHARMACOKINETICS

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20-115 mg/m^2 in phase I studies. The area under the curve (AUC) was dose proportional following doses of 70-115 mg/m^2 with infusion times of 1 to 2 hours. Docetaxel's

pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean values for total body clearance and steady state volume of distribution were 21 L/h/m^2 and 113 L, respectively. Mean total body clearance for Japanese patients dosed at the range of 10-90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations.

A study of ^{14}C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

A population pharmacokinetic analysis was carried out after TAXOTERE treatment of 535 patients dosed at 100 mg/m^2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase I studies. The pharmacokinetics of docetaxel were not influenced by age or gender and docetaxel total body clearance was not modified by pretreatment with dexamethasone. In patients with clinical chemistry data suggestive of mild to moderate liver function impairment (SGOT and/or SGPT >1.5 times the upper limit of normal [ULN] concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should, in general, not be treated with TAXOTERE.

Clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. The pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone.

The combined administration of docetaxel, cisplatin and fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug.

A population pharmacokinetic analysis of plasma data from 40 patients with hormone-refractory metastatic prostate cancer indicated that docetaxel systemic clearance in combination with prednisone is similar to that observed following administration of docetaxel alone.

A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug-interactions between docetaxel (75 mg/m²), doxorubicin (50 mg/m²), and cyclophosphamide (500 mg/m²) when administered in combination. The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy.

In vitro studies showed that docetaxel is about 94% protein bound, mainly to α_1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

In vitro drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism can be inhibited by CYP3A4 inhibitors, such as ketoconazole, erythromycin, troleandomycin, and nifedipine. Based on *in vitro* findings, it is likely that CYP3A4 inhibitors and/or substrates may lead to substantial increases in docetaxel blood concentrations. No clinical studies have been performed to evaluate this finding (see **PRECAUTIONS**).

CLINICAL STUDIES

Breast Cancer

The efficacy and safety of TAXOTERE have been evaluated in locally advanced or metastatic breast cancer after failure of previous chemotherapy (alkylating agent-containing regimens or anthracycline-containing regimens).

Randomized Trials

In one randomized trial, patients with a history of prior treatment with an anthracycline-containing regimen were assigned to treatment with TAXOTERE (100 mg/m^2 every 3 weeks) or the combination of mitomycin (12 mg/m^2 every 6 weeks) and vinblastine (6 mg/m^2 every 3 weeks). 203 patients were randomized to TAXOTERE and 189 to the comparator arm. Most patients had received prior chemotherapy for metastatic disease; only 27 patients on the TAXOTERE arm and 33 patients on the comparator arm entered the study following relapse after adjuvant therapy. Three-quarters of patients had measurable, visceral metastases. The primary endpoint was time to progression. The following table summarizes the study results (See Table 1).

Table 1-Efficacy of TAXOTERE in the Treatment of Breast Cancer Patients Previously Treated with an Anthracycline-Containing Regimen (Intent-to-Treat Analysis)

Efficacy Parameter	**Docetaxel (n=203)**	**Mitomycin/ Vinblastine (n=189)**	**p-value**
Median Survival	11.4 months	8.7 months	
Risk Ratio*, Mortality (Docetaxel: Control)	0.73		p=0.01 Log Rank
95% CI (Risk Ratio)	0.58-0.93		
Median Time to Progression	4.3 months	2.5 months	
Risk Ratio*, Progression (Docetaxel: Control)	0.75		p=0.01 Log Rank
95% CI (Risk Ratio)	0.61-0.94		
Overall Response Rate	28.1%	9.5%	p<0.0001
Complete Response Rate	3.4%	1.6%	Chi Square

*For the risk ratio, a value less than 1.00 favors docetaxel.

In a second randomized trial, patients previously treated with an alkylating-containing regimen were assigned to treatment with TAXOTERE (100 mg/m^2) or doxorubicin (75 mg/m^2) every 3 weeks. 161 patients were randomized to TAXOTERE and 165 patients to doxorubicin. Approximately one-half of patients had received prior chemotherapy for metastatic disease, and one-half entered the study following relapse after adjuvant therapy. Three-quarters of patients had measurable, visceral metastases. The primary endpoint was time to progression. The study results are summarized below (See Table 2).

Table 2-Efficacy of TAXOTERE in the Treatment of Breast Cancer Patients Previously Treated with an Alkylating-Containing Regimen (Intent-to-Treat Analysis)

Efficacy Parameter	**Docetaxel (n=161)**	**Doxorubicin (n=165)**	**p-value**
Median Survival	14.7 months	14.3 months	
Risk Ratio*, Mortality (Docetaxel: Control)	0.89		p=0.39 Log Rank
95% CI (Risk Ratio)	0.68-1.16		
Median Time to Progression	6.5 months	5.3 months	
Risk Ratio*, Progression (Docetaxel: Control)	0.93		p=0.45 Log Rank
95% CI (Risk Ratio)	0.71-1.16		
Overall Response Rate	45.3%	29.7%	p=0.004 Chi Square
Complete Response Rate	6.8%	4.2%	

*For the risk ratio, a value less than 1.00 favors docetaxel.

In another multicenter open-label, randomized trial (TAX313), in the treatment of patients with advanced breast cancer who progressed or relapsed after one prior chemotherapy regimen, 527 patients were randomized to receive TAXOTERE monotherapy 60 mg/m^2 (n=151), 75 mg/m^2 (n=188) or 100 mg/m^2 (n=188). In this trial, 94% of patients had metastatic disease and 79% had received prior anthracycline therapy. Response rate was the primary endpoint. Response rates increased with TAXOTERE dose: 19.9% for the 60 mg/m^2 group compared to 22.3% for the 75 mg/m^2 and 29.8% for the 100 mg/m^2 group; pair-wise comparison between the 60 mg/m^2 and 100 mg/m^2 groups was statistically significant, (p=0.037).

Single Arm Studies

TAXOTERE at a dose of 100 mg/m^2 was studied in six single arm studies involving a total of 309 patients with metastatic breast cancer in whom previous chemotherapy had failed. Among these, 190 patients had anthracycline-resistant breast cancer, defined as progression during an anthracycline-containing chemotherapy regimen for metastatic disease, or relapse during an anthracycline-containing adjuvant regimen. In anthracycline-resistant patients, the overall

response rate was 37.9% (72/190; 95% C.I.: 31.0-44.8) and the complete response rate was 2.1%.

TAXOTERE was also studied in three single arm Japanese studies at a dose of 60 mg/m^2, in 174 patients who had received prior chemotherapy for locally advanced or metastatic breast cancer. Among 26 patients whose best response to an anthracycline had been progression, the response rate was 34.6% (95% C.I.: 17.2-55.7), similar to the response rate in single arm studies of 100 mg/m^2.

Adjuvant Treatment of Breast Cancer

A multicenter, open-label, randomized trial (TAX316) evaluated the efficacy and safety of TAXOTERE for the adjuvant treatment of patients with axillary-node-positive breast cancer and no evidence of distant metastatic disease. After stratification according to the number of positive lymph nodes (1-3, 4+), 1491 patients were randomized to receive either TAXOTERE 75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (TAC arm), or doxorubicin 50 mg/m^2 followed by fluorouracil 500 mg/m^2 and cyclosphosphamide 500 mg/m^2 (FAC arm). Both regimens were administered every 3 weeks for 6 cycles. TAXOTERE was administered as a 1-hour infusion; all other drugs were given as IV bolus on day 1. In both arms, after the last cycle of chemotherapy, patients with positive estrogen and/or progesterone receptors received tamoxifen 20 mg daily for up to 5 years. Adjuvant radiation therapy was prescribed according to guidelines in place at participating institutions and was given to 69% of patients who received TAC and 72% of patients who received FAC.

Results from a second interim analysis (median follow-up 55 months) are as follows: In study TAX 316, the docetaxel-containing combination regimen TAC showed significantly longer disease-free survival (DFS) than FAC (hazard ratio=0.74; 2-sided 95% CI=0.60, 0.92, stratified log rank p=0.0047). The primary endpoint, disease-free survival, included local and distant recurrences, contralateral breast cancer and deaths from any cause. The overall reduction in risk of relapse was 25.7% for TAC-treated patients. (See Figure 1).

At the time of this interim analysis, based on 219 deaths, overall survival was longer for TAC than FAC (hazard ratio=0.69, 2-sided 95% CI=0.53, 0.90). (See Figure 2). There will be further analysis at the time survival data mature.

Figure 1-TAX 316 Disease Free Survival K-M curve

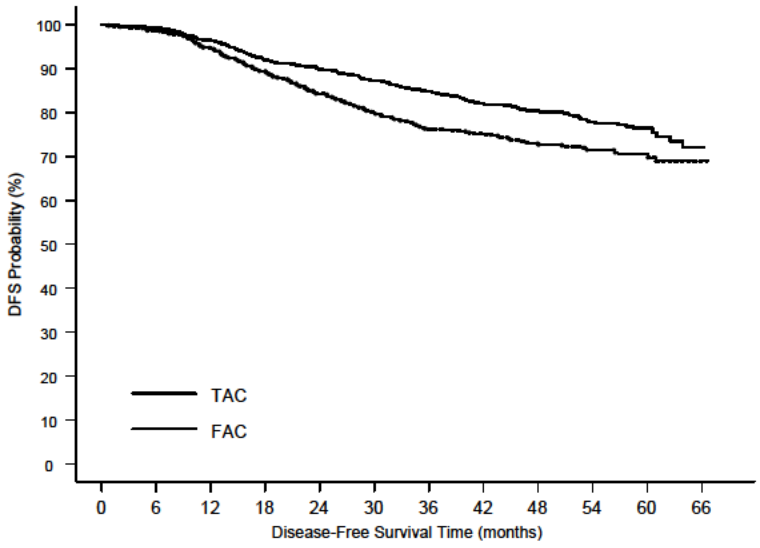
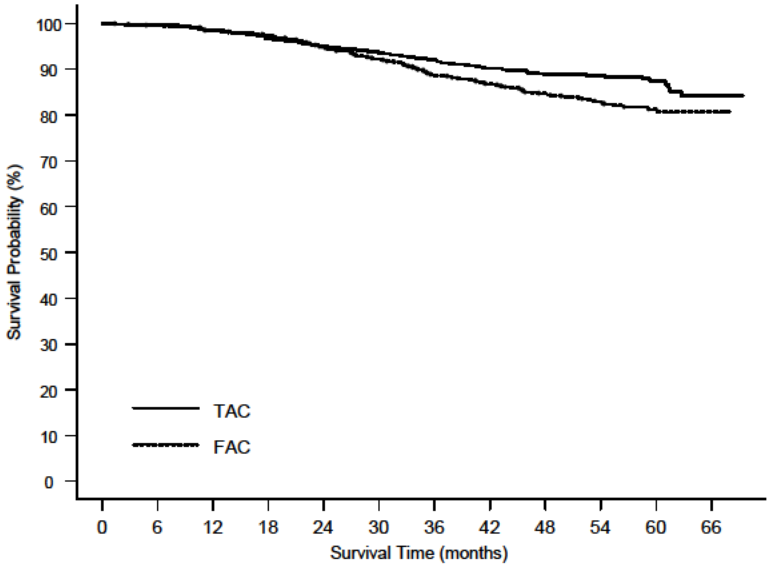


Figure 2-TAX 316 Overall Survival K-M Curve



The following table describes the results of subgroup analyses for DFS and OS (See Table 3).

Table 3-Subset Analyses-Adjuvant Breast Cancer Study

		Disease Free Survival		Overall Survival	
Patient subset	**Number of patients**	**Hazard ratio***	**95% CI**	**Hazard ratio***	**95% CI**
No. of positive nodes					
Overall	744	0.74	(0.60, 0.92)	0.69	(0.53, 0.90)
1-3	467	0.64	(0.47, 0.87)	0.45	(0.29, 0.70)
4+	277	0.84	(0.63, 1.12)	0.93	(0.66, 1.32)
Receptor status					
Positive	566	0.76	(0.59, 0.98)	0.69	(0.48, 0.99)
Negative	178	0.68	(0.48, 0.97)	0.66	(0.44, 0.98)

*****a hazard ratio of less than 1 indicates that TAC is associated with a longer disease free survival or overall survival compared to FAC.

Non-Small Cell Lung Cancer (NSCLC)

The efficacy and safety of TAXOTERE has been evaluated in patients with unresectable, locally advanced or metastatic non-small cell lung cancer whose disease has failed prior platinum-based chemotherapy or in patients who are chemotherapy-naïve.

Monotherapy with TAXOTERE for NSCLC Previously Treated with Platinum-Based Chemotherapy

Two randomized, controlled trials established that a TAXOTERE dose of 75 mg/m^2 was tolerable and yielded a favorable outcome in patients previously treated with platinum-based chemotherapy (see below). TAXOTERE at a dose of 100 mg/m^2, however, was associated with unacceptable hematologic toxicity, infections, and treatment-related mortality and this dose should not be used (see **BOXED WARNING, WARNINGS**, and **DOSAGE AND ADMINISTRATION** sections).

One trial (TAX317), randomized patients with locally advanced or metastatic non-small cell lung cancer, a history of prior platinum-based chemotherapy, no history of taxane exposure, and an ECOG performance status ≤2 to TAXOTERE or best supportive care. The primary endpoint of the study was survival. Patients were initially randomized to TAXOTERE 100 mg/m^2 or best supportive care, but early toxic deaths at this dose led to a dose reduction to TAXOTERE 75 mg/m^2. A total of 104 patients were randomized in this amended study to either TAXOTERE 75 mg/m^2 or best supportive care.

In a second randomized trial (TAX320), 373 patients with locally advanced or metastatic non-small cell lung cancer, a history of prior platinum-based chemotherapy, and an ECOG performance status ≤2 were randomized to TAXOTERE 75 mg/m^2, TAXOTERE 100 mg/m^2 and a treatment in which the investigator chose either vinorelbine 30 mg/m^2 days 1, 8, and 15 repeated every 3 weeks or ifosfamide 2 g/m^2 days 1-3 repeated every 3 weeks. Forty percent of the patients in this study had a history of prior paclitaxel exposure. The primary endpoint was survival in both trials. The efficacy data for the TAXOTERE 75 mg/m^2 arm and the comparator arms are summarized in Table 4 and in Figures 3 and 4 showing the survival curves for the two studies.

Table 4-Efficacy of TAXOTERE in the Treatment of Non-Small Cell Lung Cancer Patients Previously Treated with a Platinum-Based Chemotherapy Regimen (Intent-to-Treat Analysis)

	TAX317		**TAX320**	
	Docetaxel 75 mg/m^2 n=55	**Best Supportive Care/75 n=49**	**Docetaxel 75 mg/m^2 n=125**	**Control (V/I) n=123**
Overall Survival Log-rank Test	p=0.01		p=0.13	
Risk Ratio††, Mortality (Docetaxel: Control) 95% CI (Risk Ratio)	0.56 (0.35, 0.88)		0.82 (0.63, 1.06)	
Median Survival 95% CI	7.5 months* (5.5, 12.8)	4.6 months (3.7, 6.1)	5.7 months (5.1, 7.1)	5.6 months (4.4, 7.9)
% 1-year Survival 95% CI	37%*† (24, 50)	12% (2, 23)	30%*† (22, 39)	20% (13, 27)
Time to Progression 95% CI	12.3 weeks* (9.0, 18.3)	7.0 weeks (6.0, 9.3)	8.3 weeks (7.0, 11.7)	7.6 weeks (6.7, 10.1)
Response Rate 95% CI	5.5% (1.1, 15.1)	Not Applicable	5.7% (2.3, 11.3)	0.8% (0.0, 4.5)

* $p \leq 0.05$; † uncorrected for multiple comparisons; †† a value less than 1.00 favors docetaxel.

Only one of the two trials (TAX317) showed a clear effect on survival, the primary endpoint; that trial also showed an increased rate of survival to one year. In the second study (TAX320) the rate of survival at one year favored TAXOTERE 75 mg/m^2.

Figure 3: TAX317 Survival K-M Curves - TAXOTERE 75 mg/m^2 vs. Best Supportive Care

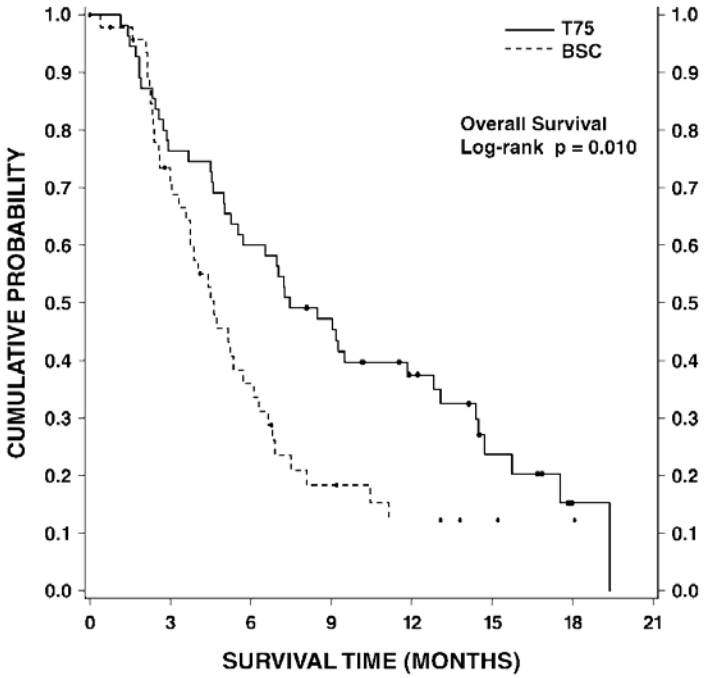
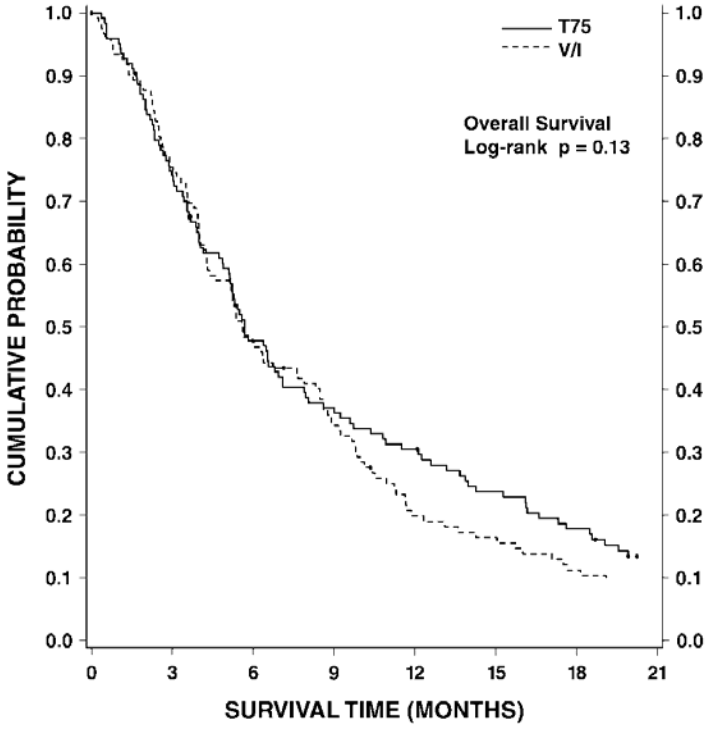


Figure 4: TAX320 Survival K-M Curves - TAXOTERE 75 mg/m^2 vs. Vinorelbine or Ifosfamide Control



Patients treated with TAXOTERE at a dose of 75 mg/m^2 experienced no deterioration in performance status and body weight relative to the comparator arms used in these trials.

Combination Therapy with TAXOTERE for Chemotherapy-Naïve NSCLC

In a randomized controlled trial (TAX326), 1218 patients with unresectable stage IIIB or IV NSCLC and no prior chemotherapy were randomized to receive one of three treatments:

TAXOTERE 75 mg/m^2 as a 1 hour infusion immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes every 3 weeks; vinorelbine 25 mg/m^2 administered over 6-10 minutes on days 1, 8, 15, 22 followed by cisplatin 100 mg/m^2 administered on day 1 of cycles repeated every 4 weeks; or a combination of TAXOTERE and carboplatin.

The primary efficacy endpoint was overall survival. Treatment with TAXOTERE+cisplatin did not result in a statistically significantly superior survival compared to vinorelbine+cisplatin (see table below). The 95% confidence interval of the hazard ratio (adjusted for interim analysis and multiple comparisons) shows that the addition of TAXOTERE to cisplatin results in an outcome ranging from a 6% inferior to a 26% superior survival compared to the addition of vinorelbine to cisplatin. The results of a further statistical analysis showed that at least (the lower bound of the 95% confidence interval) 62% of the known survival effect of vinorelbine when added to cisplatin (about a 2-month increase in median survival; Wozniak et al. JCO, 1998) was maintained. The efficacy data for the TAXOTERE+cisplatin arm and the comparator arm are summarized in Table 5.

Table 5-Survival Analysis of TAXOTERE in Combination Therapy for Chemotherapy-Naïve NSCLC

Comparison	**Taxotere+Cisplatin n=408**	**Vinorelbine+Cisplatin n=405**
Kaplan-Meier Estimate of Median Survival	10.9 months	10.0 months
p-value[a]	0.122	
Estimated Hazard Ratio[b]	0.88	
Adjusted 95% CI[c]	(0.74, 1.06)	

[a] From the superiority test (stratified log rank) comparing TAXOTERE+cisplatin to vinorelbine+cisplatin

[b] Hazard ratio of TAXOTERE+cisplatin vs. vinorelbine+cisplatin. A hazard ratio of less than 1 indicates that TAXOTERE+cisplatin is associated with a longer survival.

[c] Adjusted for interim analysis and multiple comparisons.

The second comparison in the study, vinorelbine+cisplatin versus TAXOTERE+carboplatin,did not demonstrate superior survival associated with the TAXOTERE arm (Kaplan-Meier estimate of median survival was 9.1 months for TAXOTERE+carboplatin compared to 10.0 months on the vinorelbine+cisplatin arm) and the TAXOTERE+carboplatin arm did not demonstrate preservation of at least 50% of the survival effect of vinorelbine added to cisplatin. Secondary endpoints evaluated in the trial included objective response and time to progression. There was no statistically significant difference between TAXOTERE+cisplatin and vinorelbine+cisplatin with respect to objective response and time to progression (see Table 6).

Table 6-Response and TTP Analysis of TAXOTERE in Combination Therapy for Chemotherapy-Naïve NSCLC

Endpoint	TAXOTERE+Cisplatin	Vinorelbine+Cisplatin	p-value
Objective Response Rate (95% CI)[a]	31.6% (26.5%, 36.8%)	24.4% (19.8%, 29.2%)	Not Significant
Median Time to Progression[b] (95% CI)[a]	21.4 weeks (19.3, 24.6)	22.1 weeks (18.1, 25.6)	Not Significant

[a]Adjusted for multiple comparisons.

[b]Kaplan-Meier estimates.

Prostate Cancer

The safety and efficacy of TAXOTERE in combination with prednisone in patients with androgen independent (hormone refractory) metastatic prostate cancer were evaluated in a randomized multicenter active control trial. A total of 1006 patients with Karnofsky Performance Status (KPS) ≥60 were randomized to the following treatment groups:

- TAXOTERE 75 mg/m^2 every 3 weeks for 10 cycles.
- TAXOTERE 30 mg/m^2 administered weekly for the first 5 weeks in a 6-week cycle for 5 cycles.
- Mitoxantrone 12 mg/m^2 every 3 weeks for 10 cycles.

All 3 regimens were administered in combination with prednisone 5 mg twice daily, continuously.

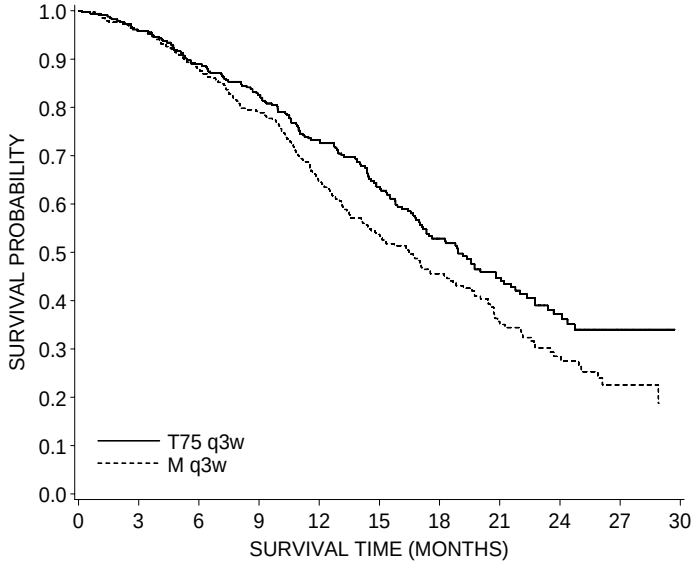
In the TAXOTERE every three week arm, a statistically significant overall survival advantage was demonstrated compared to mitoxantrone. In the TAXOTERE weekly arm, no overall survival advantage was demonstrated compared to the mitoxantrone control arm. Efficacy results for the TAXOTERE every 3 week arm versus the control arm are summarized in Table 7 and Figure 5.

Table 7-Efficacy of TAXOTERE in the Treatment of Patients with Androgen Independent (Hormone Refractory) Metastatic Prostate Cancer (Intent-to-Treat Analysis)

	TAXOTERE every 3 weeks	Mitoxantrone every 3 weeks
Number of patients	335	337
Median survival (months)	18.9	16.5
95% CI	(17.0-21.2)	(14.4-18.6)
Hazard ratio	0.761	--
95% CI	(0.619-0.936)	--
p-value*	0.0094	--

*Stratified log rank test. Threshold for statistical significance = 0.0175 because of 3 arms

Figure 5 - TAX327 Survival K-M Curves



Gastric Adenocarcinoma

A multicenter, open-label, randomized trial was conducted to evaluate the safety and efficacy of TAXOTERE for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who had not received prior chemotherapy for advanced disease. A total of 445 patients with KPS>70, were treated with either TAXOTERE (T) (75 mg/m^2 on day 1) in combination with cisplatin (C) (75 mg/m^2 on day 1) and fluorouracil (F) (750 mg/m^2 per day for 5 days) or cisplatin (100 mg/m^2 on day 1) and fluorouracil (1000 mg/m^2 per day for 5 days). The length of a treatment cycle was 3 weeks for the TCF arm and 4 weeks for the CF arm. The demographic characteristics were balanced between the two treatment arms. The median age was 55 years, 71% were male, 71% were Caucasian, 24% were 65 years of age or older, 19% had a prior curative surgery and 12% had palliative surgery. The median number of cycles administered per patient was 6 (with a range of 1-16) for the TCF arm compared to 4 (with a range of 1-12) for the CF arm. Time to progression (TTP) was the primary endpoint and was defined as time from randomization to disease progression or death from any cause within 12 weeks of the last evaluable tumor assessment or within 12 weeks of the first infusion of study drugs for patients with no evaluable tumor assessment after randomization. The hazard ratio (HR) for TTP was 1.47 (CF/TCF, 95% CI: 1.19-1.83) with a significantly longer TTP (p=0.0004) in the TCF arm. Approximately 75% of patients had died at the time of this analysis. Overall survival was significantly longer (p=0.0201) in the TCF arm with a HR of 1.29 (95% CI: 1.04-1.61). Efficacy results are summarized in Table 8 and Figures 6 and 7.

Table 8-Efficacy of TAXOTERE in the treatment of patients with gastric adenocarcinoma

Endpoint	**TCF n=221**	**CF n=224**
Median TTP (months)	5.6	3.7
(95%CI)	(4.86-5.91)	(3.45-4.47)
Hazard ratio†	1.47	
(95%CI)	(1.19-1.83)	
*p-value	0.0004	
Median survival (months)	9.2	8.6
(95%CI)	(8.38-10.58)	(7.16-9.46)
Hazard ratio†	1.29	
(95%CI)	(1.04-1.61)	
*p-value	0.0201	
Overall Response Rate (CR+PR) (%)	36.7	25.4
p-value	0.0106	

*Unstratified logrank test

†For the hazard ratio (CF/TCF), values greater than 1.00 favor the TAXOTERE arm.

Subgroup analyses were consistent with the overall results across age, gender and race.

Figure 6 - Gastric Cancer Study (TAX325) Time to Progression K-M Curve

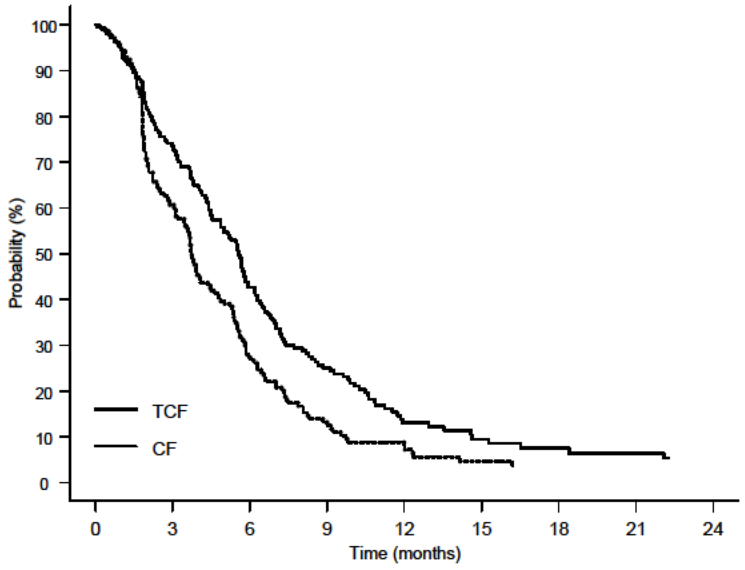
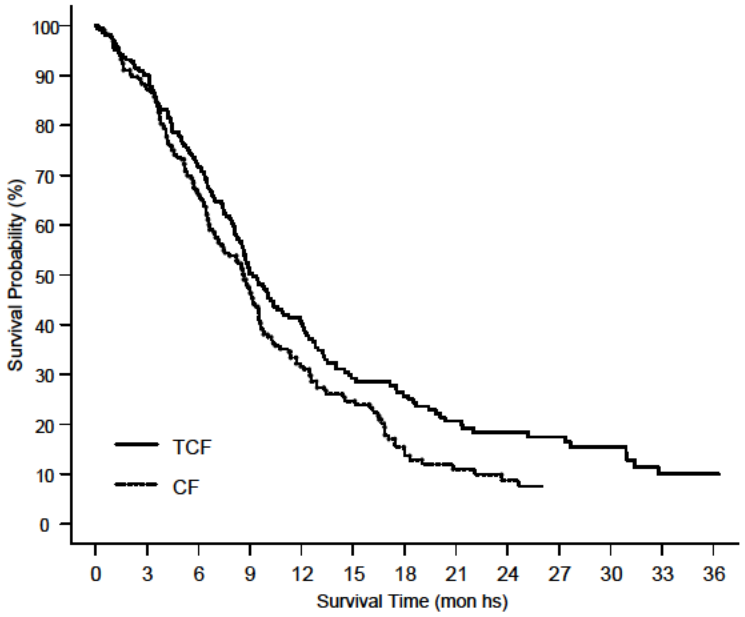


Figure 7 - Gastric Cancer Study (TAX325) Survival K-M Curve



INDICATIONS AND USAGE

Breast Cancer

TAXOTERE is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.

TAXOTERE in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.

Non-Small Cell Lung Cancer

TAXOTERE as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.

TAXOTERE in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.

Prostate Cancer

TAXOTERE in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.

Gastric Adenocarcinoma

TAXOTERE in combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

CONTRAINDICATIONS

TAXOTERE is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80.

TAXOTERE should not be used in patients with neutrophil counts of <1500 cells/mm^3.

WARNINGS

TAXOTERE should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Toxic Deaths

Breast Cancer

TAXOTERE administered at 100 mg/m^2 was associated with deaths considered possibly or probably related to treatment in 2.0% (19/965) of metastatic breast cancer patients, both previously treated and untreated, with normal baseline liver function and in 11.5% (7/61) of patients with various tumor types who had abnormal baseline liver function (SGOT and/or SGPT > 1.5 times ULN together with AP > 2.5 times ULN). Among patients dosed at 60 mg/m^2, mortality related to treatment occurred in 0.6% (3/481) of patients with normal liver function, and in 3 of 7 patients with abnormal liver function. Approximately half of these deaths occurred during the first cycle. Sepsis accounted for the majority of the deaths.

Non-Small Cell Lung Cancer

TAXOTERE administered at a dose of 100 mg/m^2 in patients with locally advanced or metastatic non-small cell lung cancer who had a history of prior platinum-based chemotherapy was associated with increased treatment-related mortality (14% and 5% in two randomized, controlled studies). There were 2.8% treatment-related deaths among the 176 patients treated at the 75 mg/m^2 dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m^2 dose level, 3 of 5 patients had a PS of 2 at study entry (see **BOXED WARNING, CLINICAL STUDIES**, and **DOSAGE AND ADMINISTRATION** sections).

Premedication Regimen

All patients should be premedicated with oral corticosteroids (see below for prostate cancer) such as dexamethasone 16 mg per day (*e.g.*, 8 mg BID) for 3 days starting 1 day prior to TAXOTERE to reduce the severity of fluid retention and hypersensitivity reactions (see **DOSAGE AND ADMINISTRATION** section). This regimen was evaluated in 92 patients with metastatic breast cancer previously treated with chemotherapy given TAXOTERE at a dose of 100 mg/m^2 every 3 weeks.

The pretreatment regimen for hormone-refractory metastatic prostate cancer is oral dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before the TAXOTERE infusion (see **DOSAGE AND ADMINISTRATION** section).

Hypersensitivity Reactions

Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by hypotension and/or bronchospasm, or generalized rash/erythema occurred in 2.2% of the 92 patients premedicated with 3-day corticosteroids. Hypersensitivity reactions requiring discontinuation of the

TAXOTERE infusion were reported in 5 out of 1260 patients with various tumor types who did not receive premedication, but in 0/92 patients premedicated with 3-day corticosteroids. Patients with a history of severe hypersensitivity reactions should not be rechallenged with TAXOTERE.

Hematologic Effects

Neutropenia (< 2000 neutrophils/mm^3) occurs in virtually all patients given 60-100 mg/m^2 of TAXOTERE and grade 4 neutropenia (< 500 cells/mm^3) occurs in 85% of patients given 100 mg/m^2 and 75% of patients given 60 mg/m^2. Frequent monitoring of blood counts is, therefore, essential so that dose can be adjusted. TAXOTERE should not be administered to patients with neutrophils < 1500 cells/mm^3.

Febrile neutropenia occurred in about 12% of patients given 100 mg/m^2 but was very uncommon in patients given 60 mg/m^2. Hematologic responses, febrile reactions and infections, and rates of septic death for different regimens are dose related and are described in **CLINICAL STUDIES**.

Three breast cancer patients with severe liver impairment (bilirubin > 1.7 times ULN) developed fatal gastrointestinal bleeding associated with severe drug-induced thrombocytopenia.

In gastric cancer patients treated with TAXOTERE in combination with cisplatin and fluorouracil (TCF), febrile neutropenia and/or neutropenic infection occurred in 12% of patients receiving G-CSF compared to 28% who did not. Patients receiving TCF should be closely monitored during the first and subsequent cycles for febrile neutropenia and neutropenic infection. (See **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION/Dosage Adjustments** sections).

Hepatic Impairment

(see **BOXED WARNING)**.

Fluid Retention

(see **BOXED WARNING)**.

Acute Myeloid Leukemia

Treatment-related acute myeloid leukemia (AML) has occurred in patients given anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast cancer. In the adjuvant breast cancer trial (TAX316, see CLINICAL STUDIES) AML occurred in 3 of 744 patients who received TAXOTERE, doxorubicin and cyclophosphamide and in 1 of 736 patients who received fluorouracil, doxorubicin and cyclophosphamide (see ADVERSE REACTIONS).

Pregnancy

TAXOTERE can cause fetal harm when administered to pregnant women. Studies in both rats and rabbits at doses ≥ 0.3 and 0.03 mg/kg/day, respectively (about 1/50 and 1/300 the daily maximum recommended human dose on a mg/m^2 basis), administered during the period of organogenesis, have shown that TAXOTERE is embryotoxic and fetotoxic (characterized by intrauterine mortality, increased resorption, reduced fetal weight, and fetal ossification delay). The doses indicated above also caused maternal toxicity.

There are no adequate and well-controlled studies in pregnant women using TAXOTERE. If TAXOTERE is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TAXOTERE.

PRECAUTIONS

General

Responding patients may not experience an improvement in performance status on therapy and may experience worsening. The relationship between changes in performance status, response to therapy, and treatment-related side effects has not been established.

Hematologic Effects

In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOTERE. Patients should not be retreated with subsequent cycles of TAXOTERE until neutrophils recover to a level > 1500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3.

A 25% reduction in the dose of TAXOTERE is recommended during subsequent cycles following severe neutropenia (< 500 cells/mm^3) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a TAXOTERE cycle (see **DOSAGE AND ADMINISTRATION** section).

Hypersensitivity Reactions

Hypersensitivity reactions may occur within a few minutes following initiation of a TAXOTERE infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required. More severe reactions, however, require the immediate discontinuation of TAXOTERE and aggressive therapy. All patients should be premedicated with an oral corticosteroid prior to the initiation of the infusion of TAXOTERE (see **BOXED WARNING** and **WARNINGS**: **Premedication Regimen**).

Cutaneous

Localized erythema of the extremities with edema followed by desquamation has been observed. In case of severe skin toxicity, an adjustment in dosage is recommended (see **DOSAGE AND ADMINISTRATION** section). The discontinuation rate due to skin toxicity was 1.6% (15/965) for metastatic breast cancer patients. Among 92 breast cancer patients premedicated with 3-day corticosteroids, there were no cases of severe skin toxicity reported and no patient discontinued TAXOTERE due to skin toxicity.

Fluid Retention

Severe fluid retention has been reported following TAXOTERE therapy (see **BOXED WARNING** and **WARNINGS**: **Premedication Regimen**). Patients should be premedicated with oral corticosteroids prior to each TAXOTERE administration to reduce the incidence and severity of fluid retention (see **DOSAGE AND ADMINISTRATION** section). Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions.

When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg.

Among 92 breast cancer patients premedicated with 3-day corticosteroids, moderate fluid retention occurred in 27.2% and severe fluid retention in 6.5%. The median cumulative dose to onset of moderate or severe fluid retention was 819 mg/m^2. 9.8% (9/92) of patients discontinued treatment due to fluid retention: 4 patients discontinued with severe fluid retention; the remaining 5 had mild or moderate fluid retention. The median cumulative dose to treatment discontinuation due to fluid retention was 1021 mg/m^2. Fluid retention was completely, but

sometimes slowly, reversible with a median of 16 weeks from the last infusion of TAXOTERE to resolution (range: 0 to 42+ weeks). Patients developing peripheral edema may be treated with standard measures, *e.g*., salt restriction, oral diuretic(s).

Neurologic

Severe neurosensory symptoms (paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of metastatic breast cancer patients, and resulted in treatment discontinuation in 6.1%. When these symptoms occur, dosage must be adjusted. If symptoms persist, treatment should be discontinued (see **DOSAGE AND ADMINISTRATION** section). Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event was available had spontaneous reversal of symptoms with a median of 9 weeks from onset (range: 0 to 106 weeks). Severe peripheral motor neuropathy mainly manifested as distal extremity weakness occurred in 4.4% (42/965).

Asthenia

Severe asthenia has been reported in 14.9% (144/965) of metastatic breast cancer patients but has led to treatment discontinuation in only 1.8%. Symptoms of fatigue and weakness may last a few days up to several weeks and may be associated with deterioration of performance status in patients with progressive disease.

Information for Patients

For additional information, see the accompanying Patient Information Leaflet.

Drug Interactions

There have been no formal clinical studies to evaluate the drug interactions of TAXOTERE with other medications. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4, such as cyclosporine, terfenadine, ketoconazole, erythromycin, and troleandomycin. Caution should be exercised with these drugs when treating patients receiving TAXOTERE as there is a potential for a significant interaction.

Carcinogenicity, Mutagenicity, Impairment of Fertility

No studies have been conducted to assess the carcinogenic potential of TAXOTERE. TAXOTERE has been shown to be clastogenic in the *in vitro* chromosome aberration test in CHO-K_1 cells and in the *in vivo* micronucleus test in the mouse, but it did not induce mutagenicity in the Ames test or the CHO/HGPRT gene mutation assays. TAXOTERE produced no impairment of fertility in rats when administered in multiple IV doses of up to 0.3 mg/kg (about 1/50 the recommended human dose on a mg/m^2 basis), but decreased testicular weights were reported. This correlates with findings of a 10-cycle toxicity study (dosing once every 21 days for 6 months) in rats and dogs in which testicular atrophy or degeneration was observed at IV doses of 5 mg/kg in rats and 0.375 mg/kg in dogs (about 1/3 and 1/15 the recommended human dose on a mg/m^2 basis, respectively). An increased frequency of dosing in rats produced similar effects at lower dose levels.

Pregnancy

Pregnancy Category D (see **WARNINGS** section).

Nursing Mothers

It is not known whether TAXOTERE is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from TAXOTERE, mothers should discontinue nursing prior to taking the drug.

Pediatric Use

The safety and effectiveness of TAXOTERE in pediatric patients have not been established.

Geriatric Use

In a study conducted in chemotherapy-naïve patients with NSCLC (TAX326), 148 patients (36%) in the TAXOTERE+cisplatin group were 65 years of age or greater. There were 128 patients (32%) in the vinorelbine+cisplatin group 65 years of age or greater. In the TAXOTERE+cisplatin group, patients less than 65 years of age had a median survival of 10.3 months (95% CI : 9.1 months, 11.8 months) and patients 65 years or older had a median survival of 12.1 months (95% CI : 9.3 months, 14 months). In patients 65 years of age or greater treated with TAXOTERE+cisplatin, diarrhea (55%), peripheral edema (39%) and stomatitis (28%) were observed more frequently than in the vinorelbine+cisplatin group (diarrhea 24%, peripheral edema 20%, stomatitis 20%). Patients treated with TAXOTERE+cisplatin who were 65 years of age or greater were more likely to experience diarrhea (55%), infections (42%), peripheral edema (39%) and stomatitis (28%) compared to patients less than the age of 65 administered the same treatment (43%, 31%, 31% and 21%, respectively).

When TAXOTERE was combined with carboplatin for the treatment of chemotherapy-naïve, advanced non-small cell lung carcinoma, patients 65 years of age or greater (28%) experienced higher frequency of infection compared to similar patients treated with TAXOTERE+cisplatin, and a higher frequency of diarrhea, infection and peripheral edema than elderly patients treated with vinorelbine+cisplatin.

Of the 333 patients treated with TAXOTERE every three weeks plus prednisone in the prostate cancer study (TAX327), 209 patients were 65 years of age or greater and 68 patients were older than 75 years. In patients treated with TAXOTERE every three weeks, the following TEAEs occurred at rates ≥ 10% higher in patients 65 years of age or greater compared to younger patients: anemia (71% vs. 59%), infection (37% vs. 24%), nail changes (34% vs. 23%), anorexia (21% vs. 10%), weight loss (15% vs. 5%) respectively.

In the adjuvant breast cancer trial (TAX316), TAXOTERE in combination with doxorubicin and cyclophosphamide was administered to 744 patients of whom 48 (6%) were 65 years of age or greater. The number of elderly patients who received this regimen was not sufficient to determine whether there were differences in safety and efficacy between elderly and younger patients.

Among the 221 patients treated with TAXOTERE in combination with cisplatin and fluorouracil in the gastric cancer study, 54 were 65 years of age or older and 2 patients were older than 75 years. In this study, the number of patients who were 65 years of age or older was insufficient to determine whether they respond differently from younger patients. However, the incidence of serious adverse events was higher in the elderly patients compared to younger patients. The incidence of the following adverse events (all grades): lethargy, stomatitis, diarrhea, dizziness, edema, febrile neutropenia/neutropenic infection occurred at rates ≥ 10% higher in patients who were 65 years of age or older compared to younger patients. Elderly patients treated with TCF should be closely monitored.

ADVERSE REACTIONS

Adverse reactions are described for TAXOTERE according to indication:

- in the treatment of breast cancer, at the maximum dose of 100 mg/m^2

- in the treatment of advanced breast cancer at doses of 60, 75 and 100 mg/m^2
- in the adjuvant therapy of breast cancer at a dose of 75 mg/m^2, in combination with doxorubicin and cyclophosphamide
- in the treatment of advanced non-small cell lung cancer after prior platinum-based chemotherapy, at a dose of 75 mg/m^2
- in the treatment of non-small cell lung cancer in patients who have not previously received chemotherapy for this condition, at a dose of 75 mg/m^2, in combination with cisplatin
- in the treatment of androgen independent (hormone refractory) metastatic prostate cancer, at a dose of 75 mg/m^2 every three weeks in combination with prednisone
- in the treatment of advanced gastric adenocarcinoma in patients who have not received prior chemotherapy for advanced disease, at a dose of 75 mg/m^2 in combination with cisplatin and fluorouracil

Monotherapy with TAXOTERE for Locally Advanced or Metastatic Breast Cancer After Failure of Prior Chemotherapy

TAXOTERE 100 mg/m^2: Adverse drug reactions occurring in at least 5% of patients are compared for three populations who received TAXOTERE administered at 100 mg/m^2 as a 1-hour infusion every 3 weeks: 2045 patients with various tumor types and normal baseline liver function tests; the subset of 965 patients with locally advanced or metastatic breast cancer, both previously treated and untreated with chemotherapy, who had normal baseline liver function tests; and an additional 61 patients with various tumor types who had abnormal liver function tests at baseline. These reactions were described using COSTART terms and were considered possibly or probably related to TAXOTERE. At least 95% of these patients did not receive hematopoietic support. The safety profile is generally similar in patients receiving TAXOTERE for the treatment of breast cancer and in patients with other tumor types (see Table 9).

Table 9-Summary of Adverse Events in Patients Receiving TAXOTERE at 100 mg/m^2

Adverse Event	All Tumor Types Normal LFTs* n=2045 %	All Tumor Types Elevated LFTs** n=61 %	Breast Cancer Normal LFTs* n=965 %
Hematologic			
Neutropenia			
<2000 cells/mm^3	95.5	96.4	98.5
<500 cells/mm^3	75.4	87.5	85.9
Leukopenia			
<4000 cells/mm^3	95.6	98.3	98.6
<1000 cells/mm^3	31.6	46.6	43.7
Thrombocytopenia			
<100,000 cells/mm^3	8.0	24.6	9.2
Anemia			
<11 g/dL	90.4	91.8	93.6
<8 g/dL	8.8	31.1	7.7

Adverse Event	All Tumor Types Normal LFTs* n=2045 %	All Tumor Types Elevated LFTs** n=61 %	Breast Cancer Normal LFTs* n=965 %
Febrile Neutropenia***	11.0	26.2	12.3
Septic Death	1.6	4.9	1.4
Non-Septic Death	0.6	6.6	0.6
Infections			
Any	21.6	32.8	22.2
Severe	6.1	16.4	6.4
Fever in Absence of Infection			
Any	31.2	41.0	35.1
Severe	2.1	8.2	2.2
Hypersensitivity Reactions			
Regardless of Premedication			
Any	21.0	19.7	17.6
Severe	4.2	9.8	2.6
With 3-day Premedication	n=92	n=3	n=92
Any	15.2	33.3	15.2
Severe	2.2	0	2.2
Fluid Retention			
Regardless of Premedication			
Any	47.0	39.3	59.7
Severe	6.9	8.2	8.9
With 3-day Premedication	n=92	n=3	n=92
Any	64.1	66.7	64.1
Severe	6.5	33.3	6.5
Neurosensory			
Any	49.3	34.4	58.3
Severe	4.3	0	5.5
Cutaneous			
Any	47.6	54.1	47.0
Severe	4.8	9.8	5.2
Nail Changes			
Any	30.6	23.0	40.5
Severe	2.5	4.9	3.7
Gastrointestinal			
Nausea	38.8	37.7	42.1
Vomiting	22.3	23.0	23.4

Adverse Event	All Tumor Types Normal LFTs* n=2045 %	All Tumor Types Elevated LFTs** n=61 %	Breast Cancer Normal LFTs* n=965 %
Diarrhea	38.7	32.8	42.6
Severe	4.7	4.9	5.5
Stomatitis			
Any	41.7	49.2	51.7
Severe	5.5	13.0	7.4
Alopecia	75.8	62.3	74.2
Asthenia			
Any	61.8	52.5	66.3
Severe	12.8	24.6	14.9
Myalgia			
Any	18.9	16.4	21.1
Severe	1.5	1.6	1.8
Arthralgia	9.2	6.6	8.2
Infusion Site Reactions	4.4	3.3	4.0

*Normal Baseline LFTs: Transaminases ≤ 1.5 times ULN or alkaline phosphatase ≤ 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN

**Elevated Baseline LFTs: SGOT and/or SGPT > 1.5 times ULN concurrent with alkaline phosphatase > 2.5 times ULN

***Febrile Neutropenia: ANC grade 4 with fever > 38°C with IV antibiotics and/or hospitalization

Hematologic: (see **WARNINGS)**.

Reversible marrow suppression was the major dose-limiting toxicity of TAXOTERE. The median time to nadir was 7 days, while the median duration of severe neutropenia (<500 cells/mm^3) was 7 days. Among 2045 patients with solid tumors and normal baseline LFTs, severe neutropenia occurred in 75.4% and lasted for more than 7 days in 2.9% of cycles.

Febrile neutropenia (<500 cells/mm^3 with fever > 38°C with IV antibiotics and/or hospitalization) occurred in 11% of patients with solid tumors, in 12.3% of patients with metastatic breast cancer, and in 9.8% of 92 breast cancer patients premedicated with 3-day corticosteroids.

Severe infectious episodes occurred in 6.1% of patients with solid tumors, in 6.4% of patients with metastatic breast cancer, and in 5.4% of 92 breast cancer patients premedicated with 3-day corticosteroids.

Thrombocytopenia (<100,000 cells/mm^3) associated with fatal gastrointestinal hemorrhage has been reported.

Hypersensitivity Reactions

Severe hypersensitivity reactions are discussed in the **BOXED WARNING, WARNINGS,** and **PRECAUTIONS** sections. Minor events, including flushing, rash with or without pruritus, chest tightness, back pain, dyspnea, drug fever, or chills, have been reported and resolved after discontinuing the infusion and appropriate therapy.

Fluid Retention: (see **BOXED WARNING**, **WARNINGS: Premedication Regimen**, and **PRECAUTIONS** sections).

Cutaneous

Severe skin toxicity is discussed in **PRECAUTIONS**. Reversible cutaneous reactions characterized by a rash including localized eruptions, mainly on the feet and/or hands, but also on the arms, face, or thorax, usually associated with pruritus, have been observed. Eruptions generally occurred within 1 week after TAXOTERE infusion, recovered before the next infusion, and were not disabling.

Severe nail disorders were characterized by hypo- or hyperpigmentation, and occasionally by onycholysis (in 0.8% of patients with solid tumors) and pain.

Neurologic: **(**see **PRECAUTIONS)**.

Gastrointestinal

Gastrointestinal reactions (nausea and/or vomiting and/or diarrhea) were generally mild to moderate. Severe reactions occurred in 3-5% of patients with solid tumors and to a similar extent among metastatic breast cancer patients. The incidence of severe reactions was 1% or less for the 92 breast cancer patients premedicated with 3-day corticosteroids.

Severe stomatitis occurred in 5.5% of patients with solid tumors, in 7.4% of patients with metastatic breast cancer, and in 1.1% of the 92 breast cancer patients premedicated with 3-day corticosteroids.

Cardiovascular

Hypotension occurred in 2.8% of patients with solid tumors; 1.2% required treatment. Clinically meaningful events such as heart failure, sinus tachycardia, atrial flutter, dysrhythmia, unstable angina, pulmonary edema, and hypertension occurred rarely. 8.1% (7/86) of metastatic breast cancer patients receiving TAXOTERE 100 mg/m^2 in a randomized trial and who had serial left ventricular ejection fractions assessed developed deterioration of LVEF by ≥ 10% associated with a drop below the institutional lower limit of normal.

Infusion Site Reactions

Infusion site reactions were generally mild and consisted of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis, extravasation, or swelling of the vein.

Hepatic

In patients with normal LFTs at baseline, bilirubin values greater than the ULN occurred in 8.9% of patients. Increases in SGOT or SGPT > 1.5 times the ULN, or alkaline phosphatase > 2.5 times ULN, were observed in 18.9% and 7.3% of patients, respectively. While on TAXOTERE, increases in SGOT and/or SGPT > 1.5 times ULN concomitant with alkaline phosphatase > 2.5 times ULN occurred in 4.3% of patients with normal LFTs at baseline. (Whether these changes were related to the drug or underlying disease has not been established.)

Hematologic and Other Toxicity: Relation to dose and baseline liver chemistry abnormalities.

Hematologic and other toxicity is increased at higher doses and in patients with elevated baseline liver function tests (LFTs). In the following tables, adverse drug reactions are compared for three populations: 730 patients with normal LFTs given TAXOTERE at 100 mg/m^2 in the randomized and single arm studies of metastatic breast cancer after failure of previous chemotherapy; 18 patients in these studies who had abnormal baseline LFTs (defined as SGOT and/or SGPT > 1.5

times ULN concurrent with alkaline phosphatase > 2.5 times ULN); and 174 patients in Japanese studies given TAXOTERE at 60 mg/m^2 who had normal LFTs (see Tables 10 and 11).

Table 10-Hematologic Adverse Events in Breast Cancer Patients Previously Treated with Chemotherapy Treated at TAXOTERE 100 mg/m^2 with Normal or Elevated Liver Function Tests or 60 mg/m^2 with Normal Liver Function Tests

	TAXOTERE 100 mg/m^2		TAXOTERE 60 mg/m^2
Adverse Event	**Normal LFTs* n=730 %**	**Elevated LFTs** n=18 %**	**Normal LFTs* n=174 %**
Neutropenia			
Any <2000 cells/mm^3	98.4	100	95.4
Grade 4 <500 cells/mm^3	84.4	93.8	74.9
Thrombocytopenia			
Any <100,000 cells/mm^3	10.8	44.4	14.4
Grade 4 <20,000 cells/mm^3	0.6	16.7	1.1
Anemia <11 g/dL	94.6	94.4	64.9
Infection* **			
Any	22.5	38.9	1.1
Grade 3 and 4	7.1	33.3	0
Febrile Neutropenia**			
By Patient	11.8	33.3	0
By Course	2.4	8.6	0
Septic Death	1.5	5.6	1.1
Non-Septic Death	1.1	11.1	0

*Normal Baseline LFTs: Transaminases ≤ 1.5 times ULN or alkaline phosphatase ≤ 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN

**Elevated Baseline LFTs: SGOT and/or SGPT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN

***Incidence of infection requiring hospitalization and/or intravenous antibiotics was 8.5% (n=62) among the 730 patients with normal LFTs at baseline; 7 patients had concurrent grade 3 neutropenia, and 46 patients had grade 4 neutropenia.

****Febrile Neutropenia: For 100 mg/m^2, ANC grade 4 and fever > 38°C with IV antibiotics and/or hospitalization; for 60 mg/m^2, ANC grade 3/4 and fever > 38.1°C

Table 11-Non-Hematologic Adverse Events in Breast Cancer Patients Previously Treated with Chemotherapy Treated at TAXOTERE 100 mg/m^2 with Normal or Elevated Liver Function Tests or 60 mg/m^2 with Normal Liver Function Tests

Adverse Event	TAXOTERE 100 mg/m^2		TAXOTERE 60 mg/m^2
	Normal LFTs* n=730 %	Elevated LFTs** n=18 %	Normal LFTs* n=174 %
Acute Hypersensitivity Reaction Regardless of Premedication			
Any	13.0	5.6	0.6
Severe	1.2	0	0
Fluid Retention* Regardless of Premedication**			
Any	56.2	61.1	12.6
Severe	7.9	16.7	0
Neurosensory			
Any	56.8	50	19.5
Severe	5.8	0	0
Myalgia	22.7	33.3	3.4
Cutaneous			
Any	44.8	61.1	30.5
Severe	4.8	16.7	0
Asthenia			
Any	65.2	44.4	65.5
Severe	16.6	22.2	0
Diarrhea			
Any	42.2	27.8	NA
Severe	6.3	11.1	
Stomatitis			
Any	53.3	66.7	19.0
Severe	7.8	38.9	0.6

*Normal Baseline LFTs: Transaminases ≤ 1.5 times ULN or alkaline phosphatase ≤ 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN

** Elevated Baseline Liver Function: SGOT and/or SGPT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN

***Fluid Retention includes (by COSTART): edema (peripheral, localized, generalized, lymphedema, pulmonary edema, and edema otherwise not specified) and effusion (pleural, pericardial, and ascites); no premedication given with the 60 mg/m^2 dose

NA = not available

In the three-arm monotherapy trial, TAX313, which compared TAXOTERE 60, 75 and 100 mg/m^2 in advanced breast cancer, the overall safety profile was consistent with the safety profile observed in previous TAXOTERE trials. Grade 3/4 or severe adverse events occurred in 49.0% of patients treated with TAXOTERE 60 mg/m^2 compared to 55.3% and 65.9% treated with 75 and 100 mg/m^2 respectively. Discontinuation due to adverse events was reported in 5.3% of patients treated with 60 mg/m^2 vs. 6.9% and 16.5% for patients treated at 75 and 100 mg/m^2 respectively. Deaths within 30 days of last treatment occurred in 4.0% of patients treated with 60 mg/m^2 compared to 5.3% and 1.6% for patients treated at 75 and 100 mg/m^2 respectively.

The following adverse events were associated with increasing docetaxel doses: fluid retention (26%, 38%, and 46% at 60, 75, and 100 mg/m^2 respectively), thrombocytopenia (7%, 11% and 12 % respectively), neutropenia (92%, 94%, and 97% respectively), febrile neutropenia (5%, 7%, and 14% respectively), treatment-related grade 3/ 4 infection (2%, 3%, and 7% respectively) and anemia (87%, 94%, and 97% respectively).

Combination Therapy with TAXOTERE in the Adjuvant Treatment of Breast Cancer

The following table presents treatment emergent adverse events (TEAEs) observed in 744 patients, who were treated with TAXOTERE 75 mg/m² every 3 weeks in combination with doxorubicin and cyclophosphamide (see Table 12).

Table 12-Clinically Important Treatment Emergent Adverse Events Regardless of Causal Relationship in Patients Receiving TAXOTERE in Combination with Doxorubicin and Cyclophosphamide (TAX 316).

	TAXOTERE 75 mg/m^2+ Doxorubicin 50 mg/m^2+ Cyclophosphamide 500 mg/m^2 (TAC) n=744 %		**Fluorouracil 500 mg/m^2+ Doxorubicin 50 mg/m^2+ Cyclophosphamide 500 mg/m^2 (FAC) n=736 %**	
Adverse Event	**Any**	**G 3/4**	**Any**	**G 3/4**
Anemia	91.5	4.3	71.7	1.6
Neutropenia	71.4	65.5	82.0	49.3
Fever in absence of infection	46.5	1.3	17.1	0.0
Infection	39.4	3.9	36.3	2.2
Thrombocytopenia	39.4	2.0	27.7	1.2
Febrile neutropenia	24.7	N/A	2.5	N/A
Neutropenic infection	12.1	N/A	6.3	N/A
Hypersensitivity reactions	13.4	1.3	3.7	0.1
Lymphedema	4.4	0.0	1.2	0.0

	TAXOTERE 75 mg/m^2+ Doxorubicin 50 mg/m^2+ Cyclophosphamide 500 mg/m^2 (TAC) n=744 %		Fluorouracil 500 mg/m^2+ Doxorubicin 50 mg/m^2+ Cyclophosphamide 500 mg/m^2 (FAC) n=736 %	
Adverse Event	**Any**	**G 3/4**	**Any**	**G 3/4**
	35.1	0.9	14.7	0.1
Fluid Retention*	26.9	0.4	7.3	0.0
Peripheral edema	12.9	0.3	8.6	0.3
Weight gain				
Neuropathy sensory	25.5	0.0	10.2	0.0
Neuro-cortical	5.1	0.5	6.4	0.7
Neuropathy motor	3.8	0.1	2.2	0.0
Neuro-cerebellar	2.4	0.1	2.0	0.0
Syncope	1.6	0.5	1.2	0.3
Alopecia	97.8	N/A	97.1	N/A
Skin toxicity	26.5	0.8	17.7	0.4
Nail disorders	18.5	0.4	14.4	0.1
Nausea	80.5	5.1	88.0	9.5
Stomatitis	69.4	7.1	52.9	2.0
Vomiting	44.5	4.3	59.2	7.3
Diarrhea	35.2	3.8	27.9	1.8
Constipation	33.9	1.1	31.8	1.4
Taste perversion	27.8	0.7	15.1	0.0
Anorexia	21.6	2.2	17.7	1.2
Abdominal Pain	10.9	0.7	5.3	0.0
Amenorrhea	61.7	N/A	52.4	N/A
Cough	13.7	0.0	9.8	0.1
Cardiac dysrhythmias	7.9	0.3	6.0	0.3
Vasodilatation	27.0	1.1	21.2	0.5
Hypotension	2.6	0.0	1.1	0.1
Phlebitis	1.2	0.0	0.8	0.0
Asthenia	80.8	11.2	71.2	5.6
Myalgia	26.7	0.8	9.9	0.0
Arthralgia	19.4	0.5	9.0	0.3
Lacrimation disorder	11.3	0.1	7.1	0.0
Conjunctivitis	5.1	0.3	6.9	0.1

* COSTART term and grading system for events related to treatment.

Of the 744 patients treated with TAC, 36.3% experienced severe TEAEs compared to 26.6 % of the 736 patients treated with FAC. Dose reductions due to hematologic toxicity occurred in 1% of cycles in the TAC arm versus 0.1% of cycles in the FAC arm. Six percent of patients treated with TAC discontinued treatment due to adverse events, compared to 1.1% treated with FAC; fever in the absence of infection and allergy being the most common reasons for withdrawal among TAC-treated patients. Two patients died in each arm within 30 days of their last study treatment; 1 death per arm was attributed to study drugs.

Fever and Infection

Fever in the absence of infection was seen in 46.5% of TAC-treated patients and in 17.1% of FAC-treated patients. Grade 3/4 fever in the absence of infection was seen in 1.3% and 0% of TAC- and FAC-treated patients respectively. Infection was seen in 39.4% of TAC-treated patients compared to 36.3% of FAC-treated patients. Grade 3/4 infection was seen in 3.9% and 2.2% of TAC-treated and FAC-treated patients respectively. There were no septic deaths in either treatment arm.

Gastrointestinal events

In addition to gastrointestinal events reflected in the table above, 7 patients in the TAC arm were reported to have colitis/enteritis/large intestine perforation vs. one patient in the FAC arm. Five of the 7 TAC-treated patients required treatment discontinuation; no deaths due to these events occurred.

Cardiovascular events

More cardiovascular events were reported in the TAC arm vs. the FAC arm; dysrhythmias, all grades (7.9% vs. 6.0%), hypotension, all grades (2.6% vs. 1.1%) and CHF (1.6% vs. 0.5%). One patient in each arm died due to heart failure.

Acute Myeloid Leukemia

Treatment-related acute myeloid leukemia (AML) is known to occur in patients treated with anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast cancer. AML occurs at a higher frequency when these agents are given in combination with radiation therapy. AML occurred in the adjuvant breast cancer trial (TAX316). The cumulative risk of developing treatment-related AML at 5 years in TAX316 was 0.4% for TAC-treated patients and 0.1% for FAC-treated patients. This risk of AML is comparable to the risk observed for other anthracyclines/cyclophosphamide containing adjuvant breast chemotherapy regimens.

Monotherapy with TAXOTERE for Unresectable, Locally Advanced or Metastatic NSCLC Previously Treated with Platinum-Based Chemotherapy

TAXOTERE 75 mg/m^2: Treatment emergent adverse drug reactions are shown in Table 13. Included in this table are safety data for a total of 176 patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who were treated in two randomized, controlled trials. These reactions were described using NCI Common Toxicity Criteria regardless of relationship to study treatment, except for the hematologic toxicities or otherwise noted.

Table 13-Treatment Emergent Adverse Events Regardless of Relationship to Treatment in Patients Receiving TAXOTERE as Monotherapy for Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy*

Adverse Event	TAXOTERE 75 mg/m^2 n=176 %	Best Supportive Care n=49 %	Vinorelbine/ Ifosfamide n=119 %
Neutropenia			
Any	84.1	14.3	83.2
Grade 3/4	65.3	12.2	57.1
Leukopenia			
Any	83.5	6.1	89.1
Grade 3/4	49.4	0	42.9
Thrombocytopenia			
Any	8.0	0	7.6
Grade 3/4	2.8	0	1.7
Anemia			
Any	91.0	55.1	90.8
Grade 3/4	9.1	12.2	14.3
Febrile Neutropenia**	6.3	NA†	0.8
Infection			
Any	33.5	28.6	30.3
Grade 3/4	10.2	6.1	9.2
Treatment Related Mortality	2.8	NA†	3.4
Hypersensitivity Reactions			
Any	5.7	0	0.8
Grade 3/4	2.8	0	0
Fluid Retention			
Any	33.5	ND††	22.7
Severe	2.8		3.4
Neurosensory			
Any	23.3	14.3	28.6
Grade 3/4	1.7	6.1	5.0
Neuromotor			
Any	15.9	8.2	10.1
Grade 3/4	4.5	6.1	3.4
Skin			
Any	19.9	6.1	16.8
Grade 3/4	0.6	2.0	0.8

Adverse Event	TAXOTERE 75 mg/m^2 n=176 %	Best Supportive Care n=49 %	Vinorelbine/ Ifosfamide n=119 %
Gastrointestinal			
Nausea			
Any	33.5	30.6	31.1
Grade 3/4	5.1	4.1	7.6
Vomiting			
Any	21.6	26.5	21.8
Grade 3/4	2.8	2.0	5.9
Diarrhea			
Any	22.7	6.1	11.8
Grade 3/4	2.8	0	4.2
Alopecia	56.3	34.7	49.6
Asthenia			
Any	52.8	57.1	53.8
Severe***	18.2	38.8	22.7
Stomatitis			
Any	26.1	6.1	7.6
Grade 3/4	1.7	0	0.8
Pulmonary			
Any	40.9	49.0	45.4
Grade 3/4	21.0	28.6	18.5
Nail Disorder			
Any	11.4	0	1.7
Severe***	1.1	0	0
Myalgia			
Any	6.3	0	2.5
Severe***	0	0	0
Arthralgia			
Any	3.4	2.0	1.7
Severe***	0	0	0.8
Taste Perversion			
Any	5.7	0	0
Severe***	0.6	0	0

*Normal Baseline LFTs: Transaminases ≤ 1.5 times ULN or alkaline phosphatase ≤ 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN

**Febrile Neutropenia: ANC grade 4 with fever > 38°C with IV antibiotics and/or hospitalization

***COSTART term and grading system

†Not Applicable; †† Not Done

Combination Therapy with TAXOTERE in Chemotherapy-Naïve Advanced Unresectable or Metastatic NSCLC

Table 14 presents safety data from two arms of an open label, randomized controlled trial (TAX326) that enrolled patients with unresectable stage IIIB or IV non-small cell lung cancer and no history of prior chemotherapy. Adverse reactions were described using the NCI Common Toxicity Criteria except where otherwise noted.

Table 14-Adverse Events Regardless of Relationship to Treatment in Chemotherapy-Naïve Advanced Non-Small Cell Lung Cancer Patients Receiving TAXOTERE in Combination with Cisplatin

Adverse Event	TAXOTERE 75 mg/m^2 + Cisplatin 75 mg/m^2 n=406 %	Vinorelbine 25 mg/m^2 + Cisplatin 100 mg/m^2 n=396 %
Neutropenia		
Any	91	90
Grade 3/4	74	78
Febrile neutropenia	5	5
Thrombocytopenia		
Any	15	15
Grade 3/4	3	4
Anemia		
Any	89	94
Grade 3/4	7	25
Infection		
Any	35	37
Grade 3/4	8	8
Fever In Absence Of Infection		
Any	33	29
Grade 3/4	< 1	1
Hypersensitivity Reaction*		
Any	12	4
Grade 3/4	3	< 1

Adverse Event	TAXOTERE 75 mg/m^2 + Cisplatin 75 mg/m^2 n=406 %	Vinorelbine 25 mg/m^2 + Cisplatin 100 mg/m^2 n=396 %
Fluid Retention**		
Any	54	42
All severe or life-threatening events	2	2
Pleural effusion		
Any	23	22
All severe or life-threatening events	2	2
Peripheral edema		
Any	34	18
All severe or life-threatening events	<1	<1
Weight gain		
Any	15	9
All severe or life-threatening events	<1	<1
Neurosensory		
Any	47	42
Grade 3/4	4	4
Neuromotor		
Any	19	17
Grade 3/4	3	6
Skin		
Any	16	14
Grade 3/4	<1	1
Nausea		
Any	72	76
Grade 3/4	10	17
Vomiting		
Any	55	61
Grade 3/4	8	16
Diarrhea		
Any	47	25
Grade 3/4	7	3
Anorexia**		
Any	42	40
All severe or life-threatening events	5	5
Stomatitis		
Any	24	21
Grade 3/4	2	1

Adverse Event	TAXOTERE 75 mg/m^2 + Cisplatin 75 mg/m^2 n=406 %	Vinorelbine 25 mg/m^2 + Cisplatin 100 mg/m^2 n=396 %
Alopecia		
Any	75	42
Grade 3	<1	0
Asthenia**		
Any	74	75
All severe or life-threatening events	12	14
Nail disorder**		
Any	14	<1
All severe events	<1	0
Myalgia**		
Any	18	12
All severe events	<1	<1

* Replaces NCI term "Allergy"
** COSTART term and grading system

Deaths within 30 days of last study treatment occurred in 31 patients (7.6%) in the docetaxel+cisplatin arm and 37 patients (9.3%) in the vinorelbine+cisplatin arm. Deaths within 30 days of last study treatment attributed to study drug occurred in 9 patients (2.2%) in the docetaxel+cisplatin arm and 8 patients (2.0%) in the vinorelbine+cisplatin arm.
The second comparison in the study, vinorelbine+cisplatin versus TAXOTERE+carboplatin (which did not demonstrate a superior survival associated with TAXOTERE, see **CLINICAL STUDIES** section) demonstrated a higher incidence of thrombocytopenia, diarrhea, fluid retention, hypersensitivity reactions, skin toxicity, alopecia and nail changes on the TAXOTERE+carboplatin arm, while a higher incidence of anemia, neurosensory toxicity, nausea, vomiting, anorexia and asthenia was observed on the vinorelbine+cisplatin arm.

Combination Therapy with TAXOTERE in Patients with Prostate Cancer

The following data are based on the experience of 332 patients, who were treated with TAXOTERE 75 mg/m² every 3 weeks in combination with prednisone 5 mg orally twice daily (see Table 15).

Table 15-Clinically Important Treatment Emergent Adverse Events (Regardless of Relationship) in Patients with Prostate Cancer who Received TAXOTERE in Combination with Prednisone (TAX 327)

	TAXOTERE 75 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=332 %		**Mitoxantrone 12 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=335 %**	
Adverse Event	**Any**	**G 3/4**	**Any**	**G 3/4**
Anemia	66.5	4.9	57.8	1.8
Neutropenia	40.9	32.0	48.2	21.7
Thrombocytopenia	3.4	0.6	7.8	1.2
Febrile neutropenia	2.7	N/A	1.8	N/A
Infection	32.2	5.7	20.3	4.2
Epistaxis	5.7	0.3	1.8	0.0
Allergic Reactions	8.4	0.6	0.6	0.0
Fluid Retention*	24.4	0.6	4.5	0.3
Weight Gain*	7.5	0.3	3.0	0.0
Peripheral Edema*	18.1	0.3	1.5	0.0
Neuropathy Sensory	30.4	1.8	7.2	0.3
Neuropathy Motor	7.2	1.5	3.0	0.9
Rash/Desquamation	6.0	0.3	3.3	0.6
Alopecia	65.1	N/A	12.8	N/A
Nail Changes	29.5	0.0	7.5	0.0
Nausea	41.0	2.7	35.5	1.5
Diarrhea	31.6	2.1	9.6	1.2
Stomatitis/Pharyngitis	19.6	0.9	8.4	0.0
Taste Disturbance	18.4	0.0	6.6	0.0
Vomiting	16.9	1.5	14.0	1.5
Anorexia	16.6	1.2	14.3	0.3
Cough	12.3	0.0	7.8	0.0
Dyspnea	15.1	2.7	8.7	0.9
Cardiac left ventricular function	9.6	0.3	22.1	1.2
Fatigue	53.3	4.5	34.6	5.1
Myalgia	14.5	0.3	12.8	0.9

	TAXOTERE 75 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=332 %		Mitoxantrone 12 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=335 %	
Adverse Event	**Any**	**G 3/4**	**Any**	**G 3/4**
Tearing	9.9	0.6	1.5	0.0
Arthralgia	8.1	0.6	5.1	1.2

*Related to treatment

Combination therapy with TAXOTERE in gastric adenocarcinoma

Data in the following table are based on the experience of 221 patients with advanced gastric adenocarcinoma and no history of prior chemotherapy for advanced disease, who were treated with TAXOTERE 75 mg/m^2 in combination with cisplatin and fluorouracil (see Table 16).

Table 16- Clinically Important Treatment Emergent Adverse Events Regardless of Relationship to Treatment in the Gastric Cancer Study

	TCF n=221		CF n=224	
Adverse Event	**Any %**	**G3/4 %**	**Any %**	**G3/4 %**
Anemia	96.8	18.2	93.3	25.6
Neutropenia	95.5	82.3	83.3	56.8
Fever in the absence of infection	35.7	1.8	22.8	1.3
Thrombocytopenia	25.5	7.7	39.0	13.5
Infection	29.4	16.3	22.8	10.3
Febrile neutropenia	16.4	N/A	4.5	N/A
Neutropenic infection	15.9	N/A	10.4	N/A
Allergic reactions	10.4	1.8	5.8	0
Fluid retention*	14.9	0	4.0	0.4
Edema*	13.1	0	3.1	0.4
Lethargy	62.9	21.3	58.0	17.9
Neurosensory	38.0	7.7	24.6	3.1
Neuromotor	8.6	3.2	7.6	2.7
Dizziness	15.8	4.5	8.0	1.8
Alopecia	66.5	5.0	41.1	1.3
Rash/itch	11.8	0.9	8.5	0.0
Nail changes	8.1	0.0	0.0	0.0

	TCF n=221		CF n=224	
Adverse Event	**Any %**	**G3/4 %**	**Any %**	**G3/4 %**
Skin desquamation	1.8	0.0	0.4	0.0
Nausea	73.3	15.8	76.3	18.8
Vomiting	66.5	14.9	73.2	18.8
Anorexia	50.7	13.1	54.0	11.6
Stomatitis	59.3	20.8	61.2	27.2
Diarrhea	77.8	20.4	49.6	8.0
Constipation	25.3	1.8	33.9	3.1
Esophagitis/dysphagia/ odynophagia	16.3	1.8	13.8	4.9
Gastrointestinal pain/cramping	11.3	1.8	7.1	2.7
Cardiac dysrythmias	4.5	2.3	2.2	0.9
Myocardial ischemia	0.9	0.0	2.7	2.2
Tearing	8.1	0	2.2	0.4
Altered hearing	6.3	0	12.5	1.8

Clinically important TEAEs were determined based upon frequency, severity, and clinical impact of the adverse event.
*Related to treatment

Post-marketing Experiences

The following adverse events have been identified from clinical trials and/or post-marketing surveillance. Because they are reported from a population of unknown size, precise estimates of frequency cannot be made.

Body as a whole: diffuse pain, chest pain, radiation recall phenomenon

Cardiovascular: atrial fibrillation, deep vein thrombosis, ECG abnormalities, thrombophlebitis, pulmonary embolism, syncope, tachycardia, myocardial infarction

Cutaneous: rare cases of bullous eruption such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis. Multiple factors may have contributed to the development of these effects. Severe hand and foot syndrome has been reported.

Gastrointestinal: abdominal pain, anorexia, constipation, duodenal ulcer, esophagitis, gastrointestinal hemorrhage, gastrointestinal perforation, ischemic colitis, colitis, intestinal obstruction, ileus, neutropenic enterocolitis and dehydration as a consequence to gastrointestinal events have been reported.

Hematologic: bleeding episodes

Hepatic: rare cases of hepatitis, sometimes fatal primarily in patients with pre-existing liver disorders, have been reported.

Neurologic: confusion, rare cases of seizures or transient loss of consciousness have been observed, sometimes appearing during the infusion of the drug.

Ophthalmologic: conjunctivitis, lacrimation or lacrimation with or without conjunctivitis. Excessive tearing which may be attributable to lacrimal duct obstruction has been reported. Rare cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during drug infusion and in association with hypersensitivity reactions have been reported. These were reversible upon discontinuation of the infusion.
Respiratory: dyspnea, acute pulmonary edema, acute respiratory distress syndrome, interstitial pneumonia. Pulmonary fibrosis has been rarely reported.
Urogenital: renal insufficiency

OVERDOSAGE

There is no known antidote for TAXOTERE overdosage. In case of overdosage, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

In two reports of overdose, one patient received 150 mg/m^2 and the other received 200 mg/m^2 as 1-hour infusions. Both patients experienced severe neutropenia, mild asthenia, cutaneous reactions, and mild paresthesia, and recovered without incident.

In mice, lethality was observed following single IV doses that were ≥154 mg/kg (about 4.5 times the recommended human dose on a mg/m^2 basis); neurotoxicity associated with paralysis, non-extension of hind limbs, and myelin degeneration was observed in mice at 48 mg/kg (about 1.5 times the recommended human dose on a mg/m^2 basis). In male and female rats, lethality was observed at a dose of 20 mg/kg (comparable to the recommended human dose on a mg/m^2 basis) and was associated with abnormal mitosis and necrosis of multiple organs.

DOSAGE AND ADMINISTRATION

Breast Cancer

The recommended dose of TAXOTERE is 60-100 mg/m^2 administered intravenously over 1 hour every 3 weeks.

In the adjuvant treatment of operable node-positive breast cancer, the recommended TAXOTERE dose is 75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 courses. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities (see also **Dosage Adjustments**).

Non-Small Cell Lung Cancer

For treatment after failure of prior platinum-based chemotherapy, TAXOTERE was evaluated as monotherapy, and the recommended dose is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m^2 in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment-related mortality in randomized, controlled trials (see **BOXED WARNING, WARNINGS** and **CLINICAL STUDIES** sections).

For chemotherapy-naïve patients, TAXOTERE was evaluated in combination with cisplatin. The recommended dose of TAXOTERE is 75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes every 3 weeks.

Prostate cancer

For hormone-refractory metastatic prostate cancer, the recommended dose of TAXOTERE is 75 mg/m^2 every 3 weeks as a 1 hour intravenous infusion. Prednisone 5 mg orally twice daily is administered continuously.

Gastric adenocarcinoma

For gastric adenocarcinoma, the recommended dose of TAXOTERE is 75 mg/m^2 as a 1 hour intravenous infusion, followed by cisplatin 75 mg/m^2, as a 1 to 3 hour intravenous infusion (both on day 1 only), followed by fluorouracil 750 mg/m^2 per day given as a 24-hour continuous intravenous infusion for 5 days, starting at the end of the cisplatin infusion. Treatment is repeated every three weeks. Patients must receive premedication with antiemetics and appropriate hydration for cisplatin administration. (See also **Dosage adjustments**).

Premedication Regimen

All patients should be premedicated with oral corticosteroids (see below for prostate cancer) such as dexamethasone 16 mg per day (*e.g.*, 8 mg BID) for 3 days starting 1 day prior to TAXOTERE administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions (see **BOXED WARNING**, **WARNINGS,** and **PRECAUTIONS** sections).

For hormone-refractory metastatic prostate cancer, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before the TAXOTERE infusion (see **WARNINGS**, and **PRECAUTIONS** sections).

Dosage Adjustments During Treatment

Breast Cancer

Patients who are dosed initially at 100 mg/m^2 and who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 for more than 1 week, or severe or cumulative cutaneous reactions during TAXOTERE therapy should have the dosage adjusted from 100 mg/m^2 to 75 mg/m^2. If the patient continues to experience these reactions, the dosage should either be decreased from 75 mg/m^2 to 55 mg/m^2 or the treatment should be discontinued. Conversely, patients who are dosed initially at 60 mg/m^2 and who do not experience febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, or severe peripheral neuropathy during TAXOTERE therapy may tolerate higher doses. Patients who develop ≥ grade 3 peripheral neuropathy should have TAXOTERE treatment discontinued entirely.

Combination Therapy with TAXOTERE in the Adjuvant Treatment of Breast Cancer

TAXOTERE in combination with doxorubicin and cyclophosphamide should be administered when the neutrophil count is ≥ 1,500 cells/mm^3. Patients who experience febrile neutropenia should receive G-CSF in all subsequent cycles. Patients who continue to experience this reaction should remain on G-CSF and have their TAXOTERE dose reduced to 60 mg/m^2. Patients who experience Grade 3 or 4 stomatitis should have their TAXOTERE dose decreased to 60 mg/m^2. Patients who experience severe or cumulative cutaneous reactions or moderate neurosensory

signs and/or symptoms during TAXOTERE therapy should have their dosage of TAXOTERE reduced from 75 to 60 mg/m². If the patient continues to experience these reactions at 60 mg/m², treatment should be discontinued.

Non-Small Cell Lung Cancer

Monotherapy with TAXOTERE for NSCLC Treatment After Failure of Prior Platinum-Based Chemotherapy

Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions, or other grade 3/4 non-hematological toxicities during TAXOTERE treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/m^2. Patients who develop ≥ grade 3 peripheral neuropathy should have TAXOTERE treatment discontinued entirely.

Combination Therapy with TAXOTERE for Chemotherapy-Naïve NSCLC

For patients who are dosed initially at TAXOTERE 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is <25,000 cells/mm^3 , in patients who experience febrile neutropenia, and in patients with serious non-hematologic toxicities, the TAXOTERE dosage in subsequent cycles should be reduced to 65 mg/m^2. In patients who require a further dose reduction, a dose of 50 mg/m^2 is recommended. For cisplatin dosage adjustments, see manufacturers' prescribing information.

Combination Therapy with TAXOTERE for Hormone-Refractory Metastatic Prostate Cancer

TAXOTERE should be administered when the neutrophil count is ≥ 1,500 cells/mm^3. Patients who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during TAXOTERE therapy should have the dosage of TAXOTERE reduced from 75 to 60 mg/m². If the patient continues to experience these reactions at 60 mg/m², the treatment should be discontinued.

Combination Therapy with TAXOTERE for gastric cancer

Patients treated with TAXOTERE in combination with cispatin and fluorouracil must receive antiemetics and appropriate hydration according to current institutional guidelines. In the study, G-CSF was recommended during the second and/or subsequent cycles in case of febrile neutropenia, or documented infection with neutropenia, or neutropenia lasting more than 7 days. If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the TAXOTERE dose should be reduced from 75 to 60 mg/m^2. If subsequent episodes of complicated neutropenia occur the TAXOTERE dose should be reduced from 60 to 45 mg/m^2. In case of Grade 4 thrombocytopenia the TAXOTERE dose should be reduced from 75 to 60 mg/m^2. Patients should not be retreated with subsequent cycles of TAXOTERE until neutrophils recover to a level > 1,500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3. Discontinue treatment if these toxicities persist. (See **WARNINGS** section).

Recommended dose modifications for gastrointestinal toxicities in patients treated with TAXOTERE in combination with cisplatin and fluorouracil are shown in table 17.

Table 17- Recommended Dose Modifications for Gastrointestinal Toxicities in Patients Treated with TAXOTERE in Combination with Cisplatin and Fluorouracil

Toxicity	Dosage adjustment
Diarrhea grade 3	First episode: reduce 5-FU dose by 20%. Second episode: then reduce TAXOTERE dose by 20%.
Diarrhea grade 4	First episode: reduce TAXOTERE and 5-FU doses by 20%. Second episode: discontinue treatment.
Stomatitis grade 3	First episode: reduce 5-FU dose by 20%. Second episode: stop 5-FU only, at all subsequent cycles. Third episode: reduce TAXOTERE dose by 20%.
Stomatitis grade 4	First episode: stop 5-FU only, at all subsequent cycles. Second episode: reduce TAXOTERE dose by 20%.

Liver dysfunction:
In case of AST/ALT > 2.5 to ≤ 5 x UNL and AP ≤ 2.5 x UNL, or AST/ALT > 1.5 to ≤ 5 x UNL and AP > 2.5 to ≤ 5 x UNL, TAXOTERE should be reduced by 20%.
In case of AST/ALT > 5 x UNL and/or AP > 5 x UNL TAXOTERE should be stopped

The dose modifications for cisplatin and fluorouracil in the gastric cancer study are provided below:

Cisplatin dose modifications and delays

Peripheral neuropathy: A neurological examination should be performed before entry in to the study, and then at least every 2 cycles and at the end of treatment. In the case of neurological signs or symptoms, more frequent examinations should be performed and the following dose modifications can be made according to NCIC-CTC grade:
• Grade 2: Reduce cisplatin dose by 20%.
• Grade 3: Discontinue treatment.

Ototoxicity: In the case of grade 3 toxicity, discontinue treatment.

Nephrotoxicity: In the event of a rise in serum creatinine ≥ grade 2 (> 1.5 x normal value) despite adequate rehydration, CrCl should be determined before each subsequent cycle and the following dose reductions should be considered (see Table 18):

Table 18 – Dose Reductions for Evaluation of Creatinine Clearance

Creatinine clearance result before next cycle	Cisplatin dose next cycle
CrCl ≥60 mL/min	Full dose of cisplatin was given. CrCl was to be repeated before each treatment cycle.
CrCl between 40 and 59 mL/min	Dose of cisplatin was reduced by 50% at subsequent cycle. If CrCl was >60 mL/min at end of cycle, full cisplatin dose was reinstituted at the next cycle. If no recovery was observed, then cisplatin was omitted from the next treatment cycle.
CrCl <40 mL/min7	Dose of cisplatin was omitted in that treatment cycle only. If CrCl was still <40 mL/min at end of cycle, cisplatin was discontinued. If CrCl was >40 and <60 mL/min at end of cycle, a 50% cisplatin dose was given at the next cycle. If CrCl was >60 mL/min at end of cycle, full cisplatin dose was given at the next cycle.

CrCl = Creatinine clearance

Fluorouracil dose modifications and treatment delays

For diarrhea and stomatitis, see Table 17.

In the event of grade 2 or greater plantar-palmar toxicity, fluorouracil should be stopped until recovery. The fluorouracil dosage should be reduced by 20%.

For other greater than grade 3 toxicities, except alopecia and anemia, chemotherapy should be delayed (for a maximum of 2 weeks from the planned date of infusion) until resolution to grade ≤ 1 and then recommenced, if medically appropriate.

For other cisplatin and fluorouracil dosage adjustments, also refer to the manufacturers' prescribing information.

Special Populations

Hepatic Impairment: Patients with bilirubin > ULN should generally not receive TAXOTERE. Also, patients with SGOT and/or SGPT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN should generally not receive TAXOTERE.

Children: The safety and effectiveness of docetaxel in pediatric patients below the age of 16 years have not been established.

Elderly: See **Precautions, Geriatric Use**. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients.

PREPARATION AND ADMINISTRATION

Administration Precautions

TAXOTERE is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing TAXOTERE solutions. The use of gloves is recommended. Please refer to **Handling and Disposal** section.

If TAXOTERE Injection Concentrate, initial diluted solution, or final dilution for intravenous infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If TAXOTERE Injection Concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

Contact of the TAXOTERE concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final TAXOTERE dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

TAXOTERE Injection Concentrate requires two dilutions prior to administration. Please follow the preparation instructions provided below. **Note:** Both the TAXOTERE Injection Concentrate and the diluent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the **entire** contents of the accompanying diluent, there is an initial diluted solution containing 10 mg/mL docetaxel.

The table below provides the fill range of the diluent, the approximate extractable volume of diluent when the entire contents of the diluent vial are withdrawn, and the concentration of the initial diluted solution for TAXOTERE 20 mg and TAXOTERE 80 mg (see table 19).

Table 19 – Initial Dilution of TAXOTERE Injection Concentrate

Product	Diluent 13% (w/w) ethanol in water for injection Fill Range (mL)	Approximate extractable volume of diluent when entire contents are withdrawn (mL)	Concentration of the initial diluted solution (mg/mL docetaxel)
Taxotere® 20 mg/0.5 mL	1.88 – 2.08 mL	1.8 mL	10 mg/mL
Taxotere® 80 mg/2 mL	6.96 – 7.70 mL	7.1 mL	10 mg/mL

Preparation and Administration

A. Initial Diluted Solution

1. TAXOTERE vials should be stored between 2 and 25°C (36 and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of TAXOTERE Injection Concentrate and diluent (13% ethanol in water for injection) vials to stand at room temperature for approximately 5 minutes.
2. Aseptically withdraw the **entire** contents of the appropriate diluent vial (approximately 1.8 mL for TAXOTERE 20 mg and approximately 7.1 mL for TAXOTERE 80 mg) into a syringe by partially inverting the vial, and transfer it to the appropriate vial of TAXOTERE Injection

Concentrate. **If the procedure is followed as described, an initial diluted solution of 10 mg docetaxel/mL will result.**

3. Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.
4. The initial diluted TAXOTERE solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

   The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

B. Final Dilution for Infusion

1. Aseptically withdraw the required amount of initial diluted TAXOTERE solution (10 mg docetaxel/mL) with a calibrated syringe and inject into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL.

   If a dose greater than 200 mg of TAXOTERE is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL TAXOTERE is not exceeded.
2. Thoroughly mix the infusion by manual rotation.
3. As with all parenteral products, TAXOTERE should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the TAXOTERE initial diluted solution or final dilution for intravenous infusion is not clear or appears to have precipitation, these should be discarded.

The final TAXOTERE dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature and lighting conditions.

Stability

TAXOTERE infusion solution, if stored between 2 and 25°C (36 and 77°F) is stable for 4 hours. Fully prepared TAXOTERE infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour i.v. administration).

HOW SUPPLIED

TAXOTERE Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, Diluent (13% ethanol in water for injection) vial. The following strengths are available:

TAXOTERE 80 mg/2 ML (NDC 0075-8001-80)

TAXOTERE (docetaxel) Injection Concentrate 80 mg/2 mL: 80 mg docetaxel in 2 mL polysorbate 80 and Diluent for TAXOTERE 80 mg (13% (w/w) ethanol in water for injection). Both items are in a blister pack in one carton.

TAXOTERE 20 mg/0.5 ML (NDC 0075-8001-20)

TAXOTERE (docetaxel) Injection Concentrate 20 mg/0.5 mL: 20 mg docetaxel in 0.5 mL polysorbate 80 and diluent for TAXOTERE 20 mg (13% (w/w) ethanol in water for injection). Both items are in a blister pack in one carton.

Storage

Store between 2 and 25°C (36 and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published[1-7]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

1.OSHA Work-Practice Guidelines for Controlling Occupational Exposure to Hazardous Drugs. *Am J Health-Syst Pharm.* 1996; 53: 1669-1685.

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4.Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.

5.National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffry, Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.

6.Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Austr*. 1983; 426-428.

7.Jones, RB, et al. Safe Handling of Chemotherapeutic Agents: A Report from the Mt. Sinai Medical Center. *CA-A Cancer Journal for Clinicians.* 1983; Sept/Oct: 258-263.

Prescribing Information as of XXXX200X

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-449/S-035

SUMMARY REVIEW

Division Director Summary Review of a New Drug Application

NDA: 20-449/S-035
Drug: Taxotere® (docetaxel) Injection Concentrate
Applicant: Aventis Pharmaceuticals Inc.
Date: March 17, 2006

This efficacy supplement requests approval of the following indication: "TAXOTERE in combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease."

Summary of Efficacy and Safety

A single, multicenter, open-label, randomized trial was conducted to evaluate the safety and efficacy of docetaxel for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who had not received prior chemotherapy for advanced disease. A total of 445 patients with KPS>70, were treated with either TCF (docetaxel 75 mg/m^2 IV on day 1, cisplatin 75 mg/m^2 IV on day 1 and fluorouracil 750 mg/m^2/day continuous IV infusion for 5 days) or CF (cisplatin 100 mg/m^2 IV on day 1 and fluorouracil 1000 mg/m^2/day continuous IV infusion for 5 days). The length of a treatment cycle was 3 weeks for the TCF arm and 4 weeks for the CF arm. The demographic characteristics were balanced between the two treatment arms. The median age was 55 years, 71% were male, 71% were Caucasian, 24% were 65 years of age or older, 19% had a prior curative surgery and 12% had palliative surgery. The median number of cycles administered per patient was 6 (with a range of 1-16) for the TCF arm compared to 4 (with a range of 1-12) for the CF arm.

Time to progression (TTP) was the primary endpoint and was defined as time from randomization to disease progression or death from any cause within 12 weeks of the last evaluable tumor assessment or within 12 weeks of the first infusion of study drugs for patients with no evaluable tumor assessment after randomization. The hazard ratio (HR) for TTP was 1.47 (CF/TCF, 95% CI: 1.19-1.83) with a significantly longer TTP (p=0.0004) in the TCF arm. Approximately 75% of patients had died at the time of this analysis. Overall survival was significantly longer (p=0.0201) in the TCF arm with a HR of 1.29 (95% CI: 1.04-1.61). Efficacy results are summarized in Table 8 and Figures 6 and 7 from the agreed upon package insert.

Table 8-Efficacy of TAXOTERE in the treatment of patients with gastric adenocarcinoma

Endpoint	**TCF n=221**	**CF n=224**
Median TTP (months)	5.6	3.7
(95%CI)	(4.86-5.91)	(3.45-4.47)
Hazard ratio†	1.47	
(95%CI)	(1.19-1.83)	
*p-value	0.0004	
Median survival (months)	9.2	8.6
(95%CI)	(8.38-10.58)	(7.16-9.46)
Hazard ratio†	1.29	
(95%CI)	(1.04-1.61)	
*p-value	0.0201	
Overall Response Rate (CR+PR) (%)	36.7	25.4
p-value	0.0106	

*Unstratified logrank test

†For the hazard ratio (CF/TCF), values greater than 1.00 favor the TAXOTERE arm.

Subgroup analyses were consistent with the overall results across age, gender and race.

Figure 6 - Gastric Cancer Study (TAX325) Time to Progression K-M Curve

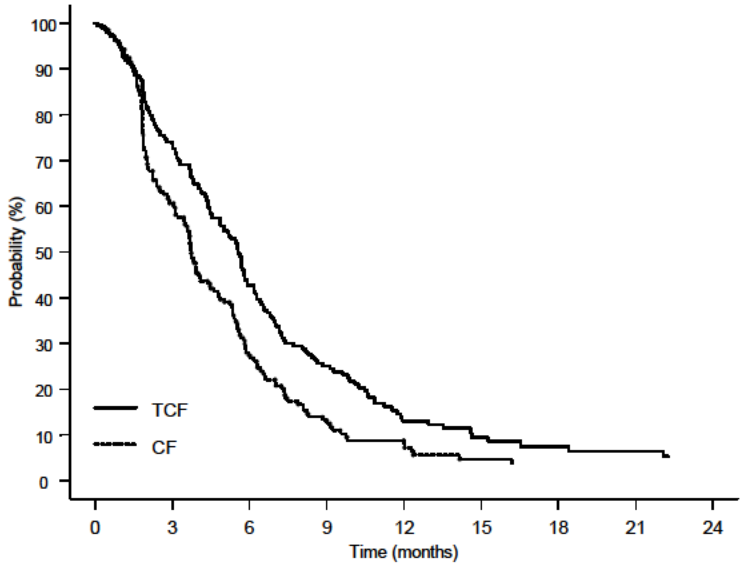
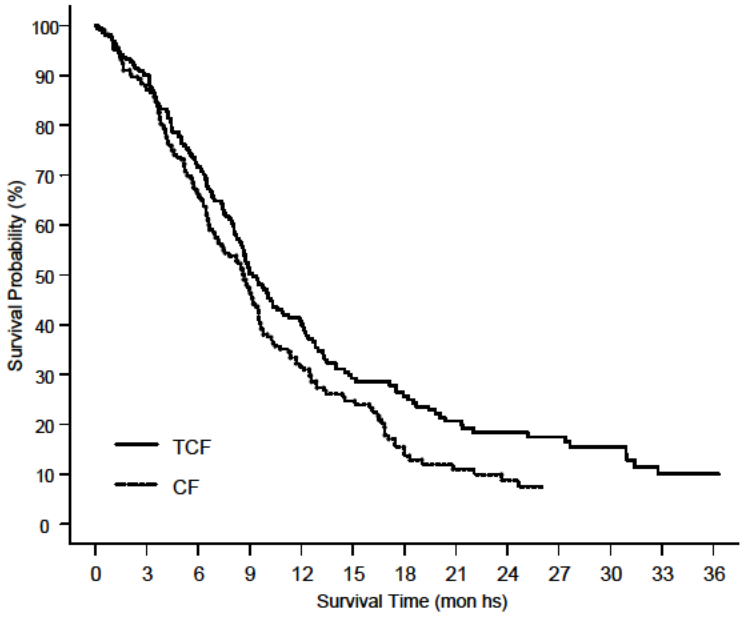


Figure 7 - Gastric Cancer Study (TAX325) Survival K-M Curve



Clinically important treatment-emergent adverse events are shown in the table below.

Table 16- Clinically Important Treatment Emergent Adverse Events Regardless of Relationship to Treatment in the Gastric Cancer Study

	TCF n=221		CF n=224	
ADVERSE EVENT	**Any %**	**G3/4 %**	**Any %**	**G3/4 %**
Anemia	96.8	18.2	93.3	25.6
Neutropenia	95.5	82.3	83.3	56.8
Fever in the absence of infection	35.7	1.8	22.8	1.3
Thrombocytopenia	25.5	7.7	39.0	13.5
Infection	29.4	16.3	22.8	10.3
Febrile neutropenia	16.4	N/A	4.5	N/A
Neutropenic infection	15.9	N/A	10.4	N/A
Allergic reactions	10.4	1.8	5.8	0
Fluid retention*	14.9	0	4.0	0.4
Edema*	13.1	0	3.1	0.4
Lethargy	62.9	21.3	58.0	17.9
Neurosensory	38.0	7.7	24.6	3.1
Neuromotor	8.6	3.2	7.6	2.7
Dizziness	15.8	4.5	8.0	1.8
Alopecia	66.5	5.0	41.1	1.3
Rash/itch	11.8	0.9	8.5	0.0
Nail changes	8.1	0.0	0.0	0.0
Skin desquamation	1.8	0.0	0.4	0.0
Nausea	73.3	15.8	76.3	18.8
Vomiting	66.5	14.9	73.2	18.8
Anorexia	50.7	13.1	54.0	11.6
Stomatitis	59.3	20.8	61.2	27.2
Diarrhea	77.8	20.4	49.6	8.0
Constipation	25.3	1.8	33.9	3.1
Esophagitis/dysphagia/odynophagia	16.3	1.8	13.8	4.9
Gastrointestinal pain/cramping	11.3	1.8	7.1	2.7
Cardiac dysrythmias	4.5	2.3	2.2	0.9
Myocardial ischemia	0.9	0.0	2.7	2.2
Tearing	8.1	0	2.2	0.4
Altered hearing	6.3	0	12.5	1.8

***Related to treatment**

Compared to patients receiving CF, patients receiving TCF had more neutropenia, fever, infection, febrile neutropenia, neutropenic infection, allergic reactions, fluid retention or peripheral edema, neurosensory toxicity, dizziness, alopecia, rash, nail changes, diarrhea, esophagitis/dysphagia/odynophagia, gastrointestinal pain or cramping, and tearing than patients receiving CF. Eighty two percent of patients on the TCF arm had grade 3 or 4 neutropenia and 32% of patients had febrile neutropenia or neutropenic infection. The most frequent causes for treatment discontinuation were GI toxicities, flu-like symptoms and neurosensory toxicity. Compared to patients receiving TCF, patients receiving CF had more thrombocytopenia, vomiting, anorexia, constipation, and altered hearing.

Clinical Review

The Clinical Review by Dr. Qin Ryan made the following recommendation on regulatory action.

> We recommend the approval of Taxotere in combination with cisplatin and fluorouracil for the following indication:
>
> "For the treatment of patients with advanced gastric adenocarcinoma, including (b) (4)
>
> This recommendation is based on the review of the results of the sNDA, discussion within the divisions and with an Oncology Drug Advisory Committee member based on the improvement in Time to Tumor Progression supported by an improvement in overall survival and an acceptable toxicity profile.

Statistical Review and Evaluation

The Statistical Review and Evaluation by Dr. Shenghui Tang provided the following conclusions and recommendations.

> In this reviewer's opinion the study results from the submitted single, randomized, open-label, parallel group, multicenter, multinational phase III study (Study 325a), support the claim of efficacy of Taxotere (docetaxel) in combination with cisplatin and 5-fluorouracil for the treatment of patients with advanced gastric adenocarcinoma with respect to time to progression (TTP) which included death from any cause. The Taxotere (docetaxel) in combination with cisplatin and 5-fluorouracil demonstrated a TTP advantage over the combination of cisplatin and 5-fluorouracil in this clinical study. Whether the endpoint and the size of the effect on this endpoint are adequate for approval is a clinical decision.

Clinical Inspection Summary

The single largest accruing site in the U.S. was inspected. The Clinical Inspection Summary provides the following overall assessment of findings and general recommendations.

> Observations noted above are based on a preliminary EIR and communications from the field investigator. No Form FDA 483 was issued upon completion of the inspection. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.
>
> The site inspected, that of Dr. Jaffer Ajani/MD Anderson Cancer Center, adhered to the applicable regulations governing the conduct of clinical investigations. The inspection of documents support that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol and signed informed consent forms. Therefore, the data submitted to the agency under NDA 20449/S-035 in support of a new indication appear to be acceptable.
>
> Observations noted above are based on the preliminary EIR and communications from field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.
>
> Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the EIR and the supporting inspection evidence and exhibits.

Study Endpoint Review

The Study Endpoint Review by William Pierce and Laurie Burke provided the following conclusions and key findings.

> Study 325A results fail to provide convincing evidence of treatment benefit favoring the Taxotere treatment arm of the study for the general concept of health-related quality of life (HRQL).[1] The EORTC QLQ-C30 was not adequately developed to measure any of the specific concepts implied by any of the domain or item scores generated by the EORTC QLQ-C30.
>
> - Study XRP6976E/325A findings are based on unblinded treatment comparisons that do not adequately control for bias in favor of the experimental treatment.
> - Results from EORTC QLQ-C30 Global Quality of Life domain or the Karnofsky Performance Scale (KPS) should not be used to support labeling claims for time to improvement in HRQL, "time to definitive deterioration of global health status" or worsening of performance status because there is no evidence that these measures are sufficiently developed to measure those general concepts nor that the instruments are

sensitive enough to detect changes that patients would considered meaningful to deterioration in HRQL or physical function, respectively.

Conclusions and recommendations are based on the sources available for review. The Sponsor provided limited information for review. Additional information readily retrieved from PubMed and previous SEALD consults also was reviewed, when available, to better understand the development and validation of the proposed endpoint measures.

Telecon with ODAC Member

The clinical team discussed the application with Dr. James Doroshow on March 2, 2006. Dr. Doroshow concurred with the Division's decision to approve the application.

Consultation from the Division of Biologic Oncology Products

(b) (4)

[redacted]

Clinical Pharmacology/Biopharmaceutics Review

The Clinical Pharmacology/Biopharmaceutics Review by Dr. Sophia Abraham made the following recommendation.

> The Supplemental NDA 20-449/SE1-035 submitted for the use of Taxotere in combination with cisplatin and 5-fluorouracil for the treatment of patients with advanced gastric adenocarcinoma is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). The following statement that was included by the Applicant in the current package insert for Taxotere is also acceptable to OCPB:
>
> **The combined administration of docetaxel, cisplatin and 5-fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug.**
>
> No action is indicated.

Chemistry Review

The Chemistry Review by Dr. Liang Zhou recommended approval noting that the information provided to claim categorical exclusion under 21 CFR Part 25.31(b) was found to be acceptable.

DDMAC Consultation

The DDMAC consultation by Joseph Grillo had several recommendations regarding the draft labeling which were considered during the labeling meetings.

Conclusion

I concur with the review team's recommendation for approval of this efficacy supplement.

Robert L. Justice, M.D., M.S.
Acting Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research

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

/s/

Robert Justice
3/17/2006 04:49:47 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-449/S-035

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA Supplement
Submission Number	20449
Submission Code	S35
Letter Date	September 23, 2005
Stamp Date	October 6, 2005
PDUFA Goal Date	March 26, 2006

Reviewer Name Qin Ryan, MD, PhD
Team Leader Amna Ibrahim
Review Completion Date March 16, 2006

Established Name	Taxotere
(Proposed) Trade Name	Taxotere
Therapeutic Class	Antineoplastic
Applicant	Sanofi Aventis
Priority Designation	P
Formulation	IV

Proposed Dosing Regimen: Taxotere 75 mg/m^2 IV over 1 hour, day 1 in combination with Cisplatin 75 mg/m^2 IV over 1-3 hours, day1 and 5-FU 750 mg/m^2/day CIV over 5 days in a 21 days cycle.

Proposed Indication: Taxotere in combination with cisplatin and 5-FU indicated for the treatment of patients with advanced gastric adenocarcinoma.

Intended Population: Patients with advanced gastric or gastroesophageal junction adenocarcinoma, who have not received chemotherapy for advanced gastric cancer.

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

We recommend the approval of Taxotere in combination with cisplatin and fluorouracil for the following indication:

"For the treatment of patients with advanced gastric adenocarcinoma, including (b) (4)

This recommendation is based on the review of the results of the sNDA, discussion within the divisions and with an Oncology Drug Advisory Committee member based on the improvement in Time to Tumor Progression supported by an improvement in overall survival and an acceptable toxicity profile.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 SUMMARY OF CLINICAL FINDINGS

1.3.1 Brief Overview of Clinical Program

A single trial, TAX 325 has been submitted to support the efficacy and safety for this sNDA. It is a randomized multicenter, open-label phase II/III trial that was conducted in patients with locally advanced or metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who had not received prior chemotherapy for advanced gastric cancer. The efficacy and safety of the phase III part (TAX325a) of the trial provides the regulatory basis for the efficacy and safety for the recommendations and will be described further.

Patients who had received prior surgery and radiation were eligible. Prior adjuvant or neoadjuvant chemotherapy was considered acceptable (except for taxanes and over 300 mg/m^2 of cisplatin) if administered more than 12 months earlier. The phase III part was stratified by liver involvement (yes/no), gastrectomy (yes/no) measurable or evaluable only disease, and weight loss ($\leq$ 5% / > 5%). The investigational arm was Taxotere 75 mg/m² in combination with cisplatin 75 mg/m² and 5-FU 750 mg/m² for 5 days administered every 3 weeks. The control arm was cisplatin 100 mg/m² and 5-FU 1000 mg/m² x 5 days, every 4 weeks. The length of a treatment cycle was 3 weeks for the TCF arm and 4 weeks for the CF arm.

Table 1: Treatment arms of the phase III part of TAX325

TCF	Docetaxel (T): 75 mg/m^2 IV administered first as a 1-hour infusion, day 1 every 3 weeks. Cisplatin (C): 75 mg/m^2, I.V. as a 3 to 4-hour infusion, day 1 every 3 weeks. 5-FU (F): 750 mg/m^2 CIV, day 1-5 every 3 weeks after the end of CDDP administration
CF	Cisplatin (C): 100 mg/m^2, day 1 as a 3 to 4-hour infusion every 4 weeks 5-FU (F): 1000 mg/m^2 CIV, day 1-5 every 4 weeks

Time to progression (TTP) was the primary endpoint and was defined as time from randomization to disease progression or death from any cause within 12 weeks of the last evaluable tumor assessment or within 12 weeks of the first infusion of study drugs for patients with no evaluable tumor assessment after randomization. Progressions were based on measurable disease, or in case of evaluable/non-evaluable disease on estimated increase in size of lesion, new lesion or clinical progression based on an external response review committee (ERRC). The ERRC could determine disease progressions based on clinical and biological information obtained from the investigator. Overall survival and response rate, quality of life were among the secondary endpoints.

A total of 457 subjects were randomized to the phase III part of the study in 39 months (November 1999 through January 2003): 227 subjects into the TCF treatment group and

230 subjects into the CF treatment group. The study was conducted in 72 centers and 16 countries. Of ITT population (n = 457), twelve patients (6 in each arm) who did not receive any treatment after randomization were excluded from the final analysis population (FAP, n = 445). The demographic characteristics were balanced between the two treatment arms. The median age was 55 years, 71% were male, 71% were caucasian, 24% were 65 years of age or older, 19% had a prior curative surgery and 12% had palliative surgery. The median number of cycles administered per patient was 6 (with a range of 1-16) for the TCF arm compared to 4 (with a range of 1-12) for the CF arm.

1.3.2 Efficacy

The main efficacy findings are summarized in the table below:

Table 2: TAX 325a Time to Tumor Progression, Overall Survival and Response Rates in the Full Analysis Population (FAP)

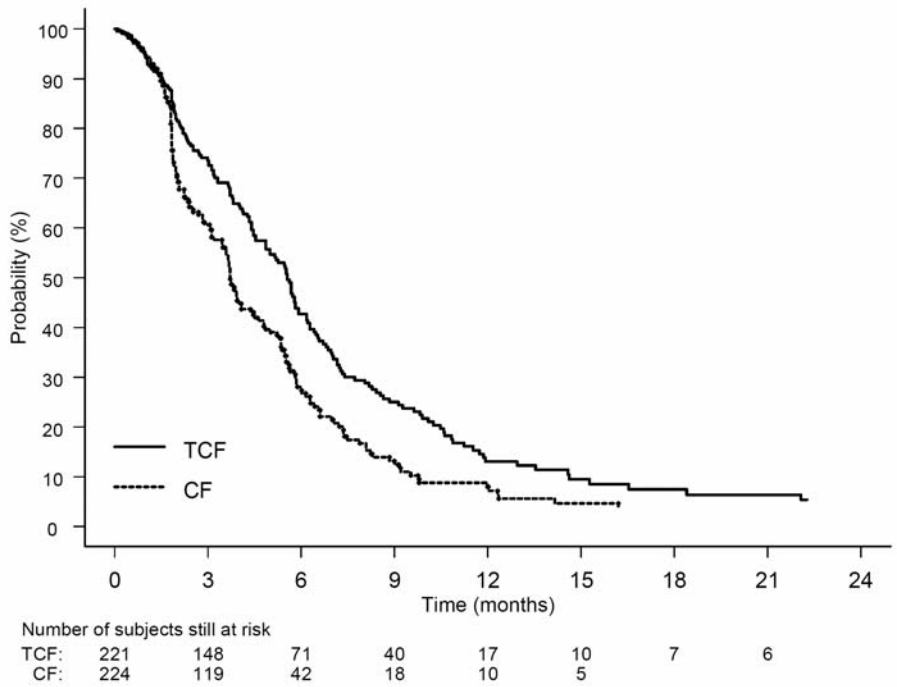
Endpoint	**TCF n=221**	**CF n=224**
Median TTP (months)	5.6	3.7
(95%CI)	(4.86-5.91)	(3.45-4.47)
Hazard ratio	1.473	
(95%CI)	(1.189-1.825)	
*p-value	0.0004	
Median survival (months)	9.2	8.6
(95%CI)	(8.38-10.58)	(7.16-9.46)
Hazard ratio	1.293	
(95%CI)	(1.041-1.606)	
*p-value	0.0201	
Overall Response Rate (CR+PR) (%)	36.7	25.4
p-value	0.0106	

*Unstratified logrank test

Approximately 75% patients had progressed or died within 12 weeks of the last tumor evaluation by the cut-off date. As shown in figure 1, the hazard ratio (HR) for TTP was 1.47 (CF/TCF, 95% CI: 1.19-1.83) with a significantly longer TTP (p=0.0004) in the TCF arm. Several sensitivity analyses using varying definitions of TTP were performed, all with similar results. Twenty one patients (TCF: n=11, CF: n=10) in the primary analysis were based on clinical progressions. A sensitivity analysis with these 21 patients censored at the last date of tumor assessment yielded results consistent with the primary analysis. Overall survival was significantly longer (p=0.0201) in the TCF arm with a HR of 1.29 (95% CI: 1.04-1.61).

TTP in the FAP was prolonged significantly in favor of TCF compared to CF with a hazard ratio of 1.473 [95% C.I.: 1.189-1.825] and p = 0.0004 (unstratified log rank). A 2-month improvement in the median TTP (from 3.7 months for the CF group to 5.6 months for the TCF group) was also noted. The end of study result, as well as the protocol-specified "325 events" result both met the nominal 0.0487 boundary set for the final analysis and confirms this conclusion. The multivariable analyses indicated that the lack of influence of the imbalance in the distribution of various baseline prognostic factors (prior gastrectomy, disease measurability, liver metastasis, weight loss, KPS, primary tumor site and age).

Figure 1: Time to progression (FAP)



TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population
Data source: TAX 325a study report, Appendix C. 2.1, Figure 4.15.

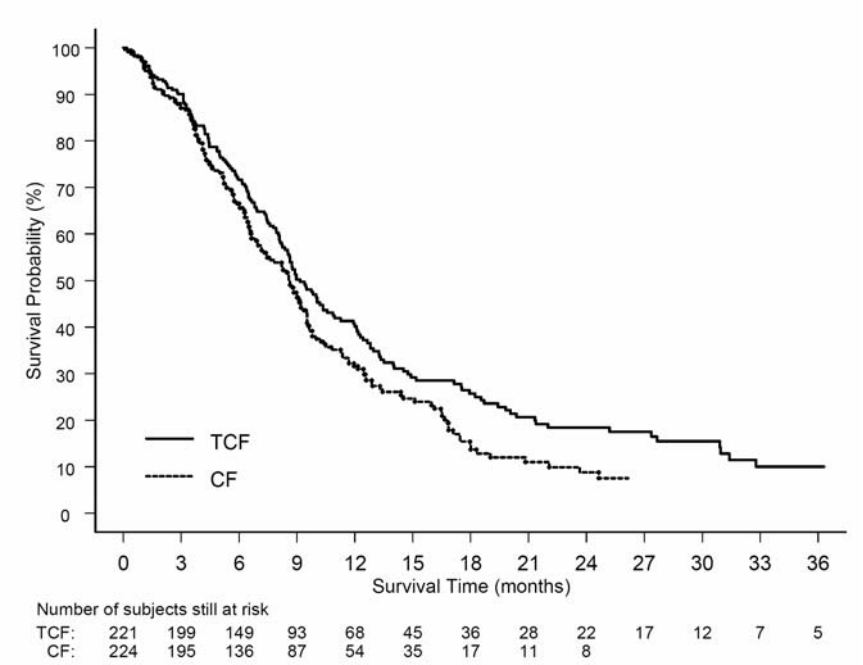
Several sensitivity analyses were conducted by the applicant and the FDA statistical reviewer. These were TTP (defined as tumor progressions only, non-progressors censored at last tumor evaluation) and PFS (defined as progressions or deaths censored at the last tumor assessments for non-progressors), both in the FAP and ITT populations. The results of these analyses remained in favor of the Taxotere combination arm.

Table 3: FDA's Unstratified Standard TTP and PFS Analyses

Analysis	Population	P value	HR (CF/TCF)	95% CI
TTP	FAP	0.0002	1.526	1.2163-1.9145
	ITT	0.0002	1.534	1.2229-1.9235
PFS	FAP	0.0039	1.343	1.0975-1.6427
	ITT	0.0096	1.2990	1.0644-1.5855

Overall survival (OS) was statistically significant in the TCF arm (log-rank test, P= 0.02, Table 1 and Figure 2) for the FAP population and a strong trend was observed in favor of the TCF arm for ITT population (Table 1). The median survival was 9.2 months in the TCF arm, compared with 8.6 months on the CF arm for the FAP. This improvement in OS was observed even though more patients received post-study chemotherapy in the control arm (CF group: 41.1% including 8.5% who received Taxotere) vs. TCF-group (32.1%).

Figure 2: Overall survival (FAP)



TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population
Data source: TAX 325a study report, Appendix C. 2.1, Figure 4.33.

Tumor Response Rate was higher in the TCF group compared to the CF group (36.7% versus 25.4%, respectively) in the FAP population (p=0.01).

1.3.3 Safety

The safety population consisted of 445 patients who received treatment; 221 in the Taxotere combination arm and 224 in the control arm. Baseline signs and symptoms were present in 84 % patients and 26.5% were grade 3 or 4 toxicities. These had a balanced distribution in the two treatment groups. These baseline signs and symptoms were not counted in the treatment-emergent AEs (AEs). Certain toxicities such as myelosuppression with or without infection or fever, diarrhea, fluid retention, neurosensory AE and alopecia were increased in the TCF arm. Most GI toxicities were greater in the control arm of CF.

Grade 3-4 AEs were experienced by 81.4% of TCF-treated subjects and 75.4% of CF-treated subjects. The most frequently (> 10%) observed grade 3-4 AEs in the TCF treatment group were cancer pain (37.1%), neutropenia (82.3%), lethargy (21.7%), stomatitis (20.4%), diarrhea (20.4%), nausea (16.3%), anorexia (15.8%), vomiting (14.9%), infection (14.9%).

Although a higher incidence of grade 3-4 AE and Serious Adverse Evenets (SAE) was seen in the TCF treatment group, the AE related mortality rate were similar in the treatment groups, with 20 (9%) for TCF-treated subjects and 26 (12%) for CF-treated subjects. The leading cause of AE related death were infection, which was fairly balanced between the two arms (3% for both arms in the safety population). Deaths on study and within 30 days of stopping treatment were 23 (10.4%) on the TCF arm and 19 (8.5%) on the CF arm.

Total treatment duration tended to be longer in the TCF treatment group (median 19 weeks) compared to the CF treatment group (16 weeks). The median relative dose intensities achieved in both treatment groups was about 90% for all drugs. The median number of cycles administered per patient was 6 (with a range of 1-16) for the TCF arm compared to 4 (with a range of 1-12) for the CF arm. More treatment cycles on the TCF arm than those on the CF arm were interrupted (10.8% vs. 4.5%), discontinued (26.7% vs 19%), dose reduced (40.7% vs 35.7%), or delayed (40.7% vs 27.1%). There were no treatment modifications due to myelosupression.

GCSF was used in less than 20% of subjects (18.6% for TCF and 8.9% for CF) and 10.0% of TCF cycles and 3.3% of CF cycles. The most frequent causes for treatment discontinuation were GI toxicities, flu-like symptoms and neurosensory toxicity. Within the TCF treatment group, infection, fever in the absence of infection, GI toxicities, and neurosensory toxicity were key AEs impacting the incidence of TE-SAE, discontinuation, or non-malignant death.

1.3.4 Dosing Regimen and Administration

See Table 1.

1.3.5 Drug-Drug Interactions

No drug-drug interactions were identified in this study.

1.3.6 Special Populations

Subjects at or over the age of 65 years appeared to be more prone to developing infections in this study. In the TCF treatment group, 21.9% of subjects age of 65 years or older (n = 54) developed grade 3-4 infection, compared to 14.4% of subjects under the age of 65 years. The majority of these grade 3-4 infections were observed during neutropenic episodes.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established Name: docetaxel
Proprietary Name: Taxotere

Applicant: Sanofi Aventis Pharmaceuticals
Route 202-206
PO Box 6800
Bridgewater, NJ 08807-2800

Drug Class: Antineoplastic

Proposed Indication:
Taxotere in combination with cisplatin and 5-FU indicated for the treatment of patients with advanced gastric adenocarcinoma, including (b) (4)

Proposed Dosage and Administration
The dosing regimen as proposed by the applicant in the label is as follows:

For gastric adenocarcinoma, the recommended dose of Taxotere is 75 mg/m2 as a 1 hour infusion, followed by cisplatin 75 mg/m2, as a 1 to 3 hour infusion (both on day 1 only), followed by 5-fluorouracil 750 mg/m2 per day given as a 24-hour continuous infusion for 5 days, starting at the end of the cisplatin infusion. Treatment is repeated every three weeks. Patients must receive premedication with antiemetics and appropriate hydration for cisplatin administration (b) (4)

Approved Indications and Usage:
Previously approved indications and regimens are listed in Table 4.

Table 4: Taxotere current indication and usage

Year of approval	*Indication*	*Dose and schedule*
1996, 1999	*locally advanced or metastatic breast cancer after failure of prior chemotherapy*	*60-100 mg/m^2 administered intravenously over 1 hour every 3 weeks*
2004	*in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer*	*75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 courses. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities*
1999	*locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy*	*75 mg/m^2 administered intravenously over 1 hour every 3 weeks*
2002	*in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition*	*75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes every 3 weeks*
2004	*in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer*	*75 mg/m^2 every 3 weeks as a 1 hour infusion. Prednisone 5 mg orally twice daily is administered continuously*

2.2 Currently Available Treatment for Proposed Indications

Gastric cancer is the second most common cause of cancer- related deaths in the world[1]. It is estimated that 755 000 new cases are diagnosed world wide annually[2]. As ranked 14th in incidence among the major types of cancers, the estimated new cases and deaths from gastric cancer in the United States for 2003 are 22400 and 12,100 respectively[3-5].

Currently, a cure for patients with gastric cancer is only for those diagnosed with early stage disease in which a complete surgical resection can be performed. Even in these patients, many (35 - 80%) will develop recurrences[6-8]. The estimated 5-year survival rates, with standard treatment modalities, by stage are: 60 - 90% for Stage I; 30 - 40% for Stage II; 10 - 25% for Stage III and < 5% for Stage IV[9, 10]. In the United States, the 5-

year survival rate for gastric cancer of all stages is only 22%. In Europe, it ranges from 27% in Italy (Romagna) to 8% in Poland[11].

Presently, the treatment of advanced gastric cancer is primarily palliative and confers a minimal impact on overall survival [10, 12, 13]. Multiple agents are active in gastric cancer, including fluoropyrimidines (such as 5-FU), platinum agents, anthracyclines, taxanes, irinotecan, gemcitabine, mitomycin-C, and etoposide[7, 14]. However, with single-agent treatment, response rate (RR) is low (from 15% to 36%) and combination treatment, such as Cisplatin + 5-FU, has been the standard in gastric cancer chemotherapy[14].

Based on the previous studies results, the applicant has designed a comparative study (TAX 325) to evaluated Taxotere add on to cisplatin and 5-FU combination, with a run in phase II to evaluated 5-FU add on to Taxotere and cisplatin combination. The result of TAX 325 study is the main key component of this NDA application.

2.3 Availability of Proposed Active Ingredient in the United States

Taxotere is presently marketed in US for 5 indications (section 2.1).

2.4 Important Issues With Pharmacologically Related Products

The dose limiting toxicity of Taxotere were myelosupression, fluid retention and fatigue.

2.5 Presubmission Regulatory Activity - Important Milestone in Taxotere Development for Gastric Cancer

1/1/1998, EOP2 meeting to discuss Taxotere development plan for gastric cancer. The proposed indication and pivotal study design were discussed.

4/8/1998, SPA meeting for TAX 325a, FDA recommended that beside the primary endpoint TTP, the study should be powered to be able to detect the deference in overall survival. FDA also recommended that phase 2 data should only be used for testing arm selection and should not be included for efficacy analysis. Applicant agreed and amended protocol.

7/8/2003, pre-sNDA meeting, the sNDA format, proposed efficacy and safety analyses were discussed and agreed by FDA.

4/4/2005 The applicant request pre-NDA meeting to discuss TAX325a result and proposed indication of taxotere in combination with cisplatin and 5-FU in advanced gastric cancer. The division has concurred with the overall concept of the sNDA proposal (b) (4)
.

2.6 Other Relevant Background Information

5/14/96 Approved for use in patients with locally advanced or metastatic breast cancer who have progressed or relapsed during anthracycline-based therapy (original NDA 20449).

(b) (4)

12/23/99 Approved for use in locally advanced or metastatic breast cancer after failure of prior chemotherapy (S-005).

12/23/99 Approved for use in locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy (S-011).

02/01/02 Approved in combination with cisplatin for the treatment of patients with unresectable locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received chemotherapy for this condition (S-018).

5/19/04 Approved for use of Taxotere q3 weeks in combination with prednisone in the treatment of metastatic hormone-refractory prostate cancer (S-028).

8/18/04 Approved for use of Taxotere in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer (S29).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This sNDA application is based on one 2 phase comparative study of TCF combination in chemotherapy naïve advanced gastric cancer patients (TAX 325 & 325a) and one TCF combination pharmacokinetic study (XRP6976E/1001). The TAX 325 study is most relevant to the proposed indication.

Table 5: Clinical Studies Included in sNDA 20491 SE 35

Study	Title	Subjects (n)
TAX 325	Open label, randomized multicenter Phase II/III study of Docetaxel in combination with Cisplatin or Docetaxel in combination with 5- Fluorouracil and Cisplatin compared to the combination of Cisplatin and 5- Fluorouracil in patients with metastatic or locally recurrent gastric cancer previously untreated with chemotherapy for advanced disease	158 (76 TC, 79 TCF)
TAX 325a		445 (221 TCF, 224 CF)
1001	A pharmacokinetic interaction study of 75 mg/m^2 of docetaxel (RP56976, Taxotere ®) plus cisplatin (75 mg/m^2) and 5- FU (750 mg/m^2/day for 5 days) in the treatment of patients with recurrent or metastatic solid tumors	12

4.3 Review Strategy

This NDA clinical review is primarily based on the efficacy and safety data of TAX 325, which is most relevant to the proposed indication. The electronic submission, with the CSRs, and other relevant portions were reviewed and analyzed.

The key review materials and activities are outlined as blow:

- the electronic submission of the NDA;
- relevant published literature;
- relevant submissions in response to medical officer's questions;
- sponsor presentation slides to FDA on Nov. 2nd, 2005;
- major efficacy and safety analyses reproduced or audited using the SAS datasets using raw data;
- other non-clinical review;
- Discussion's with consultants.

An ODAC member, Dr. James Doroshow, was consulted to discuss efficacy and safety results. Dr. Doroshow feels that the efficacy data of TAX 325a demonstrated superiority of addition Taxotere to the cisplatin and 5-FU, although whether a lower dose of Taxotere dose may be also effective which was not tested in this study. He also point out that in TAX325a study both TCF testing and control arm had better TTP than previously observed in other comparative studies, perhaps this is because TAX325a has include some patients with better prognosis (19% has curative operation and 12% had palliative operation).

(b) (4)

(b) (4)

A SEALD consult was requested to assist in evaluation the Quality of Life data. The consultant found that study 325a results fail to provide convincing evidence of treatment benefit favoring Taxotere treatment arm of the study for the general concept of health-related quality of life (HRQL). The EORTC QLQ-C30 was not adequately developed to measure any of the specific concepts implied by any of the domain or item scores generated by the EORTC QLQ-C30. Study 325a findings are based on unblind treatment comparisons that do not adequately control for bias in favor of the experimental treatment. Results from EORTC QLQ-C30 Global Quality of Life domain or the Karnofsky Performance Scale (KPS) should not be used to support labeling claims for time to improvement in HRQL, neither "time to definitive deterioration of global health status" or worsening of performance status. There is no evidence indicate that these measures are sufficiently developed to measure those general concepts nor that the instruments are sensitive enough to detect changes that patients would considered meaningful to deterioration in HRQL or physical function, respectively.

Taxotere has been marketed for other indications (section 2.1), and the results of randomized study TAX325 have not been published, except in abstract form in ASCO proceedings and are available at the ASCO website (www.ASCO.org).

4.4 Data Quality and Integrity

Data Integrity prior to sNDA submission:

In late 2002, Aventis was informed of potential data falsification at the Stratton VA Medical Center, Albany, NY. The investigator of record at the site was Dr. James Holland. Aventis attempted to conduct a for-cause audit and was unable to do so since the Veteran's Administration (VA) Inspector General had sequestered all the medical records and study information for the index studies. However, the following was known:

• A total of 6 subjects had been enrolled into the study.

• One subject (K2553), who agreed to participate on 22 May 2001, was included in the study based upon false laboratory results. This subject died on (b) (6) from toxicity on the TCF arm.

On 3 March 2003, Aventis submitted a briefing document and meeting request to IND 35 555 (Serial No. 1078) to discuss this issue with the Oncology Division of the Food and Drug Administration (FDA). Based on an expectation that reliable data from the subject study site would not be available, Aventis proposed that information collected on the subjects from the Stratton VA Medical Center would be handled in the clinical study report as follows:

• All subjects from the subject site were to be excluded from all subsequent analyses.

• All available data received on these subjects were to be summarized (as is) separately, in an appendix to the study report in tabular/listing form, including a summary of the safety and case narratives as appropriate.

The FDA indicated that the Sponsor's proposal of 03 March 2003 (Serial No. 1078) for analyses of data from studies affected by GCP compliance matters at Stratton VA Medical Center, Albany, NY would be acceptable. As a result of excluding the 6 subjects enrolled in study at this site, the effective sample size of the TAX 325 phase III study would decrease from 463 to 457.

Data quality and Integrity post sNDA submission.

A number of methods were utilized in order to evaluate the quality and integrity of the data from study TAX 325a after submission of the NDA as outlined below:

- Clinical inspections: The clinical inspection was focused on the trial TAX 325a since it provided the most crucial efficacy data for this NDA application. The Division of Scientific Investigations (DSI), Clinical Practice Branch I, conducted clinical inspection of one site of study TAX 325a in the United States. A number of factors were considered for site selection, including accrual numbers and data documentation. Conflicts of interest of investigator would be considering factor if there was any claim. However, there was no claim of conflicts of interest for study TAX 325a. The response rate was not the primary endpoint in this study and therefore, the site selection was primarily based on the accrual numbers. Only one site with highest enrollment was selected for inspection, site of principle investigator, Dr. Jaffer Ajani (MD Anderson Cancer Center, Houston, Texas). The inspectors of DSI found that trial conduction in accordance with accepted ethical standards and no major deficiency were noted.

- The medical and statistical reviewers have conducted independent efficacy and safety analyses based on the primary data submitted in SAS transport format and the JMP counterpart. Any discrepancies between the reviewers' results and those of the sponsor are disclosed in relevant sections of this joint medical/statistical review.

- Case report forms in electronic format were reviewed in selected patients. The CRF were randomly sampled at one per each country initially. Problem oriented samplings on specific files were used along the review process. There were about 30 CRFs reviewed in varying detail.

4.5 Compliance with Good Clinical Practices

According to the applicant, "Clinical trials adhered to the International Conference on Harmonization guidelines for Good Clinical Practice. Subjects and volunteers were accorded all rights granted by the Declaration of Helsinki. All protocols received approval by the appropriate governing investigational review board, ethics committee, or similar authority. Standard research methodology was utilized for the conduct and performance of each clinical trial under consideration." No major violations were found by DSI during their audit.

4.6 Financial Disclosures

Certification of financial disclosure was provided by Sanofi Aventis. There were total of 442 investigators participated TAX 325/325a trial and 402 of them claimed no financial interest in the study. Forty of them (9%) failed to disclose their financial interest due relocation during the early stage of the study and lost contact, very few of them are in US. Since the number of patient enrolled by these investigators was few, they likely did not impact on the results of this study.

Appears this way on the original

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Taxotere in combination with cisplatin and 5-FU indicated for the treatment of patients with advanced gastric adenocarcinoma, including gastroesophageal junction, who have not received chemotherapy for advanced gastric cancer.

6.1.1 Methods

TAX 325 is the major trial submitted to support the efficacy and safety for this sNDA. The phase III part of the trial, i.e.TAX325a will be reviewed in detail.

6.1.2 General Discussion of Endpoints

The prespecified primary endpoint of TAX 325a is TTP. It was defined in the original protocol as the "*time from randomization to disease progression, or death from any cause within 12 weeks of the last evaluable tumor assessment, or within 12 weeks of the first infusion of study drugs (for subjects with no evaluable tumor assessment after randomization)*". Per applicant, this prevents over-estimating TTP in subjects who miss one or more consecutive tumor assessments and then subsequently die. This endpoint could be defined differently and the results may vary depending on the definition used. To address this the applicant was requested to conduct sensitivity analyses according to the several different definitions as specified by the FDA for TTP, (TTP, with censoring at last tumor assessment) and PFS analyses (disease progression + all death with censoring of non-progressors at the last tumor assessment) in the protocol specified Full Analysis Population (FAP) and the Intent-to-Treat (ITT) population..

The disease progression is defined as follows in the original protocol:

- 25% increase in the size of at least 1 bidimensionally or measurable lesion (in comparison with the measurements at its nadir) or appearance of a new lesion.
- The occurrence of pleural effusion or ascites was also considered as PD if this was substantiated by positive cytology.
- The development of brain metastasis was considered a sign of PD, even if the malignancy was responding outside the brain.
- Pathological fracture or collapse of bone was not evidence of disease progression.

An External Response Review Committee (ERRC) was to be set up for the assessment of tumor response. This Committee was to consist of members all experts in the evaluation of gastric cancer: two expert radiologists not involved in the study and at least one investigator from the study or one medical expert. They were to meet regularly in order to

provide data on time for the selection of the test arm for phase III, the final results of the whole phase II, the phase III interim analysis and the phase III final analysis.

Should discrepancies occur between the algorithm on tumor assessment established by the RPR (Rhone-Poulenc-Rorer) statistician as a validation tool and the assessment of either the investigators or the experts investigators and/or the panel, they were to be documented and re-evaluated during a final patient assessment.

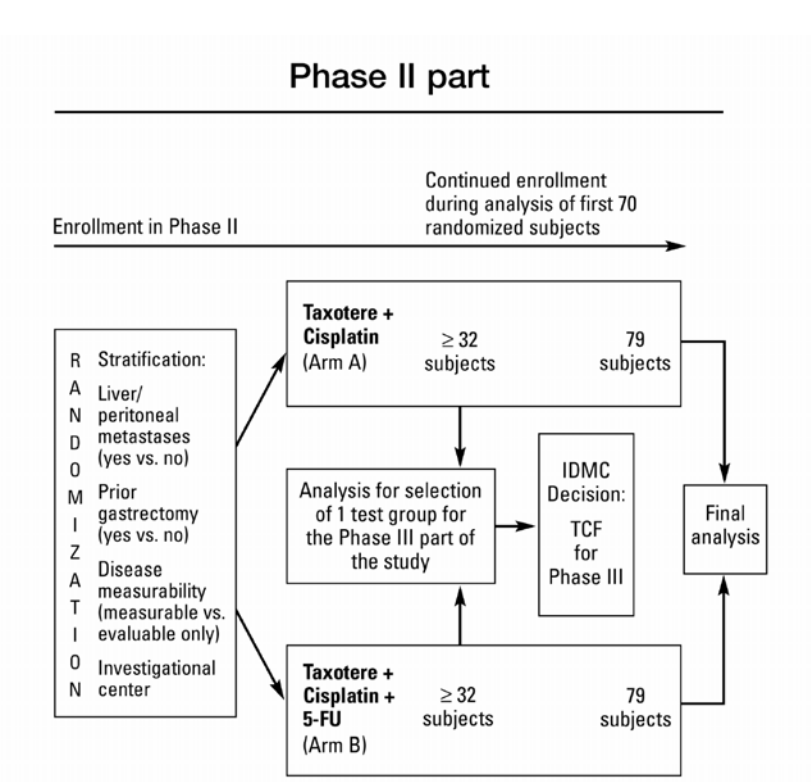
Reviewer Comments: The primary endpoint of TTP can provide proof of clinical benefit if it has large enough magnitude with an acceptable risk/benefit ratio. The progressions were not entirely based on objective events and the review of progressions was centralized, if not completely blinded. Sensitivity analyses to assess if any improvement in TTP was present if progressions were based only on objective evidence of progressions. Finally, an advantage in overall survival would provid strong support to the primary endpoint.

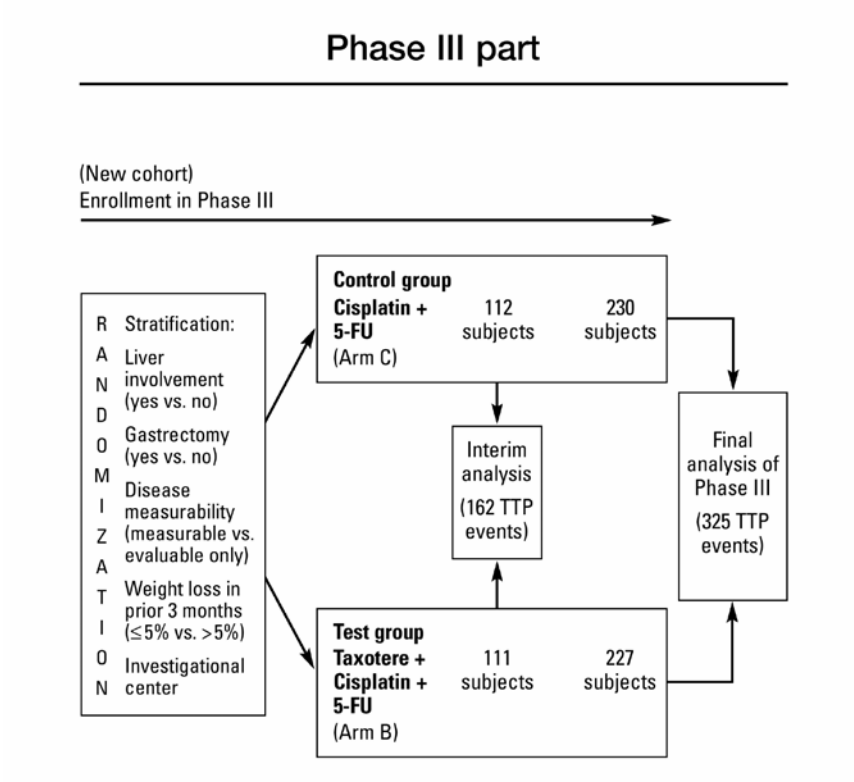
6.1.3 Study Design

TAX325A is a randomized multicenter, open-label phase II/III trial that was conducted in patients with locally advanced or metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who had not received prior chemotherapy for advanced disease. Patients who had received prior surgery and radiation were eligible. Prior adjuvant or neoadjuvant chemotherapy was considered acceptable (except for taxanes and over 300 mg/m^2 of cisplatin) if administered more than 12 months earlier. The study was stratified for the phase III part by liver involvement (yes/no), gastrectomy (yes/no) measurable or evaluable only disease, and weight loss ($\leq$ 5% / > 5%). Tumor assessments were made every 8 $\pm$ 1 week. TTP in the Full Analysis Population (FAP) was the primary endpoint. This FAP included all patients randomized who received any study drug. An External Response Review Committee (ERRC) reviewed assessment of tumor response. They provided data for the phase III interim analysis and the phase III final analysis.

Please see figure below for the TAX 325 design. This phase II part will not be discussed in any detail.

Figure 3 Phase II/III (TAX 325) Study Design





5- FU = 5- fluorouracil; TTP = Time to progression; IDMC = Independent data monitoring committee; TCF = Taxotere + cisplatin + 5-fluorouracil
Source: TAX 325 study report 5.1., Figure 1.

TTP = Time to progression; IDMC = Independent data monitoring committee; TCF = Taxotere + cisplatin + 5-FU
CF= cisplatin + 5-FU
Source: TAX 325a study report 3.2.3., Figure 1.

l

Reviewer note: This study design is adequate and well controlled and is expected to provide a reasonable assessment of clinical benefit. The study design is also intended to minimize bias through implementation of an external endpoint committee and objective assessments of tumor. Although this is an open-label study with inherent weaknesses of introduction of bias of an open-label trial, a central review was conducted with two blinded radiologists, and one study investigator or another oncologist considered a specialist in the field. This is not as optimal as a completely blinded and independent committee, however, it was centralized. In addition a positive overall survival outcome can provide support for the primary endpoint.

The **major eligibility criteria** are as follows:

- Patients with gastric adenocarcinoma including adenocarcinoma of the esophagogastric junction, histologically proven.
- Measurable and/or evaluable metastatic disease; if a single metastatic lesion is the only manifestation of the disease, cytology or histology is mandatory. Locally recurrent disease is accepted provided that there is at least one measurable lesion.
- Karnofsky performance status > 70%.
- Adequate haematological parameters (Hb > 10 g/dl, ANC > 2.0 x 109/l, platelets > 100x109/l).
- Creatinine < 1.25 x upper normal limit (UNL) or < 120 pmol/l; if creatinine value is borderline, creatinine clearance should be performed.
- Total bilirubin 1 x UNL, AST (SGOT) and ALT (SGPT) < 2.5 x UNL, alkaline phosphatase < 5 x UNL.
- No prior palliative chemotherapy, previous adjuvant (and/or neo-adjuvant) chemotherapy is allowed if more than 12 months has elapsed between the end of adjuvant (or neo-adjuvant) therapy and first relapse.
- At least 6 weeks from prior radiotherapy and 4 weeks from surgery.

- No prior treatment with taxanes.
- Prior CDDP as adjuvant (and/or neo-adjuvant) chemotherapy with cumulative dose < 300 mg/m^2.
- No known brain or leptomeningeal metastases
- No symptomatic peripheral neuropathy > grade 2 by NCIC-CTG criteria.
- No other serious illness or medical conditions:

Reviewer note: The eligibility criteria, such as the stage and severity of the disease, exclusion of prior palliative chemotherapy or taxanes, exclusion of CNS disease, are adequate for assessment of benefit for proposed indication.

The **treatment plan** is given in the table below:

Table 6:Treatment plan for TAX 325 and TAX 325a.

Phase II	
Arm	**Regimen**
Arm A:	Docetaxel: 85 mg/m^2 IV administered first as a 1-hour infusion, day l every a weeks. CDDP: 75 mg/m^2, IV as a 3 to 4-hour infusion, day 1 every 3 weeks after the end of docetaxel administration
Arm B:	Docetaxel: 75 mg/m^2 IV administered first as a 1-hour infusion, day 1 every 3 weeks. CDDP: 75 mg/m^2, I.V. as a 3 to 4-hour infusion, day 1 every 3 weeks. 5-FU: 750 mg/m^2 CIV, day 1-5 every 3 weeks after the end of CDDP administration
Phase III:	
Arm B:	Based on phase II data analysis**,** the testing arm (Arm B) used regimen of Phase II Arm B.
Arm C:	CDDP: 100 mg/m^2, day 1 as a 3 to 4-hour infusion every 4 weeks 5-FU: 1000 mg/m^2 CIV, day 1-5 every 4 weeks

Treatment was administered until the occurrence of progression, unacceptable toxicities, or withdrawal of consent. After progression, further chemotherapy treatment with taxanes or camptothecins was not recommended. Crossover was not allowed. At the end of study treatment, subjects who had progressed were followed every 3 months until death. Subjects who had not yet progressed at the end of study treatment were followed every 8 weeks until documented occurrence of progression, and then every 3 months, until death.

Reviewer note: The investigational arm is based on the findings of TAX 325, the phase II dose finding study which is adequate as a basis for doses and dose regimens used in major effectiveness study TAX 325a.

Although the dose of cisplatin and 5-FU on the control arm was 75% of that of the investigational arm, the dosing interval (schedule) of the control arm was shorter(three weeks), than that of the investigational arm (4 weeks). The dose intensity of cisplatin and 5-FU was maintained in both treatment arm at 25 mg/m2/week for cisplatin and 1250 mg/m2/week for 5-FU.

The treatment duration and follow up of this controlled study is adequate with the respect to assess benefit.

6.1.4 Efficacy Findings

The Clinical Study Protocol and SAP defined 3 populations for analysis, the Full analysis population (FAP), the Per-protocol population (PPP), and the Safety population (SP) as show in Table 7. The prespecified population for the primary analysis is FAP.

Table 7: Definition of Patient population used for Analysis.

Full Analysis Population (FAP)	all treated subjects analyzed in the treatment group to which they were assigned by randomization.
Per Protocol Population (PPP)	a subset of the FAP, consisted of subjects eligible and evaluable*, for response without a major protocol deviation during the study.
Safety Population (SP)	all subjects treated with at least 1 dose of study therapy and analyzed according to the study medication actually received.
Intent to Treat (ITT)	all patients who randomized for TAX325a

* Evaluability for response was defined in the SAP as follows: Subjects who received at least 2 cycles of study medication with at least 1 complete follow-up tumor assessment using the same imaging procedures as used at baseline for each lesion (unless early progression occurred, in which case, the subject was considered evaluable with PD). A response had to be confirmed at least 4 weeks after the first documentation of response.

Major protocol violation occurred in 6 FAP subjects, 3 did not have pathologically confirmed gastric cancer (2 on TCF arm and 1 on CF arm), 2 had ineligible liver function at enrollment (one on each arm) and one was enrolled in CF arm but accidentally received one dose of Taxotere (detailed in section 10.1.2.6). The number of subjects in various populations is shown in Table 8.

Table 8: Subject populations

Populations	Number (%) of subjects		
	TCF	CF	Total
Randomized	227 (100)	230 (100)	457 (100)
Not treated	6 (2.6)	6 (2.6)	12 (2.6)
SP (Treated)	221 (97.4)	224 (97.4)	445 (97.4)
FAP	221 (97.4)	224 (97.4)	445 (97.4)
FAP	221 (100)	224 (100)	445 (100)
Eligible	191 (86.4)	206 (92.0)	397 (89.2)
Evaluable for response	185 (83.7)	184 (82.1)	369 (82.9)
PPP	170 (76.9)	178 (79.5)	348 (78.2)

FAP = Full analysis population; PPP = Per- protocol population; CF = Cisplatin + 5- fluorouracil
Data source: TAX 325a study report Appendix C. 1.1, Table 1.01.

All treated subjects received the treatment that they were allocated at randomization. Therefore, the safety population is identical to the full analysis population.

The FAP excluded 12 randomized subjects present in the ITT population. Six patients were excluded from each arm because they did not receive therapy. The reviewer compared time to death from randomization of 12 untreated patients (Table 9). The median time to death for 6 subjects randomized to CF arm but not treated was much longer than that of TCF arm. More patients on the CF arm received other therapies and as can observed, the TTP in these excluded patients in the CF arm was much longer than those on the TCF arm.

Reviewer note: Due to a major imbalance in TTP on the two arms in the 12 excluded patients despite no administration of study drug, it is appropriate to analyze the FAP population, and conduct sensitivity analyses on the ITT populations.

Table 9: Comparison of Subjects who were Randomized but not Treated

ID	Reason of No treatment	Time to Death Days (months)	Mean (Range) Days, N = 6
TCF-randomized subjects			
H0653	Death	4	17.66 (2, 81)
K2351		2	
O7304		3	
K1509	consent withdrawn	81 (2.5)	
K6202		Lost follow up	
O3324	PD, shortly followed by death	8	
CF-randomized subjects			
F0707	consent withdrawn	426 (14)	223 (121, 426)
O3409		122 (4)	
O4706		244 (8)	
C3327	various clinical and/or laboratory abnormalities.	202 (5)	
L4405		121 (3)	
M0709		Alive in (b) (6)	

Data source: TAX 325a study report and data set.

Primary analysis: TTP

The primary analysis of the phase III part of the study was a comparison of TTP in the FAP. A total of 325 events were required to detect a statistically significant increase in TTP among TCF-treated subjects, relative to CF-treated subjects. A single interim analysis was to occur when 162 TTP events (about half that of the final analysis) had been observed with an α expenditure of 0.0036.

To test the superiority of TCF relative to CF, an unstratified log-rank test was used. Although the interim analysis conducted earlier for TTP met the pre-specified boundary criteria, the final significance level was nominally set at 0.0487 (O'Brien-Fleming type of alpha-spending function with 162/325 TTP events observed at interim). The analysis was performed with the number of pre-specified events ("325 events" analysis) and was performed, as the primary TTP analysis, to include all events in the database ("end-of-study" analysis). There was an approximately 2-month statistically significant increase in TTP in the TCF arm over the CF arm in both the 325-event analysis and the end-of-study analysis.

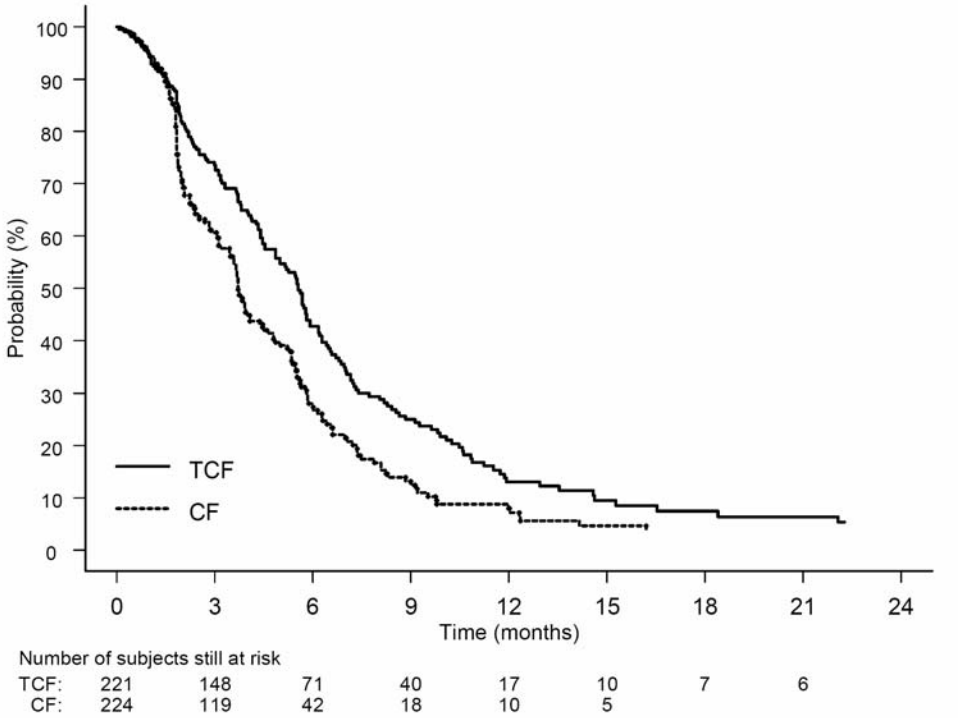
In the end of study, 341 of 445 (76.6%) subjects had a progression event, and 104 of 445 (23.4%) subjects were censored for analysis. As per applicant, the median follow-up was 13.6 months (95% CI: 11.30- 22.28). The observed median TTP was 5.6 months in the TCF group (95% CI: 4.86-5.91) and 3.7 months (95% CI: 3.45- 4.47) in the CF group as shown in Table 10 and **Error! Reference source not found.**. The difference between the 2 treatments was statistically significant (log- rank test, P= 0.0004) with an HR of 1.473 (95% CI: 1.189- 1.825). At 6 months, 42.7% of the TCF-treated subjects had no event of progression compared with 27.4% of the CF-treated subjects. These applicant analyses were verified by the FDA statistics reviewer Dr Shenghui Tang.

Table 10: Time to progression - end of study (FAP)

Event/parameter	Number (%) of subjects	
	TCF (N=221)	CF (N=224)
TTP events	167 (75.6)	174 (77.7)
Documented disease progression	149 (67.4)	155 (69.2)
Died	18 (8.1)	19 (8.5)
Censored subjects	54 (24.4)	50 (22.3)
Lost to follow-up for TTP	16 (7.2)	12 (5.4)
No event at cut-off date	16 (7.2)	18 (8.0)
Further therapy	22 (10.0)	20 (8.9)
25th percentile	2.7	1.9
Median TTP (months)	5.6	3.7
95% CI (months)	[4.86-5.91]	[3.45-4.47]
75th percentile	9.1	6.3
6-month estimate	42.7%	27.4%
P-value (Log-rank test)	0.0004	
Hazard ratio[a] (95% CI)	1.473 [1.189-1.825]	

Data source: TAX 325a study report, Appendix C. 2.1, Tables 4.14 and 4.16, and Figure 4.15.

Figure 4:Time to progression – Kaplan- Meier curve – end of study (FAP)



TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population
Data source: TAX 325a study report, Appendix C. 2.1, Figure 4.15.

Sensitivity Analyses:

a- Sensitivity analysis excluding clinical progressions:

Since the TAX 325a study endpoint included both radiological disease progression and clinical disease progression, the review team asked applicant to provide the distribution of clinical disease progression and to conduct a TTP sensitivity analysis with radiological progression only, with clinical progression censored.

Twenty one patients (TCF: n=11, CF: n=10) in the primary analysis were based on clinical progressions. In a sensitivity analysis with these 21 patients censored at the last date of tumor assessment yielded results consistent with the primary analysis. In this analysis, there were 3 patients in the TCF arm and none in the CF arm with evaluable/non-evaluable disease; 8 patients on the TCF arm and 10 on the CF arm had bidimensionally measurable disease as assessed by applicant, as shown below.

Table 11: Summary of patients with clinical progression (FAP)

Tumor characteristics	Number (%) of patients		
	TCF (N=11)	CF (N=10)	Total (N=21)
Measurability of disease			
Bidimensional	8 (72.7)	10 (100)	18 (85.7)
Evaluable only	1 (9.1)	0 (0)	1 (4.8)
Non-evaluable disease	2 (18.2)	0 (0)	2 (9.5)
TTP – CSR			
Events (progression)	11 (100)	10 (100)	21 (100)
Censored	0 (0)	0 (0)	0 (0)
TTP - sensitivity			
Events (death)	3 (27.3)	5 (50.0)	8 (38.1)
Censored	8 (72.7)	5 (50.0)	13 (61.9)

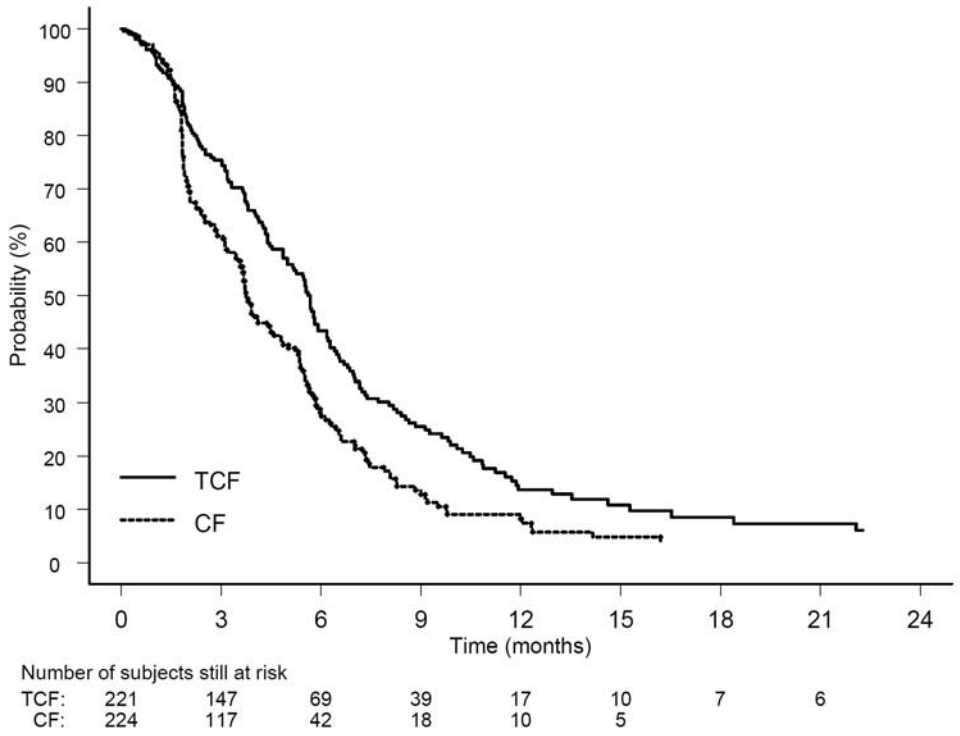
The results of a sensitivity analysis for TTP with these 21 patients with clinical progression reclassified are presented in the table and figure below:

Table 12: Time to Progression with Clinical Progression Censored (FAP)

Event/parameter	Number (%) of patients	
	TCF (N=221)	CF (N=224)
TTP events	159 (72)	169 (75)
Radiological progression	138 (62)	145 (65)
Deaths	21 (10)	24 (11)
Censored patients	62 (38)	55 (25)
25th percentile (months)	3.0	1.9
Median TTP (months)	5.6	3.7
[95% CI] (months)	[4.86-6.18]	[3.55-4.60]
75th percentile (months)	9.1	6.4
6-month estimate	43.3%	28.1%
p-value (Log-rank test)	0.0003	
Hazard ratio[a] [95% CI]	1.489 [1.197-1.852]	
Risk reduction	32.8%	

[a] Value >1 favors TCF.

Figure 5: Time to Progression with Clinical Progression Censored (FAP)



Reviewer note: The review team audited applicant's analysis and note that among 21 patients reclassified, 8 death occurred (3 in TCF and 5 in CF). Therefore, only 13 (8 in TCF and 5 in CF) events status were changed, from 'event' to 'censored', and that the sensitivity analysis is similar to the primary analysis for TTP.

b- Other Sensitivity Analyses:

At the request of the clinical reviewer, several sensitivity analyses were conducted by the applicant and the FDA statistical reviewer for TTP (TTP defined as tumor progressions only, nonprogressors censored at last tumor evaluation) in the ITT and FAP population. Sensitivity analyses were also conducted for PFS (disease progressions and deaths, patients alive without progression censored at the last tumor evaluations) in the FAP and ITT populations. The results of these analyses remained in favor of the Taxotere combination arm. (*Table 13,* Figure 7, Figure 8, Figure 9*, and Figure 10).* These results were similar to applicant's primary analysis except PFS in ITT population, which is mimicking the overall survival analysis in ITT population (dialed in next section, overall survival analysis).

Table 13: FDA's Unstratified Sensitivity TTP and PFS Analyses (FAP and ITT)

Analysis	Population	P value	HR (CF/TCF)	95 CI
TTP	FAP	0.0002	1.526	1.2163-1.9145
	ITT	0.0002	1.534	1.2229-1.9235
PFS	FAP	0.0039	1.343	1.0975-1.6427
	ITT	0.0096	1.2990	1.0644-1.5855

To address missing tumor assessments, the applicant conducted an unstratified log-rank study under the following condition: When all progressions documented more than 12 weeks after the last evaluable tumor assessment were considered progressions at 8 weeks, results were similar to the primary analysis (Figure 4), p- value = 0.0029, with Hazard Ratio of 1.383 (CF vs. TCF, 95% CI: 1.116; 1.713). This analysis indicated that effect of missing data in TTP is minimal.

As a supportive analysis for the primary endpoint of TTP, the applicant tested TTP using a stratified log-rank test in the FAP. Additionally, TTP was assessed in the PPP and for all randomized subjects. The results are summarized in the table below where the primary analysis is presented in the first row for comparison.

Table 14: Summary of end of study TTP analyses

Population	Log-rank test	*P*-value	Hazard ratio[a]	95% CI
FAP	**Unstratified**	**0.0004**	**1.473**	**[1.189 –1.825]**
FAP	Stratified [b]	<0.0001	1.603	[1.275-2.014]
PPP	Unstratified	0.0006	1.518	[1.196-1.928]
All randomized	Unstratified	0.0007	1.442	[1.166-1.784]
All randomized	Stratified [b]	<0.0001	1.564	[1.247-1.961]

a Value > 1 favors TCF
b Stratified on liver metastasis (yes, no), prior gastrectomy (yes, no), disease measurability (measurable, evaluable-only) and weight loss in prior 3 months (≤ 5%, > 5%) as specified at randomization FAP = Full analysis population; PPP = Per-protocol population; CI = Confidence interval; TTP = Time to progression
Data source: Appendix C. 2.1, Figure 4.15, Figure 4.20, Table 4a. 001, Figure 4a. 037, and Table 4a. 038.

A multivariable analyses using various stratification or prognosis factors were conducted to verify the primary analysis of TTP, as shown below:

Table 15: Multivariate analysis of TTP - end of study (FAP)

Cox Proportional Hazards Model (Full Model)[a]			
Covariate	***P* value**	**Hazard ratio[b]**	**95% CI**
Treatment group (1=CF; 0=TCF)	0.0002	1.506	[1.212–1.872]
Prior gastrectomy (1=yes; 0=no)	0.1165	0.827	[0.652–1.048]
Disease measurability (1=yes; 0=no)	0.7434	1.050	[0.784–1.406]
Liver metastasis (1=yes; 0=no)	0.6723	0.954	[0.767–1.187]
Weight loss ≤5% (1=yes; 0=no)	0.1178	0.834	[0.664–1.047]
KPS (1=90 or less; 0=100)	0.2650	1.207	[0.867–1.681]
Primary tumor site (1=distal; 0=proximal)	0.0199	1.325	[1.045–1.678]
Age (1=70 or over; 0=less than 70)	0.4491	1.148	[0.803–1.644]

a Full model containing treatment group and adjusted for 4 stratification factors (as per randomization) and 3 other pre- specified covariates.
b A hazard ratio < 1 indicates reduced risk when a covariate takes the value 1.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population; KPS = Karnofsky performance status; CI = Confidence interval
Data source: Appendix C. 2.1, Table 4a. 004.

*Reviewer note: As observed from Table 15, results of TTP cross analyses appear to be consistently in favor of TCF arm. As supportive analyses, the applicant investigated the potential effect of covariates (prognostic factors) by using Cox proportional hazards models. The results of a Cox model adjusted for 4 of the stratification factors (as per randomization, prior gastrectomy, disease measurability, liver metastasis and weight loss) and 3 other pre-specified covariates (KPS, primary tumor site, and age) for TTP in the FAP are shown in Table 66. The treatment effect was in favor of TCF (HR= 1.506, P= 0.0002), and was consistent with the unadjusted analysis in the primary analysis (*Table 10*). The only covariate that was statistically significant in this model was primary tumor site, where a distal site (i. e., body and antrum) was shown to be an adverse prognostic factor for TTP. Although the uneven distribution of primary tumor site in two arms and other prognostic factors appear to be in favor of TCF arm, the factorial analysis by primary tumor sites showed extensive overlap of the respective 95% CIs indicating the lack of influence of the imbalance in distribution of the primary tumor site between the TCF and CF arm.*

Overall Survival

OS was compared using unstratified log-rank test in the FAP and was to be performed when the protocol-specified number of events (325 deaths) observed. To adjust for the pre-specified interim analysis conducted earlier for OS, the final significance level was readjusted from prespecified 0.0487 to 0.0483 (O'Brien-Fleming type of alpha-spending function with 181/325 deaths observed at interim).

Similar to TTP, the analysis of OS was performed with exactly the number of protocol-specified events ("325 events" analysis) and as the primary presentation, updated with

more events in the database ("end-of-study" analysis). **Post-database lock**, all deaths in the FAP were ordered by date and **the 325th death** (both treatment groups combined) was found to occur on **18 April 2003**. This **cut-off date** was used for Table 16 **censoring in the 325 events analysis**. For the **end-of-study OS analysis,** the **cut-off date** was **19 May 2003**, taken conservatively as the earliest date of the reporting window (**19 May 2003**, **28 May 2003**) on the **final "Survival Update" CRF**.

The applicant conducted end of study analysis for overall survival at the time when 334 of 445 subjects (75.1%) had an event, and 111 of 445 (24.9%) subjects were censored. The median follow-up for OS was 23.4 months. Summaries of OS were performed similarly to TTP (e. g., HR, 95% CIs, medians, Kaplan-Meier curves).

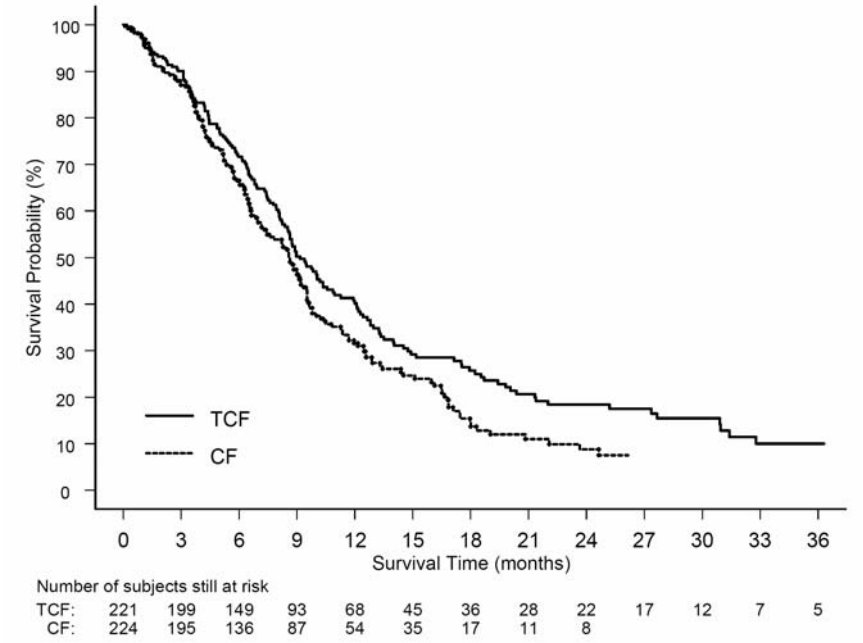
Table 16: Overall survival - end of study (FAP)

Event/parameter	Number (%) of subjects	
	TCF (N=221)	CF (N=224)
Survival event (deaths)	162 (73.3)	172 (76.8)
Censored subjects	59 (26.7)	52 (23.2)
Lost to follow-up	1 (0.5)	0 (0)
No event by cut-off date	58 (26.2)	52 (23.2)
25th percentile	5.5	4.5
Median survival (months)	9.2	8.6
[95% CI] (months)	[8.38-10.58]	[7.16-9.46]
75th percentile	18.5	14.5
1-year estimate	40.2%	31.6%
2-year estimate	18.4%	8.8%
P-value (Log-rank test)	0.0201	
Hazard ratio[a] [95% CI]	1.293 [1.041-1.606]	

a. Value > 1 favors TCF.
TCF = Taxotere + cisplatin + 5- fluorouracil; CF = Cisplatin + 5- fluorouracil; FAP = Full analysis population; CI = Confidence interval
Data source: Appendix C. 2.1, Table 4.32 and Figure 4.33.

An improvement in OS in the TCF arm supports the improvement in the FAP population.

Figure 6: Overall survival - Kaplan- Meier curve - end of study (FAP)



TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population
Data source: TAX 325a study report, Appendix C. 2.1, Figure 4.33.

Applicant also conducted supportive analyses, in which OS was tested using a stratified log-rank test in the FAP and assessed for all randomized subjects as well. The results are summarized in Table 17, in which the FAP unstratified analysis presented in top row for comparison.

Table 17: Summary of end of study OS analyses

Population	Log-rank test	*P*-value	Hazard ratio[a]	95% CI
FAP	**Unstratified**	**0.0201**	**1.293**	**[1.041 –1.606]**
FAP	Stratified[b]	0.0123	1.333	[1.064-1.671]
All randomized	Unstratified	0.0539	1.233	[0.996-1.527]
All randomized	Stratified[b]	0.0320	1.275	[1.021-1.593]

a Value > 1 favors TCF.
b Stratified on liver metastasis (yes, no), prior gastrectomy (yes, no), disease measurability (measurable, evaluable-only) and weight loss in prior 3 months (≤ 5%, > 5%) as specified at randomization.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population; OS = Overall survival; CI = Confidence interval
Data source: TAX 325a study report, Appendix C. 2.1, Figure 4.33, Table 4a. 065, Figure 4a. 097, and Table 4a. 098.

Reviewer note: The difference between the ITT and FAP is exclusion of twelve patients who did not receive any study drugs. Although these 12 excluded patients (6 on each arm) did not received any assigned treatment after randomization, the outcome and median survival of the 6 untreated patients assigned for TCF arm was much shorter than the 6 untreated patients on CF arm (17.7 days vs. 223 days), as summarized in Table 9. *It is reasonable to assess the prespecified FAP as the primary population and to conduct sensitivity analyses on the ITT population.*

Post Study Chemotherapy:

After discontinuation from study, 163 of 445 subjects (36.6%) received subsequent chemotherapeutic agents (as monotherapy or in combination chemotherapy). The number of subjects who received post-study chemotherapy was higher in the CF treatment group (92 subjects, 41.1%) than in the TCF treatment group (71 subjects, 32%). 5-FU was most common, used in 87 subjects (19.6%), followed by cisplatin, in 31 (7.0%). More subjects in the CF treatment group received taxanes than those in the TCF treatment group (CF: 10.3%; TCF: 5.0%), including Taxotere (CF: 8.5%; TCF: 2.7%). A similar rate of subjects received camptothecin in both treatment groups (9.8%; TCF: 10%).

Table 18: Post-study chemotherapy by treatment agents (FAP)

Post-study chemotherapy treatment	Number (%) of subjects	
	TCF (N=221)	CF (N=224)
Any post-study chemotherapy	71 (32.1)	92 (41.1)
Any pyrimidine analogues	59 (26.7)	58 (25.9)
5-Fluorouracil[a]	44 (19.9)	43 (19.2)
Any platinum compounds	22 (10.0)	26 (11.6)
Cisplatin[a]	14 (6.3)	17 (7.6)
Any taxanes	11 (5.0)	23 (10.3)
Taxotere[a]	6 (2.7)	19 (8.5)
Podophyllotoxin derivatives	9 (4.1)	19 (8.5)
Camptothecins	22 (10.0)	22 (9.8)
Anthracyclines	8 (3.6)	10 (4.5)

a. Drug also included in its class.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population
Data source: TAX 325a study report, Appendix C. 2.1, Table 4.37.

Reviewer note: Although more subjects on the CF arm received subsequent chemotherapy (41%) than those on the TCF arm (32%), the TCF arm demonstrated superiority in TTP in FAP and in the ITT population.

Tumor Response (RR)

Tumor RRs (CR and overall) with exact 95% CIs were calculated for each treatment group in the FAP and PPP. Comparisons between treatment groups were performed using the chi-square test. The applicant summarized best overall RRs for the FAP and the PPP are shown in Table 19. There was an approximately 10% improvement in TCF arm over CF arm (p=0.01) in the FAP population.

Table 19: Best overall response

Responses	Number (%) of subjects			
	FAP		PPP	
	TCF	CF	TCF	CF
N	221 (100)	224 (100)	170 (100)	178 (100)
Overall RR (CR+PR)	81 (36.7)	57 (25.4)	78 (45.9)	55 (30.9)
95% CI for overall response rate	[30.3%-43.4%]	[19.9%-31.7%]	[38.2%-53.7%]	[24.2%-38.2%]
P-value (Chi square test)	0.0106		0.0040	
Complete response	4 (1.8)	3 (1.3)	3 (1.8)	2 (1.1)
Partial response	77 (34.8)	54 (24.1)	75 (44.1)	53 (29.8)
No change/stable disease	67 (30.3)	69 (30.8)	63 (37.1)	68 (38.2)
Progressive disease	37 (16.7)	58 (25.9)	29 (17.1)	55 (30.9)
Not evaluable	36 (16.3)	40 (17.9)	NA	NA

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population; PPP = Per-protocol population; RR = Response rate; CR = Complete response; PR = Partial response; CI = Confidence interval; NA = Not applicable
Data source: TAX 325a study report, Appendix C. 2.1, Tables 4.40 and 4.41.

Reviewer note: The applicant's response analysis in the FAP and PPP indicated that the overall RR (CR + PR) was higher in the TCF group than in the CF group. The difference between the 2 treatment groups was statistically significant (Chi square test) in both FAP and PPP. The result of this secondary endpoint supports the efficacy of TCF.

6.1.6 Efficacy Conclusions

The major strengths of the trial and its results were:

a- This was a randomized, well-designed well-conducted trial. There were few major deviations from protocol. The primary endpoint of the study, TTP was assessed by a central review committee.

b- TTP was prolonged in the TCF arm when compared to CF (HR: 1.47, 95% CI: 1.19-1.83; p=0.0004) in the prespecified FAP. The median TTP in the TCF arm demonstrated a 2-months improvement over that of the CF arm.

c- Several sensitivity analyses were performed, and all were consistent with the primary analysis of TTP.

d- OS was statistically superior in the TCF arm when compared to CF and improved by approximately 0.5 months (HR: 1.29, 95% CI: 1.04-1.6, p=0.02) in the FAP. OS in the ITT population demonstrated a strong trend in favor of TCF (p=0.053).

e- The improvement in OS was observed despite more patients on the control arm received pot-study chemotherapy (TCF=32%; CF: 41%).

f- Response rate was improved by about 10% in the TCF arm demonstrating internal consistency of the results.

There major weakness of the trial were

a- This was an open label trial, and the external review committee was not completely blinded to the results from the investigator. However, an improvement in OS off-sets the weakness of an open-label trial.

b- Some events were based on progression in evaluable, non-evaluable disease and clinical progressions. A sensitivity analysis censoring clinical progressions at the last tumor assessments was consistent with the results of the primary analysis. The numbers of these clinical events were small.

In conclusion, the analyses of the primary and the major secondary endpoints of the study TAX 325a demonstrates clinical benefit of the TCF in the treatment of patients with advanced gastric cancer.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The TAX 325a safety data set and study report were reviewed and the major safety findings are summarized in the following sections. As described in section 6.1.4, Table 7, patient population used for safety analyses, SP, is defined as all subjects treated with at least 1 dose of study therapy and analyzed according to the study medication actually received. Since all treated subjects received the treatment were allocated at randomization, the safety population is identical to the full analysis population.

7.1.1 Deaths
The cause and incidence of death due to AE in TAX325a are summarized below:

Table 20: Death due to AE during TAX 325a Study (SP)

Body system NCICTC Terms	Death due to AE			
	TCF (n = 221)		CF (n = 224)	
	N	%	N	%
Body As A Whole	***10***	***4.52***	***7***	***3***
Cardiovascular	1	0.45	0	0
Gastrointestinal	1	0.45	0	0
Infection with neutropenia	7	3.17	7	3
Pulmonary	1	0.45	0	0
Cardiovascular System	***4***	***1.81***	***6***	***3***
Cardiovascular	4	1.81	6	3
Digestive System	***3***	***1.36***	***3***	***1***
Gastrointestinal	2	0.9	3	1
Hepatic	1	0.45	0	0
Hemic And Lymphatic System	***0***	***0***	***4***	***2***
Blood Bone Marrow	0	0	3	1
Coagulation	0	0	1	0
Metabolic And Nutritional Disorders	***1***	***0.45***	***0***	***0***
Metabolic	0	0	1	0
Genitourinary	1	0.45	0	0
Respiratory System	***2***	***0.9***	***1***	***0***
Infection without neutropenia	0	0	1	0
Pulmonary	2	0.9	0	0
Urogenital System	***0***	***0***	***4***	***2***
Genitourinary	0	0	4	2
Total	***20***	***9.05***	***26***	***12***

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population

Reviewer note: The total death rate was 9% for TCF arm and 12% for CF arm. The causes of death were fairly balanced, except thrombocytopenia (blood bone marrow) and genitourinary hemorrhage resulted death were only seen in CF arm.

To answer the question of whether addition of Taxotere to the CF combination would introduce more treatment related deaths, the applicant summarized all deaths within 60 days of randomization within 30 days and after 30 days of last treatment as follows:

Table 21: Deaths within 60 days of randomization, < 30 or > 30 days of Last Administration of Study Medication

	Number (%) of deaths		
	TCF (N=221)	CF (N=224)	Total (N=445)
Total deaths	**163 (73.8)**	**173 (77.2)**	**336 (75.5)**
Within 60 days from the randomization date	15 (6.8)	20 (8.9)	35 (7.9)
Within 30 days of last administration of study medication	23 (10.4)	19 (8.5)	42 (9.4)
Malignant disease	7 (3.2)	4 (1.8)	11 (2.5)
Toxicity from study medication	6 (2.7)	9 (4.0)	15 (3.4)
Other causes	10 (4.5)	6 (2.7)	16 (3.6)
More than 30 days after last administration of study medication	140 (63.3)	154 (68.8)	294 (66.1)
Malignant disease	129 (58.4)	145 (64.7)	274 (61.6)
Toxicity from study medication	2 (0.9)	3 (1.3)	5 (1.1)
Other causes	9 (4.1)	6 (2.7)	15 (3.4)

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population.
Data source: Appendix C.3.1, Table 10.16.

Reviewer note: The deaths within 60 days of randomization and within 30 days of last administration of study medication i.e., related to the treatment were similar between the TCF and CF arms. In contrast, deaths occurring beyond 30 days of the last administration of study medication due to disease progression were more frequent in the CF treatment group.

7.1.2 Other Serious Adverse Events

The treatment emergent severe toxicity (AEs), regardless the relation to the treatment, are summarized below, and for AEs observed greater by at least 4% are high lighted in yellow for in TCF arm, and high lighted in pink for CF arm.

Table 22: Severe Adverse Events (> 2 Incidences in SP)

Body System NCI/CTC Terms	TCF (n = 221)				CF (n = 224)			
	All Grades		**Grade 3-4**		All Grades		Grade 3-4	
	N	%	**N**	**%**	N	%	**N**	**%**
Body As A Whole								
Cancer Pain	152	68.78	**82**	**37.1**	148	66.07	**81**	**36.16**
Lethargy	168	76.02	**48**	**21.72**	155	69.2	**41**	**18.3**
Infection	55	24.89	**33**	**14.93**	46	20.54	**16**	**7.14**
Pain Chest	15	6.79	**5**	**2.26**	7	3.13	**3**	**1.34**
Fever In Absence Of Infection	85	38.46	**4**	**1.81**	52	23.21	**4**	**1.79**
Gastrointestinal Pain/Cramping	25	11.31	**4**	**1.81**	19	8.48	**9**	**4.02**
Other: Allergic Reaction	23	10.41	**4**	**1.81**	16	7.14	**0**	**0**
Other: Back Pain	4	1.81	**2**	**0.9**	2	0.89	**1**	**0.45**
Other: Pain	6	2.71	**2**	**0.9**	6	2.68	**1**	**0.45**
Cardiovascular System								
Venous	22	9.95	**19**	**8.6**	19	8.48	**17**	**7.59**
Dysrhythmias	11	4.98	**5**	**2.26**	6	2.68	**3**	**1.34**
Hypotension	27	12.22	**5**	**2.26**	17	7.59	**4**	**1.79**
Hypertension	8	3.62	**4**	**1.81**	17	7.59	**7**	**3.13**
Arterial Non Myocardial	2	0.9	**2**	**0.9**	2	0.89	**2**	**0.89**
Cardiac Function	4	1.81	**2**	**0.9**	2	0.89	**1**	**0.45**
Other: Syncope	3	1.36	**2**	**0.9**	1	0.45	**0**	**0**
Digestive System								
Diarrhea	174	78.73	**45**	**20.36**	114	50.89	**18**	**8.04**
Stomatitis	130	58.82	**45**	**20.36**	136	60.71	**60**	**26.79**
Nausea	178	80.54	**36**	**16.29**	189	84.38	**43**	**19.2**
Anorexia	148	66.97	**35**	**15.84**	155	69.2	**30**	**13.39**
Vomiting	154	69.68	**33**	**14.93**	174	77.68	**43**	**19.2**
Esophagitis/Dysphagia/Odynophagia	64	28.96	**12**	**5.43**	53	23.66	**13**	**5.8**
Gastrointestinal Bleeding	25	11.31	**8**	**3.62**	21	9.38	**9**	**4.02**
Small Bowel Obstruction	9	4.07	**6**	**2.71**	4	1.79	**3**	**1.34**
Constipation	72	32.58	**5**	**2.26**	93	41.52	**8**	**3.57**
Fistula	5	2.26	**5**	**2.26**	1	0.45	**1**	**0.45**
Heartburn	46	20.81	**3**	**1.36**	34	15.18	**0**	**0**
Helic And Lymphatic System								
Granulocytes	31	14.03	**29**	**13.12**	27	12.05	**20**	**8.93**
Platelets	11	4.98	**7**	**3.17**	12	5.36	**9**	**4.02**
Hemoglobin	12	5.43	**6**	**2.71**	11	4.91	**7**	**3.13**
White Blood Count	4	1.81	**2**	**0.9**	2	0.89	**1**	**0.45**
Metabolic And Nutritional Disorders								
Creatinine	15	6.79	**4**	**1.81**	22	9.82	**4**	**1.79**
Hyponatremia	3	1.36	**3**	**1.36**	3	1.34	**3**	**1.34**
Edema	42	19	**2**	**0.9**	37	16.52	**2**	**0.89**
Hypokalemia	2	0.9	**2**	**0.9**	1	0.45	**1**	**0.45**
Other: Dehydration	5	2.26	**2**	**0.9**	6	2.68	**1**	**0.45**
Musculoskeletal System								
Myalgia	28	12.67	**4**	**1.81**	21	9.38	**3**	**1.34**
Bone Pain	11	4.98	**3**	**1.36**	3	1.34	**0**	**0**
Nervous System								
Sensory	85	38.46	**17**	**7.69**	57	25.45	**7**	**3.13**

Body System NCI/CTC Terms	TCF (n = 221)				CF (n = 224)			
	All Grades		**Grade 3-4**		All Grades		Grade 3-4	
	N	%	**N**	**%**	N	%	**N**	**%**
Dizziness	36	16.29	**10**	**4.52**	19	8.48	**2**	**0.89**
Motor	20	9.05	**7**	**3.17**	17	7.59	**6**	**2.68**
Cortical, Somnolence	10	4.52	**6**	**2.71**	10	4.46	**7**	**3.13**
Mood	38	17.19	**6**	**2.71**	32	14.29	**2**	**0.89**
Neurologic Pain	8	3.62	**3**	**1.36**	7	3.13	0	0
Respiratory System								
Shortness Of Breath	26	11.76	**6**	**2.71**	29	12.95	**11**	**4.91**
Infection	6	2.71	**3**	**1.36**	8	3.57	**7**	**3.13**
Skin And Appendages								
Alopecia	147	66.52	**11**	**4.98**	92	41.07	**3**	**1.34**
Rash/Itch	27	12.22	**2**	**0.9**	20	8.93	**0**	**0**
Urogenital System								
Other: Creatinine Clearance Decreased	6	2.71	**3**	**1.36**	8	3.57	**0**	**0**
Other: Kidney Failure	2	0.9	**2**	**0.9**	3	1.34	**3**	**1.34**
Vaginal Hemorrhage	4	1.81	**2**	**0.9**	2	0.89	0	0

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population

Reviewer note: There were 17% more infections, 9% more neutropenia, 7% more lethargy, 5% more anorexia, and 4% more sensory neuropathy or dizziness observed in the TCF arm. More patients on the CF arm experienced stomatitis with a difference of 6%.

7.1.3 Dropouts and Other Significant Adverse Events

AEs that lead to interruption or delay of treatment, dose reduction, and termination of treatment are detailed in section 10.1.4.2.5, Table 82. More treatment modifications occurred on TCF arm than that of CF arm, interrupted (10.8% vs. 4.5%), discontinued (26.7% vs 19%), dose reduction (40.7% vs 35.7%), treatment delay (40.7% vs 27.1%), and treatment delay with dose reduction (9.5% vs 5.4%]). However, no treatment modifications were made for myelosuppression.

7.1.4 Other Search Strategies

The major concerns were neutropenic infection or fever, fluid retention, gastrointestinal and neurotoxicity.

7.1.4.1 Infection and fever with or without neutropenia

The grade 3-4 infection with or without neutropenia per subjects and cycle are summarized below:

Table 23: Subjects and cycles with grade 3-4 infection AEs (SP)

Type of AE	Number (%)					
	TCF			CF		
	Grade 3	Grade 4	Grade 3-4	Grade 3	Grade 4	Grade 3-4
Total subjects		**221 (100)**			**224 (100)**	
Regardless of relationship	22 (10.0)	14 (6.3)	36 (16.3)	11 (4.9)	12 (5.4)	23 (10.3)
Treatment related	15 (6.8)	13 (5.9)	28 (12.7)	5 (2.2)	11 (4.9)	16 (7.1)
Total cycles		**1186 (100)**			**906 (100)**	
Regardless of relationship	25 (2.1)	15 (1.3)	40 (3.4)	13 (1.4)	12 (1.3)	25 (2.8)
Treatment related	17 (1.4)	14 (1.2)	31 (2.6)	5 (0.6)	11 (1.2)	16 (1.8)

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population; AE = Adverse event; TEAE =Treatment-emergent adverse events
Data source: Appendix C.3.1, Tables 6.04, 6.05, 6.09, and 6.10.

Infections or fever without infections, regardless of neutropenia, occurred in each subject and any cycle are summarized below:

Table 24: Infection and/or fever in absence of infection by number of cycles per subject regardless of relationship to study medication and neutropenia (SP)

	Number (%) of subjects	
	TCF (N=221)	CF (N=224)
Total subjects with infection and/or fever	120 (54.3)	90 (40.2)
Subjects with 1 cycle with either event	75 (33.9)	61 (27.2)
Subjects with more than 1 cycle with either event	45 (20.4)	29 (12.9)

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population
Data source: Appendix C.3.1, Table 7.08.

The number of subjects with febrile neutropenia and/or neutropenic infection, regardless of G-CSF administration, and regardless of relationship to the study medication in the evaluable (with neutrophil counts assessed) population by subjects (Table 23) and cycles (Table 24) is summarized below:

Table 25: Febrile neutropenia and neutropenic infection in evaluable subjects (SP)

	Number (%) of subjects					
	Regardless of G-CSF		With prophylactic G-CSF		Without prophylactic G-CSF	
	TCF	CF	TCF	CF	TCF	CF
Evaluable subjects	**220 (99.5)**	**222 (99.1)**	**41 (18.6)**	**20 (8.9)**	**219 (99.1)**	**222 (99.1)**
Regardless of relationship						
Febrile neutropenia	36 (16.4)	10 (4.5)	4 (9.8)	0 (0)	33 (15.1)	10 (4.5)
Neutropenic infection	35 (15.9)	23 (10.4)	1 (2.4)	3 (15.0)	34 (15.5)	21 (9.5)
Febrile neutropenia or neutropenic infection	66 (30.0)	30 (13.5)	5 (12.2)	3 (15.0)	62 (28.3)	29 (13.1)
Related to study medication						
Febrile neutropenia	35 (15.9)	8 (3.6)	4 (9.8)	0 (0)	32 (14.6)	8 (3.6)
Neutropenic infection	31 (14.1)	20 (9.0)	1 (2.4)	3 (15.0)	30 (13.7)	18 (8.1)
Febrile neutropenia or neutropenic infection	63 (28.6)	27 (12.2)	5 (12.2)	3 (15.0)	59 (26.9)	25 (11.3)
Death from febrile neutropenia[a] or neutropenic infection[a]	5 (2.3)	7 (3.2)	0 (0)	1 (5.0)	5 (2.3)	6 (2.7)

a Regardless of relationship to study medication.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population; G-CSF = Granulocyte colony-stimulating factor
Data source: Appendix C.3.1, Tables 7.01, 7.02, and 7.03.
Note: evaluable subjects: denominator is safety population

Reviewer note: The safety population, 'SP', used by applicant to summarize neutropenic fever and infection in Table 25 was 4 subjects less (2 on each arm) than the safety population defined by protocol. However, this minor change of the denominators only minimally affected the results.

Neutropenia was observed in 95% patients (all grade) and 82.3% patients (grade 3/4) in the TCF arm vs. 83.3% patients (all grade) and 56.8% patients (grade 3/4) in the CF arm. GCSF as used in less than 20% of the patients (18.6% for TCF and 8.9% for CF). The number of deaths was similar in both arms.

Table 26: Febrile neutropenia and neutropenic infection in evaluable cycles by age (regardless of G-CSF, SP)

	Number (%) of cycles					
	Overall		Age <65 years		Age ≥65 years	
	TCF	CF	TCF	CF	TCF	CF
Evaluable cycles	**1168 (98.5)**	**891 (98.3)**	**927 (98.5)**	**686 (98.6)**	**241 (98.4)**	**205 (97.6)**
Regardless of relationship						
Febrile neutropenia	43 (3.7)	11 (1.2)	27 (2.9)	7 (1.0)	16 (6.6)	4 (2.0)
Neutropenic infection	37 (3.2)	25 (2.8)	24 (2.6)	18 (2.6)	13 (5.4)	7 (3.4)
Febrile neutropenia or neutropenic infection	80 (6.8)	36 (4.0)	51 (5.5)	25 (3.6)	29 (12.0)	11 (5.4)
Related to study medication						
Febrile neutropenia	42 (3.6)	8 (0.9)	26 (2.8)	6 (0.9)	16 (6.6)	2 (1.0)
Neutropenic infection	33 (2.8)	22 (2.5)	20 (2.2)	15 (2.2)	13 (5.4)	7 (3.4)
Febrile neutropenia or neutropenic infection	75 (6.4)	30 (3.4)	46 (5.0)	21 (3.1)	29 (12.0)	9 (4.4)

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population; G-CSF = Granulocyte colony-stimulating factor
Data source: Appendix C.3.1, Tables 7a.06, and 7.06.

Reviewer note: Death from febrile neutropenia or neutropenic infection was less frequent during cycles in which G-CSF was administered. Of the 12 subjects in this study who died from neutropenic infection or febrile neutropenia, only one had received prophylactic G-CSF during the cycle when death occurred. However, the study was not designed to examine the role of primary prophylaxis with G-CSF in TCF treated advanced gastric cancer patients.

In addition, of the 80 cycles in the TCF treatment group having febrile neutropenia and/or neutropenic infection, 30 occurred during the first treatment cycle (13.5% of the study subjects). Of the 36 cycles in the CF treatment group having febrile neutropenia and/or neutropenic infection, 18 occurred during the first treatment cycle (8%, TAX 325a study report, Appendix C.3.1, Table 7.48). (b) (4) *reviewer further requested the applicant to summarized first cycle neutropenia, neutropenic fever, and infection and verified the data as shown below:*

Table 27: First Cycle Neutropenia, Neutropenic Fever, and Infection (Evaluable Population)

Treatment/ Parameter	Number (%) of patients					
	Total evaluable	Grade 1	Grade 2	Grade 3	Grade 4	Any
TCF						
Neutropenia	220 (100)	23 (10.5)	30 (13.6)	40 (18.2)	60 (27.3)	153 (69.5)
Febrile Neutropenia	220 (100)	-	-	-	15 (6.8)	15 (6.8)
Neutropenic infection	220 (100)	-	-	4 (1.8)	11 (5.0)	15 (6.8)
CF						
Neutropenia	222 (100)	33 (14.9)	44 (19.8)	36 (16.2)	34 (15.3)	147 (66.2)
Febrile Neutropenia	222 (100)	-	-	-	7 (3.2)	7 (3.2)
Neutropenic infection	222 (100)	-	-	3 (1.4)	8 (3.6)	11 (5.0)

Data source: TAX325a data sets

Reviewer note: Although grade 3-4 neutropenia occurred on TCF arm during the first cycle are almost two fold to that of CF arm, the grade 1-3 neutropenia and grade 3 neutropenic infection were comparable between the two arms. In addition, during study TAX325a, less than 20% of subjects (18.6 for TCF and 8.9 for CF) and only 10.0% of TCF cycles and 3.3% of CF cycles prophylaxis with G-CSF after occurrence of neutropenia. (b) (4)

Subjects at or over the age of 65 years appeared to be more prone to developing infections in this study. In the TCF treatment group, 21.9% of subjects over the age of 65 years developed grade 3-4 infection, regardless of relationship to study drug, compared to 14.4% of subjects under the age of 65 years. The majority of these grade 3-4 infections were observed during neutropenic episodes.

Reviewer note: The elderly age group may thus particularly benefit from strategies that mitigate the risk of neutropenic infection.

7.1.4.2 Fluid retention

The other safety concern on TCF arm is taxotere related fluid retention, which are summarized below:

Table 28: Subjects with fluid retention (SP)

Fluid retention characteristic	Number (%) of subjects	
	TCF (N=221)	CF (N=224)
Any sign of fluid retention	33 (14.9)	9 (4.0)
Edema	29 (13.1)	7 (3.1)
Pleural effusion	2 (0.9)	1 (0.4)
Peripheral edema	2 (0.9)	1 (0.4)
Ascites	1 (0.5)	0 (0)
Face edema	1 (0.5)	0 (0)
Pericardial effusion	1 (0.5)	0 (0)

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population
Data source: Appendix C.3.1, Table 7.14.

Reviewer note: Fluid retention was predominately observed in the TCF treatment arm. In 11 subjects, the fluid retention began during Cycle 1 the incidence of fluid retention increased with increasing cumulative doses of Taxotere. It is note worthy that of the 33 TCF-treated subjects who developed fluid retention, 29 subjects (87.9%) had an onset of fluid retention when the Taxotere cumulative dose was <400 mg/m^2.

7.1.4.3 Gastrointestinal toxicity

Gastrointestinal AEs, regardless of relationship, were the most common body system in both treatment groups, with stomatitis, nausea, vomiting, and diarrhea occurring frequently in both groups. Grade 3-4 stomatitis was more frequent in the CF treatment group (27.2%) compared to the TCF treatment group (20.8%), while grade 3-4 diarrhea occurred more in the TCF treatment group (20.4%) compared to the CF treatment group (8.0%). Overall, diarrhea of any grade regardless of relationship to study medication, occurred in 77.8% of subjects in the TCF group, as compared with 49.6% in the CF group. However, in these subjects, the diarrhea appeared tolerable or manageable, since less than 5% of cycles were impacted by grade 3-4 diarrhea and only 3 subjects (1.4%) discontinued TCF due to diarrhea. Subjects in the TCF treatment group at or over the age of 65 similarly had a greater frequency of any grade diarrhea, regardless of relationship to study medication, compared to younger subjects (88.9% in subjects 65 years of age or older compared to 74.3% in subjects under age 65). The difference in frequency by age group is less for grade 3-4 diarrhea (<65years old: 19.2%, =65 years old: 24.1%). GI related AEs were the predominant reasons for dose reductions within the study (occurring in 26.7% of TCF-treated subjects and 22.3% of CF-treated subjects).

7.1.4.4 Neurotoxicity

Neurosensory adverse events are a known toxicity for both Taxotere and cisplatin. In this study, neurosensory AEs of any grade, regardless of relationship, occurred in 38.0% of TCF-treated subjects and 24.6% of CF-treated subjects. These AEs were the most frequently reported TEAE leading to treatment discontinuation among TCF subjects, with 8.6% of subjects in the TCF treatment group discontinuing treatment due to neurosensory AEs, compared to 3.6% of subjects in the CF treatment group. However, discontinuation of treatment due to neurosensory AEs occurred in later cycles, with no TCF subject discontinuing treatment due to neurosensory AEs prior to the fourth cycle.

7.1.5 Common Adverse Events

The reviewer summarized commonly seen (≥ 5%) treatment emergent AEs regardless the relationship to the study treatment in Table 29. For AEs observed 4% or more are highlighted in yellow for in TCF arm, and in pink for CF arm (Table 29).

Table 29: Common Toxicity (Treatment Emergent AEs, ≥ 5% in SP)

Body System NCI/CTC Terms	TCF (n = 221)				CF (n = 224)			
	All Grades		Grade 3-4		**All Grades**		Grade 3-4	
	N	**%**	N	%	**N**	**%**	N	%
Body As A Whole								
Lethargy	**168**	**76.02**	48	21.72	**155**	**69.2**	41	18.3
Cancer Pain	**152**	**68.78**	82	37.1	**148**	**66.07**	81	36.16
Fever In Absence Of Infection	**85**	**38.46**	4	1.81	**52**	**23.21**	4	1.79
Infection	**55**	**24.89**	33	14.93	**46**	**20.54**	16	7.14
Local Toxicity	**33**	**14.93**	0	0	**19**	**8.48**	3	1.34
Gastrointestinal Pain/Cramping	**25**	**11.31**	4	1.81	**19**	**8.48**	9	4.02
Headache	**23**	**10.41**	1	0.45	**27**	**12.05**	0	0
Other: Allergic Reaction	**23**	**10.41**	4	1.81	**16**	**7.14**	0	0
Pain Chest	**15**	**6.79**	5	2.26	**7**	**3.13**	3	1.34
Cardiovascular System								
Hypotension	**27**	**12.22**	5	2.26	**17**	**7.59**	4	1.79
Venous	**22**	**9.95**	19	8.6	**19**	**8.48**	17	7.59
Dysrhythmias	**11**	**4.98**	5	2.26	**6**	**2.68**	3	1.34
Digestive System								
Nausea	**178**	**80.54**	36	16.29	**189**	**84.38**	43	19.2
Diarrhea	**174**	**78.73**	45	20.36	**114**	**50.89**	18	8.04
Vomiting	**154**	**69.68**	33	14.93	**174**	**77.68**	43	19.2
Anorexia	**148**	**66.97**	35	15.84	**155**	**69.2**	30	13.39
Stomatitis	**130**	**58.82**	45	20.36	**136**	**60.71**	60	26.79
Constipation	**72**	**32.58**	5	2.26	**93**	**41.52**	8	3.57
Esophagitis/Dysphagia/Odynophagia	**64**	**28.96**	12	5.43	**53**	**23.66**	13	5.8
Heartburn	**46**	**20.81**	3	1.36	**34**	**15.18**	0	0
Gastrointestinal Bleeding	**25**	**11.31**	8	3.62	**21**	**9.38**	9	4.02
Flatulence	**13**	**5.88**	0	0	**21**	**9.38**	1	0.45
Other: Dyspepsia	**11**	**4.98**	0	0	**12**	**5.36**	0	0

Body System NCI/CTC Terms	TCF (n = 221)				CF (n = 224)			
	All Grades		Grade 3-4		**All Grades**		Grade 3-4	
	N	**%**	N	%	**N**	**%**	N	%
Helic And Lymphatic System								
Granulocytes	**31**	**14.03**	29	13.12	**27**	**12.05**	20	8.93
Hemoglobin	**12**	**5.43**	6	2.71	**11**	**4.91**	7	3.13
Platelets	**11**	**4.98**	7	3.17	**12**	**5.36**	9	4.02
Metabolic And Nutritional Disorders								
Edema	**42**	**19**	2	0.9	**37**	**16.52**	2	0.89
Creatinine	**15**	**6.79**	4	1.81	**22**	**9.82**	4	1.79
Myalgia	**28**	**12.67**	4	1.81	**21**	**9.38**	3	1.34
Arthralgia	**18**	**8.14**	1	0.45	**9**	**4.02**	0	0
Bone Pain	**11**	**4.98**	3	1.36	**3**	**1.34**	0	0
Nervous System								
Sensory	**85**	**38.46**	17	7.69	**57**	**25.45**	7	3.13
Insomnia	**60**	**27.15**	1	0.45	**41**	**18.3**	2	0.89
Mood	**38**	**17.19**	6	2.71	**32**	**14.29**	2	0.89
Dizziness	**36**	**16.29**	10	4.52	**19**	**8.48**	2	0.89
Motor	**20**	**9.05**	7	3.17	**17**	**7.59**	6	2.68
Respiratory System								
Cough	**27**	**12.22**	0	0	**25**	**11.16**	0	0
Shortness Of Breath	**26**	**11.76**	6	2.71	**29**	**12.95**	11	4.91
Hiccough	**23**	**10.41**	0	0	**20**	**8.93**	1	0.45
Other: Rhinitis	**14**	**6.33**	0	0	**7**	**3.13**	0	0
Skin And Appendages								
Alopecia	**147**	**66.52**	11	4.98	**92**	**41.07**	3	1.34
Rash/Itch	**27**	**12.22**	2	0.9	**20**	**8.93**	0	0
Dry Skin	**20**	**9.05**	0	0	**10**	**4.46**	0	0
Nail Changes	**18**	**8.14**	0	0	**0**	**0**	0	0
Special Senses								
Taste,Sense Of Smell Altered	**20**	**9.05**	0	0	**11**	**4.91**	0	0
Tearing	**18**	**8.14**	0	0	**5**	**2.23**	1	0.45
Altered Hearing	**17**	**7.69**	0	0	**30**	**13.39**	4	1.79

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population

Reviewer note: For incidence of common toxicities, TCF arm observed 28% more diarrhea, 25% more alopecia, 9% more insomnia, 8% more of dizziness or nail changes, 6% more tearing, 5% more fever without infection, infection, esophogitis, or heart burn, and 4% more hypotension, arthralgia, dry skin, or altered taste. Whereas the CF arm observed 9% more constipation, 8% more vomiting, and 6% more altered hearing.

7.1.7 Laboratory Findings

7.1.7.1 Hematology

The hematological safety concerns that related to myelosupressin are summarized as below:

Table 30: Leukopenia in evaluable subjects and evaluable cycles by worst grade with regard to prophylactic G-CSF (SP)

Treatment	Number (%)						
	Total evaluable	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3-4	Any grade
Subjects							
Regardless of G-CSF							
TCF	220 (99.5)	26 (11.8)	41 (18.6)	98 (44.5)	46 (20.9)	144 (65.5)	211 (95.9)
CF	223 (99.6)	40 (17.9)	70 (31.4)	51 (22.9)	19 (8.5)	70 (31.4)	180 (80.7)
Without G-CSF							
TCF	219 (99.1)	26 (11.9)	41 (18.7)	96 (43.8)	45 (20.5)	141 (64.4)	208 (95.0)
CF	223 (99.6)	40 (17.9)	71 (31.8)	51 (22.9)	18 (8.1)	69 (30.9)	180 (80.7)
With G-CSF							
TCF	41 (18.6)	5 (12.2)	15 (36.6)	14 (34.1)	3 (7.3)	17 (41.5)	37 (90.2)
CF	20 (8.9)	3 (15.0)	4 (20.0)	4 (20.0)	1 (5.0)	5 (25.0)	12 (60.0)
Cycles							
Regardless of G-CSF							
TCF	1176 (99.2)	213 (18.1)	306 (26.0)	286 (24.3)	64 (5.4)	350 (29.8)	869 (73.9)
CF	896 (98.9)	229 (25.6)	200 (22.3)	76 (8.5)	21 (2.3)	97 (10.8)	526 (58.7)
Without G-CSF							
TCF	1057 (89.1)	190 (18.0)	277 (26.2)	261 (24.7)	61 (5.8)	322 (30.5)	789 (74.6)
CF	866 (95.6)	225 (26.0)	193 (22.3)	71 (8.2)	20 (2.3)	91 (10.5)	509 (58.8)
With G-CSF							
TCF	119 (10.0)	23 (19.3)	29 (24.4)	25 (21.0)	3 (2.5)	28 (23.5)	80 (67.2)
CF	30 (3.3)	4 (13.3)	7 (23.3)	5 (16.7)	1 (3.3)	6 (20.0)	17 (56.7)

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population; G-CSF = Granulocyte colony-stimulating factor
Data source: Appendix C.3.1, Tables 8.01, 8.02, 8.03, 8.05, 8.06, and 8.07.
Note: for "total evaluable" the denominator was safety population

Reviewer note: In review of hematology laboratory findings, it is notable that 15% more any grade, 22% more grade 3, and 12% more leucopenia for subjects on TCF arm comparing to that of CF arm. Leukopenia of any grade and grade 3-4 was more frequent in TCF evaluable cycles than in CF evaluable cycles, regardless the use of G-CSF. A total of 61 subjects, 41 in the TCF treatment group and 20 in the CF treatment group, received G-CSF (13.8% of the evaluable subjects) in a total of 149 cycles (7.2% of the evaluable cycles) as secondary prophylaxes. (b) (4)

Table 31: Anemia in evaluable subjects and evaluable cycles by worst grade with regard to prophylactic EPO or RBC transfusions (SP)

Treatment	Number (%)						
	Total evaluable	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3-4	Any grade
Subjects							
Regardless of EPO/RBC							
TCF	220 (99.5)	58 (26.4)	115 (52.3)	37 (16.8)	3 (1.4)	40 (18.2)	213 (96.8)
CF	223 (99.6)	58 (26.0)	93 (41.7)	49 (22.0)	8 (3.6)	57 (25.6)	208 (93.3)
Without EPO/RBC							
TCF	220 (99.5)	61 (27.7)	114 (51.8)	35 (15.9)	3 (1.4)	38 (17.3)	213 (96.8)
CF	222 (99.1)	60 (27.0)	92 (41.4)	47 (21.2)	8 (3.6)	55 (24.8)	207 (93.2)
With EPO/RBC							
TCF	16 (7.2)	4 (25.0)	10 (62.5)	2 (12.5)	0 (0)	2 (12.5)	16 (100.0)
CF	12 (5.4)	5 (41.7)	4 (33.3)	3 (25.0)	0 (0)	3 (25.0)	12 (100.0)
Cycles							
Regardless of EPO/RBC							
TCF	1176 (99.2)	522 (44.4)	440 (37.4)	50 (4.3)	3 (0.3)	53 (4.5)	1015 (86.3)
CF	896 (98.9)	367 (41.0)	289 (32.3)	64 (7.1)	9 (1.0)	73 (8.1)	729 (81.4)
Without EPO/RBC							
TCF	1126 (94.9)	497 (44.1)	426 (37.8)	47 (4.2)	3 (0.3)	50 (4.4)	973 (86.4)
CF	871 (96.1)	357 (41.0)	280 (32.1)	61 (7.0)	9 (1.0)	70 (8.0)	707 (81.2)
With EPO/RBC							
TCF	50 (4.2)	25 (50.0)	14 (28.0)	3 (6.0)	0 (0)	3 (6.0)	42 (84.0)
CF	25 (2.8)	10 (40.0)	9 (36.0)	3 (12.0)	0 (0)	3 (12.0)	22 (88.0)

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population; EPO = Erythropoietin; RBC = Red blood cell
Data source: Appendix C.3.1, Tables 8.01, 8.02, 8.03, 8.05, 8.06 and 8.07.
Note: for "total evaluable" the denominator was safety population

Reviewer note: Anemia of all grade and Grade 3-4 was less frequent in TCF-treated subjects compared to CF-treated subjects, regardless of the use of EPO or RBC transfusions. However, the use of prophylactic EPO or RBC transfusions was infrequent in this study (occurring in only 28 evaluable subjects in 75 cycles). Regardless of the use, in the absence or in the presence of EPO/RBC transfusions, the percentage of any grade anemia was similar in both treatment groups, while grade 3-4 anemia occurred slightly more frequently in the CF treatment group.

Table 32: Thrombocytopenia in evaluable subjects and cycles by worst grade (SP)

Treatment	Number (%)						
	Total evaluable	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3-4	Any grade
Subjects							
TCF	220 (99.5)	23 (10.5)	16 (7.3)	8 (3.6)	9 (4.1)	17 (7.7)	56 (25.5)
CF	223 (99.6)	33 (14.8)	24 (10.8)	14 (6.3)	16 (7.2)	30 (13.5)	87 (39.0)
Cycles							
TCF	1176 (99.2)	63 (5.4)	35 (3.0)	10 (0.9)	11 (0.9)	21 (1.8)	119 (10.1)
CF	896 (98.9)	82 (9.2)	44 (4.9)	20 (2.2)	20 (2.2)	40 (4.5)	166 (18.5)

Thrombocytopenia: grade 1 = 75.0 x 10^9/L – 99.9 x 10^9/L, grade 2 = 50.0 x 10^9/L - 74.9 x 10^9/L, grade 3 = 25.0 x 10^9/L - 49.9 x 10^9/L, grade 4 <25.0 x 10^9/L.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population.
Data source: Appendix C.3.1, Tables 8.01, and 8.05.
Note: for "total evaluable" the denominator was safety population.

Reviewer note: Although thrombocytopenia was infrequently observed in study TAX 325a, the percentage of subjects and cycles with any grade or grade 3-4 thrombocytopenia was higher in the CF treatment group than in the TCF treatment group.

7.1.7.2 Chemistry

The laboratory testing, liver function tests and serum chemistry are summarized below:

Table 33: Liver function tests by worst grade (SP)

Test/ Treatment	Number (%) of subjects						
	Total evaluable	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3-4	Any grade
ALAT							
TCF	211 (95.5)	46 (21.8)	8 (3.8)	1 (0.5)	0 (0)	1 (0.5)	55 (26.1)
CF	213 (95.1)	25 (11.7)	7 (3.3)	2 (0.9)	0 (0)	2 (0.9)	34 (16.0)
ASAT							
TCF	211 (95.5)	52 (24.6)	5 (2.4)	3 (1.4)	0 (0)	3 (1.4)	60 (28.4)
CF	213 (95.1)	38 (17.8)	5 (2.3)	1 (0.5)	0 (0)	1 (0.5)	44 (20.7)
Alkaline phosphatase							
TCF	211 (95.5)	104 (49.3)	15 (7.1)	6 (2.8)	0 (0)	6 (2.8)	125 (59.2)
CF	209 (93.3)	87 (41.6)	13 (6.2)	5 (2.4)	0 (0)	5 (2.4)	105 (50.2)
Total bilirubin							
TCF	210 (95.0)	-	6 (2.9)	11 (5.2)	7 (3.3)	18 (8.6)	24 (11.4)
CF	214 (95.5)	-	9 (4.2)	11 (5.1)	5 (2.3)	16 (7.5)	25 (11.7)

ALT, AST, alk phosphatase: grade 1 < 2.5 x UNL, grade 2 = 2.6 - 5.0 x UNL, grade 3 = 5.1 - 2.0 x UNL, Grade 4 >20 x UNL. Bilirubin: grade 1 was not defined in NCIC-CTC scale, grade 2 <1.5 x UNL, grade 3 = 1.5 - 3.0 x UNL grade 4 > 3.0 x UNL
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population
Data source: Appendix C.3.1, Table 9.01.
Note: for "total evaluable" the denominator was safety population.

Reviewer note: Abnormal liver function test appear to be infrequent: few subjects had grade 3 abnormalities in either treatment group and no subjects had grade 4 abnormalities in AST, ALT, or alkaline phosphatase. There were no obvious differences between treatment arms.

Table 34: Selected serum chemistry by worst grade (SP)

Test/ Treatment	Number (%) of subjects						
	Total evaluable	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3-4	Any grade
Creatinine (increase)							
TCF	213 (96.4)	44 (20.7)	19 (8.9)	2 (0.9)	2 (0.9)	4 (1.9)	67 (31.5)
CF	217 (96.9)	51 (23.5)	31 (14.3)	6 (2.8)	0 (0)	6 (2.8)	88 (40.6)
Hypokalemia							
TCF	212 (95.9)	53 (25.0)	27 (12.7)	4 (1.9)	2 (0.9)	6 (2.8)	86 (40.6)
CF	216 (96.4)	25 (11.6)	25 (11.6)	5 (2.3)	4 (1.9)	9 (4.2)	59 (27.3)
Hypomagnesemia							
TCF	189 (85.5)	57 (30.2)	52 (27.5)	9 (4.8)	3 (1.6)	12 (6.3)	121 (64.0)
CF	182 (81.3)	63 (34.6)	24 (13.2)	4 (2.2)	1 (0.5)	5 (2.7)	92 (50.5)

Creatinine increased: grade 1: <1.5 x UNL, grade 2: 1.5-3.0 x UNL, grade 3: 3.1–6.0 x UNL, grade 4: >6.0 x UNL.
Hypokalemia: grade 1: 3.1–3.5 mmol/L, grade 2: 2.6–3.0 mmol/L, grade 3: 2.1–2.5, grade 4: =2.0 mmol/L.
Hypomagnesemia: grade 1: 0.70–0.58 mmol/L, grade 2: 0.57–0.38 mmol/L, grade 3: 0.37–0.30, grade 4: =0.29 mmol/L.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population
Data source: Appendix C.3.1, Table 9.01.
Note: for "total evaluable" the denominator was safety population

Reviewer note: Only few subjects presented with grade 3-4 abnormalities. There were no obvious differences between treatment groups. However, 227 patients has declined (≥ grade 1) of total protein 56%), 136 on TCF arm and 91 on CF arm (45.3%).

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The data set used for safety analysis is from TAX 325a study as detailed in the appendix, protocol review section 10.1. The patient narratives, CRFs and CTRs are well documented and organized for review.

7.2.1.1 Study type and design/patient enumeration

The detailed information of TAX325a study design, schedule, location, and treatment group are detailed in appendix 10.1, protocol review section.

Demographics

The patient characteristics of study TAX 325a are summarized below:

Table 35: Demographics at baseline (FAP)

Characteristic	Unit	TCF (N=221)	CF (N=224)	Total (N=445)
Gender				
Men	N (%)	159 (71.9)	158 (70.5)	317 (71.2)
Women	N (%)	62 (28.1)	66 (29.5)	128 (28.8)
Race				
White[a]	N (%)	157 (71.0)	158 (70.5)	315 (70.8)
Hispanic	N (%)	44 (19.9)	40 (17.9)	84 (18.9)
Asian[b]	N (%)	7 (3.2)	12 (5.4)	19 (4.3)
Black	N (%)	5 (2.3)	4 (1.8)	9 (2.0)
Other	N (%)	8 (3.6)	10 (4.5)	18 (4.0)
Age [years]	Median (range)	55 (26-79)	55 (25-76)	55 (25-79)
<65 years	N (%)	167 (75.6)	169 (75.4)	336 (75.5)
≥65 years	N (%)	54 (24.4)	55 (24.6)	109 (24.5)
KPS before first infusion	Median	90	90	90
≥90	N (%)	141 (63.8)	143 (63.8)	284 (63.8)
100	N (%)	28 (12.7)	29 (12.9)	57 (12.8)
90	N (%)	113 (51.1)	114 (50.9)	227 (51.0)
80	N (%)	77 (34.8)	78 (34.8)	155 (34.8)
70	N (%)	3 (1.4)	3 (1.3)	6 (1.3)
% Weight loss in prior 3 months	Median (range)	7 (0-37)	7 (0-35)	7 (0-37)
≤5%	N (%)	95 (43.0)	96 (42.9)	191 (42.9)
>5%, ≤10%	N (%)	64 (29.0)	67 (29.9)	131 (29.4)
>10%	N (%)	62 (28.1)	60 (26.8)	122 (27.4)
Missing value	N (%)	0 (0)	1 (0.4)	1 (0.2)
Appetite before first infusion				
Very poor	N (%)	5 (2.3)	6 (2.7)	11 (2.5)
Poor	N (%)	46 (20.8)	52 (23.2)	98 (22.0)
Fair	N (%)	76 (34.4)	62 (27.7)	138 (31.0)
Good	N (%)	86 (38.9)	97 (43.3)	183 (41.1)
Excellent	N (%)	4 (1.8)	4 (1.8)	8 (1.8)
Missing value	N (%)	4 (1.8)	3 (1.3)	7 (1.6)

a. Term on case report form was Caucasian.
b Term on case report form was Oriental.

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population; KPS = Karnofsky performance status
Data source: TAX 325a study report, Appendix C. 1.1, Table 2.01.

Reviewer Note: *Both treatment groups appear to be comparable for demographics at baseline. Most subjects in the FAP were men (71.2%) and White (70.8%). The median age of subjects was 55 years (range: 25 to 79 years) with 24.5% of subjects ≥ 65 years. There were only 3 subjects ≥ 75 years of age, 2 TCF-treated subjects and 1 CF-treated subject. The median percentage of weight loss over the 3 months preceding enrollment was 7% (range of 0% to 37%). At baseline, a weight loss of > 5% was noted in more than half (56.8%) of the subjects, and more than half (55.5%) of the subjects reported their appetite as fair, poor or very poor. The median KPS was 90, with 227 (51.0%) subjects in the FAP having a score of 90, 57 (12.8%) with a KPS of 100 and 284 (63.8%) with a score of ≥ 90. In summary, the more than 70% of FAP patients were white, male, younger than 65 years and with good performance status.*

7.2.1.3 Extent of exposure (dose/duration)

Information on chemotherapy dosage and duration are provided for the SP. The doses of each study medication were individually adjusted according to the protocol and Amendments I and II. Exposure to study medication in the treated population was measured in terms of the cumulative dose (mg/m^2), the actual dose intensity (mg/m^2/week) and the RDI, and is shown in Table 36. The median actual dose intensity for all study medications was close to the planned dose intensity. The relative dose intensities for cisplatin and 5-FU were similar for the TCF and the CF treatment groups, despite the differences in dose and cycle duration. Subjects were exposed at a similar dose intensity of 5-FU and cisplatin in both treatment groups.

Table 36: Cumulative dose, actual dose intensity, and relative dose intensity (SP)

	TCF			CF	
	Taxotere	**Cisplatin**	**5-FU**	**Cisplatin**	**5-FU**
Number of subjects who received study chemotherapy	221	221	221	224	224
Cumulative dose (mg/m^2)					
Median	431.97	383.18	18830.84	393.27	19575.27
(Minimum-maximum)	72.00-1117.00	72.00-1055.48	250.00-52691.85	73.05-996.95	1129.53-49659.16
Actual dose intensity (mg/m^2/week)					
Median	22.96	22.79	1106.67	24.07	1181.31
(Minimum-maximum)	12.08-27.88	9.22-27.88	83.33-1394.09	6.27-30.47	282.38-1523.51
Relative dose intensity					
25th percentile	0.84	0.83	0.80	0.88	0.85
Median	0.92	0.91	0.89	0.96	0.95
75th percentile	0.97	0.97	0.97	1.00	0.99

5-FU = 5-Fluorouracil; TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population Data
Source: Appendix C. 1.1, Table 3.05.

Subjects who received full doses on time would have had an intended dose intensity of 25 mg/m^2/week for Taxotere and cisplatin, and of 1250 mg/m^2/week for 5-FU. Treatment duration expressed in weeks is shown below:

Table 37: Study chemotherapy delivery-duration of treatment (SP)

	TCF	CF
Number of subjects who received study medication	221	224
Duration of chemotherapy (weeks)		
Median	19	16
(Minimum-maximum)	3-56	4-50

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population
Data source: TAX 325a study report, Appendix C. 1.1, Table 3.03.

As mentioned in the study design, , the same dose intensity of cisplatin and 5-FU was maintained in both treatment arm, 25 mg/m^2/week for cisplatin and 1250 mg/m^2/week for 5-FU. The reviewer agrees that the 2 treatment groups were similar with respect to the duration of treatment, with a median duration of chemotherapy that tended to be slightly longer in the TCF group. The median cumulative drug exposure for cisplatin and 5-FU over time was not higher in the TCF-treatment group compared to the CF-treatment group.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

1. The analysis of the safety database of TAX 325a demonstrates that the tolerability and overall safety of Taxotere (75 mg/m²) in combination with cisplatin (75 mg/m²) and 5-FU (750 mg/m² x 5 days) every 3 weeks (TCF) is generally comparable to that of cisplatin (100 mg/m²) plus 5-FU (1000 mg/m² x 5 days) every 4 weeks (CF) in the treatment of subjects with metastatic gastric cancer, with the exceptions of neutropenia, infection, diarrhea, and neurosensory toxicity.

2. Most subjects entered this study symptomatic, reflecting the advanced disease of these subjects. A total of 84% of subjects presented with one or more clinical signs or symptoms at baseline, and 26.5% of subjects had grade 3 or 4 signs or symptoms, with a balanced distribution across treatment groups. Both regimens could be delivered at planned dosages in the majority of subjects, although 41.2% of TCF-treated subjects and 36.2% of CF-treated subjects were administered reduced dosages during the course of the study. The median relative dose intensities achieved in both treatment groups was greater than 90% for all drugs except for 5-FU in TCF treatment (89%), with the predominant reason for dose adjustments being non-hematological toxicity. Total treatment duration tended to be longer in the TCF treatment group (median 19 weeks) compared to the CF treatment group (16 weeks).

3. Treatment emergent AEs (AEs), regardless of relationship to study medication, were observed in all TCF-treated subjects and in all but 3 CF-treated subjects, and in most treatment cycles for both treatment groups. They were apparent within the safety profiles of each group. Among the most frequent AEs regardless of relationship to study medication, diarrhea, neurosensory, infection and fever in the absence of infection, and alopecia, were all more frequent by >10% of subjects in the TCF treatment group than the CF treatment group.

4. NCIC-CTC grade 3-4 AEs, regardless of relationship to study medication, were experienced by 81.4% of TCF-treated subjects and 75.4% of CF-treated subjects. The 5 most frequently observed grade 3-4 AEs in the TCF treatment group, regardless of relationship to study medication, were cancer pain (37.1%), lethargy (21.7%), stomatitis (20.4%), diarrhea (20.4%), and infection (14.9%). The 5 most frequent grade 3-4 AEs observed in the CF treatment group, regardless of relationship to study medication, were cancer pain (36.2%), stomatitis (26.8%), nausea (19.2%), vomiting (19.2%), and lethargy (18.3%).

5. Although a higher incidence of grade 3-4 TEAE and TE-SAE was seen in the TCF treatment group, the TEAE related mortality rate was comparable between treatment groups, with 20 (9%) for TCF-treated subjects and 26 (12%) for CF-treated subjects. The leading cause of AE related death were infection, which was fairly balanced between the two arms (3% for both arm in SP). In addition, the death within 60 days of randomization was 6.8% for TCF-treated subjects and 8.9% of CF-treated subjects. The frequency of deaths within 30 days of last administration of study medication was also comparable, with 23 (10.4%) deaths in the TCF treatment group, and 19 (8.5%) deaths in the CF treatment group. Deaths within 30 days of the last administration of study medication from causes other than malignant disease (i.e., due to toxicity or other cause), were nearly the same in both treatment groups: 16 subjects in the TCF treatment group and 15 subjects in the CF treatment group. In contrast, deaths occurring beyond 30 days of the last administration of study medication were more frequent in the CF treatment group, and were usually attributed to malignant disease.

6. Comparing treatment modification or discontinuation between the TCF and CF arms, more treatment cycles were interrupted (10.8% vs. 4.5%), discontinued (26.7% vs 19%), dose reduction (40.7% vs 35.7%), treatment delay (40.7% vs 27.1%), and treatment delay with dose reduction (9.5% vs 5.4%). In one word, there were more treatment modification occurred on TCF arm. However, there was no treatment modification due to myelosupression. The most frequent causes for treatment discontinuation were GI toxicities, flu-like symptoms and neurosensory toxicity.

7. Overall, within the TCF treatment group, infection, fever in the absence of infection, GI toxicities, and neurosensory toxicity were key AEs impacting the incidence of TE-SAE, discontinuation, or non-malignant death.

- More infections observed on the TCF arm, occurring at any grade regardless of relationship to study medication in 29.4% of TCF-treated subjects, and in 22.8% of CF-treated subjects. Grade 3-4 infections regardless of relationship were observed in 16.3%

of TCF-treated subjects compared to 10.3% of CF-treated subjects. Fever in the absence of infection was observed in 35.7% of TCF-treated subjects and in 22.8% of CF-treated subjects. Serious infections occurred in 18.6% of TCF-treated subjects compared to 12.5% of CF-treated subjects, with 14.9% of TCF-treated subjects and 7.6% of CF-treated subjects having serious infections that were considered study-medication related. Similarly, TE-SAEs of fever in the absence of infection occurred in 16.7% of TCF-treated subjects, all being considered study-medication related, and in 4.5% of CF-treated subjects, all but one being considered study-medication related. Seven of the 16 non-malignant deaths occurring within 30 days of the last administration of study medication in the TCF treatment group were attributed to infection or moniliasis, as were 6 of the 15 non-malignant deaths in the CF treatment group, with all but one being considered related to study medication. In addition, 1 subject in the TCF treatment group and 2 subjects in CF treatment group died beyond 30 days of the last administration of study medication from infection considered related to study medication.

- Gastrointestinal AEs, regardless of relationship, were the most common body system TEAE in both treatment groups, with stomatitis, nausea, vomiting, and diarrhea occurring frequently in both groups. Grade 3-4 stomatitis was more frequent in the CF treatment group (27.2%) compared to the TCF treatment group (20.8%), while grade 3-4 diarrhea occurred more in the TCF treatment group (20.4%) compared to the CF treatment group (8.0%). Overall, diarrhea of any grade regardless of relationship to study medication, occurred in 77.8% of subjects in the TCF group, as compared with 49.6% in the CF group. However, in these subjects, the diarrhea appeared tolerable or manageable, since less than 5% of cycles were impacted by grade 3-4 diarrhea and only 3 subjects (1.4%) discontinued TCF due to diarrhea. Subjects in the TCF treatment group at or over the age of 65 similarly had a greater frequency of any grade diarrhea, regardless of relationship to study medication, compared to younger subjects (88.9% in subjects 65 years of age or older compared to 74.3% in subjects under age 65). The difference in frequency by age group is less for grade 3-4 diarrhea (<65years old: 19.2%, =65 years old: 24.1%). GI related AEs were the predominant reasons for dose reductions within the study (occurring in 26.7% of TCF-treated subjects and 22.3% of CF-treated subjects).

- Neurosensory adverse events are a known toxicity for both Taxotere and cisplatin. In this study, neurosensory AEs of any grade, regardless of relationship, occurred in 38.0% of TCF-treated subjects and 24.6% of CF-treated subjects. These AEs were the most frequently reported TEAE leading to treatment discontinuation among TCF subjects, with 8.6% of subjects in the TCF treatment group discontinuing treatment due to neurosensory AEs, compared to 3.6% of subjects in the CF treatment group. However, discontinuation of treatment due to neurosensory AEs occurred in later cycles, with no TCF subject discontinuing treatment due to neurosensory AEs prior to the fourth cycle.

8. ADDITIONAL CLINICAL ISSUES

8.6 Literature Review

Gastric cancer is the second most common cause of cancer- related deaths in the world[1]. It is estimated that 755 000 new cases are diagnosed world wide annually[2]. As ranked 14th in incidence among the major types of cancers, the estimated new cases and deaths from gastric cancer in the United States for 2003 are 22400 and 12,100 respectively[3-5].

Currently, a cure for patients with gastric cancer is only for those diagnosed with early stage disease in which a complete surgical resection can be performed. Even in these patients, many (35 - 80%) will develop recurrences[6-8]. The estimated 5-year survival rates, with standard treatment modalities, by stage are: 60 - 90% for Stage I; 30 - 40% for Stage II; 10 - 25% for Stage III and < 5% for Stage IV[9, 10]. In the United States, the 5-year survival rate for gastric cancer of all stages is only 22%. In Europe, it ranges from 27% in Italy (Romagna) to 8% in Poland[11].

Presently, the treatment of advanced gastric cancer is primarily palliative and confers a minimal impact on overall survival [10, 12, 13]. Multiple agents are active in gastric cancer, including fluoropyrimidines (such as 5-FU), platinum agents, anthracyclines, taxanes, irinotecan, gemcitabine, mitomycin-C, and etoposide[7, 14]. However, with single-agent treatment, response rate (RR) is low (from 15% to 36%) and combination treatment, such as Cisplatin + 5-FU, has been the standard in gastric cancer chemotherapy[14].

(b) (4)

The approval of 5-FU in early 60's was based on a single arm, single agent phase 2 study in patients with a wide spectrum of solid tumors, including epithelial malignancies arising in the breast, gastrointestinal tract, head and neck, and ovary, with response rate of 10-30% [15]. The clinical experience with 5-FU is particularly extensive in colorectal cancer where clinical studies directly demonstrated that continuous infusion (CIV) of 5-FU increases efficacy and lowers toxicity in comparison with bolus infusion of 5- FU[16-18].

Single-agent CIV 5-FU has been studied in gastric cancer clinical trials. A 14-subject phase II study in the late 1980s of 5-FU (initial dose of 300 mg/m^2/day) CIV in first-and second-line gastric carcinoma showed a 31% RR[19]. Grade 2-3 toxicity (mucositis, hand- foot syndrome) was observed in 7 subjects. In the single agent 5-FU arm (1000 mg/m^2/day CIV x 5) of a Korean 3 arm comparative study[20], 102 previously untreated advanced gastric cancer subjects, the RR was 26% (with a median duration of response of 31.7 weeks), median TTP was 9.1 weeks and overall survival (OS) was 30.6 weeks. Toxicity (grade $\geq$ 2) was mostly non-hematologic with nausea/vomiting in 25.5% of the subjects, alopecia in 21.3%, and stomatitis in 10.6%. These results indicate that CIV of 5-FU is feasible in gastric carcinoma, has substantial activity, and has a low incidence of severe hematologic toxicities. With 426 cycles administered, there were only 2 cases of grade 3 anemia, 1 grade 3 leukopenia, and no cases of grade 2-4 thrombocytopenia.

To achieve greater clinical benefit, combination chemotherapy has been tested in gastric cancer. 5-FU has been, almost universally, the basis for designing combination therapies for advanced gastrointestinal (GI) malignancies. Cisplatin is synergistic with 5-FU in the treatment of a large number of tumor types[21, 22]. Pre-clinical experiments have shown that this synergy is probably due to a reduction by 5-FU of the platinum- DNA adduct removal[22]. As shown in Table 38, studies of the cisplatin + 5-FU (CF) combination in gastric cancer have been published[20, 23-27]. In 3 European multicenter trials (2 phase II[24, 25] and 1 phase III[13]), the same CF regimen was evaluated: cisplatin 100 mg/m^2, day1 and 5-FU 1000 mg/m^2/day CIV for 5 days administered every 4 weeks. Comparative trials of CF and single agent 5-FU CIV in gastric cancer patients has also been reported[20, 27]. The Korean trial mentioned above is a prospective, randomized study of 5-FU and cisplatin (FP) versus 5-FU, doxorubicin, and mitomycin C (FAM) versus 5-FU alone (FU) in previously untreated patients with advanced gastric cancer is reported[20]. A total of 324 patients were entered into the trial and 295 patients (103 for FP, 98 for FAM, 94 for FU) were evaluable. Prior to randomization, the patients were stratified by performance status, presence of measurable disease, and resection of the primary tumor. The overall response rate for patients with measurable disease in the FP arm was significantly higher than in the FAM and FU arms (51% for FP; 25% for FAM; 26% for FU). The durations of response for each arm, however, were not significantly different. Even though the median time to progression for the FP arm (21.8 weeks) was statistically significant longer than that for the FAM arm (12 weeks; $P < 0.05$) and for the FU arm (9.1 weeks; $P < 0.005$), there was no statistical difference in overall survival among the three arms. In more recent Japanese prospective, randomized, controlled study[27], CF was directly compared to 5-FU CIV and with uracil and tegafur plus mitomycin (UFTM) in previously untreated subjects with advanced gastric cancer (n = 280). The UTFM arm was terminated after interim analysis due to inferior survival and uncontrollable hematologic toxicity. The RR was significantly higher with CF (34%) than with 5-FU (11%, $p< 0.0001$). Progression free survival was significantly longer with CF (3.9 months) than with 5- FU (1.9 months, $p<0.001$) but no difference in survival. In both studies, incidences of leukopenia, anemia, nausea, vomiting and peripheral neuropathy, although considered manageable, was higher with the CF combination than with 5- FU single-agent CIV.

Table 38: Published and Sponsor's Studies of cisplatin + CIV 5-FU in first line chemotherapy of Advanced Gastric Cancer

Investigator/study	*Cisplatin (mg/m^2)*	*5- FU (mg/m^2)*	*Cycle duration (weeks)*	*Patients enrolled [evaluable]*	*CR+ PR (%) [95% CI]*	*Median PFS/TTP (months) [95% CI]*	*Median survival (months) [95% CI]*
Lacave 1991 [24] Phase II	*100 D1*	*1000/day D 1-5*	*4*	*56 [53]*	*42 [28- 55]*	*NP*	*10.6 [NP]*
Rougier 1994 [25] Phase II	*100 D1*	*1000/day D 1-5*	*4*	*87 [83]*	*43 [30-56]*	*NP*	*9.0 [NP]*
Vanhoefer 2000 [13] Phase III	*100 D1*	*1000/day D 1-5*	*4*	*134 [125]*	*20 [11.5-30.0]*	*4.1[a] [3.8- 5.4]*	*7.2 [6.3-9.0]*
Kim 1993 [20] Phase III	*60 D1*	*1000 D 1-5*	*3*	*112 [103]*	*51 [NP]*	*5.0[bc] [NP]*	*8.5 [NP]*
Ohtsu 2004 [27] Phase III	*20 D 1-5*	*800 D 1-5*	*4*	*105 [99]*	*34 [25-44]*	*3.9[a] [3.1- 4.8]*	*7.3 [6.0-9.7]*

a PFS
b TTP
c 21.8 weeks in the publication
NP = Not provided; CR = Complete response; PR = Partial response; TTP = time to progression; PFS = Progression-free survival; CI = Confidence
Interval; c. i. = Continuous infusion; 5- FU = 5- fluorouracil; D = Day/Cycle

As one of the Taxanes, the activity of single-agent Taxotere in first-line chemotherapy of advanced gastric cancer subjects was demonstrated in 3 phase II clinical trials, 1 each from Europe, the United States (both 100 mg/m^2 IV every 3 weeks), and Japan (60 mg/m^2 IV every 3 weeks). In the European study[28], 8 of 33 (24%) evaluable subjects achieved a partial response (PR) with a median duration of response of 7.5 months (range, 3 to > 11). Grade 3-4 neutropenia was the major toxicity (95% of subjects) with febrile neutropenia reported in 20% of subjects and 5% of cycles. In the United States (ECOG 1293) study[29] of 41 subjects, 2 complete responses (CRs) and 5 PRs in 36 (19%) evaluable subjects were observed. Grade 4 neutropenia was reported in 88% of subjects. The dose of Taxotere was reduced in 54% of subjects. The Japanese trial[30] was a multicenter study (TAX 287) where 59 of 76 subjects were evaluable for response and 1 CR plus 13 PRs (24%) were observed. The combination of Taxotere and cisplatin has also been studied in advanced solid tumor and gastric cancer[31, 32].

In a combination with both cisplatin and 5-FU approach, the Swiss Group for Clinical Cancer Research and the European Institute of Oncology, in a phase I/II study (TAX 707) added CIV 5-FU to the Taxotere and cisplatin combination (TCF) in 43 subjects with advanced gastric cancer[33]. Each 3-week cycle consisted of Taxotere + cisplatin + protracted CIV 5-FU. The maximum tolerated dose and recommended dose was Taxotere 75 mg/m^2 and cisplatin 85 mg/m^2 on Day 1 and 300 mg/m^2/day 5-FU CIV x 2 weeks repeated every 3 weeks. The dose limiting toxicities were febrile neutropenia and mucositis and diarrhea. Main grade 3-4 toxicities by subjects reported during the study were neutropenia (79%), alopecia (46%), fatigue (23%), and diarrhea (19%). Febrile neutropenia occurred in 15% of subjects. Overall RR was 51% in measurable population (24/41) and median OS was 9.3 months. Neither full study reports nor data sets of both studies, TAX 287 and TAX 707, were included in this NDA.

Based on the previous studies results, the applicant has designed a comparative study (TAX 325) to evaluated Taxotere add on to cisplatin and 5-FU combination, with a run in phase II to evaluated 5-FU add on to Taxotere and cisplatin combination. The result of TAX 325 study is the main key component of this NDA application.

9 OVERALL ASSESSMENT

9.1 Conclusions

TAX 325 was a randomized, open label, well-designed and well-conducted trial in which the TCF regimen demonstrated superior efficacy in terms of TTP, OS and RR over CF in patients with advanced gastric carcinoma. No unexpected AE were observed on the TCF arm and overall, the toxicity was acceptable. Neutropenia, infection, diarrhea, and neurosensory toxicity were more frequent with TCF but others, such as stomatitis, anemia and thrombocytopenia, were less when compared to the CF arm. SAEs were more frequent in the TCF treatment group reflecting a greater incidence of neutropenia, fever in the absence of infection and diarrhea observed in TCF-treated subjects. (b) (4).

9.2 Recommendation on Regulatory Action

Taxotere to be approved for first line treatment in patients with advanced gastric carcinoma.

9.4 Labeling Review

Taxotere is being marketed with the present trade name for other approved indications. The proposed label change was reviewed as follows.

(b) (4)

5 Pages Immediately Following Withheld - b(4) Draft Labeling

10 APPENDICES

10.1 Review of Individual Study Reports

The study TAX 325/TAX325a is the key study of this application. Of which, the study TAX325a, the phase 3 portion of the study is most relevant to the indication. Therefore, the protocol and study result review is focused on the study TAX325a.

10.1.1 Protocol Review

10.1.1.1 Protocol Title

Open label, randomized multicenter phase II/ III study of docetaxel in combination with cisplatin or docetaxel in combination with 5-fluorouracil and cisplatin compared to the combination of cisplatin and 5-fluorouracil in patients with metastatic or locally recurrent gastric cancer previously untreated with chemotherapy for advanced disease.

10.1.1.2. Important dates

April 10, 1998: the original phase II/ III protocol (RP56976- V- 325) was implemented. During the entire study, three amendments and five administrative changes were made to the protocol.

August 17, 1999: the Independent Data Monitoring Committee (IDMC) met on August 17, 1999 and recommended to select Taxotere + cisplatin + 5-FU (TCF) as the test treatment in the phase III part of the study.

October 8, 1999: protocol Amendment 1 was issued following the recommendation by the IDMC meeting to implement TCF treatment in arm B of TAX 325a, the phase 3 part of study. In this amendment, the following items were added to the protocol:

- Along with adding a summary of the data supporting the IDMC's decision to the study protocol, the primary objective of the phase III part of the study was changed to detect a statistically significant increase in time to progression (TTP) for the test group relative to the control group. Survival became the main secondary endpoint. An increase of the sample size, calculated to have 95% power on survival to demonstrate a 1.5 hazard ratio (HR) benefit, to a total of 460 subjects (230/group), enabled a testing of both TTP and survival for statistically significance differences.
- The approximate number of study centers was changed to 75, and Mexico was added as a participating country.

- Percentage of weight loss during the last 3 months (= 5% and > 5%) was added as a stratification parameter.
- The full analysis population (FAP) and per-protocol population (PPP) were defined to replace the intent-to-treat and evaluable populations.

October 8, 1999: TAX 325a, the phase III part of the study was initiated.

March 1, 2001: Amendment 2. The following main modifications were incorporated into the protocol:

- The enrollment period was extended from 32 to 52 months (revised end date: August 2002) and the planned duration of the study from 44 to 64 months (revised end date: August 2003).
- The randomization/stratification criteria were modified from "liver and/or peritoneal metastasis" to "liver metastasis" only.
- The criteria for the evaluation of a tumor response were clarified. To be evaluable for response, a subject must have had 2 cycles of treatment except in the case of early progression and not, as previously defined, 2- 3 cycles. The tumor assessments were to be every 8 weeks (± 1 week) calculated from the date of first treatment administration.
- For the reporting of adverse events (AEs) and signs and symptoms of disease, the conventions described in the case report form (CRF) completion guidelines were to be used.

August 2003: Enrollment of the study was ended.

Cut off days:
May 20 2003 – Clinical cut off date. Data from all treatment cycles or follow-up segments that were ongoing at this date were included in the final database.
March 5 2003 – TTP cut off date. The date of the 325th event (both treatment groups combined) was used for censoring "325 event" TTP analysis.
March 7 2003 - The cut-off date for the end-of-study TTP analysis was the date of the latest occurring TTP event in the database.
(b) (6) – the date of 325th death (both treatment groups combined) was used for censoring in the 325 events OS analysis.
Mat 19 2003 – cut off date for the end-of-study OS analysis, taken conservatively as the earliest date of the reporting window (19 May 2003, 28 May 2003) on the final " Survival Update" CRF.

10.1.1.3. Study Sites:

The TAX 325, phase II part of the study, included 34 study sites. The TAX 325a, the phase 3 part of the study involved 100 study centers. The regions and countries where the study centers located are listed in the table below.

Table 39: Study Sites Location

Region	Country
Asia	Taiwan
EU	Belgium, Italy, Portugal, Spain
Eastem and Central Europe	Slovakia Republic, Russia
North America	Canada, USA
South America	Argentina, Brazil, Chile, Columbia,

10.1.1.4. Objectives

Phase II, TAX 325:
Primary Objective: to select one of the 2 test arms (docetaxel with cisplatin, docetaxel with cisplatin and 5-FU), based primarily on complete responses, to advance to a phase III survival comparison against the CDDP+ 5-FU control arm.
Secondary Objectives: to evaluate the quantitative and qualitative safety profile of the 2 test groups.

Phase III, TAX 325a:
Primary Objective: to detect a statistically significant increase in time to progression (TTP) for the selected test am relative to CDDP + 5-FU control arm.
Main Secondary Objectives: To detect a statistically significant increase in Overall survival (OS) for the test group (TCF) relative to the control group (CF).

Reviewer note: It is unusual to identify a secondary endpoint as "main" Perhaps it is due to the revision following FDA's recommendation to power the study with survival endpoint.

Other Secondary Objectives: To compare

- response rates,
- time to treatment failure,
- duration of response,
- safety profiles,
- quality of life and disease-related symptoms.
- Socio-economic data will be collected in order to be able to perform an analysis by country when necessary.

10.1.1.5. Study Design

As described in section 6.1.3 study design.

10.1.1.6. Eligibility

Inclusion Criteria

- Patient's consent form obtained, signed and dated before beginning specific protocol procedures.
- Gastric adenocarcinoma including adenocarcinoma of the esophagogastric junction, histologically proven.
- Measurable and/or evaluable metastatic disease; if a single metastatic lesion is the only manifestation of the disease, cytology or histology is mandatory. Locally recurrent disease is accepted provided that there is at least one measurable lesion (e.g. lymph node).
- Age $\geq$ 18 years.
- Karnofsky performance status > 70%.
- Life expectancy of more than 3 months.
- Adequate haematological parameters (Hb $\geq$ 10 g/dl, ANC $\geq$ 2.0 x 10^9/l, platelets > 100x10^9/l).
- Creatinine < 1.25 x upper normal limit (UNL) or < 120 pmol/l; if creatinine value is borderline, creatinine clearance should be performed.
- Total bilirubin 1 x UNL, AST (SGOT) and ALT (SGPT) < 2.5 x UNL, alkaline phosphatase < 5 x UNL.
- No prior palliative chemotherapy, previous adjuvant (and/or neo-adjuvant) chemotherapy is allowed if more than 12 months has elapsed between the end of adjuvant (or neo-adjuvant) therapy and first relapse.
- At least 6 weeks from prior radiotherapy and 4 weeks from surgery.
- Complete initial work-up within two weeks prior to inclusion for imaging and within 8 days prior to inclusion for clinical evaluation and biological work-up. Abdominal CT scan (and chest X-ray for phase II only) is mandatory.
- Able to comply with scheduled follow-up and with management of toxicity.
- Quality of life baseline questionnaire filled in before date of randomization.
- For phase II only:
  -Prothrombin time not less than 50% of lower normal value
  (This criterion applies to phase II part only).
  -Planned date of first treatment within 8 days from inclusion.
  -Chest X-ray is mandatory.

Exclusion criteria:

- Pregnant or lactating women.
- Patients (M/F) with reproductive potential not implementing adequate contraceptive measures.
- Other tumor type than adenocarcinoma (leiomyosarcoma; lymphoma).
- Any prior palliative chemotherapy. Prior adjuvant (and/or neo-adjuvant) chemotherapy with a first relapse within 12 months from the end of adjuvant (or neo-adjuvant).
- Prior treatment with taxanes. Prior CDDP as adjuvant (and/or neo-adjuvant) chemotherapy with cumulative dose > 300 mg/m^2.

- Previous or current malignancies other than gastric carcinoma, with the exception of adequately treated in situ carcinoma of the cervix uteri or non melanoma skin cancer.
- Patients with known brain or leptomeningeal metastases
- Symptomatic peripheral neuropathy > grade 2 by NCIC-CTG criteria.
- Other serious illness or medical conditions:
    - unstable cardiac disease despite treatment, myocardial infarction within 6 months prior to study entry
    - history of significant neurologic or psychiatric disorders including dementia or seizures
    - active uncontrolled infection
    - active disseminated intravascular coagulation
    - renal insufficiency (phase II only)
    - severe hypercalcemia (phase II only)
    - other serious underlying medical conditions which could impair the ability of the patient to participate in the study
- Concurrent treatment with corticosteroids (or equivalent) except as use for the prophylactic medication regimen, treatment of acute hypersensitivity reactions or unless chronic treatment (initiated > 6 months prior to study entry) at low doses (< 20 mg methyl prednisolone or equivalent).
- Definite contraindications for the use of corticosteroids.
- Creatinine dearance < 60 ml/mn (if creatinine value is borderline).
- Liver impairment with AST and/or ALT > 1.5 x UNL associated with alkaline phosphatase > 2.5 x UNL.
- Hypercalcimia not controlled by bisphosphonates and > 12mg/dl (phase III only)
- Concurrent or within 4 week period administration of any other experimental drugs.
- Concurrent treatment with any other anti-cancer therapy.
- Patients cleahy intending to withdraw from the study if not randomized in a given arm.

10.1.1.7. Treatment Plan

The regimens used for each study arms during each study phase are detailed in Table 6.

Although the dose of cisplatin and 5-FU on the Arm B was 75% of that of Arm C, the dosing interval (schedule) of Arm B was shorter, three weeks, than that of Arm C, 4 weeks. Therefore, the same dose intensity of cisplatin and 5-FU was maintained in both treatment arm, 25 mg/m^2/week for cisplatin and 1250 mg/m^2/week for 5-FU.

Neither the protocol or the study report of TAX325a has indicated there is a limitation on the maximal treatment cycles were to be administered for both study arms. Patients will continue to receive treatment if they are responding.

The pre-treatment medications are summarized below:

Table 40: Pre-treatment Medications

Corticosteroids
The following regimen was given to all subjects treated with Taxotere in order to prevent the onset of HSR and to reduce and/or delay the occurrence of skin toxicity and fluid retention related to Taxotere. Dexamethasone, 8 mg per dose for a total of 6 doses: 1. Night before chemotherapy (Day - 1). 2. Immediately upon waking the morning of chemotherapy (Day 1). 3. One hour before infusion of Taxotere (Day 1). 4. Night of chemotherapy (Day 1). 5. Morning of the day after chemotherapy (Day 2). 6. Evening of the day after chemotherapy (Day 2). If dexamethasone was not commercially available or the dosage form was too low, the equivalent medication to 8 mg of dexamethasone was: • Methylprednisolone at 40 mg per dose; • Prednisone or prednisolone at 50 mg per dose.
Antiemetic
An antiemetic medication for cisplatin was mandatory and was left to current hospital practices. One suggested premedication was: • Ondansetron: 8 mg i. v. at hour 6 (beginning of cisplatin infusion), hour 10, hour 14; and • Dexamethasone: 20 mg i. v. at hour 6 and hour 14. The use of metoclopramide was left to the investigator's judgment.
Hydration
An adequate hydration scheme was mandatory for cisplatin administration and followed current hospital practices. One suggested saline hydration schema was: • hour 0: Glucose 5% 1 L + NaCl 6 g + KCl 3 g + MgSO4: 1 vial. • hour 3: Glucose 5% 1 L + NaCl 6 g + KCl 3 g + MgSO4: 1 vial. • hour 6: Infusion of cisplatin. • hour 7: Glucose 5% 1 L + NaCl 6 g + KCl 3 g + MgSO4: 1 vial. • hour 10: Glucose 5% 1 L + NaCl 6 g + KCl 3 g + MgSO4: 1 vial. • hour 13: End of infusion.
Granulocyte-colony stimulating factor (G-CSF)
G-CSF was recommended during the second and/or subsequent cycles in case of febrile neutropenia, or documented infection with neutropenia, or neutropenia lasting more than 7 days. One suggested usage in prophylaxis was: Granocyte ® (lenogastrim): 150 µg (19.2 million International Units [MIU])/m^2/day or equivalent. 1. Starting on Day 4 following chemotherapy, G-CSF was to be administered once daily until Day 11. 2. On Day 11, a complete blood count (CBC) with differential was to be performed. If the ANC was = 1.0 x 10^9/L, then injections were to be stopped. If the ANC was < 1.0 x 10^9/L, then injections were to be continued to complete 10 days of therapy, Day 13 included.
Amifostine
The prophylactic use of amifostine (WR-2721s, Ethyol®) was not permitted.

10.1.1.8. Dose Modification

Doses were modified in the case of severe hematologic and/or non-hematologic toxicities. Toxicities were to be graded using the NCIC-CTC. Some toxicities prompted more than 1 drug in the combination to be reduced in dose, e. g., diarrhea. In the case of stomatitis and diarrhea, the first dose reduction was applied to 5-FU. If, despite the 5-FU reduction, stomatitis or diarrhea

recurred, Taxotere was then reduced. Some specific toxicities did not require any dose modification, e. g., HSRs.

If a subject experienced several toxicities and there were conflicting recommendations, the most conservative dose adjustment was recommended (a dose reduction appropriate to the most severe toxicity). Except for liver and renal function abnormalities, doses that were reduced for toxicity were not re-escalated. Two consecutive dose reductions were to be applied in case of toxicity. If, despite dose reductions and/or a maximum of 2-week delay, the same toxic complications persisted, study treatment was discontinued, unless anti-neoplastic efficacy justified continuation.

Two dose reductions might be applied to each individual drug during the study, as shown below.

Table 41: Dose adjustments for each drug in both treatment regimens

Treatment regimen	Treatment	Initial dose (mg/m^2)		Dose reduction 1 (mg/m^2)		Dose reduction 2 (mg/m^2)
TCF	Taxotere	75	→	60	→	45
	Cisplatin	75	→	60	→	45
	5-FU	750 (x 5 days)	→	600 (x 5 days)	→	450 (x 5 days)
CF	Cisplatin	100	→	80	→	65
	5-FU	1000 (x 5 days)	→	800 (x 5 days)	→	650 (x 5 days)

Data source: TAX 325a study report appendix A: Clinical study protocol Section 6.6.1

i Taxotere dose modifications and treatment delays

Myelosuppression

Table 42: Dose adjustments of Taxotere according to neutrophil and platelet nadirs

Neutrophil nadir in cycle ($\times 10^9$/L)		Platelet nadir ($\times 10^9$/L)	Taxotere dose following cycle
≥0.5	and	≥25	No change
<0.5 lasting ≤7 days without fever			No change
<0.5 lasting for more than 7 days, and/or in case of fever (single oral temperature ≥38.5°C or 3 elevations to ≥38.1°C during a 24-h period).	or	<25	First episode of febrile neutropenia or documented infection, give G-CSF in subsequent cycles. Grade 4 thrombocytopenia or second episode of febrile neutropenia (despite G-CSF), reduce Taxotere dose by 20%. Third episode of febrile neutropenia, reduce Taxotere dose again by 20%. Fourth episode of febrile neutropenia, discontinue subject from treatment.

G-CSF = Granulocyte colony stimulating factor

Febrile neutropenia was defined as grade 2 fever (single oral temperature = 38.5 °C or 3 elevations to = 38.1 °C during a 24-hour period) concomitant with grade 4 neutropenia (ANC < 0.5 x 10^9 cells/L). In case of febrile neutropenia, blood counts were to be performed every 2 days until recovery to ANC = 0.5 x 10^9 cells/L or temperature < 38.1 ° C (100.6 ° F).

Fever was graded using the NCIC-CTC criteria. The reported temperature was the oral or equivalent temperature. In cases of grade 2 fever concomitant with grade 4 neutropenia, the following approach was recommended:

• Hospital admission except where out-patient care was indicated.
• Pre-antibiotic evaluation.
• CBC with differential and blood culture should be performed.
• Start an empirical broad spectrum antibiotic therapy.

Dose adjustments were made depending on the neutrophil and platelet count on Day 21.

Table 43: Dose adjustment according to the neutrophil and platelet counts on Day 21

Counts on Day 21 Neutrophil (x 10^9/L)		Platelet (x 10^9/L)	Next Taxotere dose
> or = 1.5	and	> or = 100	Treat on time, dose adjustments according to nadir (Table 42)
< 1.5	and/or	< 100	Delay treatment a maximum of 2 weeks. Blood counts were performed twice a week until recovery. Dose adjustments were according to nadir (Table 42). If there was no recovery after 2 weeks of delay, the subject was discontinued from treatment.

Source: TAX 325a study report 3.3.3.

Cutaneous reactions

No dose modification or delay was required for grade 0, 1, or 2 cutaneous reactions. In the event of a grade 3 cutaneous reaction, the dose of Taxotere was delayed until a grade $\geq$ 1 reaction was recorded, and then the subject received a dose of Taxotere reduced by 20%. If no recovery to grade $\geq$ 1 within 2 weeks' delay was achieved, the subject was to be withdrawn from the study. In the event of a grade 4 cutaneous reaction, the subject was withdrawn from the study. Nail changes did not motivate dose modification.

Diarrhea

If diarrhea was observed, supportive treatment could be given (loperamide, rehydration). In the case of grade 3 diarrhea, 5-FU was reduced by 20%. For recurrent grade 3 diarrhea, the dose of Taxotere was reduced by 20%. In the case of grade 4 diarrhea, Taxotere and 5-FU were reduced by 20%. For recurrent grade 4 diarrhea, the subject was discontinued from the study.

Stomatitis

If stomatitis was observed, a mouth rinse was permitted as a curative or prophylactic treatment for the next cycles. In the case of grade 3 stomatitis lasting more than 48 hours, the 5-FU dose was reduced by 20%. In the case of recurrent grade 3 stomatitis, 5-FU administration was stopped at all subsequent cycles. In the case of a third episode, the Taxotere dose was reduced by 20%. In the case of grade 4 stomatitis, 5-FU administration was stopped at subsequent cycles. In the case of recurrent grade 4 stomatitis, the Taxotere dose was then reduced by 20%.

Impaired liver function

In the event of an abnormal bilirubin level (> UNL), the next cycle of treatment was delayed for a maximum of 2 weeks. If there was no recovery to $\leq$ 1 x UNL, then the subjects was withdrawn from chemotherapy.

If abnormal ALAT and/or ASAT and/or alkaline phosphatase levels were observed in the absence of progressive disease (PD), the following dose modifications were to be applied:

Table 44: Dose adjustment according to abnormal liver function tests

ALAT/ASAT (x UNL)		Alkaline phosphatase (x UNL)	Dose modification
≤1.5		≤5	No dose modification
>1.5 to ≤2.5		≤2.5	No dose modification
>2.5 to ≤5.0		≤2.5	Dose of Taxotere reduced by 20%
>1.5 to ≤5.0		>2.5 to ≤5.0	Dose of Taxotere reduced by 20%
>5.0	and/or	>5 (unless bone metastasis were present in the absence of liver disorder)	Dose delayed by a maximum of 2 weeks. If no recovery to the above values observed, the subject was discontinued from the study.

UNL = Upper normal limit

Once the Taxotere dose was reduced due to impaired liver function, no further dose reduction was recommended, providing no worsening in liver function was observed. If the liver function tests had recovered by the next cycle, the dose was re- escalated to the previous dose level.

ii Cisplatin dose modifications and delays

Peripheral neuropathy

A neurological examination was part of the physical examinations performed before entry in to the study, and then at least every 2 cycles and at the end of treatment. In the case of neurological signs or symptoms, more frequent examinations were to be performed and the following dose modification could be made according to NCIC-CTC grade:
• Grade 0 or 1: No change.
• Grade 2: Dose of cisplatin reduced by 20%.
• Grade 3: Subject withdrawn from protocol therapy.

The same guidelines also apply for subjects with grade 1 peripheral neuropathy at baseline.

Ototoxicity

In the case of grade 3 toxicity, the subject was withdrawn from the study.

Nephrotoxicity

In the event of a rise in serum creatinine ≥ grade 2 (> 1.5 x normal value) despite adequate rehydration, CrCl was to be determined before each subsequent cycle and the following dose reductions were to be considered:

Table 45: Dose Reductions for Evaluation of Creatinine Clearance

Creatinine clearance result before next cycle	Cisplatin dose next cycle
CrCl ≥60 mL/min	Full dose of cisplatin was given. CrCl was to be repeated before each treatment cycle.
CrCl between 40 and 59 mL/min	Dose of cisplatin was reduced by 50% at subsequent cycle. If CrCl was >60 mL/min at end of cycle, full cisplatin dose was reinstituted at the next cycle. If no recovery was observed, then cisplatin was omitted from the next treatment cycle.
CrCl <40 mL/min7	Dose of cisplatin was omitted in that treatment cycle only. If CrCl was still <40 mL/min at end of cycle, cisplatin was discontinued. If CrCl was >40 and <60 mL/min at end of cycle, a 50% cisplatin dose was given at the next cycle. If CrCl was >60 mL/min at end of cycle, full cisplatin dose was given at the next cycle.

CrCl = Creatinine clearance

iii 5- FU dose modifications and treatment delays

Stomatitis

If stomatitis was observed, a mouth rinse was permitted as a curative or prophylactic treatment for the next cycles. In case of grade 3 stomatitis lasting more than 48 hours, 5-FU dose was reduced by 20%. In case of recurrent grade 3 stomatitis, 5-FU administration was stopped at subsequent cycles. In case of a third episode, Taxotere dose was to be reduced by 20%. In case of grade 4 stomatitis, 5-FU administration was stopped at all subsequent cycles. In case of recurrent grade 4 stomatitis, Taxotere dose was then reduced by 20%.

Diarrhea

If diarrhea was observed, supportive treatment could be given (loperamide, rehydration). In the case of grade 3 diarrhea, 5-FU was reduced by 20%. For recurrent grade 3 diarrhea, the dose of Taxotere was reduced by 20%. In the case of grade 4 diarrhea, 5-FU and Taxotere were reduced by 20%. For recurrent grade 4 diarrhea, the subject was discontinued from the study.

Plantar-palmar syndrome • In the event of grade ≥ 2 plantar-palmar toxicity, 5-FU was stopped until recovery. The 5-FU dosage was then reduced by 20%.

Other toxic events

Other toxic events were to be managed symptomatically. For grade ≥ 3 toxicities, except alopecia and anemia, chemotherapy was delayed (for a maximum of 2 weeks from the planned date of infusion) until resolution to grade ≤ 1 and then recommenced, if medically appropriate. Dose reduction was to be discussed between the investigator and the Sponsor.

10.1.1.9. Study Assessments

The timeline for all study assessments is taken from applicant's study report:

Table 46: Overview of study assessments

Assessments	PRE-STUDY	CHEMOTHERAPY			FOLLOW-UP	
	Within x days prior to first infusion[a]	Every cycle (before next infusion)	Every 8 weeks (on Day 56, 112, 168...)	End of treatment (30 days after last infusion)	Every 8 weeks	Every 3 months until death
Informed consent	14 days prior to randomization					
History	8					
Physical exam (including weight, appetite, height and KPS)	8	X		X	X[h]	X[h]
Neurology	8		If clinically indicated			
Prior/concomitant medications	14	X		X		
AEs[b]/existing signs and symptoms	14	X		X	X[c]	X[c]
Hematology[d]	8	weekly		X		
Blood chemistry[e]	8	X		X		
Creatinine clearance	8					
Radiology and tumor measurements	14		X[f]	X	X[g]	
Quality of life	8 days prior to randomization		X[f]	X	X[h]	X[h]
Socioeconomics		X		X		X[i]
Other investigations	8		If clinically indicated			

a. Every effort was to be made to start the treatment within 48 hours after randomization.
b AEs were to be recorded and graded according to the NCIC-CTC. Investigators were to objectively report all AEs, including those not related to treatment (e. g., disease-related symptoms) in the case report form, applying conventions described in the case report form completion guidelines.
c AEs that are possibly/probably, platelet counts, and hemoglobin.
e Alkaline phosphatase, bilirubin, ASAT, ALAT, serum creatinine, calculated creatinine clearance, magnesium, potassium, total protein.
f Tumor assessments and quality of life administration were to be performed every 8 ± 1 weeks. Radiologic assessments were to be repeated a minimum of 4 weeks after initial observation of complete response or partial response.
g Tumor assessments were required every 8 ± 1 weeks in follow- up, calculated from the first treatment administration, until the documentation of progression for subjects who did not progress at end of treatment.
h Assessment of weight, appetite, KPS and quality of life administration was required every 8 ± 1 weeks in follow-up until the documentation of progression for subjects who did not progress at end of treatment and every 3 months.
i Hospital admissions were to be collected in follow- up until a second line treatment was administered, if any.
Hematological/ biochemical data will be checked by the investigator before each treatment cycle in order to assess if absolute neutrophil count is > 1.5 x 109/ L, platelets > 100 x 109/ L, and liver functions satisfactory and on Days 8, 15, and 21 for further dose adaptation.

10.1.1.9.1 Efficacy Data Assessment

10.1.1.9.1.1 Classification of lesions

All lesions were followed and measured in millimeters.

i. Bidimensionally measurable lesions

Bidimensionally measurable disease was defined as tumor masses with identifiable diameters measurable in 2 dimensions. All sites of disease were to be followed and recorded in the source documents and on the subject's CRF. Examples of such lesions, evaluated by clinical examination or imaging tools, are:
• Skin nodules or superficial lymph nodes of a minimum = 10 mm x = 10 mm.
• Lung lesions surrounded by aerated lung of a minimum = 20 mm x = 10 mm on chest X- ray, or minimum = 10 mm x = 10 mm on CT scan.
• Liver lesion, soft tissue, lymph node and masses investigated by CT scan of a minimum = 20 mm x = 10 mm.

ii. Unidimensionally measurable lesions

These included all lesions for which only 1 diameter = 20 mm on CT scan or = 10 mm on physical examination could be measured. Examples of these lesions are:
• Lung lesions not completely surrounded by aerated lung of a minimum = 20 mm on chest X-ray or minimum = 10 mm on CT scan.
• Palpable abdominal masses or soft tissue masses that could be measured only in 1 diameter.

iii. Evaluable not measurable lesions

Evaluable but not measurable lesions included:
• Bidimensionally and unidimensionally measurable lesions with 1 diameter below the cut- off sizes described above.
• Osteolytic bone metastasis.

iv. Non-evaluable lesions

Lesions that were classified as being not evaluable included:
• Osteoblastic bone metastasis.
• Malignant effusions (ascites, pleural, and pericardial effusions).
• Carcinomatous lymphangitis (skin and lung).
• Previously irradiated lesions not in progression. However, a new lesion occurring in a previously irradiated field was to be accepted as measurable or evaluable unless it was the single measurable target lesion.
• Peritoneal carcinomatosis.
• Stomach lesions (with exceptions defined by a convention endorsed by the ERRC.

10.1.1.9.1.2 Criteria for evaluation of response

i. Definition of evaluability

To be evaluable for response, a subject had to have received at least 2 cycles of treatment, with at least 1 complete follow-up tumor assessment with the same imaging procedures as at baseline for each lesion, unless early progression occurred, in which case the subject was considered evaluable and in PD. The tumor assessment for all lesions had to have been performed every 8 weeks on therapy until the documentation of the progression. Tumor response was to be reported on follow-up visits every 8 weeks, calculated from the first administration of study medication, for subjects who withdraw from the study for any reason other than tumor progression.

ii. Response criteria

All unidimensionally or bidimensionally measurable lesions were required to be measured every 8 weeks. Additional assessments were performed to confirm a response at least 28 days after the first response had been observed. Extra assessments were performed if there was a clinical suspicion of disease progression. With multiple lesions, it may not have been possible to identify each and every one. Therefore, up to 6 measurable target lesions, representative of all organs involved, were to be selected at baseline for the involved sites, giving priority to bidimensionally measurable lesions.

All subject records were to be available for source verification and submitted for external review by the ERRC.

iii. Definition of response

a. Response was defined according to standard World Health Organization (WHO) criteria as follows:

b. Bidimensionally and unidimensionally measurable lesions

Complete response: disappearance of all known disease, determined by 2 observations not less than 4 weeks apart. No new lesion could have appeared.

Partial response: in the case of bidimensionally measurable disease, decrease by $\geq$ 50% of the sum of the products of the largest perpendicular diameters of all measurable lesions as determined by 2 observations not less than 4 weeks apart. For unidimensionally measurable disease, decrease by $\geq$ 50% in the sum of the largest diameter of all lesions as determined by 2 observations not less than 4 weeks apart. It was not necessary for all lesions to have regressed to qualify for PR, but no lesion could have progressed and no new lesion could have appeared. Serial evidence of appreciable change documented by radiography or photography had to be obtained and had to be available for subsequent review. The assessment had to be objective.

No change/stable disease: for bidimensionally measurable disease < 50% decrease and < 25% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions. For unidimensionally measurable disease, < 50% decrease and < 25% increase in the diameter of all lesions. No new lesions could have appeared. The subject was to have at least 1 tumor assessment after a minimum of 36 days on study treatment from the first to be assigned to the NC category.

Progressive disease: ≥ 25% increase in the size of at least 1 bidimensionally or measurable lesion (in comparison with the measurements at its nadir) or appearance of a new lesion. The occurrence of pleural effusion or ascites was also considered as PD if this was substantiated by positive cytology. Pathological fracture or collapse of bone were not evidence of disease progression. When the progression was observed before 36 days after entry into the study, the subject was to be considered to be an "early progression."

c. Evaluable non-measurable disease

Complete response: complete disappearance of all known disease for at least 4 weeks.

Partial response: estimated decrease in tumor size of ≥ 50% for at least 4 weeks.

No change/stable disease: no significant change as assessed after a minimum of 36 days on study treatment from the first infusion. This was to include stable disease, estimated decrease of < 50% and lesions with estimated increase of < 25%.

Progressive disease: appearance of any new lesions not previously identified or an estimated increase of ≥ 25% in any existing lesions.

d. Non-evaluable lesions

Complete response: complete disappearance of all known disease for at least 4 weeks. For blastic bone lesions, bone scintigraphy also had to be normalized for 4 weeks.

No change/stable disease: neither CR nor PD in the presence of evaluable or measurable

Progressive disease: appearance of any new lesions not previously identified, or an estimated increase of ≥ 25% in any existing lesions. In the case of effusions, an increase in size alone did not determine PD in the absence of other lesions also in PD.

e. Brain metastasis

The development of brain metastasis was considered a sign of PD, even if the malignancy was responding outside the brain.

f. Overall response

The overall response in the presence of bidimensional and unidimensional measurable and non-evaluable lesions was determined according to the algorithm shown in Table 47.

Table 47: Determination of the overall response in subjects with bidimensional, unidimensional and non-evaluable lesions

Response in bidimensionally measurable [a] lesions		Response in unidimensionally measurable and evaluable [b] lesions		Response in non-evaluable lesions		Overall response
CR	+	CR	+	CR	=	CR
CR	+	Any except PD	+	Any except PD	=	PR
PR	+	Any except PD	+	Any except PD	=	PR
NC	+	Any except PD	+	Any except PD	=	NC
Any	+	PD	+	Any	=	PD
Any	+	Any	+	PD or new lesion	=	PD
PD	+	Any	+	Any	=	PD

a. Replace with "unidimensionally measurable" and "evaluable not measurable" for subjects with unidimensional and evaluable-only disease, respectively.
b Replace with "evaluable not measurable" and "osteolytic bone" for subjects with unidimensional and evaluable-only disease, respectively.
CR = Complete response, PR = Partial response, PD = Progression of disease, NC = No change/stable disease

If any lesion identified at baseline was not evaluated, then the overall response for that evaluation was to be non-evaluable.

In the case of multiple organ involvement in subjects with evaluable-only disease, the response was calculated according to the WHO criteria. If the number of CR or PR was greater than the "no change" designations, the overall response was to be PR. If the number of responses and "no change" designations were equal, the overall response was also to be PR.

g. Determination of best overall response

Best overall response was the best response recorded from the start of treatment until disease progression and before further therapy.

h. External review

Both the investigator at the time of treatment and the External Radiology Review Committee (ERRC) assessed tumor responses and progressions. Discrepancies between these assessments were categorized as follows:

Discrepancy type 1:

There were minor differences in measurement present but the ERRC's decision was not different from the investigator's for organs involved, overall response by each tumor assessment, response by each organ involved, date of disease progression, and best overall response.

Discrepancy type 2:

The ERRC's decision differed from the investigator's opinion for 1 or more of the points given above. The investigator was informed of all ERRC assessments of subjects from his center and signed the response review form to indicate that he was informed. The ERRC's assessment was used for the final evaluation (F-EVAL). The response review form, signed by the radiologists and the investigator, was to be appended to the internal subject file.

10.1.1.9.1.3 Time to progression, overall survival, duration of response, and time to treatment failure

The efficacy endpoints analyzed in this study were defined as follows:

• **Time to progression** was calculated from the day of randomization to the date of PD or death (from any cause), whichever occurred first. Subjects who had not progressed at the time of the final analysis were censored at the date of their last evaluable tumor assessment. Subjects who received non-study anti-cancer therapy before disease progression were censored at the date of the last evaluable assessment before therapy.

Reviewer Note: The primary analysis TTP here included both PD and death, therefore,can be regarded as PFS.

• **Overall survival** was defined as the time from the date of randomization to death from any cause. Subjects alive at the final analysis were to be censored at their last contact date.

• **Duration of response**: The period for CR was calculated from the date the CR was achieved to the date on which PD was first observed. For subjects who achieved a PR, only the period of overall response was to be recorded. The period of overall response was calculated from the day of randomization to the date on which disease progression was first observed or death from whatever cause.

• **Time to treatment failure** was defined as the time from the day of randomization to the date of failure (progression, relapse, death, or any other cause of treatment discontinuation).

10.1.1.9.2 Data Monitoring and Final Evaluation

Along with efficacy conventions for gastric cancer, and data that were considered final for a subject, every subject's status for study eligibility, evaluability for response and safety, and key efficacy variables derived from the tumor assessments were reviewed by a team composed of the medical officer, the study statistician, the study manager, and the study data manager. The purpose of this process, known internally as F-EVAL, is to perform a final check for the consistency of key data points used to determine subject eligibility/evaluability and to confirm efficacy endpoints described below. Where appropriate, data queries were generated and submitted for resolution to the investigational sites.

As a tool for the F-EVAL, an SAS-based algorithm for response was run on the tumor assessment data from the ERRC (or from the investigator if ERRC information was not available). The results were provided to the team along with efficacy conventions for gastric cancer, subject profiles, minor and major deviations, and other data listings. This allowed evaluation for the following parameters: primary tumor present (yes/no); extent of disease; prior adjuvant chemotherapy (yes/no) (for determination of first-line status in the study/adjuvant status of the prior therapy); eligibility and minor deviations; evaluability for response; evaluability for safety; major deviation on study; best overall response; date of first CR (or date of first PR if there was no CR); date of progression; last evaluable tumor assessment (i. e., at which all baseline lesions were assessed, using the same method of measurement as at baseline, and before the first further anti- tumor therapy and before disease progression); date and type of first further anti- cancer therapy; and cause of death. The results of the F- EVAL for these endpoints were documented in a specific F- EVAL assessment form and entered into the study database, which was then used to define analysis populations and also to derive efficacy endpoints such as TTP.

10.1.1.9.3 Adverse Event Management

The safety population (SP) includes all subjects who received at least 1 dose of study medication, analyzed as per actual treatment received. Safety procedures and assessments consisted of the following:
• Complete history of events related to malignant and non-malignant diseases.
• Full clinical examination; height and weight; assessment of residual toxicity due to prior therapies and disease symptoms according to NCIC-CTC, version 1.0; and performance status (PS) according to the KPS scale.
• Neurologic examination was required at baseline and during treatment if clinically indicated.
• Audiogram was required at baseline and during treatment if clinically indicated.
• Each subject was regularly assessed for potential AEs and disease-related signs and symptoms using the same NCIC-CTC.

10.1.1.9.4. Efficacy Endpoints

i. Primary efficacy endpoint

The primary efficacy endpoint was time to progression, calculated from the day of randomization to the date of the first TTP event.

A TTP event was defined as disease progression as determined by F-EVAL, or death from any cause, provided the death could be considered to have replaced or delayed the next planned tumor assessment under a regular follow-up scheme. A period of 12 weeks was used, corresponding to 1.5 times the planned period between 2 tumor assessments. Thus only deaths within 12 weeks of the last evaluable tumor assessment, or within 12 weeks of the first infusion of study drugs (for subjects with no evaluable tumor assessment after randomization), were considered as TTP events. This prevents over-estimating TTP in subjects who miss one or more consecutive tumor assessments and then subsequently die.

Reviewer note: This is not a standard TTP analysis, it could be considered a modified PFS because both tumor progressions and deaths are treated as events..

For the determination of censoring dates for TTP, a data cut-off date was used. Subjects were censored for TTP if they did not have a TTP event (defined above) on or before the first to occur between the data cut-off date and the date of first further anti-tumor therapy (as determined by F-EVAL). For details on the classification of censoring reasons ("no event at cut-off ," " further therapy," and " lost to follow-up").

There were 3 possible censoring dates:

- the cut-off date was used for subjects with either a TTP event or an evaluable tumor assessment after the cut-off date; otherwise,
- the date of the last evaluable tumor assessment prior to the first further anti-tumor therapy (as determined by F-EVAL); or
- the date of randomization if there was no evaluable tumor assessment after randomization and before further anti-tumor therapy.

ii. Secondary efficacy endpoints

Overall survival was defined as the time from the date of randomization to death from any cause based on information from the "Death Report Form" CRF as well as the "Survival Update" CRFs. A data cut-off date was used, and subjects known to be alive at the cut-off date were censored on that date; otherwise, subjects without a known record of death were censored on their last contact date.

Response rate was defined as the number of subjects with a best overall response of CR or PR, as determined by F-EVAL, divided by the total number of subjects in the reference population. The algorithm used for the F-EVAL determination of tumor response utilized tumor assessments prior to further therapy, and non-evaluable lesions at baseline that were not CR or PD on-study were considered NC (no change) if other measurable or evaluable lesions were also present. Additionally, subjects not evaluable for response were assigned a best overall response of NE (not evaluable).

Duration of overall response was determined in all subjects who had a best overall response of CR or PR, as determined by F-EVAL, and was calculated from the date of randomization until the date of the first TTP event or censoring, as used in the definition of TTP above. In addition, a second duration of overall response was calculated, starting from the date of the first PR or CR instead of from the date of randomization. The date of the first PR or CR was taken directly from the F-EVAL. However, subjects with a best overall response of CR were checked programmatically in case the overall response was PR before becoming CR (in this case, the date used was the latest date from the first tumor assessment that had an overall response of PR). Duration of CR was calculated as the date of first CR, as determined by F-EVAL, until the date of the first TTP event or censoring, as used in the definition of TTP given above.

Time to treatment failure was defined as the time from the day of randomization to the date of failure (defined as the first to occur among the following events: death, progression as per F-EVAL, date of concurrent anti-tumor therapy as per F-EVAL, or any other cause of treatment discontinuation). Subjects known not to have failed by the clinical cut-off date were censored on that date; otherwise, subjects known not to have failed were censored on their last evaluable tumor assessment prior to the cut-off date.

10.1.1.9.5 Safety Endpoints

10.1.1.9.5.1 Extent of exposure

Analyses of extent of exposure variables were based on study medication administration CRF data. A cycle of therapy was defined as the delivery of at least one component of the study regimen. Measures of cumulative dose, dose intensity, and relative dose intensity were determined for each of the possible components of the treatment regimens (Taxotere, cisplatin, and 5-FU).

Dose levels used for Taxotere, cisplatin, and 5-FU were derived according to the intervals given in Table 48 below. Dose reductions were determined by comparing the actual dose level between 2 subsequent cycles for each of the components. A cycle was defined to have a dose reduction if any component of the study regimen in that cycle was at least one level less than the previous cycle. Dose reduction was not defined for cycle 1.

Table 48: Dose levels for Taxotere, cisplatin and 5-FU

	Dose [mg/m^2]				
	TCF			CF	
	Taxotere	Cisplatin	5-FU	Cisplatin	5-FU
High	≥82.5	≥90	≥4500	≥120	≥6000
0	≥67.5, <82.5	≥67.5, <90	≥3375, <4500	≥90, <120	≥4500, <6000
-1	≥52.5, <67.5	≥52.5, <67.5	≥2625, <3375	≥72.5, <90	≥3625, <4500
-2	≥33.75, <52.5	≥30, <52.5	≥1700, <2625	≥50, <72.5	≥2600, <3625
Low	<33.75	<30	<1700	<50	<2600

Note: Level 0 is the intended dose and levels - 1 and - 2 correspond to 1 and 2 dose reductions, respectively. High and low are above and below these dose ranges.
5-FU = 5-fluorouracil; TCF = Taxotere + cisplatin + 5- fluorouracil; CF = Cisplatin + 5- fluorouracil.
Source: TAX325a study report.

Cycle delays were determined by comparing dates of infusion between 2 successive cycles. For TCF subjects, the cycle was considered delayed if the infusion of Taxotere in the next cycle was delivered 4 or more days after the scheduled delivery date. For CF subjects, the cycle was considered delayed if the infusion of cisplatin in the next cycle was delivered 4 or more days after the scheduled delivery date.

The denominator used for calculating the percentage of cycles with cycle delay and/or dose reduction was the total number of cycles administered (i. e., including the first cycle for dose reduction and last cycle for cycle delay).

Reasons for dose reductions and delays were summarized directly from the information provided by the investigator on the “Study medication administration” CRF page.

10.1.1.9.5.2 Adverse Events

AEs were recorded by the investigator according to the NCIC-CTC classification criteria. Unless otherwise noted, the NCIC-CTC classification (category term) was used for AE reporting. For events where the term is “other” within an NCIC- CTC classification (for instance, GI-OTH), the toxicity is presented by the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) term, for instance, “ Other: Dyspepsia” appear under Gastrointestinal.

According to CRF completion guidelines for febrile neutropenia, the investigator was not to report this toxicity using the NCIC-CTC term “ febrile neutropenia” IN- NEU) but instead to report as “ fever in the absence of infection” (FL-FEV).

Also per CRF guidelines, laboratory abnormalities were not to be reported on the AE CRF they were serious, led to treatment discontinuation, cycle delay or dose reduction, for complete list of COSTART terms identified as “laboratory

Treatment-emergent adverse events (AEs) were defined as AEs that started or worsened (i. e., increased in intensity by at least 1 grade) during the treatment period (i. e., during any of treatment cycles) and were determined programmatically, with the baseline taken as reference:

• AEs were defined as any occurrence during the treatment period of an AE (based on NCIC-CTC and COSTART terms that was either not present at baseline, or reported at baseline but had resolved baseline.

• If an AE was present at baseline and reported as ongoing during the treatment period, then was a TEAE only if the intensity increased by at least 1 grade. If this event resolved and a event with the same NCIC-CTC code and COSTART terms (any grade) was reported subsequently for that subject during the treatment period, this was also defined as a TEAE.

AEs that occurred in the follow-up-period were not considered treatment emergent. These events were used for secondary safety analyses only if they started the follow-up period, were serious, and considered related to study treatment by the or they were serious on-study and continued into the follow-up period. All follow-up AEs that did not meet either of these 2 conditions were placed in a separate dataset (study report appendix B).

Serious adverse events (TE-SAE) were defined as a TEAE considered by the investigator according to the definition given in of the protocol.

Deaths were categorized as either within 30 days after the last administration of study medication (i. e., at any time during the study and within 30 days after the last infusion including the day of infusion) or greater than 30 days from the last administration of study medication. Additionally, deaths were categorized as either within 60 days from randomization (including date of randomization) or greater than 60 days from randomization.

Cause of death (in the opinion of the investigator) was reported as either “malignant disease,” “toxicity from drug treatment,” or “Other.” Deaths within 30 days not considered related to study drug by the investigator were reassessed internally and reported in F- EVAL form.

10.1.1.9.5.3. Laboratory safety variables

Hematological abnormalities (anemia, leukopenia, neutropenia and thrombocytopenia) were graded according to NCIC-CTC criteria. Biochemical abnormalities were based on NCIC-CTC grading, when available. CrCl abnormality was defined as a value less than 60 mL/min. If “actual” and “calculated” CrCl (according to investigator) were both present on the same date, the “actual” was used. For plasma total protein, “abnormal” was taken as any value below lower normal limit (LNL).

All laboratory values recorded on-study were to be considered for worst grade on-study abnormality. Laboratory values that were obtained during the follow-up period were placed in a separate dataset.

10.1.1.9.5.4. Quality of life variables

QOL scales to be assessed (in countries where a translation was available) were the EORTC-QLQ- C30 questionnaire (version 3.0) as per the EORTC- QLQ- C30 scoring manual and the EQ-5D (5 questions plus thermometer). Further details of these instruments are described in Section 3.5.2.4.

As defined in the SAP, the primary QOL endpoint was time from randomization until a definitive 5% deterioration event in the global health status/QOL scale of the EORTC-QLQ-C30. A definitive 5% deterioration event was defined as either

1. a decrease from baseline of at least 5% in the global health status/QOL scale without any subsequent improvement to a level corresponding to < 5% deterioration from baseline; or

2. death within 12 weeks of the last evaluable questionnaire, with no further anti-tumor therapy**.**

10.1.1.10. Study Populations

The Clinical Study Protocol and SAP defined 3 populations for analysis, the Full analysis population (FAP), the Per-protocol population (PPP), and the Safety population (SP) as show in Table 7.

10.1.1.10. Statistical Methods

10.1.1.10.1. Primary efficacy evaluation

The primary analysis of the phase III part of the study was to be a comparison of TTP in the FAP. A total of 325 events were required to detect a statistically significant increase in TTP among TCF-treated subjects, relative to CF-treated subjects. A single interim analysis was to occur when 162 TTP events (about half that of the final analysis) had been observed.

To test the superiority of TCF relative to CF, an unstratified log-rank test was used. Although the interim analysis conducted earlier for TTP met the pre-specified boundary criteria, the final significance level was nominally set at 0.0487 (O'Brien-Fleming type of alpha-spending function with 162/325 TTP events observed at interim). The analysis was performed with exactly the number of protocol pre-specified events ("325 events" analysis) and was also performed, as the primary presentation of TTP, to include all events in the database ("end-of-study" analysis).

OS was to be compared using the same statistical methods (unstratified log-rank test in the FAP) as defined for TTP and to be performed when the protocol-specified number of events (325 deaths) was observed. To adjust for the pre-specified interim analysis conducted earlier for OS, the final significance level was set at 0.0483 (O'Brien-Fleming type of alpha-spending function with 181/325 deaths observed at interim).

Similar to TTP, the analysis of OS was performed with exactly the number of protocol-specified events ("325 events" analysis) and as the primary presentation, updated with more events in the database ("end-of-study" analysis). **Post-database lock**, all deaths in the FAP were ordered by date and **the 325th death** (both treatment groups combined) was found to occur on **18 April 2003**. This **cut-off date** was used for **censoring in the 325 events analysis**. For the **end-of-study OS analysis,** the **cut-off date** was **19 May 2003**, taken conservatively as the earliest date of the reporting window (**19 May 2003**, **28 May 2003**) on the **final "Survival Update" CRF**.

Summaries of OS were performed similarly to TTP (e. g., HR, 95% CIs, medians, Kaplan-Meier curves). Kaplan-Meier 1-year and 2-year survival estimates were presented.

In each analysis, reasons for censoring were summarized and the HR and 95% confidence interval (CI) were presented. Group medians (and difference in medians) with respective 95% CIs were presented. Additionally, the 25th and 75th percentile were presented as well as the 6 and 12 month Kaplan-Meier estimates of the proportion of subjects that had not yet had a TTP event in each treatment group. Kaplan-Meier curves were presented with number of subjects still at risk given at 3-month intervals underneath the x-axis. For in-text figures, the curve for each treatment group was truncated when there were less than 5 subjects still at risk in that treatment group.

As specified in the protocol and SAP, a test of non-inferiority of TCF relative to CF was to be conducted once 325 TTP events had been observed (05 March 2003). Based on the retention of at least 50% of the historical treatment effect of CF over 5-FU alone, the test arm was to be declared to be non- inferior to the control arm if the lower bound of the 2-sided 95% CI for the CF/ TCF HR exceeded 0.91 from a Cox proportional hazards model (with an indicator for the control arm as the only covariate).

10.1.1.10.2. Secondary efficacy evaluation

i. Overall Survival

OS was to be compared using the same statistical methods (unstratified log-rank test in the FAP) as defined for TTP and to be performed when the protocol-specified number of events (325 deaths) was observed. To adjust for the pre-specified interim analysis conducted earlier for OS, the final significance level was set at 0.0483 (O'Brien-Fleming type of alpha-spending function with 181/325 deaths observed at interim).

Similar to TTP, the analysis of OS was performed with exactly the number of protocol-specified events ("325 events" analysis) and as the primary presentation, updated with more events in the database ("end-of-study" analysis). **Post-database lock**, all deaths in the FAP were ordered by date and **the 325th death** (both treatment groups combined) was found to occur on **18 April 2003**. This **cut-off date** was used for **censoring in the 325 events analysis**. For the **end-of-study OS analysis,** the **cut-off date** was **19 May 2003**, taken conservatively as the earliest date of the reporting window (**19 May 2003**, **28 May 2003**) on the **final "Survival Update" CRF**.

Summaries of OS were performed similarly to TTP (e. g., HR, 95% CIs, medians, Kaplan-Meier curves). Kaplan-Meier 1-year and 2-year survival estimates were presented.

ii. Tumor Response (RR)

Tumor RRs (CR and overall) with exact 95% CIs were calculated for each treatment group in the FAP and PPP. Comparisons between treatment groups were performed using the chi-square test.

iii. Time to Treatment Failure

Summaries for **TTF** were performed similarly to TTP and OS. TTF was to be compared with the Wilcoxon test in the FAP and PPP. The cut-off date used for both of these analyses was the same date used for the end-of-study TTP (07 May 2003).

Duration of overall response (from randomization and from onset of CR/PR) was compared between treatment groups using the unstratified log-rank test in the FAP and PPP. The same cutoff date for end-of-study TTP (07 May 2003) was used. Since the number of complete responders was few, no formal analysis was performed to compare the 2 treatment groups.

10.1.1.10.3. Supportive efficacy evaluation

i. Sensitivity analyses

Supportive superiority analyses for TTP and OS (unstratified log-rank test) were to be conducted in the "all randomized" population, and only for TTP in the PPP. For these populations, "325 events" analyses in the PPP and all randomized population were based on the same cut-off date used for the "325 events" FAP analysis described above. Similarly, "end of study" analyses in these populations used the same cut-off date as for the "end of study" FAP analysis. Additionally, log-rank tests stratified by the factors used in the randomization scheme except center, were also conducted in the FAP and 'all randomized' population.

For TTP, a sensitivity analysis was to be performed to assess the impact of late documentation of progression. In this analysis, progressions documented more than 12 weeks from the last evaluable tumor assessment were to be considered as having occurred at 8 weeks after the last evaluable tumor assessment (i. e., the date when a tumor assessment was expected).

As per the SAP, supportive non-inferiority analyses for TTP and OS were performed in the PPP as well.

ii. Multivariate analyses

Multivariate analysis using Cox proportional hazards modeling was to be performed for TTP and OS to adjust the treatment effect by a set of pre-specified baseline factors. The following

baseline characteristics were included as covariates to a model containing treatment group indicator:
• Liver involvement (yes vs. no)
• Weight loss in the prior 3 months (≤ 5% vs. > 5%)
• Disease measurability (measurable vs. evaluable-only lesions)
• Prior gastrectomy (yes vs. no)
• KPS (< 100, 100)
• Age (< 70 years vs. ≥ 70 years)
• Anatomic site (proximal [EG junction + fundus] vs. distal [body +antrum]).

For the stratification factors (first 4 bullet points above), the values reported by the investigator at randomization were to be used in the model. A model with the actual values of liver involvement and disease measurability (determined by ERRC review) and prior gastrectomy and weight loss (determined by CRF information) was to be studied in a sensitivity multivariate analysis.

In a further exploratory analysis, interaction terms between treatment and each covariate listed above were to be added to the full model. Using backwards elimination, the final model was to exclude all interaction terms that were not significant at a 2-sided 10% level. Alternatively to assess interaction, a Cox proportional hazards model was fitted separately for each covariate, containing only the treatment, selected covariate, and covariate by treatment interaction terms.

For RR, a multivariate analysis was to be performed using logistic regression to similarly explore the influence of the baseline prognostic variables listed above.

iii. Subgroup analyses

For TTP and OS, the following subgroups were analyzed in the FAP and summarized using medians and corresponding 95% CIs for each treatment arm (as well as the CF:TCF HR and corresponding 95% CI) within subgroup level:
• Age (≤ 65 years, > 65 years)
• Gender (male, female, female ≥ 50 years)
• Race (Caucasian, non-Caucasian)
• Region (North America, South America, Eastern Europe, Western Europe, Asia)
• Prior gastrectomy as per randomization (yes, no)
• Measurable disease as per randomization (measurable, evaluable-only lesions)
• Liver involvement as per randomization (yes, no)
• Weight loss in prior 3 months as per randomization (≤ 5%, > 5%)
• Age (< 70 years, ≥ 70 years)
• KPS before first infusion (< 100, 100)
• Anatomic site (proximal, distal)

The overall RR in the FAP is presented by subgroups defined by selected prognostic factors at randomization (KPS, weight loss, presence of measurable disease, number of organs involved, liver involvement, anatomic site, and prior gastrectomy).

Reviewer note: Two age group definitions are given here.

iv. Proportional hazards assumption

To assess the proportional hazards assumption, plots of log (-log[survival]) against Time for TTP and OS was provided in the FAP and for TTP in the PPP.

v. Time to tumor assessments

An exploratory analysis of time to tumor assessment was performed in the FAP. This analysis used tumor assessments reviewed by the ERRC, or those by the investigator if ERRC review was unavailable, irrespective of whether the tumor assessments were evaluable or not. Tumor assessments done after progression of disease, further anti-tumor therapy, or TTP cut-off date (05 March 2003 for the 325-event analysis) were excluded. If the tumor assessment was performed over more than one day, the date of tumor assessment retained was the first day.

Kaplan-Meier curves of time to first, second and third tumor assessment were done from date of randomization and date of first i.v. and compared between treatment groups using an unstratified log-rank test.

For time to first tumor assessment, all subjects in the FAP were to be included, whereas the analyses of time to second or third tumor assessments only included subjects in the FAP who already had, respectively, a first or second tumor assessment at which PD was absent. Subjects with no first, second or third tumor assessment were to be censored at the earliest date among the date of death, date of further therapy, or cut-off date (05 March 2003).

Additionally, the duration between all evaluable tumor assessments analyzed prior to PD was summarized by treatment arm in the FAP (by ERRC and by investigator) and a histogram was constructed on the following categories: < 4 weeks, 4-6 weeks, 7-9 weeks, 10-12 weeks and > 12 weeks. For investigator assessments, the absolute value of the difference between the actual and theoretical date of tumor assessment was summarized and a histogram was constructed as follows: ≤ 7 days, 8-14 days, 15- 21 days, 22- 28 days, > 28 days. Reasons for unscheduled tumor assessments were also summarized.

10.1.1.10.4. Safety evaluation

i. Extent of exposure Summary measures of extent of exposure are presented by study medication received (SP). Summary statistics (mean, median, SD, minimum, maximum, 25th and 75th percentiles) are presented by treatment group for cycles delivered and duration of treatment. For each component of the treatment regimen (Taxotere, cisplatin, and 5-FU), summaries of cumulative dose, actual dose intensity, and relative dose intensity are presented. For cisplatin and 5-FU, median cumulative doses (mg/m^2) were plotted over time (duration of treatment in days) for each treatment group. For each treatment group, the curve for each

component (cisplatin, 5- FU) is truncated when there are less than 20 subjects still receiving that component in the arm.

Summaries of cycles of therapy, duration of treatment, cumulative dose, actual dose intensity and relative dose intensity are presented for the following subgroups: age (< 65, ≥ 65), gender (male, female, female ≥ 50 years) and race (Caucasian [White], non-Caucasian [non-White]).

ii. Adverse events

Summary measures (number, percentage) of AEs are presented in the SP. AEs (worst grade), the primary assessment of safety, were summarized by subject and cycle for each treatment group. These analyses were conducted in 2 different ways:

1. regardless of the relationship to the study medication; and
2. related (possible or probable relationship to the study medication in the opinion of the investigator).

Grade 3-4 AEs by subject with an overall incidence rate of 10% or higher in either treatment group were compared between the two treatment groups using a 2-sided Fisher's exact test. The Holm significance level ranking (step-down) method was also used, as described in the SAP. Subjects with grade 3-4 AEs were also presented by cycle number of occurrence.

AEs from the following NCIC-CTC categories were presented separately: infection (IN-*), gastrointestinal (GI-*), cardiovascular (CV-*), skin reactions (SK-*) and hypersensitivity (HS-*).

Summaries of AEs are presented for the subgroup age (< 65, ≥ 65) by subject (regardless of relation to study medication, related to study medication) and by cycle (regardless of relation to study medication, related to study medication). AEs regardless of relation to study medication are also presented by subject for the subgroups: gender (male, female, female ≥ 50 years), race (Caucasian [White], non-Caucasian [non-White]), KPS before first infusion (100 vs. < 100) and by weight loss in the prior 3 months (≤ 5% vs. > 5%).

Laboratory abnormalities recorded by the investigator as AEs were summarized separately.

As a secondary analysis, all AEs that occurred during the treatment or follow-up periods were summarized by patient.

Existing signs and symptoms at baseline were summarized by NCIC-CTC term in the FAP. According to CRF completion guidelines, baseline laboratory abnormalities were to be recorded on baseline laboratory CRFs.

iii. Serious adverse events

TE-SAEs were summarized by subject, cycle, and event for terms regardless of relationship to study medication, and by subject and event for terms related to study medication.

Additionally, all SAEs (including non-treatment emergent SAEs and SAEs occurring in the follow-up period) were summarized by subject and event, regardless of relationship to study medication. Laboratory AEs that were considered serious by the investigator were included in these summaries and listings.

TE-SAEs, regardless of relationship to study medication, were presented for subgroups: age (< 65 years, ≥ 65 years), gender (male, female, female ≥ 50 years), and race (Caucasian, non-Caucasian). TE-SAEs related to study medication were also presented for the age subgroups.

iv. Deaths

Summaries of deaths (within 30 days of last administration of study medication, and 60 days of randomization) were performed in the treated population (SP). Fisher's exact test was used to compare the 2 treatment groups on the following rates: toxic death per investigator, toxic death per Sponsor's review, death within 30 days of last administration of study medication or toxic death per investigator, and death within 30 days of last administration of study medication or toxic death per internal review.

Reviewer Note: I wonder if sponsor's review and internal review are the same.

An additional analysis of deaths within 29 days of the first infusion date in subjects that were eligible and had measurable disease was also performed.

Supportive listings on toxic deaths as well as all deaths in the SP were given.

Summaries of deaths were presented for the following subgroups: age (< 65 years, ≥ 65 years), gender (male, female, female ≥ 50 years), and race (Caucasian [White], non-Caucasian [non-White]).

v. Adverse events leading to discontinuations or deaths

AEs leading to study discontinuation (regardless of relationship to study medication, related to study medication) were summarized by treatment group in the SP. The cycle of discontinuation due to these AEs was also presented. Additional analyses included a summary of AEs leading to discontinuation or death (where the AE that led to death during the study). Listings of all discontinuations or deaths due to AEs with additional information (e. g., cycle of occurrence, grade, relationship) were also provided.

vi. Laboratory safety

Definition of laboratory parameters and toxicities are given in Section 4.1.2.5.

Baseline assessments of abnormal hematological and biochemistry values were summarized 2 ways: “before randomization” (considered the most recent value of the parameter up to and including date of randomization) and “before first infusion” (most recent value up to and including date of first infusion of study medication).

vii. Hematologic abnormalities

Analyses of hematologic abnormalities (anemia, leukopenia, neutropenia and thrombocytopenia) utilized on-study assessments and summarized as worst grade by subject and cycle, regardless of prophylactic treatment. For worst grade, a cycle was defined as evaluable if there was at least 1 blood count between Day 2 and the day of the next infusion. Analyses for leukopenia and neutropenia were also performed depending on whether a prophylactic colony-stimulating factor (e. g., G-CSF) was given during the cycle (“with G- CSF”) or not given during the cycle (“without G-CSF”). Anemia was summarized depending on whether or not prophylactic erythropoietin (EPO) or red blood cell (RBC) transfusion was given during the cycle.

Duration of grade 4 neutropenia was summarized for cycles with the toxicity and categorized into “less than or equal to 7 days,” “greater than 7 days,” or “undetermined.” The analysis was performed depending on whether or not prophylactic or curative G-CSF was given during the cycle.

Nadir of WBC and ANC (defined as lowest laboratory value in that cycle for the parameter) and days to the nadir (first infusion date of cycle to date of nadir) were summarized for cycles with any grade leukopenia and neutropenia, respectively, and at least 1 blood count between Day 6 and Day 15. The analysis was performed depending on whether or not prophylactic G-CSF was given during the cycle.

The SAP-specified analyses for recovery time for leukopenia, neutropenia, and thrombocytopenia were considered to be inappropriate due to the actual schedule of blood counts in this study. Instead, an analysis of hematologic toxicities occurring during a period defining an “end-of-cycle” was used. In the TCF treatment group, this period started on Day 19 of the cycle and finished on the day of next infusion or Day 25, whichever occurred first, while in the CF treatment group this period started on Day 25 of the cycle and finished on the day of next infusion or Day 32, whichever occurred first. The last observation in the period was retained in this analysis or cycles without curative or prophylactic treatment with any grade toxicity (greater than grade 1 for neutropenia).

viii. Biochemical abnormalities

Worst-grade analyses by subject utilized on-treatment laboratory values. A subject was considered evaluable for a given abnormality if at least one on-treatment assessment was available for that parameter. For liver function tests (serum ASAT, ALAT, alkaline phosphatase, bilirubin), the analyses were also performed separately depending on whether or not the subject had liver metastasis at baseline (for alkaline phosphatase, the analyses considered liver or bone metastasis), as determined by ERRC assessments (or investigator assessment if not available).

ix. Specific safety variables

The incidence of infection/fever in the absence of infection, and mucositis/diarrhea were summarized by subject and by cycle. The incidence of fluid retention, cardiovascular events, renal impairment events, and neurologic events were summarized by subject. The time and the cumulative dose to onset of fluid retention were analyzed using Kaplan-Meier methods.

The incidence of febrile neutropenia and neutropenic infection were presented by subject and by cycle according to whether or not prophylactic treatment with G-CSF was administered during the cycle. Cycle evaluability and grading of neutropenia as defined above for hematology was used. According to the SAP, febrile neutropenia was also summarized with the condition that the fever was related to study medication; neutropenic infection was defined similarly requiring the infection to be related to study medication. In addition, the incidence of fever or infection (regardless of relationship to study medication) with an outcome of death during febrile neutropenia or neutropenic infection, respectively, was also summarized.

10.1.1.10.5. Quality of life and clinical benefit analysis

i. Quality of life analysis

The primary analysis of QOL was the comparison between treatment groups of the time to definitive 5% deterioration on the global health status/QOL scale in the FAP using the unstratified log-rank test. Summary statistics for time to definitive 5% deterioration by treatment arm (Kaplan-Meier estimates and curves, medians with 95% CIs) were also given. Additionally, the treatment effect was estimated as the CF:TCF HR from a Cox model, adjusted for the covariates: prior gastrectomy (yes vs. no), liver involvement (yes vs. no), disease measurability (measurable vs. evaluable only lesions) and weight loss in prior 3 months ($\leq$ 5% vs. > 5%), all as specified at randomization by the investigator.

Secondary analyses of QOL using similar statistical methods were performed on the other scales of the EORTC-QLQ-C30 questionnaire (with special attention to physical functioning, social functioning, appetite loss, pain and nausea/ vomiting scales) as well as the EQ-5D thermometer. The gamma statistic of association between the global health status/QOL scores and EQ-5D visual analog scale measures was also computed.

In addition to time to 10%, 20%, and 30% definitive deterioration, secondary analyses of EORTC-QLQ-C30 questionnaire scales included analyses where the outcome was dichotomized (yes/no) for improvement and deterioration as well as an analysis of best and worst individual scores. Additionally, graphical assessments of selected EORTC-QLQ-C30 scales were performed, plotting the mean value of the scale by treatment group across time, with pseudo-CIs (mean ± 1.96 x standard error of the mean).

Using time windows defined, compliance of EORTC-QLQ-C30 (number of evaluable divided by received and exploitable questionnaires) was assessed across these periods for the following definitions of evaluability: evaluable, evaluable limited to 1 per subject per time window, and evaluable per protocol (within 1 week of theoretical completion date, before any corticosteroid premedication and self-completed).

ii. Clinical benefit analyses

The primary analysis of clinical benefit was the comparison of definite worsening of KPS between the two treatment groups using the unstratified log-rank test in the FAP. Summary measures were similar to that performed for QOL (Kaplan-Meier estimates, 95% CIs, HR using adjusted Cox model). As a measure of compliance, a summary of available KPS measures across cycles was provided.

Secondary analyses of time-to-event clinical benefit endpoints were performed similarly to the primary analysis. Summary statistics of consumption of curative analgesics and opioids were also performed by cycle for each treatment group.

As an alternative assessment of clinical benefit over time, KPS was categorized at each cycle (100 vs. < 100) and generalized estimating equation methods were used to test whether change over time in the proportion of subjects with a score of 100 differed between the treatment groups. Additionally, a similar model was fit based on 3 categories of KPS (100 vs. 70-90 vs. < 70) over time.

The time to improvement of clinical benefit parameters defined in the protocol were not analyzed because it was expected that too few events would be observed for such analyses to be meaningful. Thus, only the time to worsening of the clinical benefit endpoints was studied.

iii. Analysis of other variables

For other variables described in Section …, descriptive statistics were used to summarize the two treatment arms in the FAP (unless otherwise noted). For discontinuations due to AEs, Fisher's exact test was used to compare the rates between the 2 treatment groups.

10.1.1.10.6. Sample Size Justification

An unstratified log- rank test was used with a 2-sided 5% significance level. To show an increase in median TTP (primary endpoint) from 4 months in the control group to 6 months in the test

group with a power of 95%, a total of 325 events were required. A median follow-up of 19.5 months was expected from a uniform accrual over 15 months and a minimum follow-up of 12 months. assuming an exponential distribution, 350 subjects (175 subjects per treatment group) were required. assuming a loss to follow-up of 5%, a total of 460 subjects (230 subjects per treatment group) were required.

The study also evaluated the increase in median OS (secondary endpoint) from 8 months to 12 months with a power of 95%. A total of 325 deaths were required, using an unadjusted log rank test with a 2-sided 5% significance level. With the hypotheses of a uniform accrual and an exponential survival, 218 subjects per treatment group were required. Assuming a loss to follow-up of 5%, a total of 460 subjects (230 subjects per treatment group) were required.

Therefore, a total of 460 subjects (230 per group) were planned for phase III.

10.1.1.10.7. Interim Analysis

The study protocol included a single planned interim analysis during phase III, to support a possible early registration based on tumor response. This analysis was triggered when 162 TTP events or approximately 50% of the total expected number of events to be included in the final analysis had occurred. It was estimated that this number of events would accumulate after 272 subjects had been randomized into phase III and followed for a minimum of 2 months. Based on the observed accrual the sample size was re-estimated to be 232 subjects and this was subsequently used for the interim analysis.

10.1.2. Study Subjects and Conduct

10.1.2.1. Enrollment

A total of 457 subjects were randomized to the phase III part of the study in 39 months (November 1999 through January 2003): 227 subjects into the TCF treatment group and 230 subjects into the CF treatment group.

The study was conducted in 72 centers in 16 countries. The number of subjects according to countries (grouped by geographic regions) and randomization groups are shown below.

Table 49: Distribution of subjects by regions, countries, and randomization groups (all randomized subjects)

Region/ country	Number (%) of subjects		
	TCF (N=227)	CF (N=230)	All (N=457)
Western Europe	**77 (33.9)**	**74 (32.2)**	**151 (33.0)**
Belgium	23 (10.1)	27 (11.7)	50 (10.9)
Germany	4 (1.8)	5 (2.2)	9 (2.0)
Italy	16 (7.0)	14 (6.1)	30 (6.6)
Portugal	20 (8.8)	18 (7.8)	38 (8.3)
Spain	14 (6.2)	10 (4.3)	24 (5.3)
South America	**62 (27.3)**	**65 (28.3)**	**127 (27.8)**
Brazil	8 (3.5)	16 (7.0)	24 (5.3)
Chile	14 (6.2)	15 (6.5)	29 (6.3)
Colombia	20 (8.8)	19 (8.3)	39 (8.5)
Mexico	3 (1.3)	2 (0.9)	5 (1.1)
Peru	8 (3.5)	6 (2.6)	14 (3.1)
Venezuela	9 (4.0)	7 (3.0)	16 (3.5)
North America	**49 (21.6)**	**41 (17.8)**	**90 (19.7)**
United States	49 (21.6)	41 (17.8)	90 (19.7)
Eastern Europe	**33 (14.5)**	**39 (17.0)**	**72 (15.8)**
Russia	23 (10.1)	34 (14.8)	57 (12.5)
Slovakia	5 (2.2)	0 (0)	5 (1.1)
Turkey	5 (2.2)	5 (2.2)	10 (2.2)
Asia	**6 (2.6)**	**11 (4.8)**	**17 (3.7)**
Taiwan	6 (2.6)	11 (4.8)	17 (3.7)

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil

The number of subjects according to study centers and randomization groups are shown below.

Table 50: Distribution of subjects by countries, study center, and randomization groups

Country/ Investigator	Number (%) of subjects		
	TCF (N=227)	CF (N=230)	All (N=457)
Belgium	**23 (10.1)**	**27 (11.7)**	**50 (10.9)**
J. de Greve	3 (1.3)	2 (0.9)	5 (1.1)
E. van Cutsem	17 (7.5)	19 (8.3)	36 (7.9)
J. van Laethem	3 (1.3)	6 (2.6)	9 (2.0)
Brazil	**8 (3.5)**	**16 (7.0)**	**24 (5.3)**
A. Anelli	4 (1.8)	10 (4.3)	14 (3.1)
S. Cabral Filho	1 (0.4)	2 (0.9)	3 (0.7)
A. Malzyner	1 (0.4)	1 (0.4)	2 (0.4)
L. Olivatto	0 (0)	1 (0.4)	1 (0.2)
P. Pizao	2 (0.9)	2 (0.9)	4 (0.9)
Chile	**14 (6.2)**	**15 (6.5)**	**29 (6.3)**
M. Fodor	5 (2.2)	8 (3.5)	13 (2.8)
A. Majlis	9 (4.0)	7 (3.0)	16 (3.5)
Colombia	**20 (8.8)**	**19 (8.3)**	**39 (8.5)**
J. Martinez	2 (0.9)	6 (2.6)	8 (1.8)
C. Narvaez	6 (2.6)	4 (1.7)	10 (2.2)
F. Olivella	5 (2.2)	4 (1.7)	9 (2.0)
C. Ortiz	7 (3.1)	5 (2.2)	12 (2.6)
Germany	**4 (1.8)**	**5 (2.2)**	**9 (2.0)**
M. Clemens	2 (0.9)	3 (1.3)	5 (1.1)
C.-H. Koehne	1 (0.4)	2 (0.9)	3 (0.7)
H. Kroening	1 (0.4)	0 (0)	1 (0.2)
Italy	**16 (7.0)**	**14 (6.1)**	**30 (6.6)**
C. Barone	3 (1.3)	4 (1.7)	7 (1.5)
C. Boni	10 (4.4)	5 (2.2)	15 (3.3)
F. di Costanzo	0 (0)	1 (0.4)	1 (0.2)
F. Pasini	2 (0.9)	3 (1.3)	5 (1.1)
V. Silingardi	1 (0.4)	0 (0)	1 (0.2)
M. Tonato	0 (0)	1 (0.4)	1 (0.2)
Mexico	**3 (1.3)**	**2 (0.9)**	**5 (1.1)**
G. Morgan	1 (0.4)	0 (0)	1 (0.2)
G. Olivares	2 (0.9)	2 (0.9)	4 (0.9)
Peru	**8 (3.5)**	**6 (2.6)**	**14 (3.1)**
J. Salas	5 (2.2)	2 (0.9)	7 (1.5)
C. Vallejos	3 (1.3)	4 (1.7)	7 (1.5)
Portugal	**20 (8.8)**	**18 (7.8)**	**38 (8.3)**
C. Azevedo	5 (2.2)	3 (1.3)	8 (1.8)
S. Barroso	6 (2.6)	1 (0.4)	7 (1.5)
F. Fontes	3 (1.3)	2 (0.9)	5 (1.1)
J. Mauricio	0 (0)	1 (0.4)	1 (0.2)
F. Pimentel	1 (0.4)	1 (0.4)	2 (0.4)
M. Quina	2 (0.9)	2 (0.9)	4 (0.9)
A. Rodrigues	3 (1.3)	8 (3.5)	11 (2.4)

Country/ Investigator	Number (%) of subjects		
	TCF (N=227)	CF (N=230)	All (N=457)
Russia	**23 (10.1)**	**34 (14.8)**	**57 (12.5)**
V. Moiseyenko	14 (6.2)	14 (6.1)	28 (6.1)
S. Tjulandin	6 (2.6)	13 (5.7)	19 (4.2)
E. Voznyi	3 (1.3)	7 (3.0)	10 (2.2)
Slovakia	**5 (2.2)**	**0 (0)**	**5 (1.1)**
T. Salek	2 (0.9)	0 (0)	2 (0.4)
I. Vochyanova	3 (1.3)	0 (0)	3 (0.7)
Spain	**14 (6.2)**	**10 (4.3)**	**24 (5.3)**
M. Constenla	7 (3.1)	6 (2.6)	13 (2.8)
M. Gonzalez	2 (0.9)	2 (0.9)	4 (0.9)
C. Gravalos	2 (0.9)	2 (0.9)	4 (0.9)
J. Sastre	3 (1.3)	0 (0)	3 (0.7)
Taiwan	**6 (2.6)**	**11 (4.8)**	**17 (3.7)**
Y. Chao	5 (2.2)	8 (3.5)	13 (2.8)
J.-S. Chen	1 (0.4)	3 (1.3)	4 (0.9)
Turkey	**5 (2.2)**	**5 (2.2)**	**10 (2.2)**
E. Goker	1 (0.4)	1 (0.4)	2 (0.4)
G. Tekuzman	2 (0.9)	3 (1.3)	5 (1.1)
U. Yilmaz	2 (0.9)	1 (0.4)	3 (0.7)
United States	**49 (21.6)**	**41 (17.8)**	**90 (19.7)**
J. Ajani	19 (8.4)	12 (5.2)	31 (6.8)
L. Baez-Diaz	2 (0.9)	2 (0.9)	4 (0.9)
K. Bakri	1 (0.4)	0 (0)	1 (0.2)
A. Benson	4 (1.8)	4 (1.7)	8 (1.8)
J. Feldmann	1 (0.4)	0 (0)	1 (0.2)
FA. Greco	1 (0.4)	0 (0)	1 (0.2)
D. Haller	3 (1.3)	2 (0.9)	5 (1.1)
A. Hatfield	2 (0.9)	2 (0.9)	4 (0.9)
W. Heim	2 (0.9)	1 (0.4)	3 (0.7)
D. Howard	1 (0.4)	0 (0)	1 (0.2)
D. Kelsen	2 (0.9)	0 (0)	2 (0.4)
RJ. Kirschlin	0 (0)	2 (0.9)	2 (0.4)
R. Lilenbaum	1 (0.4)	3 (1.3)	4 (0.9)
R. Marsh	2 (0.9)	2 (0.9)	4 (0.9)
J. McCann	1 (0.4)	0 (0)	1 (0.2)
E. Mitchell	2 (0.9)	4 (1.7)	6 (1.3)
L. Pandit	2 (0.9)	3 (1.3)	5 (1.1)
J. Picus	0 (0)	1 (0.4)	1 (0.2)
C. Presant	0 (0)	1 (0.4)	1 (0.2)
A. Scholnik	1 (0.4)	0 (0)	1 (0.2)
D. Scullin	2 (0.9)	1 (0.4)	3 (0.7)
J. Thomas	0 (0)	1 (0.4)	1 (0.2)
Venezuela	**9 (4.0)**	**7 (3.0)**	**16 (3.5)**
P. Arbeloa	7 (3.1)	5 (2.2)	12 (2.6)
P. Nunez	2 (0.9)	2 (0.9)	4 (0.9)

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil

10.1.2.2. Analysis Populations

The number of subjects in various populations is shown in Table 8. All treated subjects received the treatment that they were allocated at randomization. Therefore the safety population is identical to the full analysis population.

Twelve randomized subjects, 6 in each treatment group, who did not receive therapy (Table 9). The reasons were as follows:

TCF-randomized subjects: H0653, K2351, and O7304 for death; K1509 and K6202 for consent withdrawn; and O3324 for PD, shortly followed by death.

Subject H0653: a 64-year-old man who presented at baseline with a KPS of 80, 0% weight loss, ongoing grade 2 asthenia and insomnia, grade 3 cancer pain (abdominal pain) and left pulmonary pain. The subject died due to respiratory failure 4 days after randomization.

Subject K2351: a 70-year-old man who presented at baseline with a KPS of 80, 15% weight loss; ongoing grade 3 cancer-related pain and grade 2 asthenia, dysphagia, nausea, shortness of breath, anemia and elevated alkaline phosphatase. The subject died due to malignant disease 2 days after randomization.

Subject O7304: a 37-year-old man who presented at baseline with a KPS of 80, 17% weight loss, grade 2 cancer-related pain, anorexia and dyspepsia and grade 4 obstructive jaundice. The subject died due to malignant disease 3 days after randomization.

Subject K1509: a 48-year-old woman withdrew her consent after being randomized to TCF. The subject indicated that she did not want treatment. The subject did not receive other anti-cancer therapy, and died from malignant disease 2.5 months after randomization.

Subject K6202: a 43-year-old man withdrew his consent after being randomized to TCF. The subject indicated that he wanted to be treated at another hospital and was lost to follow-up after consent was withdrawn.

Subject O3324: a 42-year-old woman who presented at baseline with ongoing grade 3 cancer-related pain and grade 3 thrombocytopenia and with grade 4 vaginal hemorrhage, started after the randomization. Tumor assessment showed ovarian metastases. She underwent surgery (ovariectomy) on Day 8 after the randomization. The subject was withdrawn from the study 19 days after randomization due to PD and died due to malignant disease 8 days later.

CF-randomized subjects: F0707, O3409, and O4706 for consent withdrawn; and C3327, L4405 and M0709 for various clinical and/or laboratory abnormalities.

Subject M0709: a 55-year-old woman who presented at baseline with a KPS of 90, 27% weight loss, grade 2 constipation and grade 3 cancer-related pain. The subject was withdrawn from the study 12 days after randomization due to grade 3 ASAT and grade 2 alkaline phosphatase.

Further chemotherapy (etoposide + 5-FU + leucovorin) started on day 19 after randomization. Subject was still alive in April 2003.

Subject L4405: a 63-year-old man presented at baseline with a KPS of 90, 20% weight loss, ongoing grade 2 anorexia and dysphagia and grade 3 cancer-related pain. After randomization, grade 3 GI hemorrhage, grade 4 anemia and grade 2 alkaline phosphatase were reported. The subject was withdrawn from the study 10 days after randomization. Further anticancer therapy (radiotherapy) started on day 20 after randomization. Subject died from malignant disease 3 months later.

Subject C3327: a 50-year-old man who presented at baseline with a KPS of 90, 0% weight loss, grade 3 cardiac dysrhythmia. The subject did not have cardiac medical history. He was withdrawn from the study 10 days after randomization due to cardiac dysrhythmia. He did not receive further anticancer therapy and was still alive more than 5 months after the date of randomization.

Subject O4706: a 63-year-old man who presented at baseline with a KPS of 90, 14% weight loss, ongoing grade 2 night sweats and grade 3 dysphagia. The subject withdrew his consent after being randomized to the control arm. Further chemotherapy (carboplatin + 5- FU, then cisplatin + irinotecan) was started on day 11 after the date of randomization. He died from malignant disease 8 months later.

Subject O3409: a 47-year-old man who presented at baseline with a KPS of 80, 8% weight loss and ongoing grade 1 cancer-related pain. The subject withdrew his consent 2 days after being randomized to the control arm. Further chemotherapy was started one month later (cisplatin + 5-FU + etoposide + folinic acid). He died from malignant disease 4 months after the date of randomization.

Subject F0707: a 38-year-old woman withdrew her consent 5 days after being randomized to the control arm. Further chemotherapy started on day 13 after randomization (etoposide + 5-FU + leucovorin). Subject died about 14 months later, from malignant disease.

Reviewer Note: Comparison of time to death from randomization on 12 untreated patients in two arms is tabulated in Table 9*. The time to death for 6 subjects randomized to CF arm but not treated was obviously much longer than that of TCF arm. Most likely that the patients who withdrew consent after randomized to CF arm received other therapies further. Therefore, for TAX 325a planned modified TTP and overall analyses, using ITT population will obviously inferior than using FAP.*

10.1.2.3. Non-eligible subjects

Overall, 48 (10.8%) subjects, 30 (13.6%) in the TCF treatment group and 18 (8.0%) in the CF treatment group, received study treatment but were considered non-eligible for the study,

primarily as a result of ERRC review of disease evaluability at baseline. The most common reason was no measurable and no evaluable metastatic disease in a total of 37 (8.3%) subjects, 22 (10.0%) TCF- treated subjects and 15 (6.7%) CF-treated subjects.

The reasons for ineligibility and the subject numbers are shown below.

Table 51: Reasons for non-eligibility (FAP)

Reasons for non-eligibility	TCF (N=221)		CF (N=224)	
	Subject No.	No. (%) of subjects	Subject No.	No. (%) of subjects
Total non-eligible subjects		**30 (13.6) [a]**		**18 (8.0) [a]**
ASAT and/or ALAT >1.5 x UNL associated with alkaline phosphatase >2.5 x UNL	C4713, C0451, I7405	3 (1.4)	C0619, O7205	2 (0.9)
ASAT or ALAT ≥5 X UNL	M6901	1 (0.5)	-	0 (0)
Calculated CrCl <57 mL/min	A4407, O0951	2 (0.9)	-	0 (0)
No measurable and no evaluable metastatic disease	A2903, C2603, E3302, H1252, H1904, H1906, I7212, K0601, K1803, K4704, L1905, L4725, M0608, M6901, M8001, N4715, P0154, P0657, P1802, P3701, P4730, P6804	22 (10.0)	E2955, E3102, E3506, F6103, G3308, L4304, M0658, O1805, O0302, O3322, P0654, P1251, P1253, P4720, P4731	15 (6.7)
Other tumor type than adenocarcinoma	A5404	1 (0.5)	O7904	1 (0.4)
Previous or current other cancer except treated in situ, cervix or non melanoma skin cancer	I3053	1 (0.5)	-	0 (0)
Total bilirubin ≥1.5 X UNL	-	0 (0)	O7205	1 (0.4)
Unstable cardiac disease, myocardial infarction, other serious medical conditions	O1609	1 (0.5)	-	0 (0)

a. Subjects M6901 and O7205 were ineligible for 2 reasons each.
FAP = Full analysis population; TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; UNL = Upper normal limit; CrCl = Creatinine clearance
Data source: TAX 325a report Appendix C. 1.1, Table 1.03.

Base on the eligibility criteria of the protocol, the applicant defined major deviations as follows:
• No histologically proven gastric adenocarcinoma.
• Not measurable and not evaluable metastatic disease.

• Locally recurrent disease without measurable lymph node.
• Other tumor type than adenocarcinoma.
• Previous or current malignancies other than gastric adenocarcinoma except adequately treated in situ carcinoma of the cervix uteri or non- melanoma skin cancer.
• Previous or history of central nervous system metastasis.
• KPS < 60.
• Symptomatic peripheral neuropathy with NCIC-CTC grade > 2.
• Active uncontrolled infection.
• Active disseminated intravascular coagulation.
• Unstable cardiac disease despite treatment, myocardial infarction within 6 months prior to study entry.
• Hgb < 6.5 g/dL.
• Neutrophils < 1.0 x 109/L.
• Platelets < 50 x109/L.
• Total bilirubin = 1.5 x UNL; ALAT or ASAT > 5 x UNL.
• Alkaline phosphatase > 5 x UNL.
• ALAT and/ or ASAT > 1.5 x UNL associated with alkaline phosphatase > 2.5 x UNL.
• Creatinine > 1.25 x UNL or 120 μ mol/L.
• Calculated CrCl < 57 mL/min.
• Prior palliative chemotherapy.
• Prior adjuvant (and/or neo-adjuvant) with a first relapse < 10 months from the end of adjuvant.
• Prior treatment with taxanes.
• Prior cisplatin with cumulative doses more > 300 mg/m2.
• Concurrent treatment with any other anti-cancer therapy.

Reviewer Note: In FAP population, TCF arm has 5.6% more ineligible patients than that of CF arm (13.6% vs. 8%). TCF arm also has 3.3% more patients who did not have either measurable or evaluable disease at baseline than that of CF arm (10% vs. 6.7%).

10.1.2.4 Subjects non-evaluable for response

Using the tumor assessment from the ERRC, except for subjects A0703, A1511, B0625, C2603, J5604, M2502, M6204, and O2301 for whom investigators' assessments were used, the F-EVAL review determined that 36 (16.3%) subjects in the TCF treatment group and 40 (17.9%) subjects in the CF treatment group were non-evaluable for response. The main reasons for non-evaluability for response were early discontinuation, (8.5%), that is, discontinuation before the second cycle, and/or no evaluable target lesions (4.3%). The most common reason for early discontinuation was AE. Reasons for non-evaluability for response were similar for the 2 treatment groups as shown below.

Table 52: Reasons for non-evaluability for response (FAP)

Reason	Number (%) of subjects		
	TCF (N=221)	CF (N=224)	Total (N=445)
Total evaluable for response by ERRC	185 (83.7)	184 (82.1)	369 (82.9)
Total non-evaluable for response by ERRC	**36 (16.3)**	**40 (17.9)**	**76 (17.1)**
Early discontinuation	17 (7.7)	21 (9.4)	38 (8.5)
Adverse event	8 (3.6)	9 (4.0)	17 (3.8)
Death (without PD)	6 (2.7)	7 (3.1)	13 (2.9)
Consent withdrawn	2 (0.9)	4 (1.8)	6 (1.4)
Lost to follow-up	1 (0.5)	0 (0)	1 (0.2)
Other [a]	0 (0)	1 (0.4)	1 (0.2)
Other reasons	12 (5.4)	12 (5.4)	24 (5.4)
No evaluable target lesions	11 (5.0)	8 (3.6)	19 (4.3)
No evaluable target and early discontinuation: consent withdrawn	1 (0.5)	1 (0.4)	2 (0.4)
No evaluable target and early discontinuation: adverse event	0 (0)	2 (0.9)	2 (0.4)
Concurrent anticancer therapy	0 (0)	1 (0.4)	1 (0.2)
Response not properly assessed	7 (3.2)	7 (3.1)	14 (3.1)

a. Subject G3321 was PD by the investigator but NE by ERRC (because no evidence of progression on surgery report)

Note: All tumor characteristics as per ERRC, except as per investigator for subjects A0703, A1511, B0625, C2603, J5604, M2502, M6204, and O2301.

FAP = Full analysis population; TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; ERRC = External Response Review Committee; PD = Pregressive disease; NE = Non-evaluable

Data source: Appendix C. 1.1, Table 1.06.

Reviewer Note: The number of patients with early discontinuation, non-evaluable response or inappropriate response assessment was relatively balanced between the two arms.

10.1.2.5 Subjects discontinued from the study

There were 430 (96.6%) subjects who had completed study medication or discontinued therapy: 216 (97.7%) TCF-treated subjects and 214 (95.5%) CF-treated subjects. The main reason was PD in both treatment groups but more CF-treated subjects discontinued due to PD (98 of 224 subjects, 43.8%), than TCF-treated subjects (66 of 221subjects, 29.9%). Discontinuation due to PD was per investigator assessment and refers to the on-treatment period. More TCF-treated subjects (48, 21.7%) withdrew consent compared to CF-treated subjects (26, 11.6%, Table 53).

The 2 treatment groups were otherwise comparable regarding reasons for discontinuation. The reasons for subject discontinuations, as reported by the investigator at the time of treatment discontinuation are shown below.

Table 53: Reason for treatment discontinuation (FAP)

Primary reason for discontinuation	Number (%) of subjects					
	TCF (N=221)		CF (N=224)		Total (N=445)	
Total discontinued	**216**	**(97.7)**	**214**	**(95.5)**	**430**	**(96.6)**
Progressive disease	66	(29.9)	98	(43.8)	164	(36.9)
Adverse event[a]	60	(27.1)	56	(25.0)	116	(26.1)
Related AE (i.e., toxicity) [b]	52	(23.5)	47	(21.0)	99	(22.2)
Not related AE	8	(3.6)	9	(4.0)	17	(3.8)
Consent withdrawn	48	(21.7)	26	(11.6)	74	(16.6)
Death	23	(10.4)	21	(9.4)	44	(9.9)
Malignant disease	7	(3.2)	5	(2.2)	12	(2.7)
Toxicity from study medication	6	(2.7)	10	(4.5)	16	(3.6)
Other	10	(4.5)	6	(2.7)	16	(3.6)
Other	14	(6.3)	11	(4.9)	25	(5.6)
Other major protocol violation	2	(0.9)	2	(0.9)	4	(0.9)
Lost to follow-up	3	(1.4)	0	(0)	3	(0.7)

a. Adverse events leading to discontinuations are discussed in Section …
b Four subjects were discontinued both for toxicity (i. e., related AE) and for not related AE but counted only in toxicity.
FAP = Full analysis population; TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; AE = Adverse event
Data source: TAX 325a study report Appendix C. 1.1, Table 1.12.

The frequencies of subjects who discontinued due to AEs were similar in the 2 treatment groups: 60 (27.1%) TCF- treated subjects and 56 (25.0%) CF- treated subjects (Fisher exact test, P= 0.666).

Other frequent reasons for treatment discontinuation were “death” and “consent withdrawn.”

i. Discontinuation due to death

There were 44 discontinuations due to death (Table 54): 12 deaths from malignant disease (7 in the TCF treatment group and 5 in the CF treatment group), 16 from toxicity from study medication (6 in the TCF treatment group and 10 in the CF treatment group), and 16 “other” (10 in the TCF treatment group and 6 in the CF treatment group). The deaths due to “other” in the TCF treatment group were pulmonary embolism (A3505, L3502, and O1609), dyspnea and chest

pain (A7106), sudden death (E0618), unknown (shortness of breath, H1906), GI bleeding (I7704), coagulopathy (K0453), unknown origin (GI- PAI, K1804) and not related AE (moniliasis, K8101). Deaths due to "other" in the CF treatment group were: pulmonary embolism (E7701 and K5402), gastrichemorrhage (K1707), unexplained death (M6204), GI bleeding (O1808), and cerebral vascular disease/respiratory failure (O7205) (TAX 325a study report Appendix C. 1.1, Table 1.19).

Table 54: Reasons for Death by Arm

Reasons of Death	Total No. Subjects	TCF No (ID)	CF No. (ID)
Deaths from malignant disease	12	7	5
Toxicity from study medication	16	6	10
Other reasons for death*	16	10	6
Total	44	23	21
*Other reasons for death			
Pulmonary embolism	5	3 (A3505, L3502, O1609)	2 (E7701, K5402)
Dyspnea and chest pain	1	1 (A7106)	-
Sudden or unexplained death	2	1 (E0618)	1 (M6204)
Unknown	2	2 (H1906, K1804)	-
GI bleeding	3	1 (I7704)	2 (K1707, O1808)
Coagulopathy	1	1 (K0453)	-
Not related AE (moniliasis,)	1	1 (K8101)	-
Cerebral vascular disease/respiratory failure	1	-	1 (O7205)

Source: TAX 325a study report Appendix C. 1.1, Table 1.19

ii. Discontinuations due to consent withdrawn

The observed rate of discontinuations for consent withdrawn (Table 55) was higher in the TCF group. It should be noted that the 48 TCF-treated subjects whom withdrew consent received a median of 6 cycles of study therapy (range: 1-16, TAX325a study report Appendix C. 1.1, Table 1.25), of which 20 subjects (41.7%) had a best overall tumor response of PR/CR and 17 subjects (35.4%) with stable disease (TAX325a study report Appendix C. 1.1, Table 1.26). Of the 26 CF-treated subjects who withdrew consent, the median number of cycles of study therapy received was 5 (range: 1-9), of whom there were 12 subjects (46.2%) with CR/PR and 8 (30.8%) with stable disease.

Table 55: Reasons for consent withdrawn by subject

TCF			Cycles	CF		
Subject no.	Best overall response[a]	Consent withdrawn comment	received	Subject no.	Best overall response[a]	Consent withdrawn comment
A1511	NE	Socioeconomic problems	1	C1705	NE	Unwillingness to continue
I7212	NE	Unwillingness to continue		F6103	NE	Patient's refusal
O1254	NE	Unacceptable traveling time		O4410	NE	Refusal of treatment
				O7208	NE	Patient decided she felt too weak to continue
				O6802	PD	Refusal of treatment
				P1253	NE	Chemotherapy made patient too ill
E3318	NC/SD	Refusal of treatment	2	G0152	NC/SD	Patient unwilling to do CDDP chemo only
G2601	PD	Patient's request				
K1809	NE	Personal reason				
K3052	NC/SD	Patient did not feel any improvement				
A2013	NC/SD	Refused therapy	3	E3304	NC/SD	Refusal of treatment
K5403	NC/SD	Patient's request				
L1103	NC/SD	Discomfort from AE, post-chemotherapy treatment				
A4407	NC/SD	Felt better and refused further treatment	4	A3401	NC/SD	Refusal of treatment
O1807	PR	Unwillingness to continue		M3054	NC/SD	Patient decided to continue treatment at other institution
P1802	PD	Unwillingness to continue		P7602	NC/SD	Patient's decision
A3317	PR	Refusal to continue chemotherapy	5	E3102	CR	Personal reasons
O1613	PR	Patient's decision		K1605	NC/SD	Patient preferred to have a CR instead of PR informed by doctor
				K1610	PR	Patient wanted to be back to work with no therapy
				L1806	PR	Unwillingness to continue
A3303	NC/SD	Refusal to comply with protocol	6	A3412	CR	Refusal of treatment
C3402	PR	Refusal of treatment		E1601	PR	Patient's request
C4301	PR	Decided not to continue		E7206	NC/SD	Unwillingness to continue
E3302	NE	Refusal of treatment		I0617	PR	No benefit expected
H1904	NE	Personal reason		I1507	PR	Unwillingness to continue

TCF			Cycles	CF		
Subject no.	Best overall response[a]	Consent withdrawn comment	received	Subject no.	Best overall response[a]	Consent withdrawn comment
K0802	NC/SD	Patient's request due to AEs		K1508	PR	Unwillingness to continue
K2353	NC/SD	Did not wish additional chemotherapy		K6001	NC/SD	Unwillingness to continue due to condition
K3313	NC/SD	Refusal of treatment				
K4302	NC/SD	Patient's decision				
K6005	PR	Unwillingness to continue				
L1905	CR	Personal reason				
L1909	PR	Patient's and family's decision				
M2002	NC/SD	Toxicity				
M2003	NC/SD	Personal reasons				
M2503	PR	Refusal of therapy				
N4715	NE	Physical and mental tiredness				
O2901	NC/SD	Patient's request				
O2902	PR	Unwillingness to continue				
P1907	NE	Unavailable due to out-of-country travel				
C2008	PR	Personal reasons	**7**	G7402	PR	Refusal of treatment
C3406	PR	Refusal of treatment		K3411	PR	Refusal of treatment
K3404	PR	Refusal of treatment				
O1552	NC/SD	Patient wants other therapy				
A1706	PR	Tired of the treatment	**8**	A3415	PR	Refusal of treatment
C3601	PR	Loss of motivation				
K4004	PR	Tiredness due to no additional benefit				
N2504	PD	Performed 8 cycles				
C3414	PR	Refusal of treatment	**9**	L1504	PR	Personal decision
K1801	PR	Unwillingness to continue				
P1908	NC/SD	Tiredness				
G5001	PR	Unwillingness to continue	**11**			
M3101	CR	Personal reasons	**14**			
O0616	NC/SD	After SAE on last chemotherapy	**16**			
48			**Total**	**26**		

Note: Reasons are summarized and adapted from literal entries.
a According to F-EVAL
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; CR = complete response, PR = partial response, NC/SD = no change/stable disease, PD = progressive disease, NE = not evaluable; SAE = Serious adverse event; AE = adverse event; CDDP = cisplatin
Data source: TAX 325a study report Appendix C. 1.1, Table 1.24.

Reviewer Note: The reviewer has verified applicant summarized reasons for discontinuation of study medication which was presented in TAX325a study report Appendix C. 1.1, Table 1.12 and sample CRFs. A listing of reasons for study discontinuation, including those described as "Other," is also examined in TAX325a study report Appendix C. 1.1, Tables 1.17, 1.19, 1.20-1.24, and 1.27. The number of subjects discontinued from study and the reason of discontinuation appeared to be balanced between the two arms. However, it is noteworthy that among patients who withdraw their consent, response rate was 41.7% for TCF and 42.2% for CF, 16 patients had CR or PR in less than or equal to 10 cycle treatment of TCF and 11 for that CF arm.

10.1.2.6. Protocol Deviations

10.1.2.6.1. Major protocol deviations at study entry (non-eligible subjects) are shown in Table 51. There were 3 subjects with major protocol deviations during the study:

TCF-treated subject **K1502** was treated despite increased liver enzymes between randomization and first administration of study medication. The subject died on Day 3 of cycle 1 from hepatic coma due to "malignant disease" according to the investigator. This case was considered as a toxic death by sponsor review. Further details on this subject are given in Safety review...

CF-treated subject **I4403** who erroneously received Taxotere one time during the second cycle. The only grade 3-4 TEAE reported for this subject during cycle 2 was cancer pain, considered not related to study treatment.

CF-treated subject **K2505** who was treated despite bilirubin and transaminases increase between randomization and first administration of study medication. Subject experienced grade 4 cancer pain, grade 4 anorexia, grade 4 vomiting and grade 4 hyperbilirubinemia. Subject discontinued treatment after cycle 1 due to adverse event (cancer pain and vomiting). He did not receive further therapy and died from malignant disease on day 47 after the last infusion.

Reviewer Note: Beside 3 patients who enrolled without pathological diagnosis (2 on TCF arm and 1 on CF arm), there were three other major protocol deviations, two received treatment (one arm each) while the liver function was abnormal, leading to grade 4 and 5 toxicity. The third incident was administration error in given taxotere for a patient on CF arm.

10.1.2.6.2. Minor protocol deviations at inclusion: Overall, 185 of 445 (41.6%) subjects (89 TCF-treated subjects and 96 CF-treated subjects) were reported to have at least 1 minor protocol deviation as summarized in Table 56. The most common minor protocol deviations were related to the timing of tumor assessment performed more than 2 weeks before first infusion (42 TCF-treated subjects, 19.0% and 43 CF- treated subjects, 19.2%) or required blood testing performed more than 1 week before randomization (33 TCF-randomized subjects, 14.9% and 37 CF-randomized subjects, 16.5%).

Table 56: Minor protocol deviations at inclusion (FAP)

Minor protocol deviation[a]	Number (%) of subjects		
	TCF	CF	Total
Full analysis population	**221 (100)**	**224 (100)**	**445 (100)**
Total with at least 1 minor protocol deviation	89 (40.3)	96 (42.9)	185 (41.6)
Tumor assessment performed >2 weeks before first administration	42 (19.0)	43 (19.2)	85 (19.1)
Biological work up performed >1 week before randomization	33 (14.9)	37 (16.5)	70 (15.7)
Reproductive potential but no adequate contraceptive measures	14 (6.3)	17 (7.6)	31 (7.0)
Definite contraindication for use of corticosteroids	10 (4.5)	8 (3.6)	18 (4.0)
Hemoglobin <10 g/dL and ≥6.5 g/dL	5 (2.3)	5 (2.2)	10 (2.2)
Calculated CrCl ≥57 mL/min and <60 mL/min	4 (1.8)	4 (1.8)	8 (1.8)
KPS of 60 or 70	2 (0.9)	2 (0.9)	4 (0.9)
Total bilirubin >1 x UNL and <1.5 x UNL	2 (0.9)	2 (0.9)	4 (0.9)
Single lesion not proven by histology or cytology	2 (0.9)	1 (0.4)	3 (0.7)
Neutrophils ≥1.0 x 10^9/L and <2.0 x 10^9/L	1 (0.5)	2 (0.9)	3 (0.7)
Prior and ongoing treatment with corticosteroids	2 (0.9)	0 (0)	2 (0.4)
Less than 6 weeks between prior radiotherapy and 1st infusion	1 (0.5)	1 (0.4)	2 (0.4)
ASAT or ALAT >2.5 x UNL and <5 x UNL	2 (0.9)	0 (0)	2 (0.4)
Symptomatic peripheral neuropathy with NCIC-CTC grade 2	1 (0.5)	1 (0.4)	2 (0.4)

a. Subjects could have more than 1 minor protocol deviation.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; UNL = Upper normal limit; KPS = Karnofsky performance status; CrCl = Creatinine clearance; FAP = Full analysis population
Data source: TAX 325a study report, appendix C. 1.1, Table 1.04.

Reviewer Note: The number of subjects with minor deviation in both arms appear to be similar.

10.1.2.7. Demographics

A summary of subject characteristics is shown in Table 35.

10.1.2.8. Baseline Characteristics

10.1.2.8.1. Baseline Tumor

A summary of tumor characteristics by treatment group is shown below.

Table 57: Tumor characteristics at baseline (FAP)

Tumor characteristics	Number (%) of subjects		
	TCF (N=221)	CF (N=224)	Total (N=445)
Histology type			
Adenocarcinoma diffuse type	92 (41.6)	77 (34.4)	169 (38.0)
Adenocarcinoma intestinal type	40 (18.1)	45 (20.1)	85 (19.1)
Linitis plastica	21 (9.5)	16 (7.1)	37 (8.3)
Adenocarcinoma, NOS	66 (29.9)	80 (35.7)	146 (32.8)
Other	2 (0.9)	6 (2.7)	8 (1.8)
Anatomic site			
Antrum	56 (25.3)	65 (29.0)	121 (27.2)
Body	97 (43.9)	86 (38.4)	183 (41.1)
Fundus	26 (11.8)	16 (7.1)	42 (9.4)
Esogastric junction	42 (19.0)	56 (25.0)	98 (22.0)
Unknown	0 (0)	1 (0.4)	1 (0.2)
Extent of disease[a]			
Metastatic	213 (96.4)	217 (96.9)	430 (96.6)
Locally recurrent	1 (0.5)	1 (0.4)	2 (0.4)
Locally advanced	5 (2.3)	5 (2.2)	10 (2.2)
No disease	2 (0.9)	1 (0.4)	3 (0.7)

a. As determined by F-EVAL.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population; NOS = Not otherwise specified
Data source: TAX 325a study report, Appendix C. 1.1, Tables 2.02 and 2.03.

A summary of disease characteristics by treatment group is shown below.

Table 58: Disease characteristics at baseline (FAP)

Tumor characteristics	Number (%) of subjects		
	TCF (N=221)	CF (N=224)	Total (N=445)
Measurability of disease[a]			
Bidimensional	185 (83.7)	195 (87.1)	380 (85.4)
Unidimensional	1 (0.5)	3 (1.3)	4 (0.9)
Evaluable only	15 (6.8)	12 (5.4)	27 (6.1)
Non-evaluable disease	18 (8.1)	13 (5.8)	31 (7.0)
No disease	2 (0.9)	1 (0.4)	3 (0.7)
Number of organs involved[a]			
1	33 (14.9)	47 (21.0)	80 (18.0)
2	86 (38.9)	76 (33.9)	162 (36.4)
>2	100 (45.2)	100 (44.6)	200 (44.9)
No organs	2 (0.9)	1 (0.4)	3 (0.7)
Organ involvement[b]			
Stomach	154 (69.7)	153 (68.3)	307 (69.0)
Lymph nodes	138 (62.4)	140 (62.5)	278 (62.5)
Liver	99 (44.8)	103 (46.0)	202 (45.4)
Peritoneum	52 (23.5)	63 (28.1)	115 (25.8)
Pleura	24 (10.9)	19 (8.5)	43 (9.7)
Lung	15 (6.8)	13 (5.8)	28 (6.3)
Adrenal gland	15 (6.8)	11 (4.9)	26 (5.8)
Ovary	11 (5.0)	13 (5.8)	24 (5.4)
Connective soft tissue	12 (5.4)	6 (2.7)	18 (4.0)
Bone	6 (2.7)	4 (1.8)	10 (2.2)

a. As determined by ERRC
b only organs in at least 2% of subjects are given
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population; ERRC = External Response Review Committee;
Data source: TAX 325a study report, Appendix C. 1.1, Tables 2.03 and 2.04.

*Reviewer Note: Most of subjects (98.2%) had adenocarcinoma of the stomach (*Table 57*). The majority of tumors were located in the body (41.1%), with the others in the antrum (27.2%), esogastric junction (22.0%), fundus (9.4%). For one subject (subject P1253), who had linitis plastica, the gastric site of primary tumor was unknown.*

There was a slight imbalance for tumor characteristics at baseline (FAP) noticed between the two treatment arms. TCF arm had 5.5% more tumors originated from body of the stomach (43.9% for TCF vs. 38.4% for CF) than that of CF arm. In addition, TCF had 3.7% less antrum disease (25.5 for TCF vs. 29% for CF) and 6% less EG junction diseases (19% for TCF vs.

38.4% for CF) than that of CF arm. In other words, the TCF arm had 3.7% more better prognosis disease and 9.7% (3.7% + 6%) worse prognosis disease than that of CF arm. However, the TCF arm did have 2.4% more linitis plastica (9.5% for TCF vs. 7.1 for CF) than that of CF arm.

With the exception of 15 subjects (3.4%), 96.6% subjects (96.6%) had metastatic disease at baseline (96.4% for TCF and 96.9 for CF). For the remaining 3.4%, ten patients (2.2%) had locally advanced disease. Two patients (0.4%) had locally recurrent disease. TCF arm had 4.4% less bidimentional measurable disease (83.7% for TCF vs. 87.1% for CF) and 0.8% less unidimentional measurable disease (0.5% for TCF vs. 1.3% for CF), resulting a total of 5.2% less measurable disease for the TCF arm. On the other hand, the TCF arm had 2.4% more non-measurable disease then that of CF arm (8.1% for TCF arm and 5.8% for CF arm). Three patients (0.7%) had no disease, two (0.9%) on TCF arm and one (0.4%) on CF arm.

There were 6% more subjects in TCF arm with 2 or more organs involved (38.9% for TCF vs. 33.9% for CF arm) than that of CF arm, most common were stomach, regional lymph nodes, and liver.

It is not clear whether these slight imbalances would have some impact in favorable outcome for TCF arm.

10.1.2.8.2. Prior cancer therapies

Prior cancer therapy that study subjects received are summarized below.

Table 59: Prior Cancer Therapies

Therapy	Number (%) of subjects		
	TCF (N=221)	CF (N=224)	Total (N=445)
Prior therapies			
Radiotherapy	5 (2.3)	5 (2.2)	10 (2.2)
Chemotherapy (Adjuvant/Neo-adjuvant)	6 (2.7)	6 (2.7)	12 (2.7)
Surgery	68 (30.8)	71 (31.7)	139 (31.2)
Complete gastrectomy	23 (10.4)	22 (9.8)	45 (10.1)
Partial gastrectomy NOS	29 (13.1)	34 (15.2)	63 (14.2)
Partial gastrectomy proximal	3 (1.4)	1 (0.4)	4 (0.9)
Partial gastrectomy distal	6 (2.7)	11 (4.9)	17 (3.8)
Other[a]	7 (3.2)	6 (2.7)	13 (2.9)
Surgery intent			
Curative	43 (19.5)	42 (18.8)	85 (19.1)
Palliative	25 (11.3)	28 (12.5)	53 (11.9)
Curative and palliative	0 (0.0)	1 (0.4)	1 (0.2)

a Details of the types of surgeries performed can be found in Appendix C. 1.1, Table 2.06 .
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population; NOS = Not otherwise specified
Data source: TAX325a study report, Appendix C. 1.1, Table 2.05.

Reviewer notes: The prior therapies (radiation, adjuvant or neo-adjuvant chemotherapy, and surgery) appear to be balanced between the two arms. Some subjects had more than one kind of prior therapy. Twelve (2.7%) subjects had received previous chemotherapy before enrollment into this study (prior chemotherapy for advanced disease was an exclusion criterion; however, previous adjuvant and/or neo-adjuvant chemotherapy was allowed if more than 12 months had elapsed between the end of the therapy and the first relapse). There were 10 (2.2%) subjects who had received Radiation therapy prior to study entry. A total of 139 (31.2%) subjects had previous surgery, which was curative in 85 subjects (19.1%) (TAX 325a study report, Appendix C. 1.1, Table 2.06). Among the 13 subjects with "other" surgery, 6 in the TCF treatment group out of 7 and 4 out of 6 in the CF-treatment group had partial or total gastrectomy combined with partial esophagectomy.

10.1.2.8.3. Timing of Prestudy Clinical Events (FAP)

A summary of the timing of clinical events prior to randomization by treatment group is shown below.

Table 60: Timing of pre-study clinical events (FAP)

Events	TCF (N=221)	CF (N=224)	Total (N=445)
Time from first diagnosis to randomization			
Median (months)	1.7	1.8	1.7
Minimum-maximum	0.1-76.1	0.1-72.3	0.1-76.1
No. (%) of subjects with surgery	68 (30.8)	71 (31.7)	139 (31.2)
Time from last surgery to randomization			
Median (months)	7.8	8.1	7.9
Minimum-maximum	0.9-76.1	0.5-72.3	0.5-76.1
No. (%) of subjects with relapse	43 (19.5)	43 (19.2)	86 (19.3)
Time from first diagnosis to relapse			
Median (months)	16.4	16.1	16.3
Minimum-maximum	3.8-75.5	3.4-70.0	3.4-75.5
Time from relapse to randomization			
Median (months)	1.4	1.0	1.2
Minimum-maximum	0.1-20.0	0.1-7.5	0.1-20.0

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population
Data source: TAX 325a study report, Appendix C. 1.1, Tables 2.02.

As per CRF filing guidelines, the date of first diagnosis was the date of biopsy or surgery that provided the original diagnosis. While the median time from first diagnosis to randomization was 1.7 months, ranged 0.1-76.1 months. About 20% of the subjects experienced relapse ranged from 3.4-75.5 months and relapse to randomization ranged 0.1-20.0 months. The median time from last surgery to randomization was approximately 8 months, but ranged 0.5-76.1 months. The timing to pre-study events appears to be balanced between the two arms.

10.1.2.8.4. Baseline signs and symptoms

Any signs and/or symptoms present at study entry, whether or not they were related to previous or ongoing therapies or disease, as well as any relevant signs and symptoms that occurred during the previous 2 weeks, were recorded at baseline. These were documented in the CRF using the same NCIC-CTC used for study medication safety evaluation.

Table 61 - Signs and symptoms at baseline in more than 1 subject, by NCIC - CTC category and selected terms (FAP)

Category (and selected terms)	Number (%) of subjects		
	TCF (N=221)	CF (N=224)	Total (N=445)
Total signs and symptoms	**188 (85.1)**	**186 (83.0)**	**374 (84.0)**
Gastrointestinal	130 (58.8)	127 (56.7)	257 (57.8)
Cancer-related symptoms	121 (54.8)	125 (55.8)	246 (55.3)
Cancer pain	121 (54.8)	124 (55.4)	245 (55.1)
Flu-like symptoms	67 (30.3)	52 (23.2)	119 (26.7)
Lethargy	55 (24.9)	49 (21.9)	104 (23.4)
Neurological	50 (22.6)	42 (18.8)	92 (20.7)
Pulmonary	19 (8.6)	15 (6.7)	34 (7.6)
Cardiovascular	9 (4.1)	13 (5.8)	22 (4.9)
Other[a]	7 (3.2)	7 (3.1)	14 (3.1)
Skin	7 (3.2)	6 (2.7)	13 (2.9)
Infection	5 (2.3)	5 (2.2)	10 (2.2)
Genitourinary	4 (1.8)	3 (1.3)	7 (1.6)
Osseous	3 (1.4)	3 (1.3)	6 (1.3)
Hypersensitivity	1 (0.5)	4 (1.8)	5 (1.1)
Endocrine	1 (0.5)	2 (0.9)	3 (0.7)
Ocular	0 (0)	2 (0.9)	2 (0.4)

a Other: including pain in chest, back, and injection site; increased salivation; and tenosynovitis.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population
Data source: TAX 325a Study Report, Appendix C. 1.1, Table 2.08.

Reviewer Note: A total of 374 (84.0%) of FAP subjects presented with clinical signs and symptoms at baseline. Signs and symptoms occurred more than 1 subject are categorized by NCIC-CTC in Table 61. The TCF arm has 7.1% more flu-like symptoms (30.3% in TCF vs. 23.2% in CF) and 4.8% more neurological symptoms (22.6% in TCF and 18.8% in CF). The most frequent symptom was lethargy. The most common signs and symptoms were GI (TCF:

58.8%; CF: 56.7%): more than half of the subjects in either treatment group presented with GI signs and symptoms at baseline, with anorexia, nausea, esophagitis/dysphagia/odynophagia, and vomiting being the most frequent. Cancer-related symptoms were the second most frequent category, which consisted of cancer pain in all but 1 subject. In the neurological category, the most frequent signs were constipation, insomnia, and mood.

Grade 3- 4 signs and symptoms at baseline in more than 1 subject in either treatment group are shown by NCIC- CTC term below.

Table 62 - Grade 3-4 signs and symptoms at baseline in more than 1 subject, by NCIC-CTC term (FAP)

Sign and symptoms	Number (%) of subjects		
	TCF (N=221)	CF (N=224)	Total (N=445)
Total grade 3-4 signs and symptoms	**61 (27.6)**	**57 (25.4)**	**118 (26.5)**
Cancer pain	45 (20.4)	45 (20.1)	90 (20.2)
Anorexia	6 (2.7)	4 (1.8)	10 (2.2)
Esophagitis/dysphagia/odynophagia	8 (3.6)	1 (0.4)	9 (2.0)
Venous	2 (0.9)	4 (1.8)	6 (1.3)
Gastrointestinal pain/cramping	0 (0)	3 (1.3)	3 (0.7)
Gastrointestinal bleeding	2 (0.9)	1 (0.4)	3 (0.7)
Bone pain	1 (0.5)	1 (0.4)	2 (0.4)
Heartburn	2 (0.9)	0 (0)	2 (0.4)
Constipation	1 (0.5)	1 (0.4)	2 (0.4)
Mood	1 (0.5)	1 (0.4)	2 (0.4)
Other: pain	2 (0.9)	0 (0)	2 (0.4)
Shortness of breath	2 (0.9)	0 (0)	2 (0.4)
Nausea	1 (0.5)	1 (0.4)	2 (0.4)

Note: signs and symptoms are ordered according to total column
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population
Data source: TAX 325a study report, Appendix C. 1.1, Table 2.11.

Reviewer Note: With cancer pain being by far the most frequent (20.2%), the treatment groups were similar with respect to grade 3-4 signs and symptoms.

10.1.2.8.5. Baseline biological parameters

i. Abnormal hematologic parameters

Both treatment groups were comparable for abnormal hematologic parameters at baseline, before first infusion, as shown below.

Table 63: Existing abnormal hematologic values at baseline before first infusion (FAP)

Hematology parameter	Number (%) of subjects		
	TCF (N=221)	CF (N=224)	Total (N=445)
Total with at least 1 abnormal parameter	**127 (57.5)**	**134 (59.8)**	**261 (58.7)**
Anemia	101 (45.7)	105 (46.9)	206 (46.3)
Leukocytosis	52 (23.5)	44 (19.6)	96 (21.6)
Leukopenia	5 (2.3)	1 (0.4)	6 (1.3)
Neutropenia	0 (0)	3 (1.3)	3 (0.7)

Note: parameters are ordered according to total column
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population
Data source: Appendix C. 1.1, Table 2.09.

Reviewer note: The most frequent hematologic abnormalities were anemia and leukocytosis in both treatment groups. All cases of abnormal hematological values were grade 1 or 0 except for 13 cases of grade 2 anemia: 6 in TCF-treated subjects and 7 in CF-treated subjects. Abnormally low levels of leukocytes and neutrophils combined accounted for abnormalities in 2% of both treatment groups. There were no subjects in either treatment group with thrombocytopenia (TAX 325a study report, Appendix C. 1.1, Table 2a. 05).

ii. Abnormal biochemical parameters

Both treatment groups were comparable for abnormal biochemical parameters at baseline, with the exception of total serum protein, for which there were slightly more subjects with abnormalities in the TCF treatment group (19.0%) than in the CF treatment group (12.9%), as shown below.

Table 64: Existing abnormal biochemical values at baseline before first infusion (FAP)

Biochemistry parameter	Number (%) of subjects		
	TCF (N=221)	CF (N=224)	Total (N=445)
At least 1 abnormal biochemical result	137 (62.0)	132 (58.9)	269 (60.4)
Alkaline phosphatase (>UNL)	93 (42.1)	92 (41.0)	185 (41.5)
ALAT (>UNL)	34 (15.4)	27 (12.1)	61 (13.7)
ASAT (>UNL)	37 (16.7)	34 (15.2)	71 (16.0)
Total serum protein (<LNL)	42 (19.0)	29 (12.9)	71 (16.0)
Missing values[a]	*27*	*21*	*48*
Magnesium (<LNL)	13 (5.9)	13 (5.8)	26 (5.8)
Missing values[a]	*53*	*47*	*100*
Potassium (<LNL)	9 (4.1)	14 (6.3)	23 (5.2)
Missing values[a]	*13*	*11*	*24*
Creatinine (>UNL)	8 (3.6)	6 (2.7)	14 (3.1)
Total serum bilirubin (>UNL)	2 (0.9)	4 (1.8)	6 (1.3)
CrCl, 40 to <60 mL/min	4 (1.8)	6 (2.7)	10 (2.2)

Note: parameters are ordered according to total column
a There were only subjects with missing values for total serum protein, magnesium, and potassium. TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population; UNL = Upper normal limit; LNL = Lower normal limit; CrCl = Creatinine clearance Data source: Appendix C. 1.1, Table 2.10.

Reviewer note: Although a large number of subjects had abnormal biochemistry values before first infusion most of these values still satisfied the inclusion criteria for that parameter. The most common abnormal parameter was increased alkaline phosphatase.

Before the treatment initiation, almost all ASAT and ALAT elevations were grade 1 in both treatment groups. Four of the 6 serum total bilirubin elevations were grade 2, and the remaining 2 elevations were grade 3, all in CF-treated subjects (4 of the subjects had liver metastasis). Low total serum protein was mostly more than 80% of the LNL, with only a few cases between 70% and 80% of the LNL: 5 cases in TCF-treated subjects and 3 cases in CF- treated subjects.

The serum creatinine level was reported abnormal in a similar number of subjects in both arms and 2 of them were > grade 1. The number of subjects with abnormal CrCl was similar in the 2 arms, with the corresponding values being between 40 and 60 mL/min. There were no subjects with CrCl less than 40 mL/min.

There were 13 subjects in each arm who had low serum magnesium at baseline (2 of grade 2 abnormalities per arm), with 22% of subjects missing this measurement. There were 9 TCF arm (2 of grade 2 and 1 grade of 3 abnormality) and 14 CF arm (3 of grade 2 and 1 grade of 3 abnormality) subjects had baseline hypokalemia (TAX 325a study report, Apendix C. 1.1, Table 2a. 06).

10.1.2.8.6. Stratification at Randomization vs. Stratification According to Baseline Characteristics

Subjects were stratified by measurable or evaluable-only lesions, liver involvement (yes vs. no), weight loss $\leq$ 5%, and prior surgery (yes vs. no). A summary of the stratification factors, as used by the investigator for the randomization and as "actual," that is, by determination from the CRF for prior surgery and weight loss and from the ERRC for tumor characteristics, are shown below.

Table 65: Baseline stratification characteristics used in randomization vs. actual (FAP)

Stratification characteristic	Number (%) of subjects					
	TCF (N=221)		CF (N=224)		Total (N=445)	
	Used in random.	Actual	Used in random.	Actual	Used in random.	Actual
Measurable disease	181 (81.9)	186 (84.2)	183 (81.7)	198 (88.4)	364 (81.8)	384 (86.3)
Liver involvement	123 (55.7)	99 (44.8)	120 (53.6)	103 (46.0)	243 (54.6)	202 (45.4)
Weight loss ≤5%	97 (43.9)	95 (43.0)	99 (44.2)	96 (42.9)	196 (44.0)	191 (42.9)
Prior surgery	75 (33.9)	68 (30.8)	73 (32.6)	71 (31.7)	148 (33.3)	139 (31.2)

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population.
Data source: Appendix C. 1.1, Table 2a. 07.

Reviewer note: The review of the baseline tumor evaluations of the ERRC indicated that some subjects would have been assigned to a different stratification group than the one assigned by the investigator. Overall, 139 (31.2%) treated subjects had a stratification different from randomization: 67 of 221 (30.3%) TCF-treated subjects, and 72 of 224 (32.1%) CF-treated subjects (TAX 325a study report, Appendix C. 1.1, Table 2a. 08). With respect to tumor characteristics only, 86 of 445 (19.3%) treated subjects incorrectly stratified, 40 of 221 (18.1%) in TCF arm and 46 of 224 (20.5%) in CF-treated subjects (TAX 325a study report, Appendix C. 1.1, Table 2a. 07). This discordance was partly caused by the fact that the stratification factor of liver/peritoneal metastases was amended to liver metastasis only during the study (TAX 325a study report, Appendix C. 1.1, Table 2a. 09).

However, the overall distributions of the "actual" stratification factors were similar between the 2 arms, except there were 4.2% less measurable disease in the TCF arm (TAX 325a study report,

Appendix C. 1.1, Table 2a. 07). The impact of any difference in incorrect stratification may be minimal, since the analyses of TTP and OS were unstratified.

10.1.2.8.7. Concomitant medication

The used of EPO or RBC transfusion for anemia and GCSF prophylaxis for neutropenia during the study were noted. Detailed review of these are in safety analysis.

10.1.2.8.8. Post study anticancer chemotherapy

Post-study anticancer chemotherapies are summarized in Table 18.

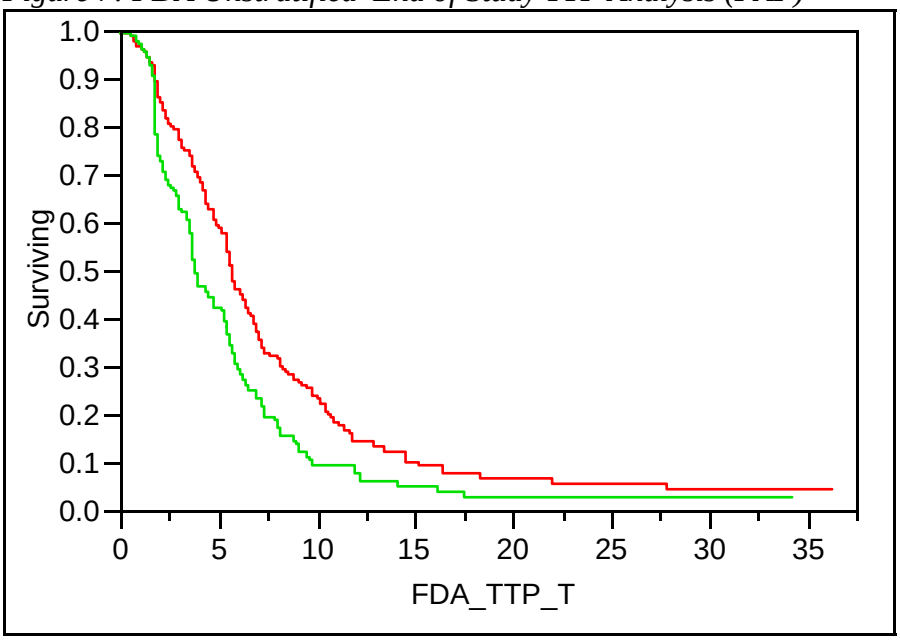
10.1.3. Efficacy Results

10.1.3.1. Primary Analysis – TTP

In the end of study, 341 of 445 (76.6%) subjects had a progression event, and 104 of 445 (23.4%) subjects were censored for analysis. As per applicant report, the median follow-up was 13.6 months (95% CI: 11.30- 22.28, TAX 325a study report, Appendix C. 1.1, Table 1.30). The observed median TTP was 5.6 months in the TCF group (95% CI: 4.86-5.91) and 3.7 months (95% CI: 3.45- 4.47) in the CF group. The difference between the 2 treatments was statistically significant (log- rank test, P= 0.0004) with an HR of 1.473 (95% CI: 1.189- 1.825) and a risk reduction of 32.1%. At 6 months, 42.7% of the TCF-treated subjects had no event of progression compared with 27.4% of the CF-treated subjects (Table 10 and Figure 4).

Reviewer note: The sponsor's non-stratified log-rank test for the TTP analyses has been verified by the statistical reviewer. In addition, per clinical reviewer request, Dr. Shenghui Tang, the statistical reviewer has conducted standard TTP (disease progression events only) and standard PFS analyses (disease progression + all death) in both FAP and ITT populations of study TAX 325a (Table 13, Figure 7 , Figure 8, Figure 9, and ***Error! Reference source not found.*** *). These results were similar to applicant's primary analysis except PFS in ITT population, which is mimicking the overall survival analysis in ITT population (dialed in next section, overall survival analysis).*

Figure 7: FDA Unstratified End of Study TTP Analysis (FAP)



Red – TCF, Green - CF

Summary

Group	N Failed	N Censored	Mean		Std Error
TCF	149	72	7.72722	Biased	0.54728
CF	155	69	5.30094	Biased	0.32521

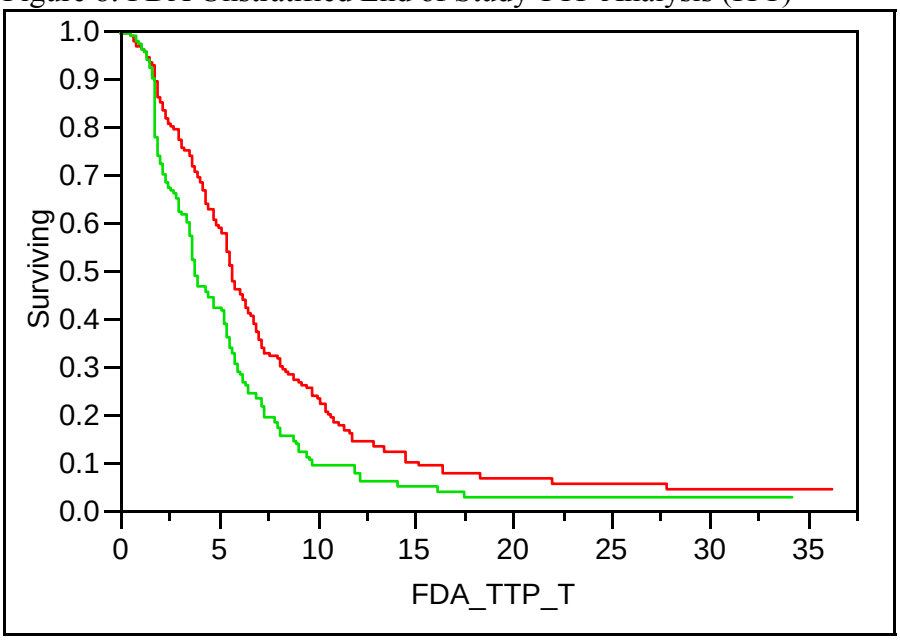
Quantiles

Group	Median Time	25% Failures	75% Failures
TCF	5.7823	3.6468	9.8234
CF	3.9097	2.037	6.9979

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	13.6393	1	0.0002
Wilcoxon	15.7069	1	<.0001

Figure 8: FDA Unstratified End of Study TTP Analysis (ITT)



Red – TCF, Green - CF

Summary

Group	N Failed	N Censored	Mean		Std Error
2-TCF	149	78	7.72722	Biased	0.54728
3-CF	156	74	5.28093	Biased	0.32416

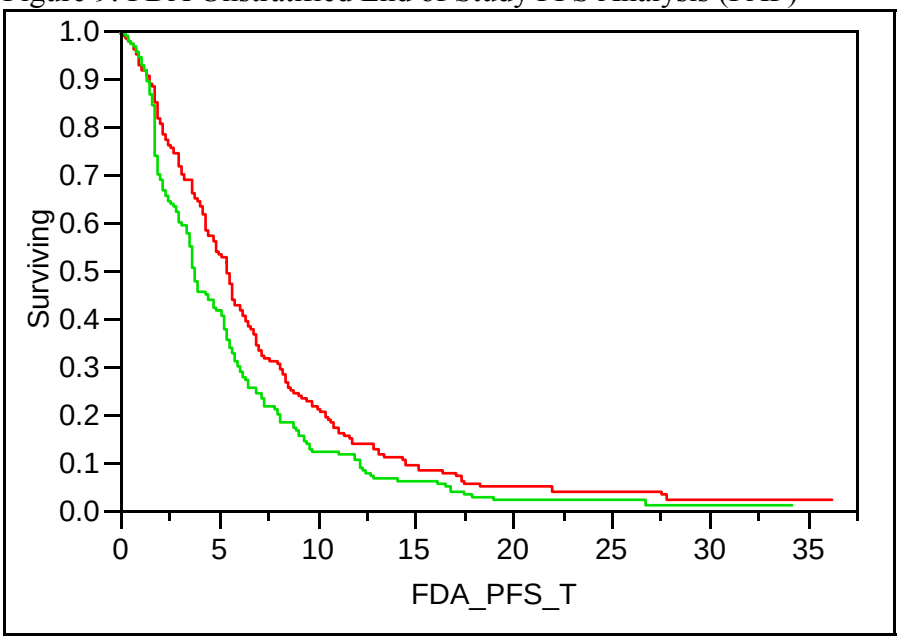
Quantiles

Group	Median Time	25% Failures	75% Failures
2-TCF	5.7823	3.6468	9.8234
3-CF	3.9097	2.037	6.6037

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	14.0132	1	0.0002
Wilcoxon	16.2715	1	<.0001

Figure 9: FDA Unstratified End of Study PFS Analysis (FAP)



Red – TCF, Green - CF

Summary

Group	N Failed	N Censored	Mean		Std Error
2-TCF	189	32	7.12768	Biased	0.45266
3-CF	193	31	5.58301	Biased	0.37503

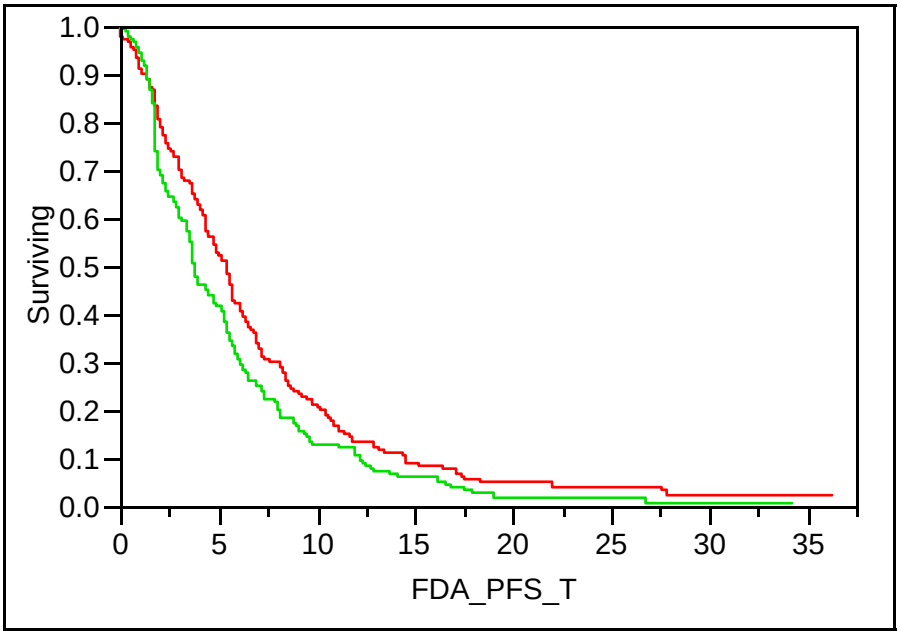
Quantiles

Group	Median Time	25% Failures	75% Failures
2-TCF	5.5524	2.8255	8.8378
3-CF	3.8439	1.8727	7.0308

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	8.3250	1	0.0039
Wilcoxon	9.9666	1	0.0016

Figure 10: FDA Unstratified End of Study PFS Analysis (ITT)



Red – TCF, Green - CF

Summary

Group	N Failed	N Censored	Mean		Std Error
2-TCF	194	33	6.98343	Biased	0.44711
3-CF	197	33	5.60273	Biased	0.36989

Quantiles

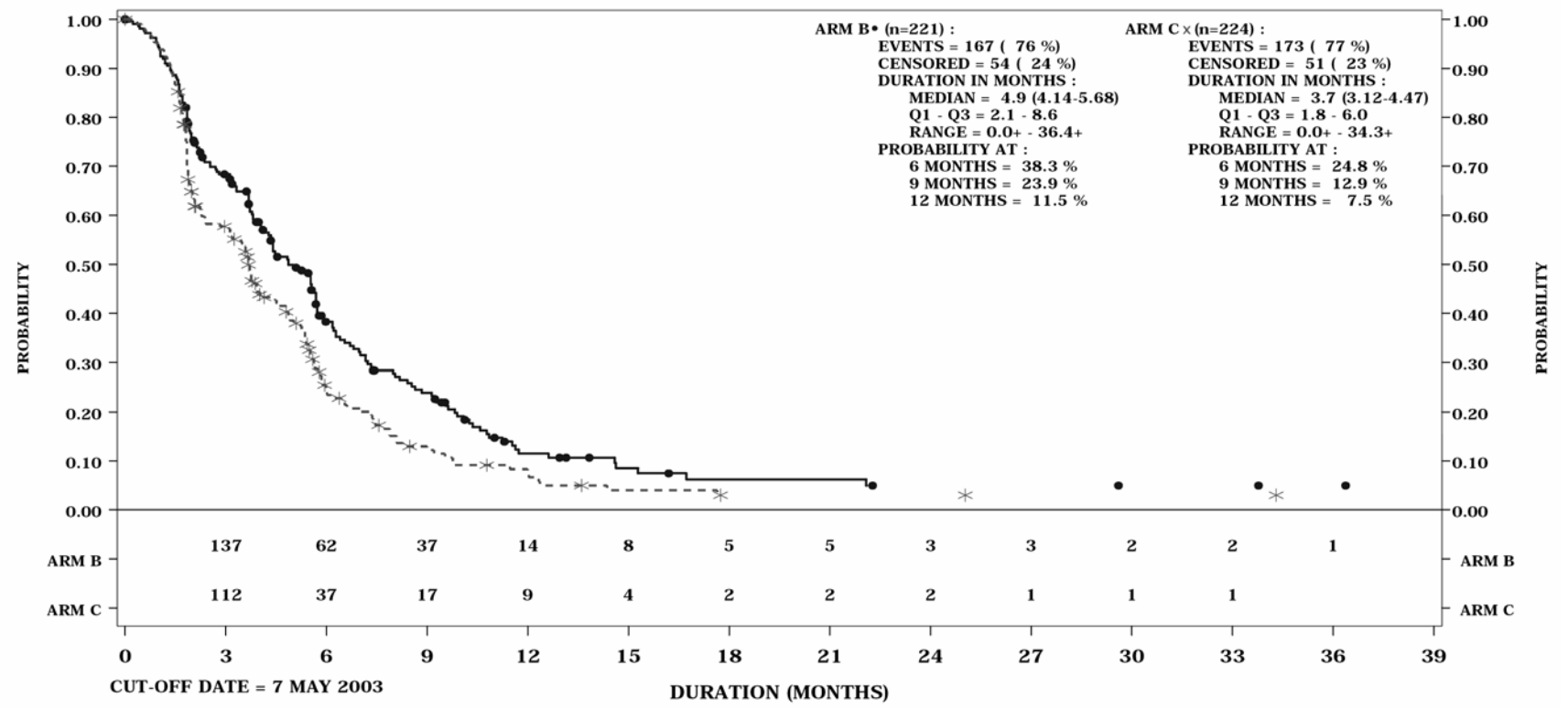
Group	Median Time	25% Failures	75% Failures
2-TCF	5.5195	2.5298	8.7392
3-CF	3.8439	1.8727	7.2279

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	6.7128	1	0.0096
Wilcoxon	7.2814	1	0.0070

To address missing tumor assessments, the applicant conducted an unstratified log-rank study under the following condition: When all progressions documented more than 12 weeks after the last evaluable tumor assessment were considered progressions at 8 weeks, results were similar to the primary analysis (Figure 11).

Figure 11: Sensitivity Analysis of Time To Progression: End of Study Kaplan Meier Curve (FAP) with Missing Evaluation Treatment.
Cox model Hazard Ratio (95% CI) on group of randomization (CF vs. TCF) : 1.383 (1.116 ; 1.713)
Risk reduction: 27.7 % - Logrank Test p- value = 0.0029
95% CI on difference of medians (TCF - CF): 1.2 (0.3 ; 2.4)



Data source: TAX325a study report, Appendix C. 2.1, Table 4a. 032, and Figure 4a. 033.

Reviewer note: This analysis indicated that effect of missing data in TAX 325a study to TTP is minimal.

The treatment effect was very similar in a Cox proportional hazards model that only included the 4 stratification factors and also in a model that used the "actual" values for the stratification factors rather than those specified by the investigator at randomization (Table 66).

Table 66: TTP Covatiates analyses with Four Stratification Factors

Covariates Included In The Cox Proportional Hazards Model	As Per Randomization[a]		Actual[b]	
	Hazard Ratio (95% CI)	P- Value	Hazard Ratio (95% CI)	P- Value
Group Of Randomization (CF vs. TCF)	1.488 (1.199 - 1.846)	0.0003	1.502 (1.201 - 1.878)	0.0004
Prior Surgery	0.831 (0.656 - 1.053)	0.1254	0.844 (0.660 - 1.080)	0.1774
Measurable Disease	1.024 (0.767 - 1.367)	0.8728	1.183 (0.723 - 1.935)	0.5048
Liver Involvement	0.952 (0.766 - 1.183)	0.6595	1.021 (0.818 - 1.274)	0.8554
Weight Loss ≤ 5% (As Per Randomization)	0.827 (0.661 - 1.034)	0.0961	0.855 (0.678 - 1.078)	0.1853

a. FAP N = 445, 341 events and 104 censored
b. PPP, N = 410, 322 events and 88 censored.
Data source: TAX 325a study report: Appendix C. 2.1, Table 4a. 003 and 4a. 007

Reviewer Note: The primary analysis and the sensitivity analyses appear to be consistently support the superior efficacy of the TCF arm. Although the concerning issue for TTP analyses in this study was that and the actual timing of tumor assessments. The applicant anticipated the potential effect of different cycle lengths (every 3 weeks for the test group, every 4 weeks for the control group) on the analysis of TTP by requesting in the protocol that tumor assessments be made irrespective of the actual chemotherapy timing, and at fixed 8-week intervals for both treatment groups. Evidence of progression (for example, as suggested by the clinical condition of the subject) could have resulted in an ad hoc tumor assessment. Consequently, it is important to assess if the actual tumor assessment pattern was similar across treatment arms and if it was different, to determine the extent of the difference.

The analyses of whether there is a difference in the time from randomization to first, second, and third tumor assessments are shown below.

Table 67: Time from randomization to first, second, and third tumor assessments (FAP)

Tumor	Number of subjects		Median in days [95% CI]		Log rank	HR[a]
Assessment	TCF	CF	TCF	CF	*P*-value	[95% CI]
First	221	224	58 [58- 59]	57 [57- 58]	0.0729	1.196 [0.983-1.454]
Second	168	140	111 [104-113]	112 [109-113]	0.2457	1.151 [0.907-1.460]
Third	127	91	163 [150-170]	170 [165-174]	0.2334	0.838 [0.626-1.121]

a HR greater than 1 indicates CF assessed earlier
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; CI = Confidence interval; HR = Hazard ratio; FAP = Full analysis population
Data source: TAX 325a study report, Appendix C. 2.1, Figures 4a. 057, 4a. 060, 4a. 063.

Reviewer note: The median times from randomization to first, second, and third tumor assessment were similar between the groups, and all log-rank tests comparing treatments was insignificant at the 5% level (although the time from randomization to first tumor assessment was borderline, p = 0.0729).

The applicant also conducted TTP analyses in subgroups, which are considered exploratory.

As per the protocol statistic analysis plan, the applicant conducted a "325 event" analysis of TTP (325 of 445, 73.0% subjects experience an event and 120 of 445, 27% subjects censored) and results shown in Table 68. In addition, the median follow-up was 11.3 months (95% CI: 10.78-16.20, TAX 325a study report, Appendix C. 1.1, Table 1.30).

Table 68: Time to progression - 325 events (FAP)

Event/parameter	Number (%) of subjects	
	TCF (N=221)	CF (N=224)
TTP events	156 (70.6)	169 (75.4)
Documented disease progression	139 (62.9)	150 (67.0)
Died	17 (7.7)	19 (8.5)
Censored subjects	65 (29.4)	55 (24.6)
Lost to follow-up for TTP	15 (6.8)	11 (4.9)
No event at cut-off date	29 (13.1)	24 (10.7)
Further therapy	21 (9.5)	20 (8.9)
25th percentile	2.7	1.9
Median TTP (months)	5.7	3.7
[95% CI] (months)	[4.99-6.21]	[3.45-4.07]
75th percentile	9.8	6.3
6-month estimate	43.8%	26.8%
P-value (Log-rank test)	0.0001	
Hazard ratio[a] [95% CI]	1.537 [1.234-1.915]	
Risk reduction	34.9%	

a. Value > 1 favors TCF.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population; TTP = Time to progression; CI = Confidence interval
Data source: TAX 325a study report, Appendix C. 2.1, Tables 4.01, 4.03and Figure 4.02.

Reviewer note: The results of this analysis are consistent to the end of study TTP analysis. The observed median TTP was 5.7 months in the TCF group (95% CI: 4.99-6.21) and 3.7 months

(95% CI: 3.45-4.07) in the CF group as shown in Table 68. The difference between the 2 treatment groups was statistically significant (log- rank test, p = 0.0001) and an HR of 1.537 (95% CI: 1.234- 1.915). The p = 0.0001 is much smaller than prespecified alpha spending, 0.0487.

10.1.3.2. Secondary Analysis

10.1.3.2.1. Overall Survival

The applicant conducted end of study analysis for overall survival at the time that a total 334 of 445 subjects (75.1%) had an event, and 111 of 445 (24.9%) subjects were censored (Table 16 and Figure 6).

Reviewer note: The applicant analysis (FAP) indicated that the difference between the 2 arms was statistically significant (log-rank test, p = 0.0201) with an HR of 1.293 (95% CI: 1.041-1.606) and a risk reduction of 22.7%. The observed median OS was 9.2 months for the TCF group (95% CI: 8.38- 10.58) and 8.6 months in the CF group (95% CI: 7.16- 9.46). The 1- year survival estimate was 40.2% in the TCF group and 31.6% in the CF group. The 2- year survival estimate was 18.4% in the TCF group and 8.8% in the CF group. These data are consistent with the TTP finding.

Applicant also conducted supportive analyses, in which OS was tested using a stratified log-rank test in the FAP and assessed for all randomized subjects as well. The results are summarized in Table 17, in which the FAP unstratified analysis presented in top row for comparison.

*Reviewer note: The applicant results for OS were consistent in the table above as a similar treatment effect was observed across analyses except unstratified OS analysis in ITT population. It is concerning that the applicant's unstratified overall survival analysis in ITT population just trending but not statistically significant favoring the TCF arm (*Figure 12*). As mentioned before, the difference between the ITT and AFP is exclusion of twelve patients. Although these 12 excluded patients (6 on each arm) did not received any assigned treatment after randomization, the median survival of the 6 untreated patients assigned for TCF arm was much shorter than the 6 untreated patients on CF arm (17.7 days vs 223 days;* Table 9*).*

The applicant also conducted exploratory subgroup analyses of OS. The HRs for OS according to the age, gender, race as well as other stratification or predefined subgroups showed extensive overlap of the respective 95% CIs, thus indicating the lack of any influence of these factors on the results (Table 69).

Figure 12: Applicant's Unstratified Overall Survival Analysis: End Of Study Kaplan Meier Curve By Group of Randomization (All Randomized Population)
Cox model Hazard Ratio (95% CI) on group of randomization (CF vs. TCF) : 1.233 (0.996 ; 1.527)
Risk reduction: 18.9 % - Logrank Test p - value = 0.0539
95% CI on difference of medians (TCF - CF) : 0.4 (-0.8; 2.5)

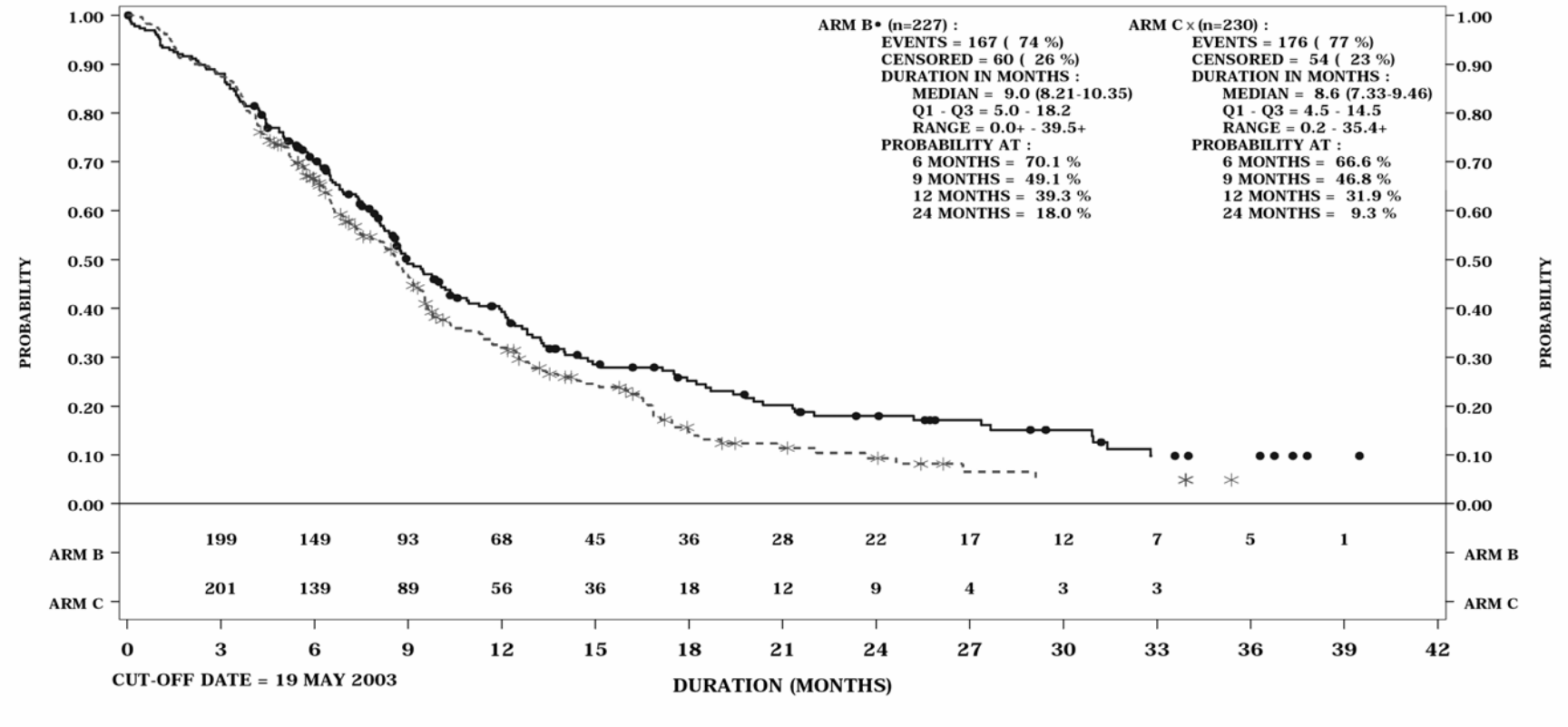


Table 69: Subgroup analyses of overall survival - end of study (FAP)

Subgroup	Number of subjects		Hazard ratio[a]	95% CI
	TCF	CF		
Total FAP	**221**	**224**	**1.293**	**[1.041 –1.606]**
Gender				
Male	159	158	1.160	[0.898-1.500]
Female	62	66	1.803	[1.193-2.724]
Female ≥50 years	30	35	2.086	[1.172-3.714]
Age				
<65 years	167	169	1.331	[1.038-1.707]
≥65 years	54	55	1.185	[0.760-1.849]
<70 years	193	202	1.308	[1.040-1.645]
≥70 years	28	22	1.154	[0.585-2.278]
Race				
Caucasian (white)	157	158	1.378	[1.058-1.795]
Non-Caucasian	64	66	1.109	[0.756-1.626]
Region				
North America	47	40	1.173	[0.735-1.874]
South America	60	63	1.145	[0.767-1.709]
Western Europe	76	74	1.725	[1.146-2.597]
Eastern Europe	32	37	1.082	[0.617-1.897]
Asia	6	10	0.407	[0.129-1.286]
Prior gastrectomy[b]				
Yes	75	73	1.093	[0.741-1.610]
No	146	151	1.428	[1.099-1.856]
Measurable disease[b]				
Measurable	181	183	1.407	[1.105-1.791]
Evaluable-only lesions	40	41	0.832	[0.499-1.386]
Liver involvement[b]				
Yes	123	120	1.127	[0.844-1.506]
No	98	104	1.533	[1.103-2.129]
Weight loss[b]				
≤5%	97	99	1.418	[1.008-1.995]
>5%	124	125	1.207	[0.911-1.598]
KPS before first infusion				
<100	193	195	1.283	[1.020-1.615]
100	28	29	1.402	[0.725-2.709]
Anatomical site				
Distal	153	151	1.279	[0.986-1.658]
Proximal	68	72	1.310	[0.881-1.950]

a. Value > 1 favors TCF.
b Per randomization.

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population; CI = Confidence interval; KPS = Karnofsky performance status
Data source: TAX 325a study report, Appendix C. 2.1, Figures 4.33, 4a. 075, 4a. 077, 4a. 079, 4a. 081, 4a. 083, 4a. 085, 4a. 087, 4a. 089, 4a. 091, 4a. 093, 4a. 095.

Reviewer note: The factorial analysis by primary tumot sites showed extensive overlap of the respective 95% CIs indicating the lack of influence of the imbalance in distribution of the primary tumor site between the TCF and CF arm.

Considering the clinical relevance of the age in the context of the overall risk/benefit response, the analysis of OS by age is presented in more detail below.

Table 70: Summary statistics for OS by age - end of study (FAP)

Parameter	Number (%) of subjects			
	<65 years		≥65 years	
	TCF (N=167)	CF (N=169)	TCF (N=54)	CF (N=55)
OS events	124 (74.3)	130 (76.9)	38 (70.4)	42 (76.4)
Censored subjects	43 (25.7)	39 (23.1)	16 (29.6)	13 (23.6)
Median OS (months)	9.0	8.5	10.1	9.6
[95% CI] (months)	[8.25-10.87]	[7.13-9.13]	[6.51-13.24]	[6.54-12.55]
1-year estimate	39.0%	28.1%	43.4%	41.7%
Hazard ratio[a] [95% CI]	1.331 [1.038-1.707]		1.185 [0.760-1.849]	
Risk reduction	24.9%		15.6%	

a. Value > 1 favors TCF.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population; OS = Overall survival; CI = Confidence interval
Data source: TAX 325a study report, Appendix C. 2.1, Table 4a. 074 and Figure 4a. 075.

Reviewer note: Although it is under powered, the analysis of OS by age group showed a consistent benefit in the TCF treatment group for both elderly subjects (≥ 65 years of age) and non-elderly subjects (< 65 years of age).

The applicant performed "325 events" analysis for OS following the SAP, with exactly 325 death events (18.46- 25.13).). When 325 of 445 (73.0%) subjects had an event, 120 of 445 (27.0%) subjects were censored. The median follow-up time was 22.34 months (18.46- 25.13).

Table 71: Overall survival - 325 events (FAP)

Event/parameter	Number (%) of subjects	
	TCF (N=221)	CF (N=224)
Survival event (deaths)	156 (70.6)	169 (75.4)
Censored subjects	65 (29.4)	55 (24.6)
Lost to follow-up	1 (0.5)	0 (0)
No event by cut-off date	64 (29.0)	55 (24.6)
25th percentile	5.5	4.5
Median survival (months)	9.2	8.6
[95% CI] (months)	[8.38-10.94]	[7.16-9.46]
75th percentile	18.5	14.4
1-year estimate	40.6%	31.3%
2-year estimate	18.6%	8.1%
P-value (log-rank test)	0.0111	
Hazard ratio[a] [95% CI]	1.328 [1.066-1.655]	
Risk reduction	24.7%	

a. Value > 1 favors TCF.
TCF = Taxotere + cisplatin + 5- fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population; CI = Confidence interval
Data source: TAX 325a study report, Appendix C. 2.1, Tables 4.24 and 4.26, and Figure 4.25.

Reviewer note: The applicant's "325 event" analysis of OS indicated there is a statistically significant difference (log-rank test, p = 0.0111) between the 2 treatments, with an HR of 1.328 (95% CI: 1.066-1.655) and a risk reduction of 24.7%. The applicant's results for the end of study and the "325 events" analysis are very similar.

10.1.3.2.2. Response Rate

The applicant summarized best overall RRs for the FAP and the PPP are shown in Table 19.

Reviewer note: The applicant's response analysis in the FAP and TTP indicated that the overall RR (CR + PR) was higher in the TCF group than in the CF group. The difference between the 2 treatment groups was only statistically significant (Chi square test) in PPP. The number and percentage of subjects with NC/SD was similar in both treatment groups. The number and percentage of subjects with PD was lower in the TCF group than in the CF group.

10.1.3.2.3. Duration of the Response

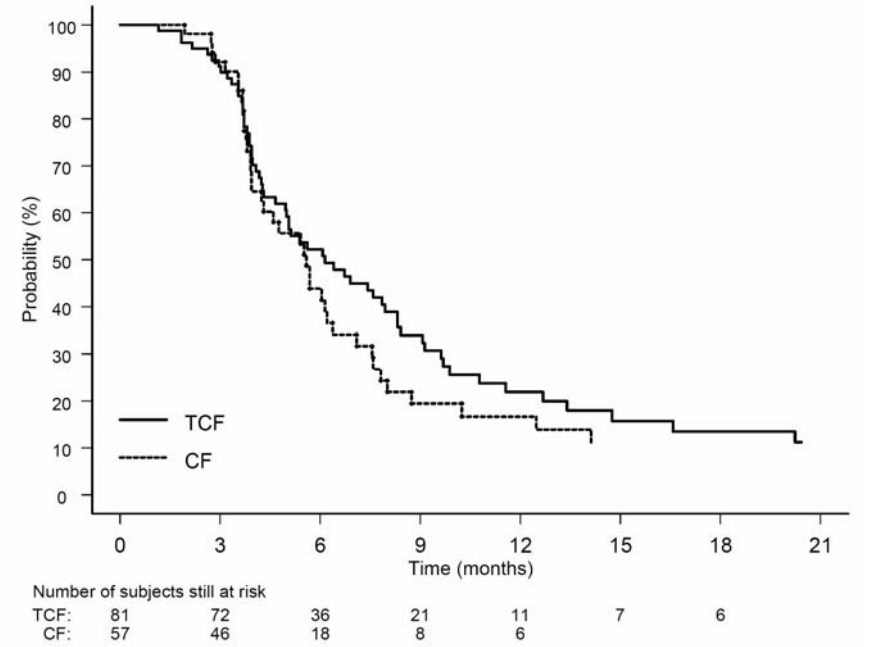
Of the 138 subjects with applicant reported objective response, 101 (73.2%) were subsequently observed to progress and 37 subjects (26.8%) were censored (Table 72 and Figure 13).

Table 72: Summary statistics for overall response duration - from onset of PR/CR (FAP)

Event/parameter	TCF (N=81)	CF (N=57)
Overall response duration event	61 (75.3)	40 (70.2)
Censored subjects	20 (24.7)	17 (29.8)
Lost to follow-up	4 (4.9)	5 (8.8)
No event by cut-off date	10 (12.3)	12 (21.1)
Further therapy	6 (7.4)	0 (0)
25th percentile	3.9	3.8
Median overall response duration (months)	6.1	5.6
95% CI (months)	[4.96–8.31]	[4.24–6.37]
75th percentile	10.8	7.8
6-month estimate	52.2%	43.8%
P-value (Log-rank test)	0.3175	
Hazard ratio[a] [95% CI]	1.226 [0.821–1.831]	
Risk reduction	18.4%	

a Value > 1 favors TCF.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population; CR = Complete response; PR = Partial response; CI = Confidence interval Data source: TAX 325a study report, Appendix C. 2.1, Tables 4.48, 4.50 and Figure 4.49.

Figure 13: Duration of response from onset of PR/CR - Kaplan- Meier curve (FAP)



TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population; CR = Complete response; PR = Partial response
Data source: TAX 325a study report, Appendix C. 2.1, Figure 4.49.

Reviewer note: Base on applicant's response duration analysis, the difference between the 2 groups was not statistically significant (log-rank test, p = 0.3175) with an HR of 1.226 (95% CI: 0.821- 1.831). The median overall response duration, as defined from the onset of PR/CR, was 6.1 months in the TCF group (95% CI: 4.96 - 8.31) and 5.6 months in the CF group (95% CI: 4.24- 6.37). A duration of response (from onset of PR/CR) longer than 9 months was achieved by 21 subjects in the TCF group and 8 subjects in the CF group.

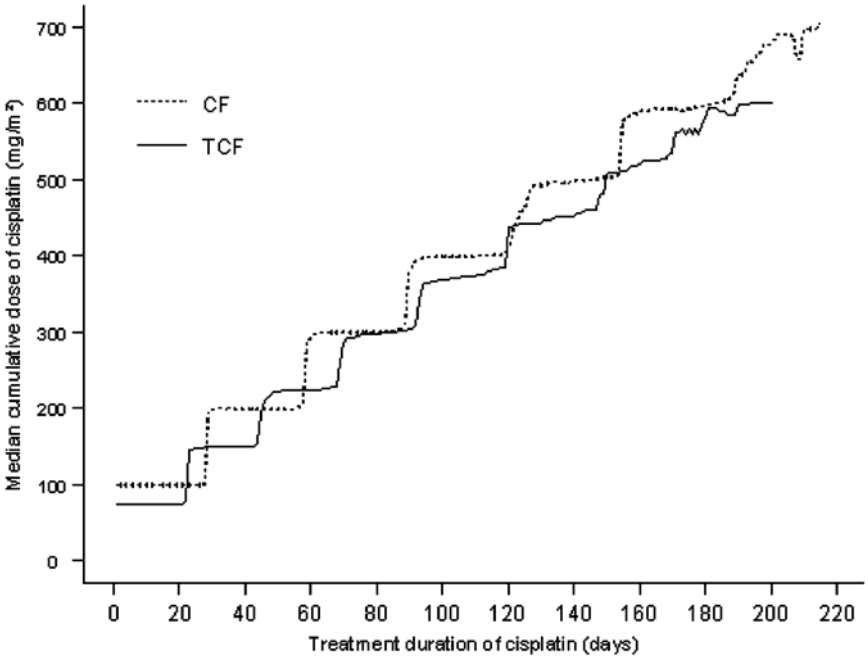
10.1.4. Safety Results

10.1.4.1. Drug Exposure

10.1.4.1.1. Administration of Investigational Product
The median interval between randomization and first administration of study medication was 1 day in both treatment groups. In 309 (69.4%) subjects, the interval was between 0 and 2 days, and in 131 (29.4%) subjects between 3 and 7 days. All but 5 (1.1%) subjects received their first study-medication infusion within 7 days of their randomization (TAX 325a study report, Appendix C. 1.1, Table 1.05).

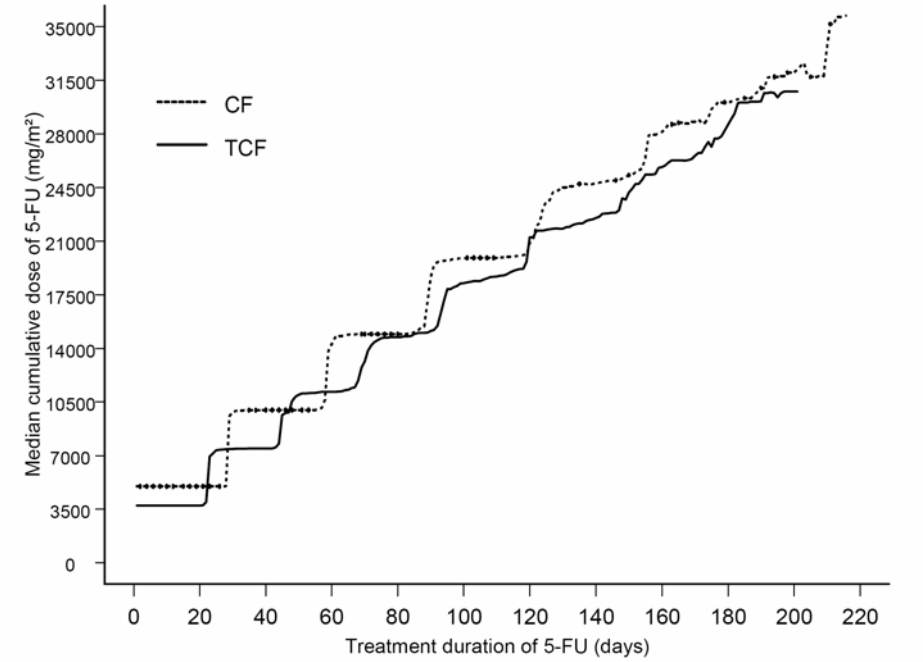
10.1.4.1.2. Dosage and duration
See section 7.2.1.3. for thedetail, the cumulative dose of Cisplatin and 5-FU are analyzed below:

Figure 14: Median cumulative dose of cisplatin (FAP)



FAP = Full analysis population; TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5- fluorouracil
Data source: TAX325a study report, Appendix C. 1.1, Table 3.34 and figure 3.35.

Figure 15: Median cumulative dose of 5- FU (FAP)



FAP = Full analysis population; TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; 5-FU = 5- fluorouracil
Data source: TAX 325a study report, Appendix C. 1.1, Table 3.36 and Figure 3.37

10.1.4.1.3. Cycles administered

The number of cycles of study chemotherapy received per subject by treatment group is summarized in Table 73.

Table 73: Study chemotherapy delivery - number of cycles by subject (SP)

	TCF	CF
Number of subjects	221	224
Number of cycles received	1186	906
Number of cycles by subject		
Median	6	4
Minimum-maximum	1-16	1-12
Number of cycles received	No. (%) of subjects	No. (%) of subjects
1	221 (100.0)	224 (100.0)
2	199 (90.0)	193 (86.2)
3	178 (80.5)	155 (69.2)
4	160 (72.4)	128 (57.1)
5	144 (65.2)	89 (39.7)
6	116 (52.5)	67 (29.9)
7	66 (29.9)	26 (11.6)
8	41 (18.6)	15 (6.7)
9	20 (9.0)	5 (2.2)
10	15 (6.8)	2 (0.9)
11	11 (5.0)	1 (0.4)
12	6 (2.7)	1 (0.4)
13	3 (1.4)	0 (0)
14	3 (1.4)	0 (0)
15	2 (0.9)	0 (0)
16	1 (0.5)	0 (0)

SP = Safety population; TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil.
Data source: Appendix C. 1.1, Tables 3.01 and 3.04.

Reviewer Note: It appears that patients on TCF arm received more cycles than patients on the CF arm. Theses may suggest that 75% cisplatin and 5-FU given every 3 weeks, or TCF regimen is better tolerated than 100% dose of cisplatin and 5-FU every 4 weeks. However, comparisons between the treatment arms based on cycles should be made with caution as the cycles were of different lengths.

10.1.4.1.4. Cycle Delays

In both treatment groups, the initiation of a cycle could be delayed up to 2 weeks to allow for recovery from cutaneous reactions, impaired liver function or other toxic events. Cycle delays beyond 2 weeks were an indication for therapy discontinuation.

Reviewer Note: Table 74 and Table 75 summarize the number of subjects with cycle delays and the number of cycles delayed in each treatment group as well as the reasons for cycle delay as determined by investigators. The reviewer aggress that there were more TCF-treated subjects (63.8%) with at least one cycle delay than CF-treated subjects (42.4%). There were more TCF-treated subjects (35.3%) with more than 1 cycle delay than CF-treated subjects (20.1%) (TAX325a study report, Appendix C. 1.1, Table 3.18).

Table 74: Study chemotherapy delivery - number of subjects with cycle delay (SP)

Reason	Number (%) of subjects	
	TCF	CF
Number of subjects	**221 (100)**	**224 (100)**
Number of subjects with at least 1 cycle delay	141 (63.8)	95 (42.4)
Reasons for cycle delay[a]		
AE unrelated to study medication	20 (9.0)	15 (6.7)
AE related to study medication		
Hematologic toxicity[b]	27 (12.2)	26 (11.6)
Non-hematologic toxicity	44 (19.9)	16 (7.1)
Both toxicities	3 (1.4)	3 (1.3)
Other[c]	86 (38.9)	60 (26.8)

a. Subjects with more than 1 cycle delay may have more than 1 reason for cycle delay.
b Hematologic toxicity includes infection, febrile neutropenia and fever.
c For example, personal problems, logistical issues, error, vacation.
TCF = Taxotere + cisplatin + 5- fluorouracil; CF = Cisplatin + 5- fluorouracil; SP = Safety population
Data source: Appendix C. 1.1, , Table 3.18.

Table 75: Study chemotherapy delivery - number of cycles with cycle delay (SP)

Reason	Number (%) of cycles	
	TCF	CF
Number of cycles administered	**1186 (100)**	**906 (100)**
Number of cycles delayed	289 (24.4)	167 (18.4)
By 4 to 7 days	186 (15.7)	115 (12.7)
By 8 to 14 days	81 (6.8)	45 (5.0)
By >14 days	22 (1.9)	7 (0.8)
Reason for cycle delay		
AE unrelated to study medication	22 (1.9)	16 (1.8)
AE related to study medication		
Hematologic toxicity[a]	30 (2.5)	34 (3.8)
Non-hematologic toxicity	64 (5.4)	22 (2.4)
Both toxicities	3 (0.3)	3 (0.3)
Other[b]	170 (14.3)	92 (10.2)

a. Hematologic toxicity includes infection, febrile neutropenia and fever.
b For example, personal problems, logistical issues, error, vacation, etc.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; AE = Adverse event; SP = Safety population
Data source: Appendix C. 1.1, Tables 3.21 and 3.22.

Reviewer Note: There were more cycle delays due to only non-hematological toxicity in TCF-treated subjects (44, 19.9%) than in CF-treated subjects (16, 7.1%). Similarly, there were more subjects with "Other" as the reason for the cycle delay in TCF-treated subjects (86, 38.9%) than in CF-treated subjects (60, 26.8%]), likely related to the shorter cycle.

The most frequent treatment related AEs leading to cycle delay were tabulated below by the reviewer (Appendix C. 1.1 Table 3.19 and 3.20, Sample CRF reviewed):

Table 76: The most frequent treatment related AEs leading to cycle delay

AEs	TCF-treated subjects (%)	CF- treated subjects (%)
Lethargy	20 (9.0)	7 (3.1)
infection	7 (3.2)	3 (1.3)
granulocytes	12 (5.4)	20 (8.9),
stomatitis	10 (4.5)	8 (3.6)
platelets	-	3 (1.3)

Data Source: Appendix C. 1.1 Table 3.19 and 3.20, Sample CRFs

10.1.4.1.5. Dose reductions

Table 77 summarizes the number of treatment cycles with dose reduction, as well as the reasons for dose reduction, as determined by investigators.

Table 77: Study chemotherapy delivery - number of subjects with dose reduction (SP)

Reason	Number (%) of subjects	
	TCF	CF
Number of subjects	221 (100.0)	224 (100.0)
Number of subjects with at least 1 dose reduction	91 (41.2)	81 (36.2)
Number of subjects with 1 dose reduction	56 (25.3)	57 (25.4)
Number of subjects with 2 dose reductions	28 (12.7)	19 (8.5)
Number of subjects with >2 dose reductions	7 (3.2)	5 (2.2)
Reason for dose reduction [a]		
AE unrelated to study medication	1 (0.5)	1 (0.4)
AE related to study medication		
Hematologic toxicity	8 (3.6)	2 (0.9)
Non-hematologic toxicity	65 (29.4)	66 (29.5)
Both toxicities	11 (5.0)	4 (1.8)
Other	2 (0.9)	1 (0.4)
Unknown[b]	12 (5.4)	12 (5.4)

a. Subjects with more than1 dose reduction may have more than 1 reason for dose reduction.
b Calculated dose reduction only – no corresponding reason.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; AE = Adverse event; SP = Safety population
Data source: Appendix C. 1.1, Table 3.09.

Reviewer Note: Treatment related AEs were the most frequent reason for dose reduction (TAX 325a study report, Appendix C. 1.1, Table 3.12). The main reason for dose reduction was non-hematological toxicity for both treatment groups (TCF: 29.4%; CF: 29.5%). The main non-hematological toxicity leading to dose reduction was GI related AEs for both treatment groups (TCF: 26.7%; CF: 22.3%): mainly stomatitis (13.6%) and diarrhea (12.2%) for TCF-treated subjects and stomatitis (19.2%) for CF- treated subjects. The second most common type of non-hematological toxicity leading to dose reduction was neurological toxicity (7.2%) in TCF-treated subjects and genitourinary toxicity (11.2%) in CF-treated subjects. There were few dose reductions due to hematological toxicity in CF- treated subjects (2, 0.9%), but more of those reductions were in the TCF-treated subjects (8, 3.6%). Similarly, there were more subjects with

both hematological and non-hematological toxicities leading to dose reduction in TCF-treated subjects (1, 5.0%) than in CF-treated subjects (4, 1.8%). However, in general, toxicities were leading to dose reduction more than cycle delays.

Dose reductions by study medication, categorized by the number of dose reductions are shown below.

Table 78: Subjects with dose reductions by study medication (SP)

Reduction	Number (%) of subjects				
	TCF (N=221)			CF (N=224)	
	Taxotere	Cisplatin	5-FU	Cisplatin	5-FU
No dose reduction	185 (83.7)	179 (81.0)	151 (68.3)	184 (82.1)	159 (71.0)
At least 1 dose reduction	36 (16.3)	42 (19.0)	70 (31.7)	40 (17.9)	65 (29.0)
Only 1 dose reduction	34 (15.4)	34 (15.4)	60 (27.1)	29 (12.9)	57 (25.4)
More than 1 dose reduction	2 (0.9)	8 (3.6)	10 (4.5)	11 (4.9)	8 (3.6)

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; 5-FU = 5-fluorouracil; SP = Safety population
Data source: Appendix C. 1.1, Table 3.10.

Reviewer Note: In both treatment groups, the 5-FU dose was reduced more often than the other medication. In the TCF treatment group, it was reduced in 70 (31.7%) subjects, compared to Taxotere in 36 (16.3%) subjects and cisplatin in 42 (19.0%) subjects. In the CF treatment group, it was reduced in 65 (29.0%) subjects, compared to cisplatin in 40 (17.9%) subjects.

10.1.4.1.6. Cycle delays or dose reductions

The numbers of subjects and cycles with either cycle delays or dose reductions is summarized below.

Table 79: Study chemotherapy delivery - number of subjects and cycles with cycle delay or dose reduction (SP)

	Number (%)	
	TCF	**CF**
Number of subjects who received study chemotherapy	**221 (100.0)**	**224 (100.0)**
Number of subjects with at least 1 cycle delay	141 (63.8)	95 (42.4)
Number of subjects with no cycle delay or dose reduction	59 (26.7)	100 (44.6)
Number of subjects with cycle delay only	71 (32.1)	43 (19.2)
Number of subjects with dose reduction only	21 (9.5)	29 (12.9)
Number of subjects with both cycle delay and dose reduction	70 (31.7)	52 (23.2)
Number of cycles administered	**1186 (100.0)**	**906 (100.0)**
Number of cycles with no delay or dose reduction	814 (68.6)	672 (74.2)
Number of cycles with delay only	238 (20.1)	123 (13.6)
Number of cycles with dose reduction only	83 (7.0)	67 (7.4)
Number of cycles with both delay and dose reduction	51 (4.3)	44 (4.9)

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population
Data source: TAX 325a study report, Appendix C. 1.1, Tables 3.18, 3.27 and 3.30.

Reviewer Note: Overall, the CF treatment group required fewer treatment schedule modifications (cycle delay or dose reduction) by subject (44.6%), compared with 26.7% of TCF-treated subjects. The percentage of cycles that required no delay or dose reduction, however, was only slightly higher in the CF treatment group (74.2%) than in the TCF treatment group (68.6%).

10.1.4.2. Safety Profiles

Of 457 randomized subjects, 12 subjects (6 from each treatment group) did not receive study medication. This resulted in an SP of 445 treated subjects: 221 TCF-treated subjects and 224 CF-treated subjects. As recorded at baseline, with a total of 374 (84.0%) of SP subjects presenting with clinical signs and symptoms at study entry. Baseline signs and symptoms were not considered treatment-emergent adverse events (AEs) according to the protocol, unless they worsened following treatment.

10.1.4.2.1 All Worst AEs per Each Subject Regardless the Relation to the Study Drug
The reviewer has summarized all treatment emergent worst AEs of every subject in SP regardless relationship to the study treatment under body systems below and under NCI/CTC terms by body system.

Table 80: Reviewer's Summary of All Worst AEs Emerged during the Study Summarized in Body System (SP)

Body System NCI/CTC Terms	TCF (n = 221)				CF (n = 224)			
	All Grades		Grade 3-4		All Grades		Grade 3-4	
	N	%	N	%	N	%	N	%
Body As A Whole	638	288.69	193	87.33	533	237.95	166	74.11
Cardiovascular System	97	43.89	41	18.55	95	42.41	44	19.64
Digestive System	1056	477.83	239	108.14	1032	460.71	236	105.36
Endocrine System	1	0.45	0	0	2	0.89	1	0.45
Helic And Lymphatic System	64	28.96	46	20.81	58	25.89	40	17.86
Metabolic And Nutritional Disorders	85	38.46	19	8.6	84	37.5	21	9.38
Musculoskeletal System	60	27.15	9	4.07	35	15.63	3	1.34
Nervous System	283	128.05	52	23.53	216	96.43	31	13.84
Respiratory System	140	63.35	12	5.43	122	54.46	22	9.82
Skin And Appendages	249	112.67	15	6.79	149	66.52	5	2.23
Special Senses	72	32.58	2	0.9	57	25.45	6	2.68
Urogenital System	48	21.72	11	4.98	44	19.64	10	4.46
Total	2793	1263.8	639	289.13	2427	1083.48	585	261.17

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population

Reviewer note: It is clear that most AEs were observed in digestive system, followed by body as a whole, nervous system and skin and appendages for both arms. The incidence of digestive system toxicity was similar in both arms, whereas the TCF arm appears to have more AEs of body as a whole, nervous system and skin and appendage observed. The total number AEs and severe AEs observed in TCF arm were slightly more than that of CF arm.

Table 81: Reviewer's Summary of All Worst Treatment Emergent AEs (SP) in NCI CTC Terms by Body system

Body System NCI/CTC Terms	TCF (n = 221)				CF (n = 224)			
	All Grades		Grade 3-4		All Grades		Grade 3-4	
	N	%	N	%	N	%	N	%
Body As A Whole								
Lethargy	168	76.02	48	21.72	155	69.2	41	18.3
Cancer Pain	152	68.78	82	37.1	148	66.07	81	36.16
Fever In Absence Of Infection	85	38.46	4	1.81	52	23.21	4	1.79
Infection	55	24.89	33	14.93	46	20.54	16	7.14
Local Toxicity	33	14.93	0	0	19	8.48	3	1.34
Gastrointestinal Pain/Cramping	25	11.31	4	1.81	19	8.48	9	4.02
Headache	23	10.41	1	0.45	27	12.05	0	0
Other: Allergic Reaction	23	10.41	4	1.81	16	7.14	0	0
Pain Chest	15	6.79	5	2.26	7	3.13	3	1.34
Rigors/Chills	10	4.52	0	0	3	1.34	0	0
Genito-Urinary Pain	7	3.17	1	0.45	3	1.34	0	0
Other: Pain	6	2.71	2	0.9	6	2.68	1	0.45
Other: Accidental Injury	4	1.81	1	0.45	2	0.89	0	0
Other: Back Pain	4	1.81	2	0.9	2	0.89	1	0.45
Other: Abdominal Pain	3	1.36	0	0	2	0.89	0	0
Other: Abdomen Enlarged	2	0.9	0	0	3	1.34	0	0
Other: Flu Syndrome	2	0.9	0	0	4	1.79	0	0
Other: Injection Site Pain	2	0.9	0	0	1	0.45	0	0
Other: Reaction Unevaluable	2	0.9	0	0	2	0.89	1	0.45
Skin Pain	2	0.9	1	0.45	3	1.34	0	0
Stomatitis	2	0.9	1	0.45	2	0.89	2	0.89
Toothache	2	0.9	0	0	3	1.34	1	0.45
Arthralgia	1	0.45	1	0.45	0	0	0	0
Ascites	1	0.45	0	0	0	0	0	0
Bone Pain	1	0.45	1	0.45	1	0.45	1	0.45
Edema	1	0.45	0	0	0	0	0	0
Motor	1	0.45	0	0	1	0.45	0	0
Neurologic Pain	1	0.45	1	0.45	0	0	0	0
Other: Chest Pain	1	0.45	0	0	0	0	0	0
Other: Malaise	1	0.45	0	0	0	0	0	0
Other: Moniliasis	1	0.45	1	0.45	1	0.45	0	0
Other: Mucous Membrane Disorder	1	0.45	0	0	0	0	0	0
Other: Neoplasm	1	0.45	0	0	0	0	0	0
Other: Face Edema	0	0	0	0	1	0.45	0	0
Other: Hernia	0	0	0	0	1	0.45	1	0.45
Other: Infection Fungal	0	0	0	0	2	0.89	0	0
Pulmonary Pain	0	0	0	0	1	0.45	1	0.45
Cardiovascular System								
Hypotension	27	12.22	5	2.26	17	7.59	4	1.79
Venous	22	9.95	19	8.6	19	8.48	17	7.59
Dysrhythmias	11	4.98	5	2.26	6	2.68	3	1.34
Hypertension	8	3.62	4	1.81	17	7.59	7	3.13
Cardiac Function	4	1.81	2	0.9	2	0.89	1	0.45
Sinus Tachycardia	4	1.81	0	0	7	3.13	1	0.45
Bruising/Bleeding	3	1.36	0	0	3	1.34	0	0

Body System NCI/CTC Terms	TCF (n = 221)				CF (n = 224)			
	All Grades		Grade 3-4		All Grades		Grade 3-4	
	N	%	N	%	N	%	N	%
Other: Syncope	3	1.36	2	0.9	1	0.45	0	0
Arterial Non Myocardial	2	0.9	2	0.9	2	0.89	2	0.89
Hemorrhage Resulting From Thrombocytopenia	2	0.9	1	0.45	1	0.45	0	0
Ischemia Myocardial	2	0.9	0	0	6	2.68	5	2.23
Local Toxicity	2	0.9	0	0	0	0	0	0
Other: Pallor	2	0.9	0	0	1	0.45	0	0
Pericardial	2	0.9	1	0.45	0	0	0	0
Other: Cardiovascular Disorder	1	0.45	0	0	1	0.45	0	0
Other: Hemorrhage	1	0.45	0	0	0	0	0	0
Other: Subarachnoid Hemorrhage	1	0.45	0	0	0	0	0	0
Dizziness	0	0	0	0	2	0.89	2	0.89
Gastrointestinal Bleeding	0	0	0	0	1	0.45	0	0
Other: Atrial Fibrillation	0	0	0	0	1	0.45	1	0.45
Other: Bradycardia	0	0	0	0	1	0.45	0	0
Other: Cardiomegaly	0	0	0	0	1	0.45	0	0
Other: Heart Arrest	0	0	0	0	1	0.45	1	0.45
Other: Peripheral Vascular Disorder	0	0	0	0	1	0.45	0	0
Other: Vascular Disorder	0	0	0	0	3	1.34	0	0
Other: Vasculitis	0	0	0	0	1	0.45	0	0
Digestive System								
Nausea	178	80.54	36	16.29	189	84.38	43	19.2
Diarrhea	174	78.73	45	20.36	114	50.89	18	8.04
Vomiting	154	69.68	33	14.93	174	77.68	43	19.2
Anorexia	148	66.97	35	15.84	155	69.2	30	13.39
Stomatitis	130	58.82	45	20.36	136	60.71	60	26.79
Constipation	72	32.58	5	2.26	93	41.52	8	3.57
Esophagitis/Dysphagia/Odynophagia	64	28.96	12	5.43	53	23.66	13	5.8
Heartburn	46	20.81	3	1.36	34	15.18	0	0
Gastrointestinal Bleeding	25	11.31	8	3.62	21	9.38	9	4.02
Flatulence	13	5.88	0	0	21	9.38	1	0.45
Other: Dyspepsia	11	4.98	0	0	12	5.36	0	0
Proctitis	10	4.52	1	0.45	6	2.68	0	0
Small Bowel Obstruction	9	4.07	6	2.71	4	1.79	3	1.34
Fistula	5	2.26	5	2.26	1	0.45	1	0.45
Gastritis/Ulcer	2	0.9	0	0	2	0.89	0	0
Other: Colitis	2	0.9	1	0.45	0	0	0	0
Other: Oral Moniliasis	2	0.9	0	0	3	1.34	1	0.45
Other: Cholestatic Jaundice	1	0.45	1	0.45	0	0	0	0
Other: Gastrointestinal Disorder	1	0.45	0	0	2	0.89	2	0.89
Other: Gingivitis	1	0.45	0	0	1	0.45	0	0
Other: Gum Hemorrhage	1	0.45	0	0	0	0	0	0
Other: Hepatic Failure	1	0.45	1	0.45	0	0	0	0
Other: Hepatitis	1	0.45	0	0	0	0	0	0
Other: Hyperchlorhydria	1	0.45	0	0	0	0	0	0
Other: Intestinal Perforation	1	0.45	1	0.45	0	0	0	0
Other: Intestinal Ulcer	1	0.45	1	0.45	0	0	0	0
Other: Tooth Disorder	1	0.45	0	0	0	0	0	0
Tooth Decay	1	0.45	0	0	1	0.45	0	0

Body System NCI/CTC Terms	TCF (n = 221)				CF (n = 224)			
	All Grades		Grade 3-4		All Grades		Grade 3-4	
	N	%	N	%	N	%	N	%
Bilirubin	0	0	0	0	1	0.45	1	0.45
Infection	0	0	0	0	2	0.89	1	0.45
Other: Eructation	0	0	0	0	2	0.89	0	0
Other: Jaundice	0	0	0	0	1	0.45	1	0.45
Other: Pancreatitis	0	0	0	0	2	0.89	0	0
Other: Perforated Stomach Ulcer	0	0	0	0	1	0.45	1	0.45
Other: Tongue Disorder	0	0	0	0	1	0.45	0	0
Endocrine System								
Other: Hyperthyroidism	1	0.45	0	0	0	0	0	0
Other: Diabetes Mellitus	0	0	0	0	2	0.89	1	0.45
Helic And Lymphatic System								
Granulocytes	31	14.03	29	13.12	27	12.05	20	8.93
Hemoglobin	12	5.43	6	2.71	11	4.91	7	3.13
Platelets	11	4.98	7	3.17	12	5.36	9	4.02
White Blood Count	4	1.81	2	0.9	2	0.89	1	0.45
Other: Hypervolemia	3	1.36	0	0	1	0.45	0	0
Prothrombin Time	2	0.9	1	0.45	2	0.89	1	0.45
Partial Thromboplastin Time	1	0.45	1	0.45	1	0.45	0	0
Other: Pancytopenia	0	0	0	0	1	0.45	1	0.45
Rigors/Chills	0	0	0	0	1	0.45	1	0.45
Metabolic And Nutritional Disorders								
Edema	42	19	2	0.9	37	16.52	2	0.89
Creatinine	15	6.79	4	1.81	22	9.82	4	1.79
Other: Dehydration	5	2.26	2	0.9	6	2.68	1	0.45
Hyponatremia	3	1.36	3	1.36	3	1.34	3	1.34
Alkaline Phosphatase	2	0.9	1	0.45	0	0	0	0
Bilirubin	2	0.9	0	0	1	0.45	1	0.45
Hypocalcemia	2	0.9	1	0.45	1	0.45	1	0.45
Hypokalemia	2	0.9	2	0.9	1	0.45	1	0.45
Other: Electrolyte Abnormality	2	0.9	1	0.45	0	0	0	0
Transaminase Sgot	2	0.9	0	0	1	0.45	1	0.45
Transaminase Sgpt	2	0.9	0	0	1	0.45	1	0.45
Hypoglycemia	1	0.45	1	0.45	3	1.34	0	0
Hypomagnesemia	1	0.45	1	0.45	1	0.45	1	0.45
Local Toxicity	1	0.45	0	0	0	0	0	0
Other: Hyperkalemia	1	0.45	1	0.45	0	0	0	0
Other: Hypernatremia	1	0.45	0	0	0	0	0	0
Weight Loss	1	0.45	0	0	0	0	0	0
Hyperglycemia	0	0	0	0	5	2.23	4	1.79
Other: Cachexia	0	0	0	0	2	0.89	1	0.45
Musculoskeletal System								
Myalgia	28	12.67	4	1.81	21	9.38	3	1.34
Arthralgia	18	8.14	1	0.45	9	4.02	0	0
Bone Pain	11	4.98	3	1.36	3	1.34	0	0
Other: Arthrosis	1	0.45	0	0	0	0	0	0
Other: Joint Disorder	1	0.45	0	0	0	0	0	0
Other: Pathological Fracture	1	0.45	1	0.45	1	0.45	0	0
Other: Tenosynovitis	0	0	0	0	1	0.45	0	0
Nervous System								

Body System NCI/CTC Terms	TCF (n = 221)				CF (n = 224)			
	All Grades		Grade 3-4		All Grades		Grade 3-4	
	N	%	N	%	N	%	N	%
Sensory	85	38.46	17	7.69	57	25.45	7	3.13
Insomnia	60	27.15	1	0.45	41	18.3	2	0.89
Mood	38	17.19	6	2.71	32	14.29	2	0.89
Dizziness	36	16.29	10	4.52	19	8.48	2	0.89
Motor	20	9.05	7	3.17	17	7.59	6	2.68
Cortical,Somnolence	10	4.52	6	2.71	10	4.46	7	3.13
Neurologic Pain	8	3.62	3	1.36	7	3.13	0	0
Flushing	6	2.71	0	0	2	0.89	0	0
Personality Change	5	2.26	1	0.45	2	0.89	0	0
Extrapyramidal/Involuntary Movement	3	1.36	0	0	4	1.79	1	0.45
Mouth,Nose Dryness	3	1.36	0	0	11	4.91	0	0
Other: Increased Salivation	3	1.36	0	0	3	1.34	0	0
Liver	1	0.45	1	0.45	0	0	0	0
Other: Abnormal Gait	1	0.45	0	0	0	0	0	0
Other: Leg Cramps	1	0.45	0	0	0	0	0	0
Other: Tremor	1	0.45	0	0	2	0.89	0	0
Other: Urinary Retention	1	0.45	0	0	0	0	0	0
Other: Vertigo	1	0.45	0	0	1	0.45	0	0
Cerebellar	0	0	0	0	1	0.45	1	0.45
Hot Flashes	0	0	0	0	1	0.45	0	0
Infection	0	0	0	0	1	0.45	1	0.45
Myalgia	0	0	0	0	2	0.89	0	0
Other: Amnesia	0	0	0	0	1	0.45	0	0
Other: Encephalopathy	0	0	0	0	1	0.45	1	0.45
Small Bowel Obstruction	0	0	0	0	1	0.45	1	0.45
Respiratory System								
Cough	27	12.22	0	0	25	11.16	0	0
Shortness Of Breath	26	11.76	6	2.71	29	12.95	11	4.91
Hiccough	23	10.41	0	0	20	8.93	1	0.45
Other: Rhinitis	14	6.33	0	0	7	3.13	0	0
Other: Epistaxis	10	4.52	0	0	8	3.57	0	0
Hay Fever	9	4.07	0	0	6	2.68	0	0
Infection	6	2.71	3	1.36	8	3.57	7	3.13
Other: Pharyngitis	6	2.71	0	0	3	1.34	0	0
Pleural Effusion	3	1.36	0	0	2	0.89	0	0
Voice Changes	3	1.36	0	0	2	0.89	0	0
Other: Pneumothorax	2	0.9	1	0.45	2	0.89	1	0.45
Dyspnea	1	0.45	0	0	0	0	0	0
Gastrointestinal Pain/Cramping	1	0.45	0	0	0	0	0	0
Hemoptysis	1	0.45	0	0	3	1.34	0	0
Other: Apnea	1	0.45	1	0.45	2	0.89	2	0.89
Other: Asthma	1	0.45	0	0	0	0	0	0
Other: Bronchitis	1	0.45	0	0	0	0	0	0
Other: Laryngitis	1	0.45	0	0	0	0	0	0
Other: Pleural Effusion	1	0.45	0	0	0	0	0	0
Other: Respiratory Distress Syndrome	1	0.45	1	0.45	0	0	0	0
Pneumonitis Non Infectious	1	0.45	0	0	0	0	0	0

Body System NCI/CTC Terms	TCF (n = 221)				CF (n = 224)			
	All Grades		Grade 3-4		All Grades		Grade 3-4	
	N	%	N	%	N	%	N	%
Stomatitis	1	0.45	0	0	0	0	0	0
Other: Lung Disorder	0	0	0	0	1	0.45	0	0
Other: Sputum Increased	0	0	0	0	3	1.34	0	0
Pulmonary Edema	0	0	0	0	1	0.45	0	0
Skin And Appendages								
Alopecia	147	66.52	11	4.98	92	41.07	3	1.34
Rash/Itch	27	12.22	2	0.9	20	8.93	0	0
Dry Skin	20	9.05	0	0	10	4.46	0	0
Nail Changes	18	8.14	0	0	0	0	0	0
Sweating	9	4.07	1	0.45	7	3.13	0	0
Skin Changes	8	3.62	0	0	10	4.46	1	0.45
Desquamation	4	1.81	0	0	1	0.45	0	0
Other: Herpes Simplex	4	1.81	0	0	3	1.34	0	0
Infection	3	1.36	0	0	0	0	0	0
Other: Skin Ulcer	3	1.36	1	0.45	0	0	0	0
Other: Rash	2	0.9	0	0	0	0	0	0
Other: Eczema	1	0.45	0	0	0	0	0	0
Other: Pruritus	1	0.45	0	0	0	0	0	0
Other: Skin Disorder	1	0.45	0	0	2	0.89	1	0.45
Rash	1	0.45	0	0	0	0	0	0
Other: Exfoliative Dermatitis	0	0	0	0	2	0.89	0	0
Other: Skin Atrophy	0	0	0	0	1	0.45	0	0
Proctitis	0	0	0	0	1	0.45	0	0
Special Senses								
Taste,Sense Of Smell Altered	20	9.05	0	0	11	4.91	0	0
Tearing	18	8.14	0	0	5	2.23	1	0.45
Altered Hearing	17	7.69	0	0	30	13.39	4	1.79
Vision	5	2.26	0	0	4	1.79	0	0
Conjunctivitis/Keratitis	3	1.36	0	0	3	1.34	1	0.45
Eye Pain	3	1.36	1	0.45	0	0	0	0
Dry Eye	2	0.9	0	0	1	0.45	0	0
Neurologic Pain	1	0.45	1	0.45	0	0	0	0
Other: Ear Disorder	1	0.45	0	0	0	0	0	0
Other: Eye Disorder	1	0.45	0	0	0	0	0	0
Other: Eye Hemorrhage	1	0.45	0	0	0	0	0	0
Other: Diplopia	0	0	0	0	1	0.45	0	0
Other: Eye Pain	0	0	0	0	1	0.45	0	0
Other: Papilledema	0	0	0	0	1	0.45	0	0
Urogenital System								
Other: Creatinine Clearance Decreased	6	2.71	3	1.36	8	3.57	0	0
Urinary Frequency	6	2.71	1	0.45	6	2.68	1	0.45
Vaginal Hemorrhage	4	1.81	2	0.9	2	0.89	0	0
Amenorrhea	3	1.36	0	0	0	0	0	0
Genito-Urinary Pain	3	1.36	0	0	0	0	0	0
Other: Oliguria	3	1.36	0	0	2	0.89	0	0
Creatinine	2	0.9	1	0.45	4	1.79	2	0.89
Cystitis	2	0.9	0	0	3	1.34	0	0
Hematuria	2	0.9	0	0	1	0.45	1	0.45

Body System NCI/CTC Terms	TCF (n = 221)				CF (n = 224)			
	All Grades		Grade 3-4		All Grades		Grade 3-4	
	N	%	N	%	N	%	N	%
Incontinence	2	0.9	0	0	2	0.89	0	0
Infection	2	0.9	0	0	1	0.45	0	0
Other: Acute Kidney Failure	2	0.9	0	0	0	0	0	0
Other: Kidney Failure	2	0.9	2	0.9	3	1.34	3	1.34
Vaginitis	2	0.9	0	0	1	0.45	0	0
Metrorrhagia	1	0.45	1	0.45	0	0	0	0
Other: Dysuria	1	0.45	0	0	0	0	0	0
Other: Kidney Pain	1	0.45	0	0	0	0	0	0
Other: Scrotal Edema	1	0.45	0	0	0	0	0	0
Other: Toxic Nephropathy	1	0.45	0	0	2	0.89	1	0.45
Other: Urinary Tract Infection	1	0.45	1	0.45	0	0	0	0
Ureteral Obstruction	1	0.45	0	0	0	0	0	0
Impotence/Libido	0	0	0	0	1	0.45	0	0
Other: Cervix Neoplasm	0	0	0	0	1	0.45	0	0
Other: Genital Edema	0	0	0	0	1	0.45	0	0
Other: Impotence	0	0	0	0	1	0.45	1	0.45
Other: Kidney Tubular Disorder	0	0	0	0	1	0.45	0	0
Other: Mastitis	0	0	0	0	1	0.45	1	0.45
Other: Polyuria	0	0	0	0	1	0.45	0	0
Other: Urine Abnormality	0	0	0	0	2	0.89	0	0

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population

Reviewer note: As mentioned in the protocol deviation section, one subject in the CF treatment group (subject I4403) received Taxotere at cycle 2, and was included and analyzed within the SP of the CF treatment group. The only grade 3-4 TEAE reported for this subject during cycle 2 was cancer pain, considered not related to study treatment. The incident of accidental taxotere administration did not appear have any impact to the safety.

10.1.4.2.2 Common Toxicities

See section 7.1.5.

10.1.4.2.3 Severe Adverse Events

See section 7.1.2.

10.1.4.2.4 Death

See section 7.1.1.

10.1.4.2.5 AEs that lead to Treatment Modification

AEs that clinically significant enough to course treatment modification were summarized below:

Table 82: AEs that Lead to Treatment Modification (SP)

Body System NCI/CTC Terms	TCF (n =221)										CF (n = 224)									
	Interuppted		Discontinued		Reduced dose		Delayed		Dose reduced and discontinued		Interuppted		Discontinued		Reduced dose		Delayed		Dose reduced and discontinued	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Body As A Whole	***11***	***4.98***	***20***	***9.05***	***10***	***4.52***	***33***	***14.93***	***5***	***2.26***	***5***	***2.26***	***9***	***4.07***	***5***	***2.26***	***19***	***8.6***	***1***	***0.45***
Cancer Related Symptoms	0	0	1	0.45	0	0	1	0.45	0	0	2	0.9	1	0.45	0	0	1	0.45	0	0
Cardiovascular	1	0.45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dentition	0	0	0	0	0	0	1	0.45	0	0	0	0	0	0	0	0	0	0	0	0
Flu-Like Symptoms	1	0.45	11	4.98	4	1.81	21	9.5	3	1.36	0	0	6	2.71	2	0.9	8	3.62	1	0.45
Gastrointestinal	1	0.45	0	0	1	0.45	0	0	0	0	0	0	0	0	2	0.9	0	0	0	0
Hypersensitivity	7	3.17	1	0.45	0	0	0	0	0	0	2	0.9	0	0	0	0	0	0	0	0
Infection	0	0	6	2.71	5	2.26	8	3.62	2	0.9	1	0.45	2	0.9	1	0.45	8	3.62	0	0
Neurologic	1	0.45	1	0.45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Osseous	0	0	1	0.45	0	0	1	0.45	0	0	0	0	0	0	0	0	0	0	0	0
Skin	0	0	0	0	0	0	1	0.45	0	0	0	0	0	0	0	0	2	0.9	0	0
Cardiovascular System	***3***	***1.36***	***2***	***0.9***	***0***	***0***	***5***	***2.26***	***0***	***0***	***1***	***0.45***	***6***	***2.71***	***0***	***0***	***1***	***0.45***	***0***	***0***
Cardiovascular	3	1.36	2	0.9	0	0	5	2.26	0	0	1	0.45	6	2.71	0	0	1	0.45	0	0
Digestive System	***3***	***1.36***	***14***	***6.33***	***46***	***20.81***	***12***	***5.43***	***10***	***4.52***	***1***	***0.45***	***6***	***2.71***	***0***	***0***	***1***	***0.45***	***0***	***0***
Gastrointestinal	2	0.9	10	4.52	46	20.81	12	5.43	10	4.52	4	1.81	9	4.07	42	19	3	1.36	7	3.17
Hepatic	0	0	2	0.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Infection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.45	0	0
Neurologic	1	0.45	2	0.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Endocrine System	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***1***	***0.45***	***0***	***0***
Metabolic	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.45	0	0
Helic And Lymphatic System	***0***	***0***	***5***	***2.26***	***5***	***2.26***	***20***	***9.05***	***1***	***0.45***	***0***	***0***	***3***	***1.36***	***1***	***0.45***	***26***	***11.76***	***1***	***0.45***
Blood Bone Marrow	0	0	4	1.81	5	2.26	20	9.05	1	0.45	0	0	3	1.36	1	0.45	25	11.31	1	0.45
Coagulation	0	0	1	0.45	0	0	0	0	0	0	0	0	0	0	0	0	1	0.45	0	0
Metabolic And Nutritional	***3***	***1.36***	***4***	***1.81***	***9***	***4.07***	***4***	***1.81***	***0***	***0***	***0***	***0***	***8***	***3.62***	***11***	***4.98***	***1***	***0.45***	***2***	***0.9***

Body System NCI/CTC Terms	TCF (n =221)										CF (n = 224)									
	Interuppted		Discontinued		Reduced dose		Delayed		Dose reduced and discontinued		Interuppted		Discontinued		Reduced dose		Delayed		Dose reduced and discontinued	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Disorders																				
Genitourinary	0	0	4	1.81	7	3.17	1	0.45	0	0	0	0	6	2.71	11	4.98	0	0	2	0.9
Hepatic	1	0.45	0	0	2	0.9	2	0.9	0	0	0	0	1	0.45	0	0	0	0	0	0
Metabolic	2	0.9	2	0.9	0	0	0	0	0	0	0	0	1	0.45	0	0	1	0.45	0	0
Weight	0	0	0	0	0	0	1	0.45	0	0	0	0	0	0	0	0	0	0	0	0
Musculoskeletal System	***0***	***0***	***1***	***0.45***	***1***	***0.45***	***2***	***0.9***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***
Flu-Like Symptoms	0	0	1	0.45	1	0.45	2	0.9	0	0	0	0	0	0	0	0	0	0	0	0
Nervous System	***1***	***0.45***	***16***	***7.24***	***14***	***6.33***	***3***	***1.36***	***2***	***0.9***	***0***	***0***	***7***	***3.17***	***6***	***2.71***	***2***	***0.9***	***0***	***0***
Infection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.45	0	0
Neurologic	1	0.45	16	7.24	14	6.33	3	1.36	2	0.9	0	0	7	3.17	6	2.71	2	0.9	0	0
Respiratory System	***2***	***0.9***	***0***	***0***	***0***	***0***	***8***	***3.62***	***1***	***0.45***	***0***	***0***	***0***	***0***	***0***	***0***	***3***	***1.36***	***0***	***0***
Flu-Like Symptoms	0	0	0	0	0	0	2	0.9	0	0	0	0	0	0	0	0	1	0.45	0	0
Hypersensitivity	1	0.45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Infection	0	0	0	0	0	0	2	0.9	1	0.45	0	0	0	0	0	0	2	0.9	0	0
Pulmonary	1	0.45	0	0	0	0	4	1.81	0	0	0	0	0	0	0	0	0	0	0	0
Skin And Appendages	***1***	***0.45***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***2***	***0.9***	***1***	***0.45***	***0***	***0***
Hypersensitivity	1	0.45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Skin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0.9	1	0.45	0	0
Special Senses	***0***	***0***	***1***	***0.45***	***0***	***0***	***1***	***0.45***	***0***	***0***	***0***	***0***	***7***	***3.17***	***0***	***0***	***1***	***0.45***	***0***	***0***
Neurologic	0	0	1	0.45	0	0	0	0	0	0	0	0	7	3.17	0	0	0	0	0	0
Ocular	0	0	0	0	0	0	1	0.45	0	0	0	0	0	0	0	0	1	0.45	0	0
Urogenital System	***0***	***0***	***1***	***0.45***	***5***	***2.26***	***2***	***0.9***	***2***	***0.9***	***0***	***0***	***0***	***0***	***12***	***5.43***	***1***	***0.45***	***1***	***0.45***
Endocrine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.45	0	0
Genitourinary	0	0	1	0.45	5	2.26	1	0.45	2	0.9	0	0	0	0	12	5.43	0	0	0	0
Infection	0	0	0	0	0	0	1	0.45	0	0	0	0	0	0	0	0	0	0	1	0.45
Total.	***24***	***10.86***	***59***	***26.7***	***90***	***40.72***	***90***	***40.72***	***21***	***9.5***	***10***	***4.52***	***42***	***19***	***79***	***35.75***	***60***	***27.15***	***12***	***5.43***

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population

10.1.4.2.6 Laboratory Abnormalities - Hematology

i. Neutropenia

The hematological safety concerns that related to myelosupressin are summarized below:

Table 83: Leukopenia in evaluable subjects and evaluable cycles by worst grade with regard to prophylactic G-CSF (SP)

Treatment	Number (%)						
	Total evaluable	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3-4	Any grade
Subjects							
Regardless of G-CSF							
TCF	220 (99.5)	26 (11.8)	41 (18.6)	98 (44.5)	46 (20.9)	144 (65.5)	211 (95.9)
CF	223 (99.6)	40 (17.9)	70 (31.4)	51 (22.9)	19 (8.5)	70 (31.4)	180 (80.7)
Without G-CSF							
TCF	219 (99.1)	26 (11.9)	41 (18.7)	96 (43.8)	45 (20.5)	141 (64.4)	208 (95.0)
CF	223 (99.6)	40 (17.9)	71 (31.8)	51 (22.9)	18 (8.1)	69 (30.9)	180 (80.7)
With G-CSF							
TCF	41 (18.6)	5 (12.2)	15 (36.6)	14 (34.1)	3 (7.3)	17 (41.5)	37 (90.2)
CF	20 (8.9)	3 (15.0)	4 (20.0)	4 (20.0)	1 (5.0)	5 (25.0)	12 (60.0)
Cycles							
Regardless of G-CSF							
TCF	1176 (99.2)	213 (18.1)	306 (26.0)	286 (24.3)	64 (5.4)	350 (29.8)	869 (73.9)
CF	896 (98.9)	229 (25.6)	200 (22.3)	76 (8.5)	21 (2.3)	97 (10.8)	526 (58.7)
Without G-CSF							
TCF	1057 (89.1)	190 (18.0)	277 (26.2)	261 (24.7)	61 (5.8)	322 (30.5)	789 (74.6)
CF	866 (95.6)	225 (26.0)	193 (22.3)	71 (8.2)	20 (2.3)	91 (10.5)	509 (58.8)
With G-CSF							
TCF	119 (10.0)	23 (19.3)	29 (24.4)	25 (21.0)	3 (2.5)	28 (23.5)	80 (67.2)
CF	30 (3.3)	4 (13.3)	7 (23.3)	5 (16.7)	1 (3.3)	6 (20.0)	17 (56.7)

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population; G-CSF = Granulocyte colony-stimulating factor
Data source: Appendix C.3.1, Tables 8.01, 8.02, 8.03, 8.05, 8.06, and 8.07.
Note: for "total evaluable" the denominator was safety population

Reviewer note: Leukopenia of any grade and grade 3-4 was more frequent in TCF evaluable cycles (95.5% and 29.8%) than in CF evaluable cycles (80.7% and 10.8%), regardless the use of G-CSF. A total of 61 subjects, 41 in the TCF treatment group and 20 in the CF treatment group, received G-CSF (13.8% of the evaluable subjects) in a total of 149 cycles (7.2% of the evaluable cycles) as secondary prophylaxes. (b) (4)

(b) (4)

ii. Anemia

Table 84: Anemia in evaluable subjects and evaluable cycles by worst grade with regard to prophylactic EPO or RBC transfusions (SP)

Treatment	Number (%)						
	Total evaluable	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3-4	Any grade
Subjects							
Regardless of EPO/RBC							
TCF	220 (99.5)	58 (26.4)	115 (52.3)	37 (16.8)	3 (1.4)	40 (18.2)	213 (96.8)
CF	223 (99.6)	58 (26.0)	93 (41.7)	49 (22.0)	8 (3.6)	57 (25.6)	208 (93.3)
Without EPO/RBC							
TCF	220 (99.5)	61 (27.7)	114 (51.8)	35 (15.9)	3 (1.4)	38 (17.3)	213 (96.8)
CF	222 (99.1)	60 (27.0)	92 (41.4)	47 (21.2)	8 (3.6)	55 (24.8)	207 (93.2)
With EPO/RBC							
TCF	16 (7.2)	4 (25.0)	10 (62.5)	2 (12.5)	0 (0)	2 (12.5)	16 (100.0)
CF	12 (5.4)	5 (41.7)	4 (33.3)	3 (25.0)	0 (0)	3 (25.0)	12 (100.0)
Cycles							
Regardless of EPO/RBC							
TCF	1176 (99.2)	522 (44.4)	440 (37.4)	50 (4.3)	3 (0.3)	53 (4.5)	1015 (86.3)
CF	896 (98.9)	367 (41.0)	289 (32.3)	64 (7.1)	9 (1.0)	73 (8.1)	729 (81.4)
Without EPO/RBC							
TCF	1126 (94.9)	497 (44.1)	426 (37.8)	47 (4.2)	3 (0.3)	50 (4.4)	973 (86.4)
CF	871 (96.1)	357 (41.0)	280 (32.1)	61 (7.0)	9 (1.0)	70 (8.0)	707 (81.2)
With EPO/RBC							
TCF	50 (4.2)	25 (50.0)	14 (28.0)	3 (6.0)	0 (0)	3 (6.0)	42 (84.0)
CF	25 (2.8)	10 (40.0)	9 (36.0)	3 (12.0)	0 (0)	3 (12.0)	22 (88.0)

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population; EPO = Erythropoietin; RBC = Red blood cell
Data source: Appendix C.3.1, Tables 8.01, 8.02, 8.03, 8.05, 8.06 and 8.07.
Note: for "total evaluable" the denominator was safety population

Reviewer note: Anemia of all grade and Grade 3-4 was less frequent in TCF-treated subjects (86.3% and 18.2%) compared to CF-treated subjects (96.8% and 25.6%), regardless of the use of EPO or RBC transfusions. However, the use of prophylactic EPO or RBC transfusionswas infrequent in this study (occurring in only 28 evaluable subjects in 75 cycles). Regardless of the use, in the absence or in the presence of EPO/RBC transfusions, the percentage of any grade anemia was similar in both treatment groups, while grade 3-4 anemia occurred slightly more frequently in the CF treatment group.

iii. Thrombocytopenia

Table 85: Thrombocytopenia in evaluable subjects and cycles by worst grade (SP)

Treatment	Number (%)						
	Total evaluable	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3-4	Any grade
Subjects							
TCF	220 (99.5)	23 (10.5)	16 (7.3)	8 (3.6)	9 (4.1)	17 (7.7)	56 (25.5)
CF	223 (99.6)	33 (14.8)	24 (10.8)	14 (6.3)	16 (7.2)	30 (13.5)	87 (39.0)
Cycles							
TCF	1176 (99.2)	63 (5.4)	35 (3.0)	10 (0.9)	11 (0.9)	21 (1.8)	119 (10.1)
CF	896 (98.9)	82 (9.2)	44 (4.9)	20 (2.2)	20 (2.2)	40 (4.5)	166 (18.5)

Thrombocytopenia: grade 1 = 75.0 x 10^9/L – 99.9 x 10^9/L, grade 2 = 50.0 x 10^9/L - 74.9 x 10^9/L, grade 3 = 25.0 x 10^9/L - 49.9 x 10^9/L, grade 4 <25.0 x 10^9/L.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population.
Data source: Appendix C.3.1, Tables 8.01, and 8.05.
Note: for "total evaluable" the denominator was safety population.

Reviewer note: Although thrombocytopenia was infrequently observed in studyTAX 325a, the percentage of subjects and cycles with any grade or grade 3-4 thrombocytopenia was higher in the CF treatment group (any grade: subjects 39.0%, cycles 18.5%) than in the TCF treatment group (any grade: subjects 25.5%, cycles 10.1%).

10.1.4.2.7 Laboratory Abnormalities - Chemistry

i. Liver Function Test

The laboratory testing, liver function tests and serum chemistry are summarized below:

Table 86: Liver function tests by worst grade (SP)

Test/ Treatment	Number (%) of subjects						
	Total evaluable	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3-4	Any grade
ALAT							
TCF	211 (95.5)	46 (21.8)	8 (3.8)	1 (0.5)	0 (0)	1 (0.5)	55 (26.1)
CF	213 (95.1)	25 (11.7)	7 (3.3)	2 (0.9)	0 (0)	2 (0.9)	34 (16.0)
ASAT							
TCF	211 (95.5)	52 (24.6)	5 (2.4)	3 (1.4)	0 (0)	3 (1.4)	60 (28.4)
CF	213 (95.1)	38 (17.8)	5 (2.3)	1 (0.5)	0 (0)	1 (0.5)	44 (20.7)
Alkaline phosphatase							
TCF	211 (95.5)	104 (49.3)	15 (7.1)	6 (2.8)	0 (0)	6 (2.8)	125 (59.2)
CF	209 (93.3)	87 (41.6)	13 (6.2)	5 (2.4)	0 (0)	5 (2.4)	105 (50.2)
Total bilirubin							
TCF	210 (95.0)	-	6 (2.9)	11 (5.2)	7 (3.3)	18 (8.6)	24 (11.4)
CF	214 (95.5)	-	9 (4.2)	11 (5.1)	5 (2.3)	16 (7.5)	25 (11.7)

ALT, AST, alk phosphatase: grade 1 < 2.5 x UNL, grade 2 = 2.6 - 5.0 x UNL, grade 3 = 5.1 - 2.0 x UNL, Grade 4 >20 x UNL. Bilirubin: grade 1 was not defined in NCIC-CTC scale, grade 2 <1.5 x UNL, grade 3 = 1.5 - 3.0 x UNL grade 4 > 3.0 x UNL
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population
Data source: Appendix C.3.1, Table 9.01.
Note: for "total evaluable" the denominator was safety population.

Reviewer note: Abnormal liver function test appear to be infrequent: few subjects had grade 3 abnormalities in either treatment group and no subjects had grade 4 abnormalities in AST, ALT, or alkaline phosphatase. There were no obvious differences between treatment arms.

ii Most Frequent Abnormal Serum Chemistry

Table 87: Selected serum chemistry by worst grade (SP)

Test/ Treatment	Number (%) of subjects						
	Total evaluable	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3-4	Any grade
Creatinine (increase)							
TCF	213 (96.4)	44 (20.7)	19 (8.9)	2 (0.9)	2 (0.9)	4 (1.9)	67 (31.5)
CF	217 (96.9)	51 (23.5)	31 (14.3)	6 (2.8)	0 (0)	6 (2.8)	88 (40.6)
Hypokalemia							
TCF	212 (95.9)	53 (25.0)	27 (12.7)	4 (1.9)	2 (0.9)	6 (2.8)	86 (40.6)
CF	216 (96.4)	25 (11.6)	25 (11.6)	5 (2.3)	4 (1.9)	9 (4.2)	59 (27.3)
Hypomagnesemia							
TCF	189 (85.5)	57 (30.2)	52 (27.5)	9 (4.8)	3 (1.6)	12 (6.3)	121 (64.0)
CF	182 (81.3)	63 (34.6)	24 (13.2)	4 (2.2)	1 (0.5)	5 (2.7)	92 (50.5)

Creatinine increased: grade 1: <1.5 x UNL, grade 2: 1.5-3.0 x UNL, grade 3: 3.1–6.0 x UNL, grade 4: >6.0 x UNL.
Hypokalemia: grade 1: 3.1–3.5 mmol/L, grade 2: 2.6–3.0 mmol/L, grade 3: 2.1–2.5, grade 4: =2.0 mmol/L.
Hypomagnesemia: grade 1: 0.70–0.58 mmol/L, grade 2: 0.57–0.38 mmol/L, grade 3: 0.37–0.30, grade 4: =0.29 mmol/L.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population
Data source: Appendix C.3.1, Table 9.01.
Note: for "total evaluable" the denominator was safety population

Reviewer note: Only few subjects presented with grade 3-4 abnormalities. There were no obvious differences between treatment groups. However, 227 patients has declined (≥ grade 1) of total protein 56%), 136 on TCF arm and 91 on CF arm (45.3%)

10.1.4.2.8 Special Safety Analyses

See section 7.1.4.

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APPLICATION NUMBER:

NDA 20-449/S-035

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #1	1. ORGANIZATION ONDQA Division IV Branch VIII	2. NDA NUMBER 20-449
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Aventis Pharmaceuticals P.O Box 9720 Kansas City, MO 64134-0720 Attention: Dhiren N. Shah Director, Regulatory CMC Tel: (816)-966-5100		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S)
6. NAME OF DRUG Taxotere®	7. NONPROPRIETARY NAME docetaxel	SE1-035 9-23-05 SE1-035 (SU) 1-20-06
8. SUPPLEMENT PROVIDES FOR: a new indication for the treatment of patients with gastric cancer		9. AMENDMENTS DATES
10. PHARMACOLOGICAL CATEGORY antineoplastic	11. HOW DISPENSED RX x OTC ___	12. RELATED IND/NDA/DMF
13. DOSAGE FORM(S) injection concentrate	14. POTENCY 20 mg and 80 mg vials	
15. CHEMICAL NAME AND STRUCTURE See PDR		16. RECORDS AND REPORTS CURRENT YES___NO___ REVIEWED YES___NO___

17. COMMENTS

See page 2
cc:
NDA 20-449
HFD-150/Div. File
HFD-150/ LZhou
HFD-150/HPatel
HFD-150/AStaten
R/D Init. by:

18. CONCLUSIONS AND RECOMMENDATIONS

Approval is recommended.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Liang Zhou, Ph.D.		2/1/06

DISTRIBUTION ORIGINAL JACKET x DIVISION FILE x REVIEWER x CSO x SUP. CHEMIST x

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-449/S-035

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA /Serial Number:	20-449 /S035
Drug Name:	Taxotere
Applicant:	Sanofi-Aventis
Indication(s):	Advanced Gastric Adenocarcinoma
Date(s):	Submission Date: September 26, 2005
	PDUFA Date: March 26, 2006
	Review Completion Date: March 10, 2006
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Shenghui Tang, Ph.D.
Concurring Reviewer:	Mark Rothmann, Ph.D., Acting Team Leader
	Aloka Chakravarty, Ph.D., Director
Medical Division:	Oncology Drug Products (HFD-150)
Clinical Team:	Qin Ryan, M.D. & Ramzi Dagher, M.D.
Project Manager:	Ms. Ann Staten
Keywords:	Superiority, log-rank test

Table of Contents

1 Executive Summary

This is a review of NDA20-449/S035 for the use of Taxotere (docetaxel) in combination with cisplatin and 5-fluorouracil for the treatment of patients with (b) (4) gastric cancer previously untreated with chemotherapy for advanced disease.

1.1 Conclusions and Recommendations

In this reviewer's opinion the study results from the submitted single, randomized, open-label, parallel group, multicenter, multinational phase III study(Study 325a), support the claim of efficacy of Taxotere (docetaxel) in combination with cisplatin and 5-fluorouracil for the treatment of patients with advanced gastric adenocarcinoma with respect to time to progression (TTP) which included death from any cause. The Taxotere (docetaxel) in combination with cisplatin and 5-fluorouracil demonstrated a TTP advantage over the combination of cisplatin and 5-fluorouracil in this clinical study. Whether the endpoint and the size of the effect on this endpoint are adequate for approval is a clinical decision.

1.2 Brief Overview of Clinical Studies

This NDA submission is to support the use of Taxotere (docetaxel) in combination with cisplatin and 5-fluorouracil for the treatment of patients with (b) (4) gastric cancer previously untreated with chemotherapy for advanced disease. The submitted study was a randomized, open-label, parallel group, multicenter, multinational phase III study (Study 523a) performed in Asia, Western and Eastern Europe, and North and South America. It is the only randomized phase III pivotal study conducted to establish efficacy and safety of Taxotere (docetaxel) in combination with cisplatin and 5-fluorouracil for the treatment of patients with advanced gastric adenocarcinoma.

Patients were centrally randomized (1:1) to either the test group (Taxotere combined with cisplatin and 5-fluorouracil (TCF)) or the control group (cisplatin combined with 5-fluorouracil (CF)) using a biased-coin minimization method with the following stratification factors: liver metastasis (yes/no), prior gastrectomy (yes/no), disease measurability (measurable vs. evaluable-only lesions), weight loss in prior 3 months (≤5% vs. >5%), and investigational center.

Treatment was administered up to progression, unacceptable toxicities, or consent withdrawn. After documented progression, subjects were followed every 3 months until death. Subjects who discontinued their treatment but had not yet progressed were followed every 8 weeks, until documented progression and then every 3 months until death.

In Study 325a, one interim analysis was planned to be performed when 162 TTP events occurred, and the final analysis was planned to be performed when exactly 325 TTP events occurred. In August 2002, the results from the interim analysis were reviewed by the IDMC. Because the difference in overall survival was not statistically significant, it was decided not to stop the study at that point. As of May 7, 2003, a total of 341 TTP events occurred and the final analysis for TTP was performed.

The submission includes a total of 457 patients randomized to the phase III study: 227 patients into the TCF treatment group and 230 patients into the CF treatment group. Twelve randomized subjects, 6 in each treatment group, did not receive therapy. Therefore, a total of 445 treated patients were included in the final TTP analysis in which, 341 of 445 (76.6%) subjects had an event, and 104 of 445 (23.4%) subjects were censored. The results of the TTP analysis led to the submission of this application.

1.3 Statistical Issues and Findings

In this NDA submission, Study 325a was the only randomized pivotal phase III study conducted to establish efficacy and safety. The efficacy analysis for the data collected until the cut-off date of May 7, 2003 included 167 events (75.6%) for TTP in the TCF arm and 174 events (77.7%) for TTP in the CF arm. A total of 341 TTP events (76.6%) occurred at the time of TTP analysis.

Statistical Issues:

The study protocol included a single planned interim analysis during the phase III study. This analysis was triggered when 162 TTP events had occurred. An O'Brien-Fleming stopping boundary was used with the Lan-DeMets method for the interim analysis of superiority of TTP. The nominal significance levels for the interim and final analysis of TTP was 0.0036 and 0.0487, respectively.

The interim analysis included 115 TCF-treated patients and 117 CF-treated patients. The results from this interim analysis showed the observed median TTP was 5.2 months in the TCF treatment group [95% CI: 4.34-6.80] and 3.7 months [95% CI 3.06-4.80] in the CF treatment group. The difference between the 2 groups (log-rank test, P=0.0008; HR=0.587, TCF vs. CF) met the pre-specified boundary for superiority set for the interim analysis (0.0036). The median OS was also longer for the TCF group (10.2 months, [95% CI: 8.51-12.29]) compared to the CF group (8.5 months, [95% CI: 6.64-9.53]) but the observed difference (log-rank test, P=0.0064, HR=0.664, TCF vs. CF) did not meet the pre-specified boundary. At the time of the interim analysis (data cutoff of June 4, 2002), 181 deaths were observed. The nominal significance levels for the interim and final

OS analysis were 0.0053 and 0.0483, respectively. Because the difference in OS was not statistically significant, it was decided not to stop the study at this point.

Only deaths within 12 weeks of the last evaluable tumor assessment, or within 12 weeks of the first infusion of study drugs (for subjects with no evaluable tumor assessment after randomization), were considered as TTP events. This definition is different from the definition of PFS which includes all deaths.

The TTP analysis in the ITT patient population supported the findings from the TTP analysis in the full analysis population (FAP). The OS analysis in the ITT patient population showed that the p-value was 0.0536, which was greater than the nominal significance level for the final analysis (0.0483), while the OS analysis in the FAP showed that the p-value was 0.0199. However, the hazard ratios from both FAP and ITT analyses were similar. The observed median OS was 0.1314 months for the 6 patients excluded from the FAP in the TCF group and 8.0821months for the 6 patients excluded from the FAP in the CF group.

Findings:

Patients were assessed for tumor response and progression (defined according to WHO criteria) every 8 ±1 weeks. All tumor assessments were to be reviewed by an External Response Review Committee (ERRC). As stated in the protocol, the primary TTP analysis of the phase III study was performed in Full Analysis Population (FAP) which consisted of all treated subjects analyzed in the treatment group to which they were assigned by randomization. The TCF and CF groups were compared using a 2-sided log-rank test with $\alpha = 0.0487$ to adjust for one interim TTP analysis. A total of 341 TTP events occurred at the time of analysis. The hazard ratio for recurrence or death in the TCF arm, as compared with the CF arm, was 0.679 (p-value=0.0004, Table 1). The TTP analysis in the ITT patient population also supported the findings.

Table 1. Primary Efficacy TTP Analysis

	TCF	**CF**
Number of patients (FAP)	221	224
Number of events (%)	167 (75.6%)	174 (77.7%)
Median[1] (months), 95% CI	5.6, (4.86,5.91)	3.7, (3.45, 4.47)
Unstratified Logrank test	P=0.0004	
Hazard ratio (95% CI)[2]	0.679 (0.548, 0.841)	
Number of patients (ITT)	227	230
Number of events (%)	171 (75.3%)	175 (76.1%)
Median[1] (months), 95% CI	5.5, (4.53,5.82)	3.7, (3.45, 5.32)
Unstratified Logrank test	P=0.0007	
Hazard ratio (95% CI)[2]	0.693 (0.561, 0.858)	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the CFT arm, as compared with the CF arm.

2 Introduction

2.1 Overview

The sponsor is seeking approval of using Taxotere (docetaxel) in combination with cisplatin and 5-fluorouracil for the treatment of patients with (b) (4) gastric cancer previously untreated with chemotherapy for advanced disease.

The submitted study was a randomized, open-label, parallel group, multicenter, multinational phase III study performed in Asia, Western and Eastern Europe, and North and South America. It is the only randomized phase III pivotal study conducted to establish efficacy and safety of Taxotere (docetaxel) in combination with cisplatin and 5-fluorouracil for the treatment of patients with advanced gastric adenocarcinoma. Patients were centrally randomized (1:1) to either the test group (Taxotere combined with cisplatin and 5-fluorouracil (TCF)) or the control group (cisplatin combined with 5-fluorouracil (CF)) using a biased-coin minimization method with the following stratification factors: liver metastasis (yes/no), prior gastrectomy (yes/no), disease measurability (measurable vs. evaluable-only lesions), weight loss in prior 3 months (≤5% vs. >5%), and investigational center.

2.1.1 Background

Gastric cancer is the second most common cause of cancer-related deaths in the world. It is estimated that 755000 new cases are diagnosed annually. However, the incidence and mortality rates of gastric cancer vary greatly amongst regions. Over the past 7 decades, these rates have decreased progressively in North America and Western Europe but they are still high in Eastern Europe, South America, and Asia. The estimated new cases and deaths from gastric cancer in the United States for 2003 are 22400 and 12100 respectively.

Currently, a cure for patients with gastric cancer is only possible for those diagnosed with early stage disease in whom a complete surgical resection can be performed. Even in these patients, many (35-80%) will develop recurrences. The estimated 5-year survival rates, with standard treatment modalities, by stage are: 60-90% for Stage I; 30-40% for Stage II; 10-20% for Stage III and <5% for Stage IV. In the United States, the 5-year survival rate for gastric cancer of all stages is only 22%. In Europe, it ranges from 27% in Italy to 8% in Poland. The short life expectancy of patients with advanced gastric cancer indicates that new treatment modalities are urgently needed.

Adequate treatment for advanced disease remains elusive. A few chemotherapy agents (5-FU, cisplatin, anthracyclines, mitomycin-C, and etoposide) have shown

activity in gastric cancer. However, with single-agent treatment, response rate (RR) is low (from 15% to 36%) and combination treatment has been the standard in gastric cancer chemotherapy.

5-FU is (b) (4) It has been, almost universally, the basis for designing combination therapies for advanced gastrointestinal (GI) malignancies.

The activity of single-agent Taxotere in first-line chemotherapy of advanced gastric cancer subjects was shown in 3 phase II clinical trials, 1 each from Europe, the United States (both 100 mg/m2 intravenous [i.v.] every 3 weeks), and Japan (60 mg/m² i.v. every 3 weeks). In the European study, 8 of 33 (24%) evaluable subjects achieved a partial response (PR) with a median duration of response of 7.5 months (range, 3 to >11). Grade 3-4 neutropenia was the major toxicity (95% of subjects) with febrile neutropenia reported in 20% of subjects and 5% of cycles. In the United States (Eastern Cooperative Oncology Group [ECOG 1293]) study of 41 subjects, 2 complete responses (CRs) and 5 PRs in 36 (19%) evaluable subjects were achieved. Median progression-free survival was 2.8 months. Grade 4 neutropenia was reported in 88% of subjects. The dose of Taxotere was reduced in 54% of subjects. The Japanese trial was a multicenter study (TAX 287) where 59 of 76 subjects were evaluable for response and 1 CR plus 13 PRs (24%) were achieved. These data demonstrate that Taxotere has activity in gastric cancer.

The results of the phase II studies suggested that this agent is one of the most active therapies in gastric cancer and led to the design of Study 325, which was a phase II/III study. The principal goal of the phase II part of the study was to select 1 of 2 test treatments: Taxotere + cisplatin (TC) and Taxotere + cisplatin + 5-FU (TCF). In the phase III part of Study 325, the selected test treatment was compared on TTP and OS to a control regimen of cisplatin 100 mg/m2/day and 5-FU 1000 mg/m2/day over 5 days c.i. in patients with metastatic or locally recurrent gastric cancer, previously untreated with chemotherapy for advanced disease. According to the protocol, patients participating in the phase II part of the study would not be included in the phase III part (Study 325a).

The final analysis of the phase II part of this study showed that TCF had an overall RR of 55.0% versus 31.3% in TC, and TTP was 5.9 months with TCF versus 5.0 months with TC. The IDMC recommended TCF as the test treatment for the phase III part of the study (Study 325a) which compared the safety and efficacy of the control regimen CF to the test TCF treatment regimen in patients with metastatic or locally recurrent gastric cancer previously untreated with chemotherapy for advanced disease.

Enrollment in Study 325a began on November 29, 1999. Patients were centrally randomized (1:1) to either the test group TCF or the control group CF using a biased-coin minimization method with the following stratification factors: liver metastasis (yes/no), prior gastrectomy (yes/no), disease measurability (measurable vs. evaluable-only lesions), weight loss in prior 3 months (≤5% vs. >5%), and investigational center.

In the protocol, one interim analysis was planned to be performed when 162 TTP events occurred, and the final analysis was planned to be performed when 325 TTP events occurred. In August 2002, the results from the interim analysis were reviewed by the IDMC. Because the difference in overall survival was not statistically significant, it was decided not to stop the study at that point. As of May 7, 2003, a total of 341 TTP events occurred and the final analysis for TTP was performed. A total of 457 patients were randomized to the phase III study: 227 subjects into the TCF treatment group and 230 subjects into the CF treatment group. Twelve randomized subjects, 6 in each treatment group, did not receive therapy. Therefore, a total of 445 treated patients were included in the final TTP analysis in which, 341 of 445 (76.6%) subjects had an event, and 104 of 445 (23.4%) subjects were censored. The results of the TTP analysis led to the submission of this application.

The review will focus on the phase III part of the study (Study 325a) for evaluation of the use of Taxotere (docetaxel) in combination with cisplatin and 5-fluorouracil for the treatment of patients with metastatic or locally recurrent gastric cancer previously untreated with chemotherapy for advanced disease.

2.1.2 Statistical Issues

The study protocol included a single planned interim analysis during the phase III study. This analysis was triggered when 162 TTP events had occurred. An O'Brien-Fleming stopping boundary was used with the Lan-DeMets method for the interim analysis of superiority of TTP. The nominal significance levels for the interim and final analysis of TTP was 0.0036 and 0.0487, respectively.

The interim analysis included 115 TCF-treated patients and 117 CF-treated patients. The results from this interim analysis showed the observed median TTP was 5.2 months in the TCF treatment group [95% CI: 4.34-6.80] and 3.7 months [95% CI 3.06-4.80] in the CF treatment group. The difference between the 2 groups (log-rank test, P=0.0008; HR=0.587, TCF vs. CF) met the pre-specified boundary for superiority set for the interim analysis (0.0036). The median OS was also longer for the TCF group (10.2 months, [95% CI: 8.51-12.29]) compared to the CF group (8.5 months, [95% CI: 6.64-9.53]) but the observed difference (log-rank test, P=0.0064, HR=0.664, TCF vs. CF) did not meet the pre-specified boundary. At the time of the interim analysis (data cutoff of June 4, 2002), 181

deaths were observed. The nominal significance levels for the interim and final OS analysis were 0.0053 and 0.0483, respectively. Because the difference in OS was not statistically significant, it was decided not to stop the study at this point.

Only deaths within 12 weeks of the last evaluable tumor assessment, or within 12 weeks of the first infusion of study drugs (for subjects with no evaluable tumor assessment after randomization), were considered as TTP events. This definition is different from the definition of PFS which includes all deaths.

The TTP analysis in the ITT patient population supported the findings from the TTP analysis in the full analysis population (FAP). The OS analysis in the ITT patient population showed that the p-value was 0.0536, which was greater than the nominal significance level for the final analysis (0.0483), while the OS analysis in the FAP showed that the p-value was 0.0199. However, the hazard ratios from both FAP and ITT analyses were similar. The observed median OS was 0.1314 months for the 6 patients excluded from the FAP in the TCF group and 8.0821months for the 6 patients excluded from the FAP in the CF group.

2.2 Data Sources

Data and electronic documents used for this review are located on the network with path \\CDSESUB1\N20449\S_035\2005-09-23" in the EDR.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

The sponsor has submitted results of analyses from a randomized, open-label, parallel group, multicenter, multinational phase III study (Study 325a) designed to assess the efficacy and safety of Taxotere (docetaxel) in combination with cisplatin and 5-fluorouracil for the treatment of patients with advanced gastric adenocarcinoma. The main focus of this review will be on the results from the analyses, particularly on the efficacy aspect of this study.

3.1.1.1 Study Design

Study 325a was a prospective, randomized, open-label, parallel group, multicenter, multinational phase III study performed in Asia, Western and Eastern Europe, and North and South America. It was designed to primarily compare the TTP between the test group (TCF treatment regimen) and the control group (CF treatment regimen) in patients with metastatic or locally recurrent gastric cancer previously untreated with chemotherapy for advanced disease.

Enrollment in Study 325a began on November 29, 1999. Patients were centrally randomized (1:1) to either the test group TCF or the control group CF using a biased-coin minimization method with the following stratification factors: liver metastasis (yes/no), prior gastrectomy (yes/no), disease measurability (measurable vs. evaluable-only lesions), weight loss in prior 3 months (≤5% vs. >5%), and investigational center.

Patients were randomly (1:1) assigned to either the 3-drug test treatment regimen (TCF; selected in phase II part of the study) or the 2-drug control regimen (CF). Subjects receiving the TCF treatment regimen were to be administered 75 mg/m^2 of Taxotere i.v. on Day 1, 75 mg/m^2 of cisplatin i.v. on Day 1, followed by 750 mg/m^2 /day of 5-FU c.i. for 5 days, from Day 1 to Day 5. Subjects receiving the CF treatment regimen were to be administered 100 mg/m^2 of cisplatin i.v. on Day 1, followed by 1000 mg/m^2 /day of 5-FU c.i. for 5 days, from Day 1 to Day 5. Because of the existing clinical experience at the time of the study initiation, TCF cycles were to be repeated every 3 weeks and CF cycles every 4 weeks. The same intended dose intensity of cisplatin and 5-FU was maintained in both treatment groups (25 mg/m^2/week for cisplatin and 1250 mg/m^2 /week for 5-FU).

Treatment was administered until the occurrence of progression, unacceptable toxicities, or withdrawal of consent. After progression, further chemotherapy treatment with taxanes or camptothecins was not recommended. Crossover was not allowed. At the end of study treatment, patients who had progressed were followed every 3 months until death. patients who had not yet progressed at the end of study treatment were followed every 8 weeks until documented occurrence of progression, and then every 3 months, until death. The study design for Study 325a is shown in Figure 1.

Reviewer's Comments:

One interim analysis was planned to be performed when 162 TTP events occurred, and the final analysis was planned to be performed when exactly 325 TTP events occurred. In August 2002, the results from the interim analysis were reviewed by the IDMC. Because the difference in overall survival was not statistically significant, it was decided not to stop the study at that point. As of May 7, 2003, a total of 341 TTP events occurred and the final analysis for TTP was performed. The results of the TTP analysis led to the submission of this application.

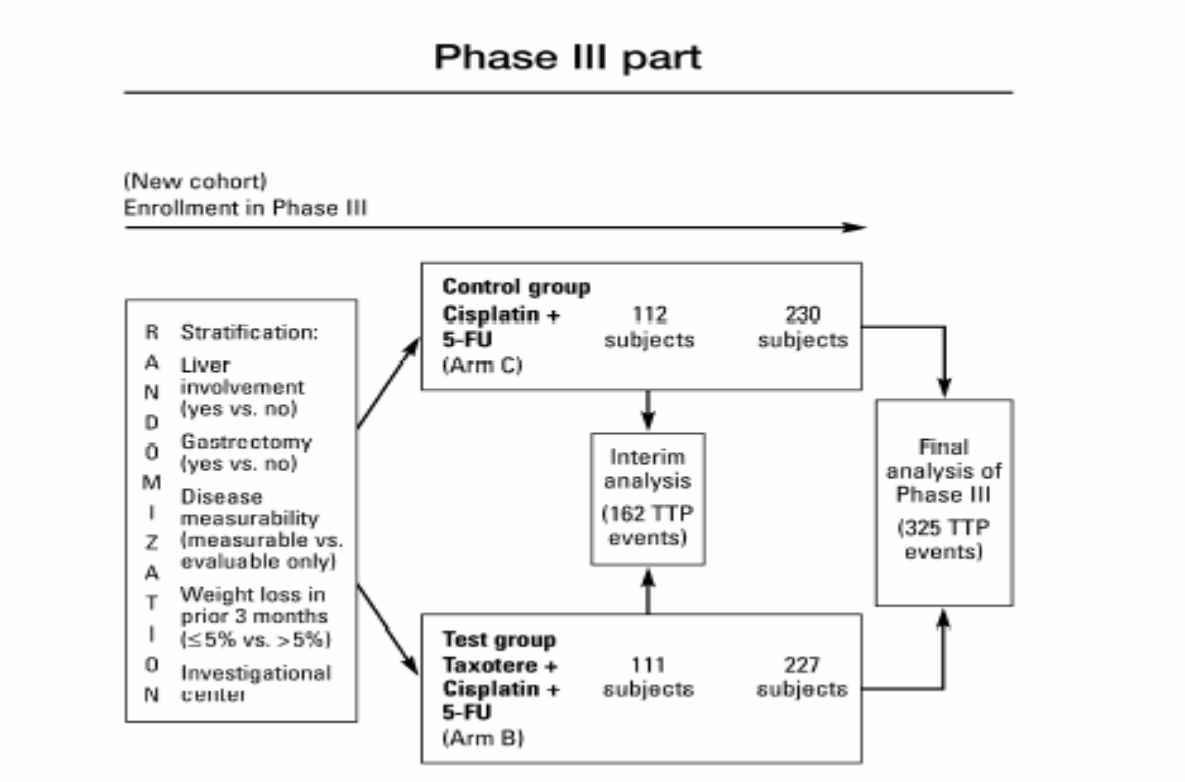

Figure 1. Study Design for Study 325a

3.1.1.2 Study Objectives

Study 325a was designed to assess the efficacy and safety of Taxotere (docetaxel) in combination with cisplatin and 5-fluorouracil for the treatment of patients with advanced gastric adenocarcinoma.

3.1.1.3 Efficacy Endpoints

Primary efficacy endpoint was time to progression (TTP), calculated from the day of randomization to the date of the first TTP event. A TTP event was defined as disease progression, or death from any cause. A period of 12 weeks was used, corresponding to 1.5 times the planned period between 2 tumor assessments. Thus only deaths within 12 weeks of the last evaluable tumor assessment, or within 12 weeks of the first infusion of study drugs (for subjects with no evaluable tumor assessment after randomization), were considered as TTP events. This prevents over-estimating TTP in subjects who miss one or more consecutive tumor assessments and then subsequently die.

For the determination of censoring dates for TTP, a data cut-off date was used. There were three possible censoring dates: 1) the cut-off date was used for

subjects with either a TTP event or an evaluable tumor assessment after the cut-off date; otherwise; 2) the date of the last evaluable tumor assessment prior to the first further anti-tumor therapy; 3) the date of randomization if there was no evaluable tumor assessment after randomization and before further anti-tumor therapy.

Survival is the main secondary endpoint in the phase III part. It will be measured from the date of randomization to the date of death from whatever cause. Response rate and duration of response were among other secondary endpoints. Response rate was defined as the number of subjects with a best overall response of CR or PR divided by the total number of subjects in the full analysis population. Duration of response was calculated as the date of first response until the date of the first TTP event or censoring.

Reviewer's Comment:

Only deaths within 12 weeks of the last evaluable tumor assessment, or within 12 weeks of the first infusion of study drugs (for subjects with no evaluable tumor assessment after randomization), were considered as TTP events. This definition is different from the definition of PFS which includes all deaths.

3.1.1.4 Sample Size Considerations

Assuming the use of an unadjusted logrank test with a two-sided 5% significance level to show a difference in TTP distributions corresponding to an increase in median TTP from 4 months in the control arm to 6 months in the test arm with a power of 95%, a total of 325 events were required. A median follow-up of 19.5 months was anticipated from a uniform accrual over 15 months and a minimum follow-up of 12 months. Assuming an exponential distribution, 350 patients (175 / arm) were required. Assuming a loss to follow-up of 5 %, a total of 370 patients (185 / arm) would be included.

It was also desirable to show a difference in overall survival distributions (main secondary endpoint) corresponding to an increase in median overall survival from 8 months to 12 months with a 95% power. A total of 325 deaths are required, assuming the use of a unadjusted logrank test with a two-sided 5% significance level.

Reviewer's Comment:

The study protocol included a single planned interim analysis during the phase III study. This analysis was triggered when 162 TTP events had occurred. An O'Brien-Fleming stopping boundary was used with the Lan-DeMets method for the interim analysis of superiority of TTP. The nominal significance levels for the interim and final analysis of TTP was 0.0036 and 0.0487, respectively.

The interim analysis included 115 TCF-treated patients and 117 CF-treated patients. The results from this interim analysis showed the observed median TTP was 5.2 months in the TCF treatment group [95% CI: 4.34-6.80] and 3.7 months [95% CI 3.06-4.80] in the CF treatment group. The difference between the 2 groups (log-rank test, *P*=0.0008; HR=1.704) met the pre-specified boundary for superiority set for the interim analysis (0.0036). The median OS was also longer for the TCF group (10.2 months, [95% CI: 8.51-12.29]) compared to the CF group (8.5 months, [95% CI: 6.64-9.53]) but the observed difference (log-rank test, *P*=0.0064, HR=1.505) did not meet the pre-specified boundary (0.0053). Because the difference in OS was not statistically significant, it was decided not to stop the study at this point.

As of May 7, 2003, the data cut-off date, a total of 341 TTP events occurred and the final analysis for TTP was performed. A total of 457 patients were randomized to the phase III study: 227 subjects into the TCF treatment group and 230 subjects into the CF treatment group. Twelve randomized subjects, 6 in each treatment group, did not receive therapy. Therefore, a total of 445 treated patients were included in the final TTP analysis in which, 341 of 445 (76.6%) subjects had an event, and 104 of 445 (23.4%) subjects were censored. The results of the TTP analysis led to the submission of this application.

3.1.1.5 Efficacy Analysis Methods

The primary analysis of the phase III study 352a was to be a comparison of TTP in the full analysis population (FAP). One interim analysis was performed when 162 TTP events occurred. The final significance level was nominally set at 0.0487 to adjust for the interim analysis. The cut-off date for the end-of-study TTP analysis was the date of the latest occurring TTP event in the database, which was 07 May 2003.

To test the superiority of TCF relative to CF with respect to TTP, an unstratified log-rank test was used. Kaplan–Meier survival curves were produced. Overall survival was compared using the same statistical methods.

Tumor response rates with exact 95% CIs were calculated for each treatment group in the FAP. Comparisons between treatment groups were performed using the chi-square test. Duration of overall response (from randomization and from onset of CR/PR) was compared between treatment groups using the unstratified log-rank test in the FAP.

Reviewer's Comments:

At the time of the interim analysis (data cutoff of June 4, 2002), 181 deaths were observed. This represented an information fraction of 0.5569, i.e., 181 divided by the 325, the required number of events needed for the survival analysis. The nominal significance levels for the interim and final OS analysis were 0.0053 and 0.0483, respectively.

3.1.1.6 Sponsor's Results and Statistical Reviewer's Findings/ Comments

The submission includes a total of 457 patients randomized to the phase III study: 227 subjects into the TCF treatment group and 230 subjects into the CF treatment group. Twelve randomized subjects, 6 in each treatment group, did not receive therapy. Therefore, a total of 445 treated patients were included in the final TTP analysis in which, 341 of 445 (76.6%) subjects had an event, and 104 of 445 (23.4%) subjects were censored. The results of the TTP analysis led to the submission of this application. The following list showed the 12 patients who did not receive therapy and the reasons:

TCF-randomized subjects: H0653, K2351, and O7304 for death; K1509 and K6202 for consent withdrawn; and O3324 for PD, shortly followed by death.

Subject H0653: a 64-year-old man who presented at baseline with a KPS of 80, 0% weight loss, ongoing grade 2 asthenia and insomnia, grade 3 cancer pain (abdominal pain) and left pulmonary pain. The subject died due to respiratory failure 4 days after randomization.

Subject K2351: a 70-year-old man who presented at baseline with a KPS of 80, 15% weight loss; ongoing grade 3 cancer-related pain and grade 2 asthenia, dysphagia, nausea, shortness of breath, anemia and elevated alkaline phosphatase. The subject died due to malignant disease 2 days after randomization.

Subject O7304: a 37-year-old man who presented at baseline with a KPS of 80, 17% weight loss, grade 2 cancer-related pain, anorexia and dyspepsia and grade 4 obstructive jaundice. The subject died due to malignant disease 3 days after randomization.

Subject K1509: a 48-year-old woman withdrew her consent after being randomized to TCF. The subject indicated that she did not want treatment. The subject did not receive other anti-cancer therapy, and died from malignant disease 2.5 months after randomization.

Subject K6202: a 43-year-old man withdrew his consent after being randomized to TCF. The subject indicated that he wanted to be treated at another hospital and was lost to follow-up after consent was withdrawn.

Subject O3324: a 42-year-old woman who presented at baseline with ongoing grade 3 cancerrelated pain and grade 3 thrombocytopenia and with grade 4 vaginal hemorrhage, started after the randomization. Tumor assessment showed ovarian metastases. She underwent surgery (ovariectomy) on Day 8 after the randomization. The subject was withdrawn from the study 19 days after randomization due to PD and died due to malignant disease 8 days later.

CF-randomized subjects: F0707, O3409, and O4706 for consent withdrawn; and C3327, L4405 and M0709 for various clinical and/or laboratory abnormalities.

Subject M0709: a 55-year-old woman who presented at baseline with a KPS of 90, 27% weight loss, grade 2 constipation and grade 3 cancer-related pain. The subject was withdrawn from the study 12 days after randomization due to grade 3 ASAT and grade 2 alkaline phosphatase. Further chemotherapy (etoposide + 5-FU + leucovorin) started on day 19 after randomization. Subject was still alive in April 2003.

Subject L4405: a 63-year-old man presented at baseline with a KPS of 90, 20% weight loss, ongoing grade 2 anorexia and dysphagia and grade 3 cancer-related pain. After randomization, grade 3 GI hemorrhage, grade 4 anemia and grade 2 alkaline phosphatase were reported. The subject was withdrawn from the study 10 days after randomization. Further anticancer therapy (radiotherapy) started on day 20 after randomization. Subject died from malignant disease 3 months later.

Subject C3327: a 50-year-old man who presented at baseline with a KPS of 90, 0% weight loss, grade 3 cardiac dysrhythmia. The subject did not have cardiac medical history. He was withdrawn from the study 10 days after randomization due to cardiac dysrhythmia. He did not receive further anticancer therapy and was still alive more than 5 months after the date of randomization.

Subject O4706: a 63-year-old man who presented at baseline with a KPS of 90, 14% weight loss, ongoing grade 2 night sweats and grade 3 dysphagia. The subject withdrew his consent after being randomized to the control arm. Further chemotherapy (carboplatin + 5-FU, then cisplatin + irinotecan) was started on day 11 after the date of randomization. He died from malignant disease 8 months later.

Subject O3409: a 47-year-old man who presented at baseline with a KPS of 80, 8% weight loss and ongoing grade 1 cancer-related pain. The subject withdrew his consent 2 days after being randomized to the control arm. Further chemotherapy was started one month later (cisplatin + 5- FU + etoposide + folinic acid). He died from malignant disease 4 months after the date of randomization.

Subject F0707: a 38-year-old woman withdrew her consent 5 days after being randomized to the control arm. Further chemotherapy started on day 13 after randomization (etoposide + 5-FU + leucovorin). Subject died about 14 months later, from malignant disease.

3.1.1.6.1 Baseline Characteristics

The baseline Characteristics of the overall population are presented in Table 2.

Reviewer's Comments:
In the overall patient population the baseline characteristics appear to be balanced between the two treatment arms.

Table 2. Baseline Characteristics of the Patients in the Study 325a

Characteristic	TCF (N=221)	CF (N=224)	ALL (N=445)
Age — yr			
Mean (SD)	54.4(11.9)	54.6(11.4)	54.5(11.6)
Median (Range)	55 (26–79)	55 (25–76)	55 (25-79)
Age grouped — no. (%)			
<65	167 (75.6)	169 (75.4)	336 (75.5)
+65	54 (24.4)	55 (24.6)	109 (24.5)
Sex — no. (%)			
Male	159 (71.0)	158 (70.5)	317 (71.2)
Female	62 (28.1)	66 (29.5)	128 (28.8)
Race — no. (%)			
Caucasian	157 (71.0)	158 (70.5)	315 (70.8)
Black	5 (2.3)	4 (1.8)	9 (2.0)
Oriental/Asian	7 (3.2)	12 (5.4)	19 (4.3)
Hispanic	44 (19.9)	40 (17.9)	84 (18.9)
Others	8 (3.6)	10 (4.5)	18 (4.0)
Karnofsky performance status (KPS)— no. (%)			
100	28 (12.7)	29 (12.9)	57 (12.8)
90	113 (51.1)	114 (50.9)	227 (51.0)
80	77 (34.8)	78 (34.8)	155 (34.8)
70	3 (1.4)	3 (1.3)	6 (1.3)
% Weight loss in prior 3 months — no. (%)			
≤5%	95 (43.0)	96 (42.9)	191 (42.9)
>5%, ≤10%	64 (29.0)	67 (29.9)	131 (29.4)
>10%	62 (28.1)	60 (26.8)	122 (27.4)
Missing value	0 (0)	1 (0.4)	1 (0.2)
Extent of disease*a* — no. (%)			
Metastatic	213 (96.4)	217 (96.9)	430 (96.6)
Locally recurrent	1 (0.5)	1 (0.4)	2 (0.4)
Locally advanced	5 (2.3)	5 (2.2)	10 (2.2)
No disease	2 (0.9)	1 (0.4)	3 (0.7)
Measurability of disease— no. (%)			
Bidimensional	158 (83.7)	195 (87.1)	380 (85.4)
Unidimensional	1 (0.5)	3 (1.3)	4 (0.9)
Evaluable only	15 (6.8)	12 (5.4)	27 (6.1)
Non-evaluable disease	18 (8.1)	13 (5.8)	31 (7.0)
No disease	2 (0.9)	1 (0.4)	3 (0.7)
Number of organs involved — no. (%)			
0	2 (0.9)	1 (0.4)	3 (0.7)
1	33 (14.9)	47 (21.0)	80 (18.0)
2	86 (38.9)	76 (33.9)	162 (36.4)
>2	100 (45.2)	100 (44.6)	200 (44.9)

3.1.1.6.2 Primary Efficacy Analyses

The primary TTP analysis of the phase III study was performed in the full analysis population (FAP) which consisted of all treated subjects analyzed in the treatment group to which they were assigned by randomization. Patients were assessed for tumor response and progression (defined according to WHO criteria) every 8 ±1 weeks. All tumor assessments were to be reviewed by an External Response Review Committee (ERRC). The TCF and CF groups were compared using a 2-sided log-rank test with $\alpha = 0.0487$ to adjust for one interim TTP analysis.

A total of 445 treated patients were included in the final TTP analysis: 221 patients in the TCF treatment group and 224 patients in the CF treatment group. There were 167 events (75.6%) for TTP in the TCF arm and 174 events (77.7%) for TTP in the CF arm. A total of 341 TTP events (76.6%) occurred at the time of TTP analysis. The hazard ratio for recurrence or death in the TCF arm, as compared with the CF arm, was 0.679 (p-value=0.0004, Table 2, Figure 2).

Table 3. Primary Efficacy TTP Analysis

	TCF	**CF**
Number of patients (FAP)	221	224
Number of events (%)	167 (75.6%)	174 (77.7%)
Median[1] (months), 95% CI	5.6, (4.86,5.91)	3.7, (3.45, 4.47)
Untratified Logrank test	P=0.0004	
Hazard ratio (95% CI)[2]	0.679 (0.548, 0.841)	
Number of patients (ITT)	227	230
Number of events (%)	171 (75.3%)	175 (76.1%)
Median[1] (days), 95% CI	5.5, (4.53,5.82)	3.7, (3.45, 5.32)
Unstratified Logrank test	P=0.0007	
Hazard ratio (95% CI)[2]	0.693 (0.561, 0.858)	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the CFT arm, as compared with the CF arm.

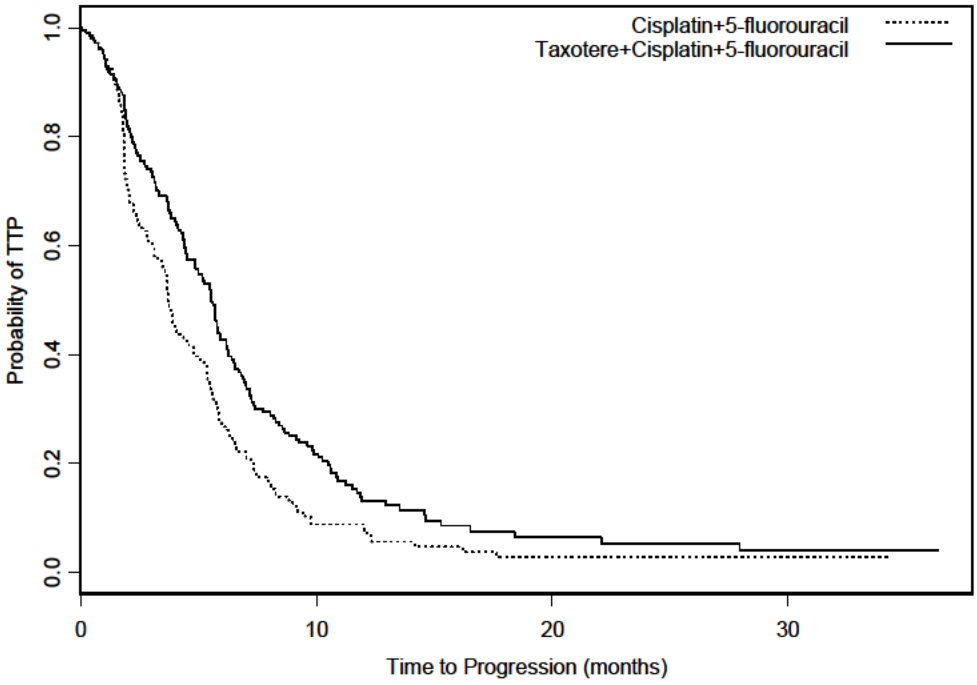

Figure 2: Kaplan-Meier Curves for TTP in the FAP

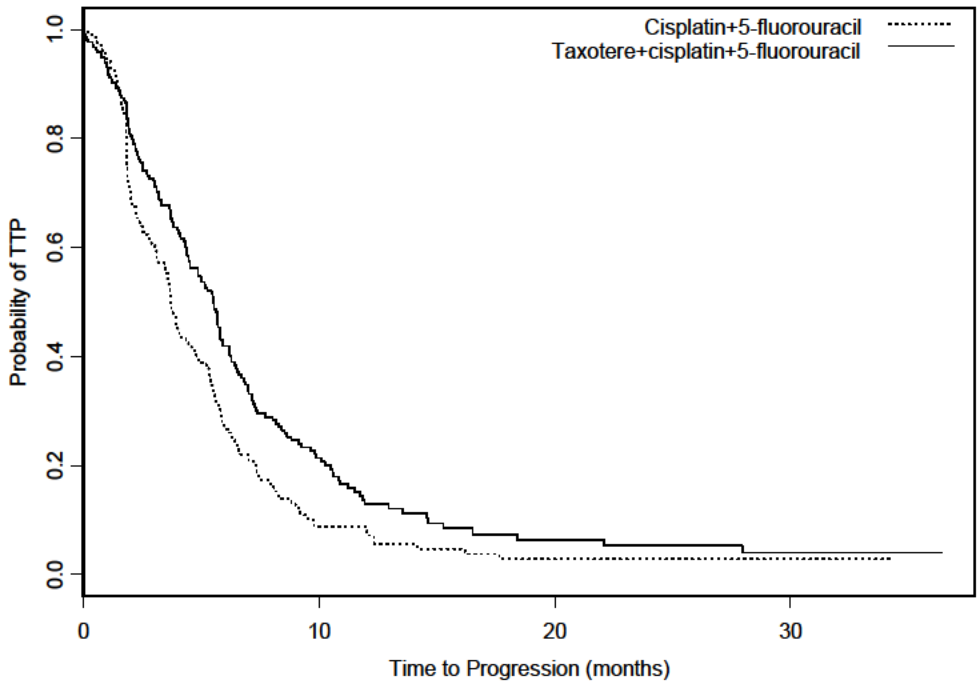

Figure 3: Kaplan-Meier Curves for TTP in ITT population

Reviewer's Comments:

The TTP analysis in the ITT patient population also supported the findings. It included 457 patients: 227 patients in the TCF treatment group and 230 patients in the CF treatment group. There were 171 events (75.3%) for TTP in the TCF arm and 175 events (76.1%) for TTP in the CF arm. A total of 346 TTP events (75.7%) occurred at the time of the ITT analysis. The hazard ratio for recurrence or death in the TCF arm, as compared with the CF arm, was 0.693 (p-value= 0.0007, Table 1, Figure 3).

This reviewer performed a standard TTP analysis where TTP was based on the time from randomization to radiological progression. In the absence of progression, patients should be censored at the last complete tumor assessment. Results were similar to the primary analysis (unstratified log-rank test in FAP P=0.0002, HR=0.655, [95% CI: 0.522-0.822]). A standard PFS analysis was also performed in which time from randomization to the first event of radiological progression or death is analyzed. Patients are censored at the date of last complete tumor assessment. Again, results were similar to the primary analysis (unstratified log-rank test in FAP P=0.0039, HR=0.745, [95% CI: 0.609-0.911]).

3.1.1.6.3 Secondary Efficacy Analyses

Overall Survival

At the time of the interim analysis for TTP (data cutoff of June 4, 2002), 181 deaths were observed. This represented an information fraction of 0.5569, i.e., 181 divided by the 325, the required number of events needed for the survival analysis. According to the O'Brien-Fleming type of alpha spending function, the nominal significance levels for OS were 0.0053 for the interim analysis and 0.0483 for the final analysis. Patients still alive at the time of OS analysis are censored at their last date of follow-up.

A total of 334 of 445 (75.1%) subjects in the full analysis population had an event, and 111 of 445 (24.9%) subjects were censored. The median follow-up for OS was 23.4 months. The hazard ratio for death in the TCF arm, as compared with the CF arm, was 0.774 (p-value=0.0199, Table XX). However, the OS analysis in the ITT patient population showed that the hazard ratio for death in the TCF arm, as compared with the CF arm, was 0.8109 (p-value=0.0536, Table 4, Figure 4, 5).

Table 4. Primary Efficacy OS Analysis

	TCF	**CF**
Number of patients (FAP)	221	224
Number of events (%)	162 (73.3%)	172 (76.8%)
Median[1] (months), 95% CI	9.2, (8.38,10.58)	8.6, (7.16, 9.46)
Unstratified Logrank test	P=0.0199	
Hazard ratio (95% CI)[2]	0.774 (0.623, 0.961)	
Number of patients (ITT)	227	230
Number of events (%)	167 (73.6%)	176 (76.5%)
Median[1] (months), 95% CI	8.97, (8.12,10.35)	8.57, (7.16, 9.46)
Unstratified Logrank test	P=0.0536	
Hazard ratio (95% CI)[2]	0.8109 (0.655, 1.004)	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the CFT arm, as compared with the CF arm.

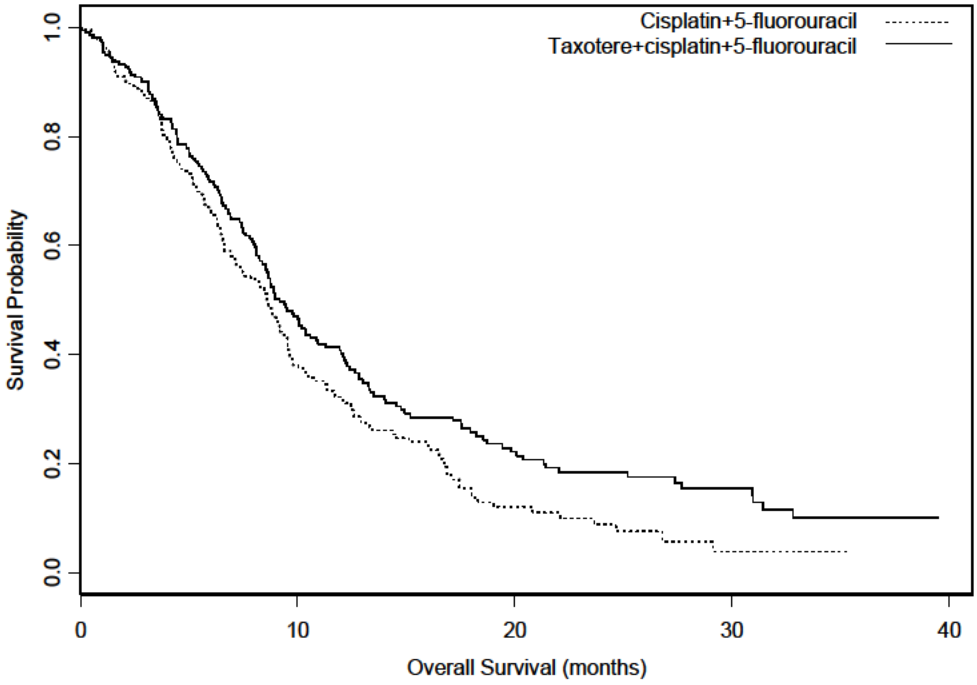

Figure 4: Kaplan-Meier Curves for OS in the FAP

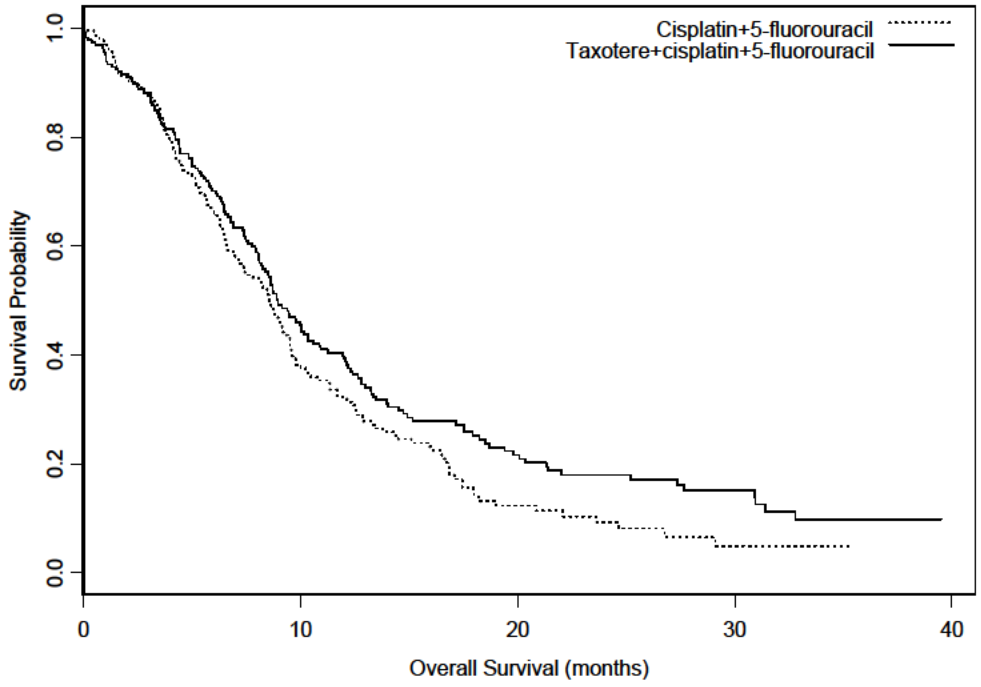

Figure 5: Kaplan-Meier Curves for OS in ITT Population

Reviewer's Comments:

The OS analysis in the ITT patient population showed that the p-value was 0.0536, which was greater than the nominal significance level for the final analysis (0.0483). The observed median OS was 0.1314 months for the 6 patients excluded from the FAP in the TCF group and 8.0821months for the 6 patients excluded from the FAP in the CF group.

Response Rate and Duration of Response

The best overall response rates for the full analysis population were shown in Table 5. The overall response rates (CR + PR) were 36.7% [95% CI: 30.3%-43.4%]) in the TCF group and 25.4% [95% CI: 19.9%-31.7%] in the CF group. The p-value from a Chi square test for the difference between the 2 treatment groups was 0.0106). The numbers of patients with progressive disease were 37 [16.7%] in the TCF group and 58 [25.9%] in the CF group.

Of the 138 subjects with an overall response, 101 (73.2%) were subsequently observed to progress and 37 subjects (26.8%) were censored. The median overall response duration (from the onset of PR/CR), was 6.1 months in the TCF group

[95% CI: 4.96-8.31] and 5.6 months in the CF group [95% CI: 4.24-6.37]. The p-value from a log-rank test for the difference between the 2 groups was 0.3175.

Table 5. Response Rates and Duration of Response

	TCF N=221	**CF N=224**
Response		
Complete response	4 (1.8%)	3 (1.3%)
Partial response	77 (34.8%)	54 (24.1%)
No change/stable disease	67 (30.3%)	69 (30.8%)
Progressive disease	37 (16.7%)	58 (25.9%)
Not evaluable	36 (16.3%)	40 (17.9%)
Overall response rate (RR)[a] [95% CI]	81 (36.7%) [30.3%-43.4%]	57 (25.4%) [19.9%-31.7%]
χ^2 test	P-value[b]=0.0106	
Duration of Response		
Number of responsers	81	57
Number of events (%)	61 (75.3%)	40 (70.2%)
Median[c] (days), 95% CI	6.1, (4.96,8.31)	5.6, (4.24, 6.37)

[a] RR = CR + PR; [b] not adjusted for multiple analyses; [c] Kaplan-Meier Estimates.

3.2 Evaluation of Safety

Please refer to Clinical Review of this application for safety evaluation.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

For each subgroup population, a separate unadjusted log-rank test was performed; Hazard ratios were estimated. The subgroup analyses were performed in both the full analysis population and the ITT population. Results from TTP analyses by gender (male vs. female) were presented in Tables 6-7; results from TTP analyses by race (Caucasian and Non-Caucasian) were presented in Tables 8-9; results from TTP analyses by age (< 65 years vs. ≥ 65 years were presented in Tables 10-11.

Table 6. TTP Analyses by Gender in FAP

	TCF	CF
Gender		
Male		
Number of patients (FAP)	159	158
Number of events (%)	120 (75.5%)	121 (76.6%)
Median (months), 95% CI[1]	5.6 (4.5, 6.2)	3.8 (3.5, 4.9)
Hazard ratio [95% CI][2]	0.73 (0.57, 0.94)	
Unstratified log-rank test	P-value[3]=0.0141	
Female		
Number of patients (FAP)	62	66
Number of events (%)	47 (75.8%)	53 (80.3%)
Median (months), 95% CI[1]	5.6 (3.8, 7.0)	3.7 (2.5, 4.4)
Hazard ratio (95% CI)[2]	0.55 (0.36, 0.82)	
Unstratified log-rank test	P-value[3]=0.0030	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the TCF arm, as compared with the CF arm; [3:] not adjusted for multiple analyses.

Table 7. TTP Analyses by Gender in ITT population

	TCF	CF
Gender		
Male		
Number of patients (ITT)	163	162
Number of events (%)	123 (75.5%)	122 (75.3%)
Median (months), 95% CI[1]	5.5 (4.5, 5.9)	3.8 (3.2, 4.9)
Hazard ratio [95% CI][2]	0.75 (0.58, 0.96)	
Unstratified log-rank test	P-value[3]=0.0216	
Female		
Number of patients (ITT)	64	68
Number of events (%)	48 (75.0%)	53 (77.9%)
Median (months), 95% CI[1]	5.6 (3.8, 6.9)	3.7 (2.5, 4.4)
Hazard ratio (95% CI)[2]	0.56 (0.37, 0.83)	
Unstratified log-rank test	P-value[3]=0.0038	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the TCF arm, as compared with the CF arm; [3:] not adjusted for multiple analyses.

Table 8. TTP Analyses by Age in FAP

	TCF	CF
Age		
<65		
Number of patients (FAP)	167	169
Number of events (%)	131 (78.4%)	136 (80.5%)
Median (months), 95% CI[1]	5.5 (4.5, 5.9)	3.7 (3.1, 4.5)
Hazard ratio (95% CI)[2]	0.674 (0.53, 0.86)	
Unstratified log-rank test	P-value[3]=0.0014	
>=65		
Number of patients (FAP)	54	55
Number of events (%)	36 (66.7%)	38 (69.1%)
Median (months), 95% CI[1]	5.8 (3.3, 7.7)	3.8 (2.2, 5.5)
Hazard ratio (95% CI)[2]	0.686 (0.43, 0.1.087)	
Unstratified log-rank test	P-value[3]=0.1053	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the TCF arm, as compared with the CF arm; [3]: not adjusted for multiple analyses.

Table 9. TTP Analyses by Age in ITT population

	TCF	CF
Age		
<65		
Number of patients (ITT)	172	175
Number of events (%)	134 (77.9%)	137 (78.3%)
Median (months), 95% CI[1]	5.5 (4.5, 5.8)	3.7 (3.1, 4.4)
Hazard ratio (95% CI)[2]	0.688 (0.54, 0.88)	
Unstratified log-rank test	P-value[3]=0.0021	
>=65		
Number of patients (ITT)	55	55
Number of events (%)	37 (67.3%)	38 (69.1%)
Median (months), 95% CI[1]	5.8 (3.3, 7.7)	3.8 (2.2, 5.5)
Hazard ratio (95% CI)[2]	0.708 (0.45, 1.12)	
Unstratified log-rank test	P-value[3]=0.1346	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the TCF arm, as compared with the CF arm; [3]: not adjusted for multiple analyses.

Table 10. TTP Analyses by Race in FAP

	TCF	CF
Race		
Caucasian		
Number of patients (FAP)	157	158
Number of events (%)	120 (76.4%)	118 (74.5%)
Median (months), 95% CI[1]	5.6 (4.5, 6.2)	3.7 (3.5, 4.8)
Hazard ratio [95% CI][2]	0.713 (0.55, 0.92)	
Unstratified log-rank test	P-value[3]=0.0091	
Non-Caucasian		
Number of patients (FAP)	64	66
Number of events (%)	47 (73.4%)	56 (84.8%)
Median (months), 95% CI[1]	5.8 (4.04, 6.87)	3.45 (2.23, 4.80)
Hazard ratio (95% CI)[2]	0.597 (0.400, 0.884)	
Unstratified log-rank test	P-value[3]=0.0092	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the TCF arm, as compared with the CF arm; [3:] not adjusted for multiple analyses.

Table 11. TTP Analyses by Race in ITT Population

	TCF	CF
Race		
Caucasian		
Number of patients (ITT)	159	163
Number of events (%)	121 (76.1%)	118 (72.4%)
Median (months), 95% CI[1]	5.5 (4.5, 6.2)	3.7 (3.5, 4.8)
Hazard ratio [95% CI][2]	0.715 (0.55, 0.92)	
Unstratified log-rank test	P-value[3]=0.0096	
Non-Caucasian		
Number of patients (ITT)	68	67
Number of events (%)	50 (73.5%)	56 (83.6%)
Median (months), 95% CI[1]	5.6 (3.7, 6.6)	3.45 (2.23, 4.80)
Hazard ratio (95% CI)[2]	0.637 (0.43, 0.94)	
Unstratified log-rank test	P-value[3]=0.0209	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the TCF arm, as compared with the CF arm; [3:] not adjusted for multiple analyses.

Reviewer's Comments:

Subgroup analyses are consistent with the overall analysis across gender, race and age groups.

5 Summary and Conclusions

This NDA submission is to support the use of Taxotere (docetaxel) in combination with cisplatin and 5-fluorouracil for the treatment of patients with (b) (4) gastric cancer previously untreated with chemotherapy for advanced disease. The submitted study was a randomized, open-label, parallel group, multicenter, multinational phase III study (Study 523a) performed in Asia, Western and Eastern Europe, and North and South America. It is the only randomized phase III pivotal study conducted to establish efficacy and safety of Taxotere (docetaxel) in combination with cisplatin and 5-fluorouracil for the treatment of patients with advanced gastric adenocarcinoma.

The submission includes a total of 457 patients randomized to the phase III study: 227 patients into the TCF treatment group and 230 patients into the CF treatment group. Twelve randomized subjects, 6 in each treatment group, did not receive therapy. Therefore, a total of 445 treated patients were included in the final TTP analysis in which, 341 of 445 (76.6%) subjects had an event, and 104 of 445 (23.4%) subjects were censored. The results of the TTP analysis led to the submission of this application.

5.1 Statistical Issues and Collective Evidence

In this NDA submission, Study 325a was the only randomized pivotal phase III study conducted to establish efficacy and safety. The efficacy analysis for the data collected until the cut-off date of May 7, 2003 included 167 events (75.6%) for TTP in the TCF arm and 174 events (77.7%) for TTP in the CF arm. A total of 341 TTP events (76.6%) occurred at the time of TTP analysis.

The primary TTP analysis of the phase III study was performed in full analysis population (FAP) which consisted of all treated subjects analyzed in the treatment group to which they were assigned by randomization. The TCF and CF groups were compared using a 2-sided log-rank test with $\alpha = 0.0487$ to adjust for one interim TTP analysis. The hazard ratio for recurrence or death in the TCF arm, as compared with the CF arm, was 0.679 (p-value=0.0004). The TTP analysis in the ITT patient population also supported the findings.

Statistical Issues:

The study protocol included a single planned interim analysis during the phase III study. This analysis was triggered when 162 TTP events had occurred. An O'Brien-Fleming stopping boundary was used with the Lan-DeMets method for the interim analysis of superiority of TTP. The nominal significance levels for the interim and final analysis of TTP was 0.0036 and 0.0487, respectively.

The interim analysis included 115 TCF-treated patients and 117 CF-treated patients. The results from this interim analysis showed the observed median TTP was 5.2 months in the TCF treatment group [95% CI: 4.34-6.80] and 3.7 months [95% CI 3.06-4.80] in the CF treatment group. The difference between the 2 groups (log-rank test, P=0.0008; HR=0.587, TCF vs. CF) met the pre-specified boundary for superiority set for the interim analysis (0.0036). The median OS was also longer for the TCF group (10.2 months, [95% CI: 8.51-12.29]) compared to the CF group (8.5 months, [95% CI: 6.64-9.53]) but the observed difference (log-rank test, P=0.0064, HR=0.664, TCF vs. CF) did not meet the pre-specified boundary. At the time of the interim analysis (data cutoff of June 4, 2002), 181 deaths were observed. The nominal significance levels for the interim and final OS analysis were 0.0053 and 0.0483, respectively. Because the difference in OS was not statistically significant, it was decided not to stop the study at this point.

Only deaths within 12 weeks of the last evaluable tumor assessment, or within 12 weeks of the first infusion of study drugs (for subjects with no evaluable tumor assessment after randomization), were considered as TTP events. This definition is different from the definition of PFS which includes all deaths.

The TTP analysis in the ITT patient population supported the findings from the TTP analysis in the full analysis population (FAP). The OS analysis in the ITT patient population showed that the p-value was 0.0536, which was greater than the nominal significance level for the final analysis (0.0483), while the OS analysis in the FAP showed that the p-value was 0.0199. However, the hazard ratios from both FAP and ITT analyses were similar. The observed median OS was 0.1314 months for the 6 patients excluded from the FAP in the TCF group and 8.0821months for the 6 patients excluded from the FAP in the CF group.

5.2 Conclusions and Recommendations

In this reviewer's opinion the study results from the submitted single, randomized, open-label, parallel group, multicenter, multinational phase III study(Study 325a), support the claim of efficacy of Taxotere (docetaxel) in combination with cisplatin and 5-fluorouracil for the treatment of patients with advanced gastric adenocarcinoma with respect to time to progression (TTP) which included death from any cause. The Taxotere (docetaxel) in combination with cisplatin and 5-fluorouracil demonstrated a TTP advantage over the combination of cisplatin and 5-fluorouracil in this clinical study. Whether the endpoint and the size of the effect on this endpoint are adequate for approval is a clinical decision.

SIGNATURES/DISTRIBUTION LIST

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HFD-700/R. O'Neill
HFD-700/L. Patrician

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-449/S-035

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	20-449/SE1-035
BRAND NAME:	Taxotere
GENERIC NAME:	Docetaxel (b) (4)
DOSAGE FORM/ STRENGTH:	40 mg/ml Docetaxel (b) (4) in Single-Dose Vials for Intravenous Injection
INDICATION:	Advanced Gastric Adenocarcinoma
SUBMISSION DATE:	23-Sep-2005
SUBMISSION TYPE:	NDA-Supplement
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1. EXECUTIVE SUMMARY

The purpose of this Supplemental New Drug Application (NDA 20-449/SE1-035) is to seek approval for the use of Taxotere (docetaxel (b) (4) in combination with cisplatin and 5-fluorouracil (5-FU) for the first-line treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastro-esophageal junction, who have not received prior chemotherapy for advanced disease.

In support of this new indication, the Applicant submitted a pivotal Phase 2/3 study (Study XRP6976E/325), with a Phase 2 part called Study TAX325 and a Phase 3 part called Study TAX325A. In the Phase 3 Study TAX325A, 445 patients with advanced gastric adenocarcinoma were randomized to receive either of the following treatments:

TCF (n=221): Taxotere 75 mg/m^2 given as a 1-hour infusion on Day 1 followed by cisplatin 75 mg/m^2 as a 1- to 3-hour infusion after the end of the Taxotere infusion, and then followed by 5-FU 750 mg/m^2/day as a 24-hour infusion on Day 1 immediately after the end of the cisplatin infusion to Day 5 every 3 weeks (1 cycle).

CF (n=224): Cisplatin 100 mg/m^2 as a 1- to 3-hour infusion on Day 1 followed by 5-FU 1000 mg/m^2/day as a 24-hour continuous infusion on Day 1 immediately after the end of the cisplatin infusion to Day 5 every 4 weeks (1 cycle).

The primary efficacy endpoint was Time to Progression (TTP). According to the Applicant, the observed median TTP was longer for TCF-treated patients (5.6 months) than for CF-treated patients (3.7 months). This difference was statistically significant [*P*=0.0004, hazard ratio = 1.5, 95% CI=1.2-1.8%] with a median follow-up period of 13.6 months. In general, the two treatment groups had comparable drug-related adverse events.

In addition, a separate pharmacokinetic interaction study (Study XRP6976E/1001) was conducted in 12 patients with solid tumors. In this study, patients were randomized (1:1) to receive Taxotere and cisplatin either without 5-FU (TC) or with 5-FU (TCF) in cycle 1 and were then crossed over to the alternate regimen in cycle 2. Each treatment cycle lasted 3 weeks. The double combination (TC) consisted of docetaxel 75 mg/m² given as a 1-hour infusion on Day 1 followed by cisplatin 75 mg/ m² as a 3-hour infusion 15 minutes after the end of docetaxel infusion. The triple combination (TCF) consisted of docetaxel 75 mg/m² given as a 1-hour infusion on Day 1 followed by cisplatin 75 mg/m² as a 3-hour infusion 15 minutes after the end of docetaxel infusion then followed by 5-FU 750 mg/m²/day as a continuous 24-hour infusion for 5 days immediately after the end of cisplatin infusion. The results of this study indicate that 5-FU had no effect on the pharmacokinetics of docetaxel and cisplatin when the three drugs were given in combination to 12 patients with solid tumors. The combination of docetaxel and cisplatin had no effect on the pharmacokinetics of 5-FU.

In addition, published data indicate that the pharmacokinetics of a combination of cisplatin and docetaxel were consistent with those for single agents, suggesting no major pharmacokinetic interaction between both drugs. The current package insert for Taxotere also indicates that the pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone.

1.1 RECOMMENDATION

The Supplemental NDA 20-449/SE1-035 submitted for the use of Taxotere in combination with cisplatin and 5-fluorouracil for the treatment of patients with advanced gastric adenocarcinoma is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). The following statement that was included by the Applicant in the current package insert for Taxotere is also acceptable to OCPB:

The combined administration of docetaxel, cisplatin and 5-fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug.

No action is indicated.

1.2 PHASE 4 COMMITMENTS

[None]

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The potential for drug-drug interactions between Taxotere, cisplatin, and 5-FU was assessed in a separate pharmacokinetic study (Study XRP6976E/1001). Study XRP6976E/1001 was an open-label, single-center, randomized, cross-over study in 12 patients with solid tumors. Patients were randomized (1:1) to receive Taxotere + cisplatin either without 5-FU (TC) or with 5-FU (TCF) in cycle 1 and were crossed over to the alternate regimen in cycle 2. Each treatment cycle lasted 3 weeks. The double combination (TC) consisted of docetaxel 75 mg/m² given as a 1-hour infusion on Day 1 followed by cisplatin 75 mg/m² as a 3-hour infusion 15 minutes after the end of docetaxel infusion. The triple combination (TCF) consisted of docetaxel 75 mg/m² given as a 1-hour infusion on Day 1 followed by cisplatin 75 mg/m² as a 3-hour infusion 15 minutes after the end of docetaxel infusion then followed by 5-FU 750 mg/m²/day as a continuous 24-hour infusion for 5 days immediately after the end of cisplatin infusion. The results of this study indicate that 5-FU had no effect on the pharmacokinetics of docetaxel and cisplatin when the three drugs were given in combination to 12 patients with solid tumors. The combination of docetaxel and cisplatin had no effect on the pharmacokinetics of 5-FU.

In addition, published data [Millward MJ et al., Phase 1 trial of docetaxel and cisplatin in previously untreated patients with advanced non-small-cell lung cancer. J Clin Oncol 15:750-758, 1997] indicate that the pharmacokinetics of a combination of cisplatin and docetaxel were consistent with those for single agents, suggesting no major pharmacokinetic interaction between both drugs when given in combination. The current package insert for Taxotere also indicates that the pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone.

2 QUESTION BASED REVIEW

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dose for the advanced gastric adrenocarcinoma indication is Taxotere 75 mg/m^2 as a 1-hour infusion, followed by cisplatin 75 mg/m^2 as a 1- to 3-hour infusion (both on Day 1 only), followed by 5-fluorouracil 750 mg/m^2/day as a continuous 24-hour infusion for 5 days, starting at the end of the cisplatin infusion. The treatment is to be repeated every three weeks.

2.2 General clinical pharmacology

2.2.1 What are the design features of the clinical studies used to support dosing or claims?

In support of the use of Taxotere in combination with cisplatin and 5-FU for the first-line treatment of patients with advanced gastric adenocarcinoma, the Applicant conducted a pivotal Phase 2/3 study, Study XRP6976/325 (with a Phase 2 part called Study TAX325 and a Phase 3 part called Study TAX325A).

Study TAX325 was an open-label, prospective, multi-center, multi-national, parallel-group, Phase 2 study in 155 chemotherapy-naive patients with metastatic or locally recurrent gastric adenocarcinoma to determine the regimen that will be tested in the Phase 3 part of the study (Study TAX325A). Patients were randomized to receive either of the following two treatments:

TCF (n=79): Taxotere 75 mg/m^2 as a 1-hour infusion on Day 1 followed by cisplatin 75 mg/m^2 as a 1- to 3-hour infusion after the end of Taxotere infusion, then followed by 5-FU 750 mg/m^2/day as a continuous 24-hour infusion for 5 days after the end of cisplatin infusion on Day 1. This schedule was repeated every 3 weeks (1 cycle).

TC (n=76): Taxotere 85 mg/m^2 as a 1-hour infusion on Day 1 followed by cisplatin 75 mg/m^2 as a 1-3 hours infusion after the end of Taxotere infusion. This schedule was repeated every 3 weeks (1 cycle).

The primary endpoint was overall response rate (Complete+Partial). The overall response rate was greater in the TCF-treated group, 43% [95% CI: 32-55%] than in the TC-treated group, 26% [95% CI: 17-38%]. Based on these results, the TCF treatment was selected to be tested in the Phase 3 part of the study (Study TAX325A).

Study TAX325A was an open-label, prospective, multi-center, multi-national, parallel-group, randomized, comparative Phase 3 study in 445 patients with metastatic or locally recurrent gastric cancer previously untreated with chemotherapy for advanced disease. Patients were randomized to receive either of the following two treatments:

TCF (n=221): Taxotere 75 mg/m^2 as a 1-hour infusion on Day 1 followed by cisplatin 75 mg/m^2 as a 1- to 3-hour infusion after the end of the Taxotere infusion; then followed by 5-FU 750 mg/m^2/day as a continuous 24-hour infusion over 5 days on Day 1 after the end of the cisplatin infusion. The schedule was repeated every 3 weeks (1 cycle).

CF (n=224): Cisplatin 100 mg/m^2 as a 1- to 3-hour on Day 1 followed By 5-FU 1000 mg/m^2/day as a continuous 24-hour infusion for 5 days on Day 1 after the end of the cisplatin infusion on Day 1. This schedule was repeated every 4 weeks (1 cycle). The primary efficacy endpoint was Time to Progression (TTP), calculated from the day of randomization to the date of the first TTP event. A TTP event was defined as disease progression as determined by “Final Evaluation”, or death from any cause.

According to the Applicant, the observed median TTP was 5.6 months in the TCF-treated group [95% CI: 4.8-5.9 months] and 3.7 months [95% CI: 3.5-4.5 months] in the CF-treated group. The difference between the two treatments was statistically significant (*P*=0.0004) with a Hazard Ratio [HR] of 1.5 [95% CI: 1.2-1.8%] (see Table below).

Table 1 - Time to progression at the end of study

Parameter	TCF (n=221)	CF (n=224)
Median TTP (months)	5.6	3.7
95% CI (months)	[4.8-5.9]	[3.5-4.5]
P-value (Log-rank test)	0.0004	
HR (95% CI)	1.5 [1.2-1.8%]	

The secondary efficacy endpoint was overall survival (OS) defined as the time from the date of randomization to death from any cause. According to the Applicant, the observed median OS was 9.2 months for the TCF-treated group [95% CI: 8.4-10.6

months] and 8.6 months in the CF-treated group [95% CI: 7.2-9.5 months]. The difference between the two treatment groups was statistically significant (*P*=0.0201) with an HR of 1.3 [95% CI: 1.0-1.6%] (see Table below).

Table 2 – Overall survival at the end of the study

Parameter	TCF (n=221)	CF (n=224)
Median survival (months)	9.2	8.6
[95% CI] (months)	[8.4-10.6]	[7.2-9.5]
P-value (Log-rank test)	0.0201	
Hazard Ratio [95% CI]	1.3 [1.0-1.6%]	

In general, the two treatment groups were similar for treatment-emergent adverse events (TEAEs) for most grade 3-4, with the exception of diarrhea (TCF: 20%; CF: 8%), infection (TCF: 13%; CF: 7%), and neurosensory (TCF: 8%; CF: 3%). The treatment groups had comparable grade 3-4 TEAEs for lethargy (TCF: 18%; CF: 14%), stomatitis (TCF: 21%; CF: 27%), anorexia (TCF: 10%; CF: 9%), nausea (TCF: 14%; CF: 17%), and vomiting (TCF: 15%; CF: 17%).

Based on the results of this study, the Applicant updated the current package insert for Taxotere (see Appendix 1).

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint used in the pivotal Phase 3 part of Study TAX325 was the comparison of the Time to Progression (TTP) for the triple combination (Taxotere +cisplatin+5-FU) versus the double combination (cisplatin+5-FU) in the intent-to-treat population. The basis for selecting TTP as a primary endpoint in the pivotal Phase 3 study is that TTP is a robust endpoint to demonstrate efficacy with the advantage of evaluation of the true effect of the tested drugs without interference of subsequent therapies.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Plasma concentrations of docetaxel, unbound platinum, and 5-FU were measured in the pharmacokinetic Study XRP6976E/1001 using validated assay methods (see Section 2.6 of this review).

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy*?*

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.2.4.3 Does this drug prolong the QT or QTc interval?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.2.5 What are the PK characteristics of the drug and its major metabolite?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.2.5.1 What are the single dose and multiple dose PK parameters?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.2.5.3 What are the characteristics of drug absorption?

[NOT APPLICABLE]

2.2.5.4 What are the characteristics of drug distribution?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.2.5.6 What are the characteristics of drug metabolism?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.2.5.7 What are the characteristics of drug excretion?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.2.5.9 How do the PK parameters change with time following chronic dosing?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups?

2.3.2.1 Elderly
2.3.2.2 Pediatric patients
2.3.2.3 Gender
2.3.2.4 Race
2.3.2.5 Renal impairment
2.3.2.6 Hepatic impairment

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?

[None]

2.3.2.7 What pregnancy and lactation use information is there in the application?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Docetaxel is a substrate of CYP 3A4 and 3A5 enzymes. Neither cisplatin nor 5-FU is a substrate of any CYP enzymes.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

The proposed label specifies that Taxotere (docetaxel) is to be administered in combination with cisplatin and 5-FU for the first-line treatment of patients with advanced gastric adenocarcinoma. In support of this new indication, the Applicant submitted a separate PK study (Study XRP6976E/1001) to examine the potential for drug-drug interactions between docetaxel, cisplatin, and 5-FU when given in combination to patients with solid tumors. [Note: Tumor type has no effect on the pharmacokinetics of docetaxel (PDR®)].

Study XRP6976E/1001 was an open-label, single-center, randomized, two-period, crossover study in 12 patients with solid tumors (6 males and 6 females). Patients were randomized (1:1) to receive either the double combination of docetaxel+ cisplatin in Cycle 1 followed by the triple combination, docetaxel+cisplatin+5-FU in Cycle 2. Patients were then crossed over to the alternate regimen in each cycle. Each treatment cycle lasted 3 weeks. The double combination consisted of docetaxel 75 mg/m² given as a 1-hour infusion on Day 1 followed by cisplatin 75 mg/m² as a 3-hour infusion 15 minutes after the end of docetaxel infusion. The triple combination consisted of docetaxel 75 mg/m² given as a 1-hour infusion on Day 1 followed by cisplatin 75 mg/m² as a 3-hour infusion 15 minutes after the end of docetaxel infusion then followed by 5-FU 750 mg/m² as a continuous infusion for 5 days immediately after the end of cisplatin infusion. Blood samples for PK analysis were collected at Cycles 1 and 2 from each patient for up to 24 hours after the end of 1-hour docetaxel infusion, up to 21 hours after the end of 3-hour cisplatin infusion, and up to 96 hours during and up to 2 hours after the end of the 5-day 5-FU infusion. Plasma samples were assayed for docetaxel, unbound platinum, and 5-FU using validated assay methods (see Section 2.6 of this review).

The PK parameters of docetaxel, unbound platinum, and 5-FU were estimated using non-compartmental methods. In addition, individual docetaxel total clearance (CL) was estimated using POSTHOC (Bayesian) analysis and the previously published population PK model [Bruno R et al., A population pharmacokinetic model for docetaxel (Taxotere): model building and valiation. J Pharmacokinet Biopharm 1996;24:153-72]. According to this analysis, the population PK parameters were fixed at the values reported in the population PK model, and only the individual CL values were estimated (MAXEVALS=0 in NONMEM).

Results:

A summary of the non-compartmental PK parameters for docetaxel, unbound platinum, and 5-FU is shown in the Tables and Figures below.

Effect of 5-FU on Docetaxel and Cisplatin:

Table 3 - Arithmetic Mean±SD (%CV) Non-Compartmental PK Parameters for Docetaxel Following Administration of 75 mg/m² Docetaxel over 1-Hour Infusion

Parameter	TC (n=12)	TCF (n=12)
C_{max} (ng/ml)	2717±591 (22%)	2706±715 (26%)
AUC_{inf} (ng•h/ml)	3518±733 (21%)	3442±970 (28%)
Non-Compartment CL (L/h/m²)	22.2±5.6 (25%)	23.2±6.0 (26%)
Bayesian CL (L/h/m²)	20.6±6.7 (32%)	22.4±6.8 (30%)
t½ (h)	11.7±7.1 (60%)	11.8±11.5 (97%)
V_{ss} (L/ m²)	103±81 (78%)	113±125 (110%)

Table 4 – Docetaxel Treatment Comparison

Parameter	Treatment	N	Bayesian Geometric Mean	%CV	TCF/TC Ratio (%)	90% Confidence Interval
CL ($L/h/m^2$)	TCF	12	21.6	30%	110%	98 – 123%
	TC	12	19.6	33%		

There was no statistically significant difference in docetaxel plasma clearance (CL) when given in combination with cisplatin and 5-FU (TCF) and when given in combination with cisplatin only (TC). The 90% confidence interval for CL values was between the acceptance criteria of 80-125%.

Docetaxel mean plasma concentration/time profiles were comparable following the two treatment combinations (see Figure below).

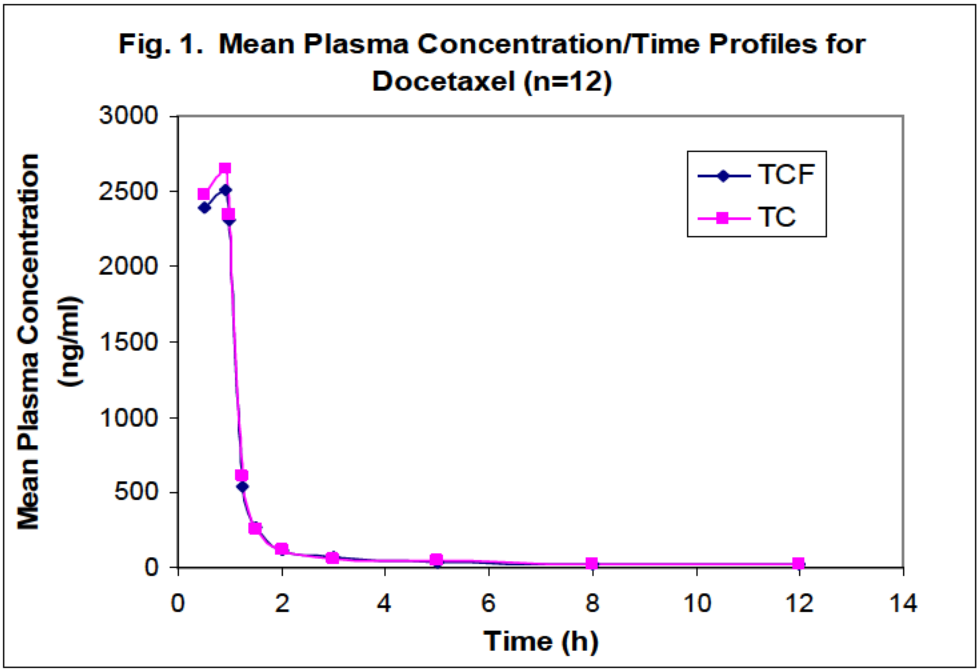


Table 5 - Arithmetic Mean ± SD (%CV) Non-Compartmental PK Parameters for Unbound Platinum Following Administration of 75 mg/m² Cisplatin over 3-Hour Infusion

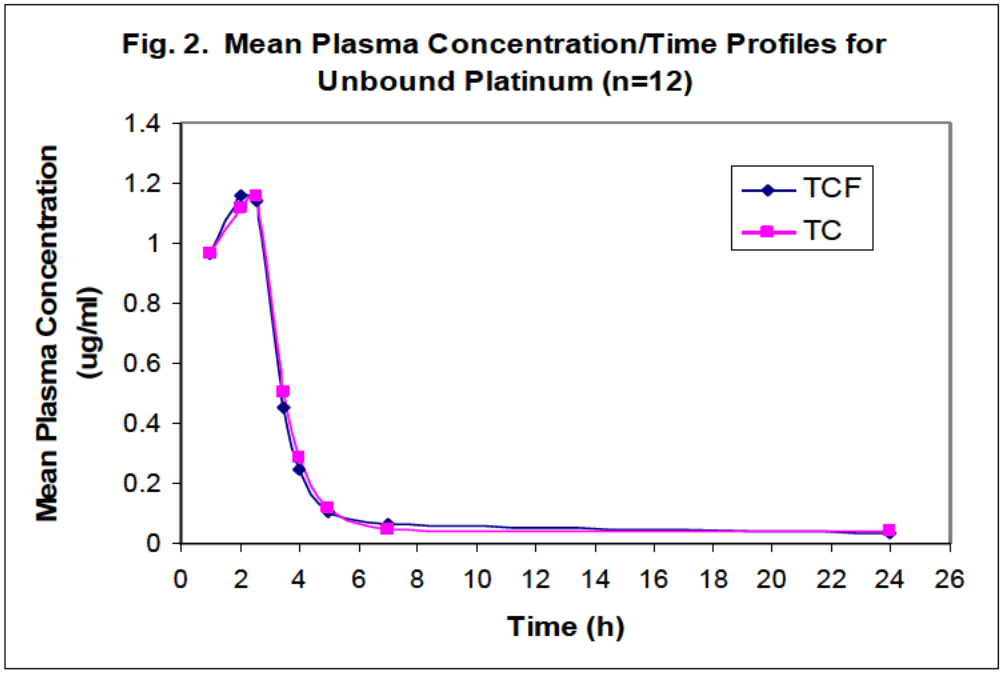
Parameter	TC (n=12)	TCF (n=12)
C_{max} (µg/ml)	1.2±0.2 (16%)	1.2±0.2 (15%)
AUC_{inf} (µg•h/ml)	4.7±1.2 (25%)	4.4±1.1 (24%)
CL (L/h/m^2)	16.7±4.1 (24%)	17.7±4.7 (26%)
t½ (h)	8.7±8.1 (93%)	6.2±4.9 (79%)
V_{ss} (L/m^2)	88±76 (86%)	65±40 (61%)

Table 6 – Unbound Platinum Treatment Comparison

Parameter	Treatment	N	Geometric Mean	CV (%)	TCF/TC Ratio (%)	90% Confidence Interval
CL (L/h/m^2)	TCF	12	17.3	26%	105%	88 – 125%
	TC	12	16.4	24%		

There was no statistically significant difference in CL of unbound platinum following either the TC or TCF combination. The 90% confidence interval for CL values was between the acceptance criteria of 80-125%.

Mean plasma concentration/time profiles of unbound platinum were comparable following the two treatment combinations (see Figure below).



Effect of Docetaxel and Cisplatin on 5-FU:

Table 7 - Arithmetic Mean ± SD (%CV) Non-Compartmental PK Parameters for 5-FU Following a Continuous Infusion of 750 mg/m² 5-FU for 5 Days

Parameter	TCF (n=12)
C_{ss} (ng/mL)	265±61 (23%)
CL ($L/h/m^2$)	121±39 (32%)
V_{ss} (L/m^2)	784±597 (76%)

In this study, the mean CL of 5-FU of 121 $L/h/m^2$ is within the range of previously-reported CL values for 5-FU as a monotherapy following continuous 24-hour infusion for 5 days at doses of 10-175 mg/kg and 300-500 mg/m^2 (CL= 32-243 $L/h/m^2$, n=2-28) [Diasio RB and Harris BE, Clinical pharmacology of 5-fluorouracil. Clin Pharmacokinet 16:215-237, 1989]. The mean CL of 5-FU in this study is also comparable to the mean 5-FU CL value when 5-FU was given in combination with docetaxel (CL=104±15 $L/h/m^2$, n=4) at the same dose (750 mg/m^2/day as a continuous 24-hour infusion for 5 days) [Neste EVD et al., A Phase 1 and pharmacokinetics study of docetaxel administered in combination with continuous intravenous infusion of 5-fluorouracel in patients with advanced solid tumors. Clin Cancer Res 6:64-71, 2000].

In conclusion, the results of this study indicate that 5-FU had no effect on the pharmacokinetics of docetaxel and cisplatin when the three drugs were given in combination to 12 patients with solid tumors. The combination of docetaxel and cisplatin had no effect on the pharmacokinetics of 5-FU.

In addition, published data [Millward MJ et al., Phase 1 trial of docetaxel and cisplatin in previously untreated patients with advanced non-small-cell lung cancer. J Clin Oncol 15:750-758,1997] indicate that the pharmacokinetics of a combination of cisplatin and docetaxel were consistent with those for single agents, suggesting no major pharmacokinetic interaction between both drugs when given in combination. The current package insert for Taxotere also indicates that the pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Dexamethasone (8 mg) was administered on Days 1 and 2 of each treatment cycle to reduce the risk of allergic reactions and fluid retention. In case of febrile neutropenia or neutropenia lasting > 5 days in Cycle 1, granulocyte colony-stimulating factor (G-CSF) support was to be administrated. Prophylactic antiemetics (e.g., granisetron, ondansetron), antiallergics, antibiotics were to be administered.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

Refer to the original NDA 20-449 (Submission Date: 27-July-1994)

2.5 General Biopharmaceutics [NOT APPLICABLE]

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

2.5.2.1.1 What data support or do not support a waiver of in vivo BE data?
2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?
2.5.4 When would a fed BE study be appropriate and was one conducted?
2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Docetaxel, unbound platinum from cisplatin, and 5-FU were the active moieties measured in plasma samples.

2.6.2 Which metabolites have been selected for analysis and why?

No metabolites for docetaxel and 5-FU were measured in plasma samples.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total (bound+unbound) drug concentrations of docetaxel and 5-FU were measured in plasma samples. Unbound platinum from cisplatin is an atom and it does not bind to plasma proteins.

2.6.4 What bioanalytical methods are used to assess concentrations?

The assays for docetaxel, unbound platinum, and 5-FU were validated according to the Food and Drug Administration guidance on Bioanalytical Method Validation (2001).

Docetaxel plasma concentrations were measured using a validated high performance liquid chromatography (HPLC) with ultraviolet (UV) detection [Loos WJ et al., Sensitive determination of docetaxel in human plasma by liquid-liquid extraction and reversed-phase high-performance liquid chromatography. J Chromatgr B Biomed Sci Appl 693:437-441, 1997]. Docetaxel and paclitaxel (used as an internal standard) are extracted from human plasma samples using n-butylchloride and acetonitril and then analyzed using HPLC with UV detection at 230 nm.

Unbound platinum plasma concentrations were measured using a validated flameless atomic absorption spectrometry [Kloft A, et al. Determination of platinum complexes in clinical samples by a rapid flameless atomic absorption spectrometry assay. Ther Drug Monit 21:631-637, 1999]. Platinum concentrations in plasma ultrafiltrates were measured with a Zeeman Atomic Absorption Spectrometer with an AS-72 autosampler (b) (4) The absorbance of atomized platinum was measured at 265 nm.

5-FU plasma concentrations were measured using a validated HPLC with UV detection [Loos WJ et al., Determination of 5-fluorouracil in microvolumes of human plasma by solvent extraction and high-performance liquid chromatography. J Chromatogr B Biomed Sci Appl 735:293-297, 1999]. 5-FU and 5-Chlorouracil (used as an internal standard) were extracted from plasma samples using ethylacetate and then analyzed by HPLC with UV detection at 266 nm.

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

Calibration curves for docetaxel were linear over the concentration range of 15-2000 ng/ml.

Calibration curves for unbound platinum were linear over the concentration range of 0.03-0.6 µg/mL. Plasma samples with unbound platinum concentrations higher than 0.6 µg/mL were diluted to cover the calibration range.

Calibration curves for 5-FU were linear over the concentration range of 50-1000 ng/mL.

2.6.4.2 What are the lower and upper limits of quantification (LLOQ)?

The LLOQ were 15 ng/mL, 0.03 µg/mL, and 50 ng/mL for docetaxel, unbound platinum, and for 5-FU, respectively.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

For **Docetaxel**: The within- and between-run precision at five tested Quality Control Sample concentrations were < 5.4%, while the average accuracy ranged from 96.5-102.1%.

For **Unbound Platinum**: The within- and between-run precision were <12.8%, while the average accuracy ranges from 94.8-102%.

For **5-FU**: The within- and between-run precision at quality control concentrations were < 6.3%, while the accuracy ranged from 98.8-104.1%.

3. OCPB Labeling Recommendations

[None]

Based on the results from the pharmacokinetic Study XRP6976E/1001, the Applicant included the following statement in the current package insert for Taxotere which is acceptable to OCPB:

The combined administration of docetaxel, cisplatin and 5-fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug.

4. Appendices

4.1 Proposed Package Insert

57 Pages Immediately Followith Withheld - b(4) Draft Labeling

4.2 Cover Sheet and OCPB Filing/Review Form

I. Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	20-449/SE1-035	**Brand Name**	Taxotere
OCPB Division (II, II, III)	Dpe1	**Generic Name**	Docetaxel
Medical Division		**Drug Class**	Taxenes
OCPB Reviewer	Sophia Abraham	**Indication(s)**	Advanced Gastric Adenocarcinoma
OCPB Team Leader	Brian Booth	**Dosage Form**	Injection
		Dosing Regimen	Docetaxel 75 mg/m^2 in combination with cisplatin 75 mg/m^2 and 5-FU 750 mg/m^2
Date of Submission	23-Sep-2005	**Route of Administration**	IV infusion
Estimated Due Date of OCPB Review	03-Jan-2006	**Sponsor**	Sanofi Aventis
PDUFA Due Date	25-Mar-2006	**Priority Classification**	1P
Division Due Date	04-Mar-2006		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
II. Patients-				
single dose:				

multiple dose:	**1**			
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
Renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments		
	"X" if yes	***Comments***
Application filable ?	**x**	
Comments sent to firm?	**NAI**	
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 20-449/SE1-035, OODP (Staten), DCP5 (Huang, Rahman, Booth, Abraham), CDR

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/s/

Sophia Abraham
3/9/2006 11:21:39 AM
BIOPHARMACEUTICS

Brian Booth
3/9/2006 02:56:16 PM
BIOPHARMACEUTICS

Shiew-Mei Huang
3/16/2006 10:41:07 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-449/S-035

OTHER REVIEW(S)

Division of Drug Marketing, Advertisement, and Communications

Enforcement Branch II

Internal Consult

****Pre-decisional Agency Information****

To: Qin Ryan, MD, Medical Officer, DODP

From: Joseph A. Grillo, Regulatory Review Officer, DDMAC
Iris Masucci, Labeling Reviewer, DDMAC

CC: Ann Staten, Project Manager, DODP

Date: March 1, 2006

Re: NDA # 20-449
MACMIS # 14094
Taxotere® (docetaxel) Injection Concentrate
Comments on draft Labeling

In response to your consult request via email on October 26, 2005, we have reviewed the draft Labeling and offer the following comments:

(b) (4)

1 Page Immediately Following Withheld - b(4) Draft Labeling

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/s/

Joseph Grillo
3/1/2006 10:23:59 AM
DDMAC REVIEWER

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2005.002.A.00170
APPLICATION TYPE	NDA
SUBMISSION NUMBER	20449
SUBMISSION CODE	035
LETTER DATE	September 23, 2005
STAMP DATE	September 26, 2005
PDUFA GOAL DATE	March 25, 2006
DATE OF CONSULT REQUEST	November 4, 2005
REVIEW DIVISION	DODP
MEDICAL TEAM LEADER	Amna Ibrahim
REVIEW DIVISION PM	Ann Staten
SEALD REVIEWER(S)	William Pierce/Laurie Burke
REVIEW COMPLETION DATE	March 1, 2006
ESTABLISHED NAME	Taxotere
TRADE NAME	Docetaxel
THERAPEUTIC CLASS	Cytotoxic
APPLICANT	Aventis Pharmaceuticals, Inc.
PRIORITY DESIGNATION	S
ENDPOINT(S) CONCEPT(S)	Time to worsening in performance status, clinical benefit, "quality of life"
INSTRUMENT(S)	EORTC QLQ-C30; Karnofsky Performance Status (KPS); EQ-5D Health State Thermometer
FORMULATION	Concentrate for Injection, 20mg and 80mg
DOSING REGIMEN	75 mg/m2 Taxotere as 1 hour continuous infusion followed by 75mg/m2 1-3 hour infusion cisplatin on day 1; 750mg/m2 per day infusion of 5-fluorouracil day 1-5 starting at end of cisplatin infusion (Repeat treatment every 3 weeks)
INDICATION	In combination with cisplatin and 5-fluorouracil for the treatment of advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction who have not received prior chemotherapy
PATIENT POPULATION	≥18 years of age, KPS > 70 with histologically proven gastric adenocarcinoma and adenocarcinoma of the esophagogastric junction

STUDY ENDPOINT REVIEW

Table of Contents

1 EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Drug Oncology Products (DODP) regarding the adequacy of study endpoints to support labeling statements for Taxotere® in combination with cisplatin and 5- fluorouracil for the treatment of advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction who have not received prior chemotherapy for advanced disease. The review of NDA 20449 SN 035 data [1] and other documents identified that address the development and validation of the EORTC QLQ-C30 as a measure of time to worsening in "Global Quality of Life" and the Karnofsky Performance Status (KPS) as a component of the composite time to worsening "clinical benefits" measure (b) (4)

Conclusions and Key Findings:

Study 325A results fail to provide convincing evidence of treatment benefit favoring the Taxotere treatment arm of the study for the general concept of health-related quality of life (HRQL).[1] The EORTC QLQ-C30 was not adequately developed to measure any of the specific concepts implied by any of the domain or item scores generated by the EORTC QLQ-C30.

- Study XRP6976E/325A findings are based on unblinded treatment comparisons that do not adequately control for bias in favor of the experimental treatment.
- Results from EORTC QLQ-C30 Global Quality of Life domain or the Karnofsky Performance Scale (KPS) should not be used to support labeling claims for time to improvement in HRQL, "time to definitive deterioration of global health status" or worsening of performance status because there is no evidence that these measures are sufficiently developed to measure those general concepts nor that the instruments are sensitive enough to detect changes that patients would considered meaningful to deterioration in HRQL or physical function, respectively.

Conclusions and recommendations are based on the sources available for review. The Sponsor provided limited information for review. Additional information readily retrieved from PubMed and previous SEALD consults also was reviewed, when available, to better understand the development and validation of the proposed endpoint measures.

1 ***Health-related quality of life (HRQL)*** — A multidomain concept that represents the patient's overall perception of the impact of an illness and its treatment. An HRQL measure captures, at a minimum, physical, psychological (including emotional and cognitive), and social functioning. Claiming a statistical and meaningful improvement in HRQL implies: (1) that the instrument measures all HRQL domains that are important to interpreting change in how the study population feels or functions as a result of treatment; and (2) that improvement was demonstrated in all of the important domains. An HRQL instrument is a particular type of patient-reported outcome (PRO) instrument.

2 Pages Immediately Following Withheld - b(4)

(b) (4)

3 BACKGROUND (RELEVANT TO ENDPOINT ISSUES)

3.1 Product Information

Taxotere is an antineoplastic agent which blocks cells in the M phase of the cell cycle by interfering with microtubule structure and function.

3.2 Proposed Indication

This NDA is for an extension of the indication of Taxotere in combination with cisplatin and 5-FU for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

3.3 Study Design Summary

Study XRP6976E/325A was a multinational, open-label, randomized multicenter phase III (325A) study of docetaxel in combination with 5-fluorouracil and cisplatin compared to the combination of cisplatin and 5-fluorouracil in patients with metastatic or locally recurrent gastric cancer previously untreated with chemotherapy for advanced disease. The primary goal of the study was to detect a statistically significant increase in time to progression (TTP) of disease for

the test group (Taxotere® combined with cisplatin and 5-fluorouracil [TCF]) relative to the control group (cisplatin combined with 5-fluorouracil [CF]). Secondary endpoints included overall survival (OS), response rate (RR), time to treatment failure (TTF), duration of responses, safety profiles, quality of life (QoL), and disease-related symptoms.

Subjects were centrally randomized (1:1) and stratified for liver metastasis, prior gastrectomy, disease measurability, weight loss in prior 3 months, and investigational center.
Treatment was administered up to progression, unacceptable toxicities, or consent withdrawn. After documented progression, subjects were followed every 3 months until death. Subjects who discontinued their treatment but had not yet progressed were followed every 8 weeks, until documented progression and then every 3 months until death. Subjects were to be ≥18 years of age with histologically proven gastric adenocarcinoma, including adenocarcinoma of the esophagogastric junction and have a Karnofsky performance status (KPS) of >70.
Subjects were assessed for tumor response and progression (defined according to WHO criteria) every 8 ±1 weeks. [1]

3.4 EORTC QLQ-C30, EuroQoL EQ-5D, Karnofsky Performance Status (KPS) Background

The EORTC QLQ-C30 (version 3.0) is a cancer specific self administered core questionnaire comprised of 30 questions and provides a multi-dimensional assessment of health related quality of life. The sponsor extracted scale scores from the initial 30 items including five functional scales (Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, Social functioning), selected symptom scales, and the global health status/QoL scale. The scores of the scales were calculated per the scoring procedure defined in the EORTC QLQ-C30 Scoring Manual and range from 0 to 100 after linear transformation.

The KPS is an instrument that rates patients according to 11 levels ("%") of performance status. Each level is based on a combination of symptoms, activity, and need for assistance. 100% criteria are "Normal; no complaints; no evidence of disease." 0% criteria is "Dead." (See Appendix 4 for the full KPS scale.)

The EQ-5D is a self administered instrument comprised of five questions and a visual analog scale (health state thermometer) which represents a rating of the patient's health state today. The sponsor has reported results from the health state thermometer in this submission.

3.5 Health Related Quality of life and Clinical Benefit Endpoints

These instruments were completed every 8 (± 1) weeks until progression and every 3 months thereafter. The "primary" HRQL endpoint specified in the SAP was the Global health status / QoL scale of the EORTC QLQ-C30. The physical functioning, social functioning, appetite loss, pain and nausea/vomiting scales were defined as secondary parameters and the sponsor proposed that these were the most specific to the gastric cancer setting and the most sensitive to a potential treatment effect. The other secondary quality of life parameters comprising the other EORTC QLQ-C30 scales and the EQ-5D scales were analyzed for a descriptive purpose, in order to interpret more specifically the results of the primary analysis.[5]

The "clinical benefit" endpoints were defined as the following:

- (Primary)- Time to definitive worsening of Karnofsky performance status defined as a definitive decrease in performance status by at least one Karnofsky category compared to baseline.
- Time to definitive weight loss- actual weight reported in the CRF defined as a definitive decrease in weight by at least 5% compared to baseline. The analysis was also prespecified as an endpoint.
- Time to definitive worsening of appetite- The following scale was used:
    - During the past week, my appetite has been
        1. Very poor
        2. Poor
        3. Fair
        4. Good
        5. Excellent

    Worsening is defined as a decrease of appetite by at least 1 category compared to baseline.
- Pain-free survival using the NCIC-CTC grade 0 cancer pain at baseline as the interval from randomization to the appearance of grade 1 or greater cancer pain.
- Time to first cancer pain related opioid intake performed in patients with a baseline NCIC-CTC grade for cancer pain strictly below 3. Following NCIC-CTC cancer pain grade 3 definition, the date of event will be the date when an opioid intake is first reported in the same cycle as a cancer pain grade 3 or above.

3.6 Statistical procedures (relevant to this consult)

The prespecified HRQL endpoints were time from randomization until a definitive 5% deterioration event in the global quality of life domain from the EORTC QLQ-C30, time to 5% deterioration of the EORTC QLQ-C30 functional (physical and social), and symptom (nausea/vomiting, pain, and appetite loss) domains. A "definitive" decrease in a parameter (any single parameter) was defined as no later increase above the defined threshold observed within the course of the study before any further anticancer therapy.

Non-parametric confidence intervals (CIs) were calculated for the medians. Hazard ratios and corresponding 95% CIs were also calculated. TTP and OS were also compared between groups with the stratified log rank test and the Cox proportional hazards model. RR was analyzed using the chi-square test and selected safety endpoints were analyzed using Fisher's exact test. HRQL and clinical benefit time-to-event endpoints were analyzed similarly to secondary efficacy endpoints. The HRQL analyses was performed on the full analysis population.

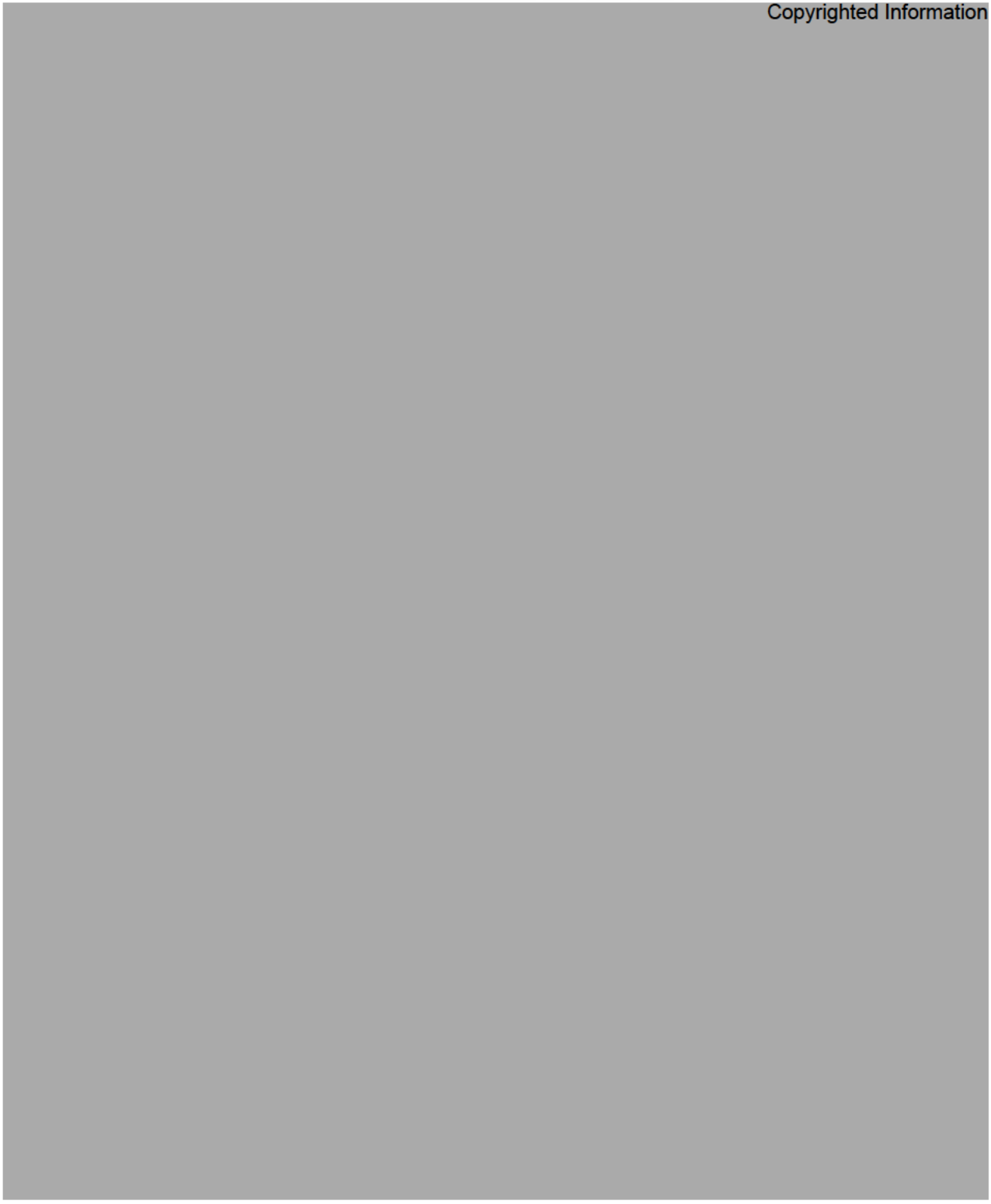
"Clinical benefit" analyses were performed on the full-analysis population using Kaplan-Meier analyses for the time to definitive worsening of Karnofsky Performance Status, time to definitive weight loss, time to definitive worsening of appetite, pain free survival, and time to first cancer pain related opioid intake. Unadjusted log rank tests and Cox models with score tests will be used to compare the treatment groups. Patients that have not worsened as of the cutoff date will be censored at the date of their last assessment before cutoff, or at the date of cutoff if assessments are available after cutoff. Patients receiving any further anti-tumor therapy before definitive worsening will be censored at the date of their last assessment before therapy.

Changes in Karnofsky performance scores were analyzed over time in two different ways

one with the scores collapsed into 2 categories at each cycle (100 *vs.* < 100) and one with the scores collapsed into 3 categories (100 *vs.* 70-90 *vs.* < 70). In each case, the data will be analyzed using generalized estimating equation methods to model whether the proportion of patients with a 100 scores changes over time between the treatment groups. [5]

4 APPENDICES

4.1 EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC) QLQ-C30 [6]



4.2 Karnofsky Performance Scale (KPS)

Definition	%	Criteria
Able to carry on normal activity and to work. No special care is needed	100	Normal; no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort, some signs or symptoms of disease
Unable to work. Able to live at home, care for most personal needs. A varying amount of assistance is needed	70	Cares for self. Unable to carry on normal activity or to do active work
	60	Requires occasional assistance, but is able to care for most of his needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospitalization is indicated although death not imminent
	20	Very sick; hospitalization necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

4.3 EuroQoL Group (EQ-5D)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own heal state today.

Mobility

- I have no problems in walking about ❑
- I have some problems in walking about ❑
- I am confined to bed ❑

Self-Care

- I have no problems with self-care ❑
- I have some problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

- I have no problems with performing my usual activities ❑
- I have some problems with performing my usual activities ❑
- I am unable to perform my usual activities ❑

Pain/Discomfort

- I have no pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have extreme pain or discomfort ❑

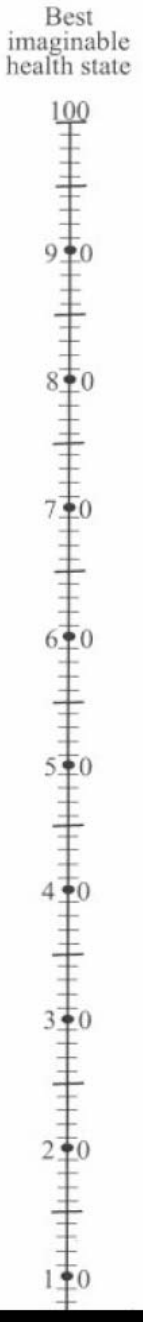
Anxiety/Depression

- I am not anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



5 REFERENCES

[1] NDA 20449, Serial No. 035, Taxotere® in combination with cisplatin and 5- fluorouracil for the treatment of advanced gastric adenocarcinoma. September 23, 2005. Aventis Pharmaceuticals, Inc.

[2] SEALD Endpoint Review. (b) (4)

[2] Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001 Jul;33(5):337-43.

[3] The EuroQol Group. EQ-5D. http://www.euroqol.org/web/. Accessed November 29, 2005.

[5] NDA 20449, Serial No. 035, Statistical Analysis Plan (SAP). September 23, 2005

[6] EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER. Group for research in Quality of Life. http://www.eortc.be/home/qol/default.htm. Accessed January 24, 2006.

drafted: 02/17/06 wp
comments: 02/21/06 js
revised: 02/21/06 wp
revised: 03/01/06 lb

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/s/

Laurie Burke
3/1/2006 03:50:46 PM
INTERDISCIPLINARY

PROJECT MANAGER REVIEW OF LABELING

NDA 20-449/S-035

Drug:	**Taxotere (docetaxel) Concentrate for Injection, 20 mg and 80 mg**
Applicant:	**Aventis**
Submission Date:	**September 23, 2005**
Receipt Date:	**September 25, 2006**

BACKGROUND:

On March 1, 2005, Aventis submitted a Changes Being Effected supplement containg FPL to the electronic document room that provides for changes to the package insert ADVERSE REACTIONS to include new adverse events, resulting from entries into the Aventis post-marketing surveillance database. In addition, a statement regarding a dose reduction for patients who experience stomatitis while receiving the adjuvant treatment for breast cancer has been added to the DOSAGE AND ADMINISTRATION/Dosage Adjustments During Treatment section.

This Changes Being Effected supplement 033 was approved on August 11, 2005.

On September 23, 2005, Aventis submitted supplement 035. This new supplement (S-035) provides for the following new proposed indication: "Taxotere in combination with cisplatin and 5-fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced (b) (4)

DOCUMENTS REVIEWED:

I compared the electronic Word version of the proposed draft package insert text submitted September 23, 2005 for S-035 against the electronic version of the final printed labeling for S-033 submitted on March 1, 2005.

REVIEW:

The only changes in the new version are those the sponsor proposes for this supplement.

CONCLUSION - RECOMMENDED REGULATORY ACTION:

The proposed draft package insert text submitted on September 23, 2005 with tracked changes is attached.

With the concurrence of the Medical and Clinical Pharmacology reviewers, this labeling may be approved (see their reviews).

__ ***{See appended electronic signature page}***_
Ann Staten, Regulatory Health Project Manager
___***{See appended electronic signature page}***_
Dotti Pease, Chief, Project Manager Staff

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/s/

Ann Staten

1/25/2006 02:51:13 PM

CSO

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE:	January 31, 2006
TO:	Ann Staten, Project Manager Qin Ryan, M.D., Medical Reviewer Division of Oncology Drug Products, HFD-150
THROUGH:	Leslie K. Ball, M.D. Branch Chief Good Clinical Practice Branch 2, HFD-47 Division of Scientific Investigations
FROM:	Lauren Iacono-Connors, Ph.D. Reviewer, Good Clinical Practice Branch II (HFD-47) Division of Scientific Investigations
SUBJECT:	Evaluation of Domestic Clinical Inspection
NDA:	20-449/S-035
APPLICANT:	Aventis Pharmaceuticals, Inc.
DRUG:	Taxotere® (docetaxel)
THERAPEUTIC CLASSIFICATION:	Priority Review
INDICATION:	Treatment of advanced gastric adenocarcinoma of the gastroesophageal junction in patients who have not received prior chemotherapy for advanced gastric cancer.
CONSULTATION REQUEST DATE:	October 26, 2005
DIVISION ACTION GOAL DATE:	March 26, 2006
PDUFA DATE:	March 26, 2006

I. BACKGROUND:

Drug Product:

Docetaxel (Taxotere®) is an antineoplastic agent that is currently approved for the treatment of breast cancer, non-small cell lung cancer and prostate cancer. This agent of the toxoid family corrupts cellular function by disrupting macromolecular/microtubular networks essential to cell division phases of mitosis and interphase. The sponsor, Aventis Pharmaceutical, Inc., seeks to add to the current indication of Taxotere® to include the treatment of gastric adenocarcinoma when used in combination with Cisplatin and 5-Fluorouracil.

The safety and efficacy data submitted under NDA 20449/S-035 to support the above indication are drawn from a single, prospective, multicenter, multinational, parallel-group, open-label, randomized comparative analysis, pivotal phase II/III study; XRP6976E/325.

Protocol XRP6976E/325A:

The phase III component of the study referred to as XRP6976E/325A, is entitled, "Open label, randomized multicenter Phase II/III study of Docetaxel in combination with Cisplatin or Docetaxel in combination with 5-Fluorouracil and Cisplatin compared to the combination of Cisplatin and 5-Fluorouracil in patients with metastatic or locally recurrent gastric cancer previously untreated with chemotherapy for advanced disease." The study seeks to demonstrate an increase in time to progression (TTP: the primary efficacy endpoint and objective) from 4 months in the control group to 6 months in the test group with 95% certainty. Therefore, the study had to record at least 325 events to achieve the target power of 95%. The secondary objective of increased overall survival (OS) time from 8 to 12 months between the control group and the study group required a minimum of 325 deaths. A total of 460 subjects were planned for enrollment to achieve both primary and secondary objectives.

The site selected for inspection is one of 72 study centers in 16 countries including the United States, and one of 22 domestic sites. The clinical investigator/site was selected for inspection because it represents the single largest accruing site within the United States with 55 subjects/total of 457 randomized subjects in this multicenter, international study. Of those 55 subjects randomized into XRP6976E/325 31 were enrolled into the phase III component of the study, protocol XRP6976E/325A, and are the target subjects for the inspection.

Inspection instructions:

The purpose of the inspection was to validate the reliability of the efficacy data generated at this site; integral in the conduct of a clinical investigator inspection in accordance with the Bioresearch Monitoring Compliance Program 7348.811. Data produced at this site is intended to be representative of the totality of efficacy data submitted to the agency in support of the new indication, NDA 20449/S-035, for Taxotere® (docetaxel).

II. RESULTS:

Name	City, State	Protocol	Inspection Date	EIR Received Date	Classification
Jaffer Ajani, M.D.	Houston, TX	XRP6976 E/325A	December 20-21, and 28-29, 2005	Pending from Dallas-DO	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

A. Protocol # XRP6976E/325A

1. **Jaffer Ajani, M.D.**
   MD Anderson Cancer Center
   Department of GI Oncology
   1515 Holcombe Blvd.
   Houston, TX 77030

   a. What was inspected?

   The study records of 8 of the 31 subjects enrolled into the phase III study were audited. In addition to the clinical investigator inspection Bioresearch Monitoring Compliance Program, 7348.811, the FDA investigator focused on the consistency between subject case report forms, source documents and sponsor data listings submitted to the agency in support of NDA 20449/S-035.

   b. Limitations of inspection: None

   c. General observations/commentary:

   In addition to the routine clinical investigator compliance program assessments, the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. With respect to the efficacy data, no discrepancies were observed. Source data including subject randomization, medical history, histopathology lab reports, tumor measurements, periodic assessments and response, CT scans, EKGs, QOL surveys, and labs were audited for 8 subjects. CRFs were assessed for data consistency with the source documents. SAE/AE reporting for each audited subject to source documents and verified. No discrepancies were observed. No Form FDA 483 was issued upon completion of the inspection.

   The EIR is currently being finalized and will be submitted to DSI upon completion. The observations noted above are based on the preliminary EIR and communication from the field investigator, Ms. Andrea Branche. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

   d. Assessment of data integrity: The data from Dr. Jaffer Ajani's site, associated with protocol XRP6976E/325A, submitted to the agency in support of efficacy supplement NDA 20449/S-035, is reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Observations noted above are based on a preliminary EIR and communications from the field investigator. No Form FDA 483 was issued upon completion of the inspection. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

The site inspected, that of Dr. Jaffer Ajani/MD Anderson Cancer Center, adhered to the applicable regulations governing the conduct of clinical investigations. The inspection of documents support that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol and signed informed consent forms. Therefore, the data submitted to the agency under NDA 20449/S-035 in support of a new indication appear to be acceptable.

Observations noted above are based on the preliminary EIR and communications from field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the EIR and the supporting inspection evidence and exhibits.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Lauren Iacono-Connors
1/31/2006 01:35:49 PM
UNKNOWN

Leslie Ball
2/1/2006 01:08:09 PM
MEDICAL OFFICER

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

FROM:	Joseph Gootenberg, Team Leader, DBOP
TO:	Qin Ryan, Medical Officer, DDOP
SUBJECT:	DDOP/OODP requested consult for sNDA 20449
SUBMIT DATE:	10-JAN-06
RECEIPT DATE	10-JAN-06
PRODUCT:	Taxotere
SPONSOR:	Aventis
DATE:	9-MAR-06

OODP/ DBOP CONSULT
sNDA: Taxotere for Advanced Gastric Cancer

sNDA:	**20449**
SUBMISSION DATE:	**25-SEPT-05**
PRODUCT:	**Taxotere**
SPONSOR:	**Aventis**
CLINICAL REVIEW:	**Joe Gootenberg**
CONSUMER SAFETY OFFICER	**Ann Staten**

sNDA TITLE: Taxotere for (b) (4) **Treatment of Gastric Carcinoma**

Material reviewed: DDOP provided briefing document accompanying consult request

DBOP comments to DDOP questions

DDOP consult discussion and question

(b) (4)

1 Page Immediatly Following Withheld-b(4) Draft Labeling

(b) (4)

[redacted]

3/9/06

Joseph E. Gootenberg M.D., Clinical Team Leader, DBOP, date

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/s/

Ann Staten

3/13/2006 07:04:05 AM

CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-449/S-035

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 20-449 SUPPL # 035 HFD # 150

Trade Name Taxotere

Generic Name docetaxel

Applicant Name sanofi-aventis

Approval Date, If Known 3-22-06

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-449 Taxotere (docetaxel)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

TAX325 and TAX325a

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

TAX325 and TAX325a

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 35,555	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 35,555	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Ann Staten, RD
Title: Senior Project Manager
Date: February 22, 2006

Name of Office/Division Director signing form: Robert L. Justice, MD
Title: Acting Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Robert Justice

3/22/2006 05:07:10 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 20-449 **Supplement Type (e.g. SE5):** SE1 **Supplement Number:** 035

Stamp Date: 9-26-05 **Action Date:** PDUF=3-25-05

HFD 150 **Trade and generic names/dosage form:** Taxotere (docetaxel)

Applicant: Aventis **Therapeutic Class:** 1

Indication(s) previously approved: Breast , NSCLC, Prostate

Number of indications for this application(s): 1

Is there a full waiver for this indication (check one)?

x Yes: Please proceed to Section A.

❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

❑ **Products in this class for this indication have been studied/labeled for pediatric population**
x Disease/condition does not exist in children
❑ **Too few children with disease to study**
❑ **There are safety concerns**
❑ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

❑ **Products in this class for this indication have been studied/labeled for pediatric population**
❑ **Disease/condition does not exist in children**
❑ **Too few children with disease to study**
❑ **There are safety concerns**
❑ **Adult studies ready for approval**
❑ **Formulation needed**
❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 20-449/S-035
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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/s/

Ann Staten

11/16/2005 10:45:47 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (*Division/Office)* DBOP, Karen Jones.			FROM: DDOP, Ann Staten for Qin Ryan, MD	
DATE 1-10-06	IND NO.	NDA NO. 20-449/S-035	TYPE OF DOCUMENT new sNDA	DATE OF DOCUMENT 9-23-05
NAME OF DRUG Taxotere (docetaxel)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE PDUFA date = 3-25-06
NAME OF SPONSOR: Aventis				

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL	PRE-NDA MEETING	RESPONSE TO DEFICIENCY LETTER (fax)
PROGRESS REPORT	END OF PHASE II MEETING	FINAL PRINTED LABELING
NEW CORRESPONDENCE	RESUBMISSION	LABELING REVISION
DRUG ADVERTISING	SAFETY/EFFICACY	ORIGINAL NEW CORRESPONDENCE
ADVERSE REACTION REPORT	PAPER NDA	FORMULATIVE REVIEW
MANUFACTURINGCHANGE/ADDITION	CONTROL SUPPLEMENT	■OTHER *(SPECIFY BELOW)*
MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER	CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER

III. BIOPHARMACEUTICS

DISSOLUTION	DEFICIENCY LETTER RESPONSE
BIOAVAILABILTY STUDIES	PROTOCOL-BIOPHARMACEUTICS
PHASE IV STUDIES	IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	SUMMARY OF ADVERSE EXPERIENCE
CASE REPORTS OF SPECIFIC REACTIONS*(List below)*	POISON RISK ANALYSIS
COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

9 CLINICAL	9 PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please see attached consult from Dr. Ryan and refer to the EDR for the sNDA. Jeff Summers was involved in the pre-sNDA meeting.

SIGNATURE OF REQUESTER Ann Staten	METHOD OF DELIVERY *(Check one)* ☐ FAX ■ DFS email
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

1 Page Immediately Following Withheld - b(4) Draft Labeling

Summary of sNAD 20449

Application Type	NDA Supplement
Submission Number	20449
Submission Code	S35
Submission location:	EDR
Submission Date	September 23, 2005
PDUFA Goal Date	March 26, 2006
Reviewer Name	Qin Ryan, MD, PhD
Team Leader	Amna Ibrahim
Established Name	Taxotere
Trade Name	Taxotere
Therapeutic Class	Antineoplastic
Applicant	Sanofi Avemtis
Priority Designation	P
Formulation	IV

Pivotal Study:
Study TAX 325 is an open label, phase 2/ 3 study comparing taxotere (75 mg/ m2 IV, D1,) cisplatin (75 mg/ m2 IV d1), and 5- FU (750 mg/ m2/ day x5 CIV), q3w, versus cisplatin (100 mg/ m2 d1) and 5- FU (1000 mg/ m2/ d CIV 5 days) q3w, in metastatic or locally recurrent gastric adenocarcinoma patients whose disease was evaluable or measurable.

Efficacy:
The final analysis is based on TTP (primary endpoint based on radiological response by WHO response criteria) and OS (secondary endpoint).

Endpoints	TCF	CF	HR/p value
Median TTP (Months)	5.6	3.7	1.473 / 0.0004
ITT Median Survival (months)	9.0	8.6	1.233/ 0.0539
FAP Median survival (months)	9.2	8.6	1.293 / 0.02
ORR	36.7	25.4	Logrank 1.226 / 0.31 χ^2 p = 0.01

FAP: Patients randomized and treated according to assigned therapy.

Safety:
Febrile neutropenia or neutropenic infection rate (%)

	TCF (%) n= 221	CF (%) n= 224
Neutropenia (grade3/4)	181 (82.3)	126 (56.8)
Neutropenic fever or infection with GCSF	5/41 (12.2)	3/20 (15.0)
Neutropenic fever or infection without GCSF	62/219 (28.3)	29/222 (13.1)

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/s/

Ann Staten
1/10/2006 03:30:21 PM
Doc room - please log this as a consult
to the division of biologic oncology products Thanks!

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 20-449	Efficacy Supplement Type SE-1	Supplement Number S-035	
Drug: Taxotere (docetaxel)		Applicant: Aventis	
RPM: Ann Staten		HFD-150	Phone # 301.796.1468

Application Type: **(X)** 505(b)(1) **( )** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **( )** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	**( )** Standard **(X)** Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	
❖ Special programs (indicate all that apply)	**(X)** None Subpart H **( )** 21 CFR 314.510 (accelerated approval) **( )** 21 CFR 314.520 (restricted distribution) **( )** Fast Track **( )** Rolling Review **( )** CMA Pilot 1 **( )** CMA Pilot 2
❖ User Fee Information	
• User Fee	**(X)** Paid UF ID number 3006165_____
• User Fee waiver	**( )** Small business **( )** Public health **( )** Barrier-to-Innovation **( )** Other (specify) _____
• User Fee exception	**( )** Orphan designation **( )** No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) **( )** Other (specify) _____
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	**( )** Yes **(X)** No

• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(x) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(x) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) (x) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).*	**( )** Yes **( )** No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	**( )** Yes **( )** No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	**( )** Yes, Application #_____ **(x)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	2-1-06;

General Information	
❖ Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X)** Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**(X)** None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	1-25-06 (PM review); DDMAC & SEALD 3-1-06; DBOP 3-9-06
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	n/a
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	n/a
• Applicant proposed	n/a
• Reviews	n/a
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	n/a
• Documentation of discussions and/or agreements relating to post-marketing commitments	n/a
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	1-30-98; 4-8-98
• Pre-NDA meeting (indicate date)	7-8-03; 4-4-05
• Pre-Approval Safety Conference (indicate date; approvals only)	3-2-06
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	Dr. Doroshow tcon 3-2-06
• 48-hour alert	n/a
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	n/a

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	X 3-1-06
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	n/a
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	n/a
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	n/a
❖ Statistical review(s) *(indicate date for each review)*	X 3-15-06
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X 3-16-06
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	n/a
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	2-1-06
• Bioequivalence studies	n/a
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	EA only
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	2-1-06
• Review & FONSI *(indicate date of review)*	n/a
• Review & Environmental Impact Statement *(indicate date of each review)*	n/a
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	n/a
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	n/a
❖ Nonclinical inspection review summary	n/a
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	n/a
❖ CAC/ECAC report	n/a

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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

/s/

Ann Staten

3/23/2006 09:50:06 AM

MEMORANDUM OF TELEPHONE CONVERSATION
DIVISION OF ONCOLOGY DRUG PRODUCTS

DATE: March 2, 2006 (10:30am-11:00am)

SUBJECT: NDA 20-449/S-035 Taxotere (docetaxel)

Discussion:

Dr. James Doroshow was consulted regarding the supplemental application for Taxotere in combination with cisplatin and 5-fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease. Dr. Doroshow concurred with the Division's decision to approve this application.

Ann Staten, RD
Regulatory Health Project Manager

Qin Ryan, MD
Medical Reviewer

Attachment: FDA review summary (handout)

BRIEFING DOCUMENT FOR SNDA 20449

TAXOTERE IN GASTRIC CANCER

Teleconference with ODAC Consultant

March 2, 2006

Proposed Indication:

Taxotere in combination with cisplatin and 5-fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

Proposed Dosing Regimen:

The dosing regimen as proposed by the applicant in the label is as follows:

(b) (4)

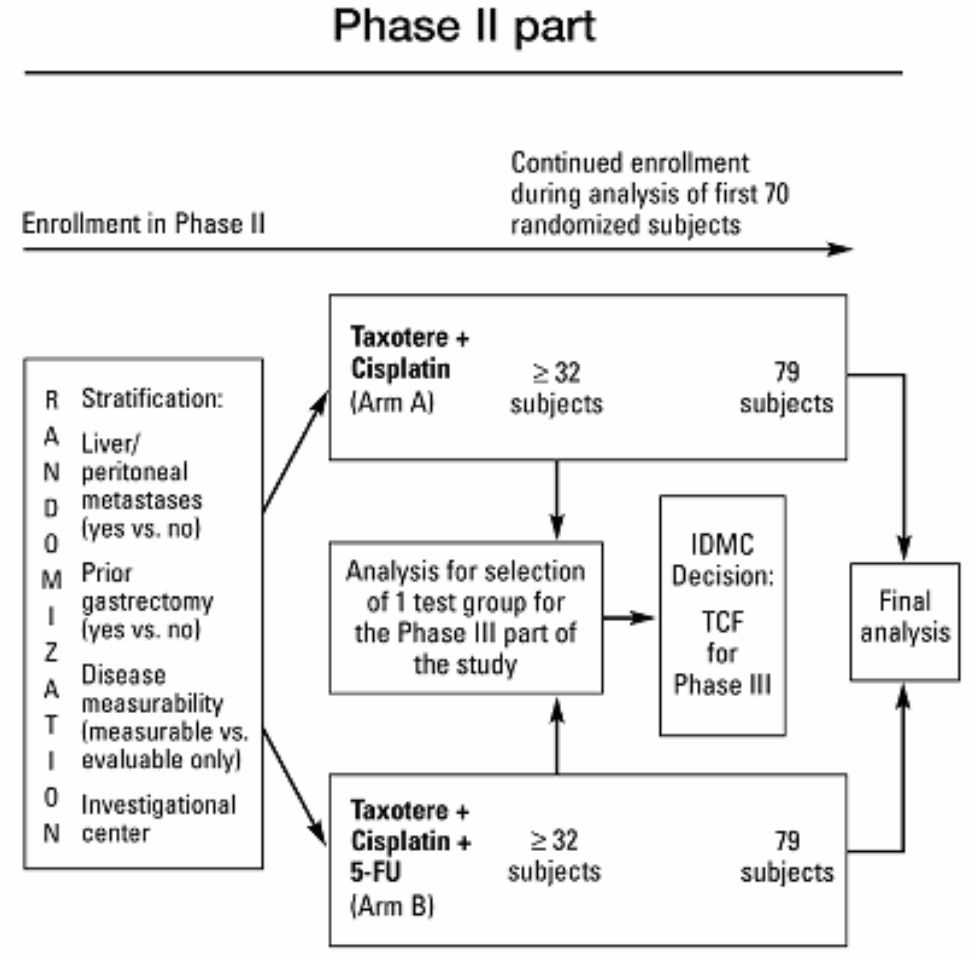
[redacted]

Summary of Clinical Findings

1. Brief Overview of Clinical Program

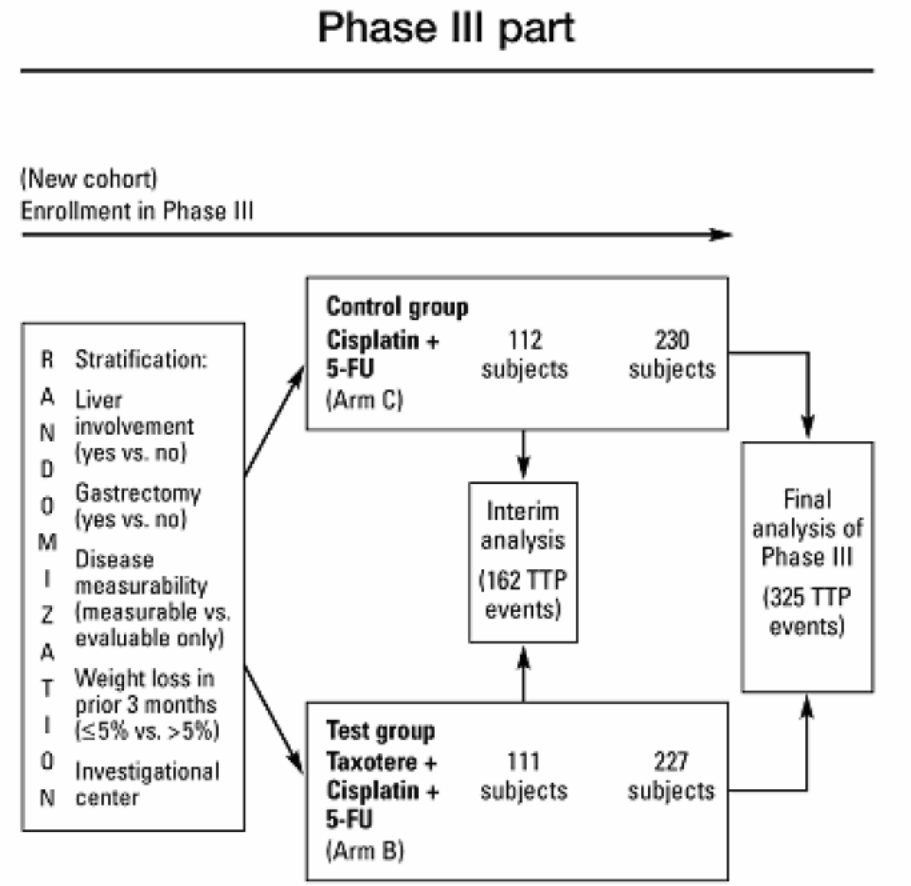
TAX 325 is the major trial submitted to support the efficacy and safety for this sNDA. It is a randomized multicenter, open-label phase II/III trial that was conducted in patients with locally advanced or metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who had not received prior chemotherapy for advanced disease. Patients who had received prior surgery and radiation were eligible. Prior adjuvant or neoadjuvant chemotherapy was considered acceptable (except for taxanes and over 300 mg/m^2 of cisplatin) if administered more than 12 months earlier. The study was stratified for the phase III part by liver involvement (yes/no), gastrectomy (yes/no) measurable or evaluable only disease, and weight loss ($\leq$ 5% / > 5%). The schema of the phase II and phase III parts of the protocol are given in figures 1 and 2 below.

Figure 1: TAX 325 Study Design



5- FU = 5- fluorouracil; TTP = Time to progression; IDMC = Independent data monitoring committee; TCF = Taxotere + cisplatin + 5-fluorouracil
Source: TAX 325 study report 5.1., Figure 1.

Figure 2: TAX 325a Study Design.



5- FU = 5- fluorouracil; TTP = Time to progression; IDMC = Independent data monitoring committee; TCF = Taxotere + cisplatin + 5-fluorouracil
Source: TAX 325a study report 3.2.3., Figure 1.

Two treatment regimens were evaluated in the phase II part. Based on the results of phase II, the investigational arm for the phase III portion of the study was chosen. See table 1.

Table 1: Treatment plan for TAX 325 and TAX 325a

Phase II	
Arm	**Regimens**
Arm A:	Docetaxel: 85 mg/m^2 IV administered first as a 1-hour infusion, day l every three weeks. CDDP: 75 mg/m^2, IV as a 3 to 4-hour infusion, day 1 every 3 weeks after the end of docetaxel administration
Arm B:	Docetaxel: 75 mg/m^2 IV administered first as a 1-hour infusion, day 1 every 3 weeks. CDDP: 75 mg/m^2, I.V. as a 3 to 4-hour infusion, day 1 every 3 weeks. 5-FU: 750 mg/m^2 CIV, day 1-5 every 3 weeks after the end of CDDP administration
Phase III:	
Arm B: TCF	Based on phase II data analysis, the testing arm (Arm B) used regimen of Phase II Arm B.
Arm C: CF	CDDP: 100 mg/m^2, day 1 as a 3 to 4-hour infusion every 4 weeks 5-FU: 1000 mg/m^2 CIV, day 1-5 every 4 weeks

The primary analysis was a comparison of TTP in the full analysis population (FAP) for the phase III part. Please see table 3 for the definition of patient populations analyzed. The sample size was calculated to demonstrate an increase in the median over all survival from 8 months to 12 months with a 95% power. Three hundred and twenty five deaths were required, using an unadjusted logrank test with a two-sided 5% significance level.

Definition of TTP

TTP was defined in the study report as time from randomization to disease progression, or death from any cause within 12 weeks of the last evaluable tumor assessment, or within 12 weeks of the first infusion of study drugs (for subjects with no evaluable tumor assessment after randomization).

A total of 457 subjects were randomized to the phase III part of the study in 39 months from November 1999 through January 2003; 227 subjects into the TCF treatment group and 230 subjects into the CF treatment group. The study was conducted in 72 centers and 16 countries. Of ITT population, twelve patients (6 in each arm) who did not receive any treatment after randomization were excluded from the final analysis population (FAP).

Table 2: Definition of Patient population used for Analysis.

Full Analysis Population (FAP)	all treated subjects analyzed in the treatment group to which they were assigned by randomization.
Per Protocol Population (PPP)	a subset of the FAP, consisted of subjects eligible and evaluable, for response without a major protocol deviation during the study.
Safety Population (SP)	all subjects treated with at least 1 dose of study therapy and analyzed according to the study medication actually received.
Intent to Treat (ITT)	all patients who randomized for TAX325a

Table 3: Subject populations

Populations	Number (%) of subjects		
	TCF	CF	Total
Randomized	227 (100)	230 (100)	457 (100)
Not treated	6 (2.6)	6 (2.6)	12 (2.6)
SP (Treated)	221 (97.4)	224 (97.4)	445 (97.4)
FAP	221 (97.4)	224 (97.4)	445 (97.4)
FAP	221 (100)	224 (100)	445 (100)
Eligible	191 (86.4)	206 (92.0)	397 (89.2)
Evaluable for response	185 (83.7)	184 (82.1)	369 (82.9)
PPP	170 (76.9)	178 (79.5)	348 (78.2)

FAP = Full analysis population; PPP = Per- protocol population; CF = Cisplatin + 5- fluorouracil
Data source: TAX 325a study report Appendix C. 1.1, Table 1.01.

2 Efficacy

Approximately 75% patients had progressed or died within 12 weeks of the last tumor evaluation by the cut-off date. TTP in the FAP was prolonged significantly in favor of TCF compared to CF with a hazard ratio of 1.473 [1.189-1.825] and p = 0.0004 (unstratified log rank). It was associated with a 2- month improvement in the median TTP (from 3.7 months for the CF group to 5.6 months for the TCF group). The end of study result, as well as the protocol-specified “325 events” result both met the nominal 0.0487 boundary set for the final analysis and confirm this conclusion. Please see table 4 and Figure 3.

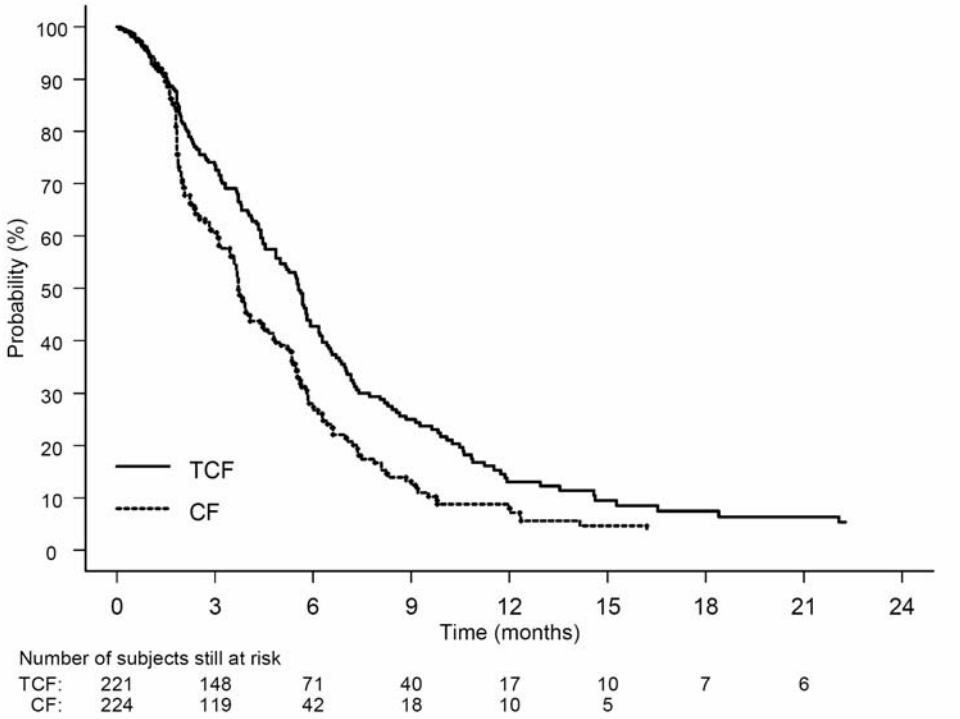
At the request of the clinical team, several sensitivity analyses were conducted by the applicant and the FDA statistical reviewer for TTP (this time defined as tumor progressions only, censored at last tumor evaluation) in the ITT and FAP population. Sensitivity analyses were also conducted for PFS (disease progressions and deaths by the last tumor evaluations) in the FAP and ITT populations. The results of these analyses remained in favor of the Taxotere combination arm.

Table 4: Time to progression - end of study (FAP)
Applicant table

Event/parameter	Number (%) of subjects	
	TCF (N=221)	CF (N=224)
TTP events	167 (75.6)	174 (77.7)
Documented disease progression	149 (67.4)	155 (69.2)
Died	18 (8.1)	19 (8.5)
Censored subjects	54 (24.4)	50 (22.3)
Lost to follow-up for TTP	16 (7.2)	12 (5.4)
No event at cut-off date	16 (7.2)	18 (8.0)
Further therapy	22 (10.0)	20 (8.9)
25th percentile	2.7	1.9
Median TTP (months)	5.6	3.7
95% CI (months)	[4.86-5.91]	[3.45-4.47]
75th percentile	9.1	6.3
6-month estimate	42.7%	27.4%
P-value (Log-rank test)	0.0004	
Hazard ratio[a] (95% CI)	1.473 [1.189-1.825]	
Risk reduction	32.1%	

a. Value > 1 favors TCF.

Figure 3: Time to progression – Kaplan- Meier curve – end of study (FAP)



TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population
Data source: TAX 325a study report, Appendix C. 2.1, Figure 4.15.

Table 5: FDA's Untratified Standard TTP and PFS Analyses (FAP and ITT)

Analysis	Population	P value	HR (CF/TCF)	95 CI
TTP	FAP	0.0002	1.526	1.2163-1.9145
	ITT	0.0002	1.534	1.2229-1.9235
PFS	FAP	0.0039	1.343	1.0975-1.6427
	ITT	0.0096	1.2990	1.0644-1.5855

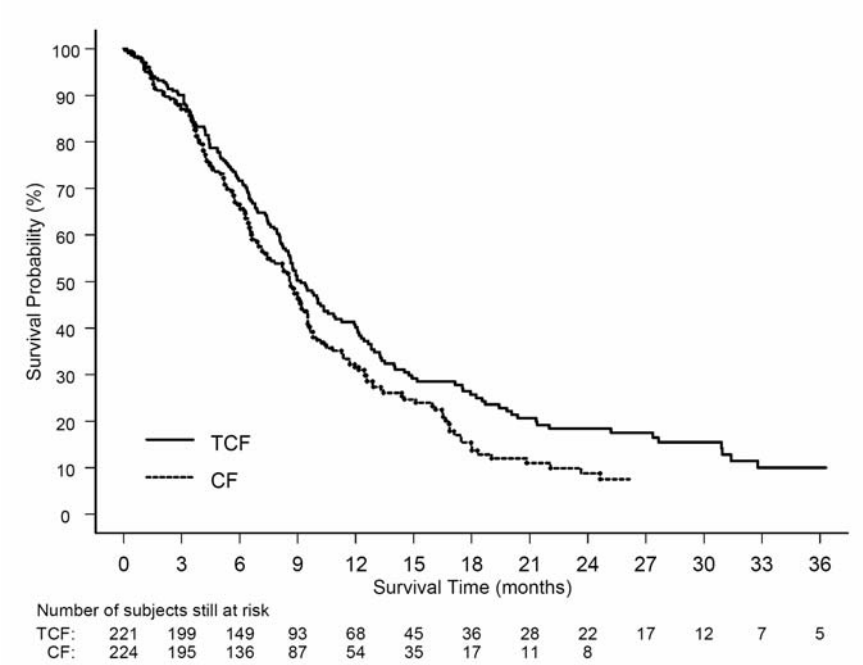
Overall survival (OS) was statistically better in the TCF arm (unstratified log-rank test, P= 0.0201) for the FAP population and a strong trend was observed in favor of the TCF arm for ITT population. The median survival was 9.2 months in the TCF arm, compared with 8.6 months on the CF arm for the FAP. This improvement in OS occurred despite the higher rate of post-study chemotherapy in the control arm (CF group: 41.1% including 8.5% who received Taxotere vs. TCF-group: 32.1%).

Table 6: Overall survival - end of study (FAP)

Event/parameter	Number (%) of subjects	
	TCF (N=221)	CF (N=224)
Survival event (deaths)	162 (73.3)	172 (76.8)
Censored subjects	59 (26.7)	52 (23.2)
Lost to follow-up	1 (0.5)	0 (0)
No event by cut-off date	58 (26.2)	52 (23.2)
25th percentile	5.5	4.5
Median survival (months)	9.2	8.6
[95% CI] (months)	[8.38-10.58]	[7.16-9.46]
75th percentile	18.5	14.5
1-year estimate	40.2%	31.6%
2-year estimate	18.4%	8.8%
P-value (Log-rank test)	0.0201	
Hazard ratio[a] [95% CI]	1.293 [1.041-1.606]	
Risk reduction	22.7%	

a. Value > 1 favors TCF.
TCF = Taxotere + cisplatin + 5- fluorouracil; CF = Cisplatin + 5- fluorouracil; FAP = Full analysis population; CI = Confidence interval
Data source: Appendix C. 2.1, Table 4.32 and Figure 4.33.

Figure 4: Overall survival - Kaplan- Meier curve - end of study (FAP)



TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population
Data source: TAX 325a study report, Appendix C. 2.1, Figure 4.33.

Table 7: Summary of end of study OS analyses

Population	Log-rank test	*P*-value	Hazard ratio[a]	95% CI
FAP	**Unstratified**	**0.0201**	**1.293**	**[1.041 –1.606]**
FAP	Stratified[b]	0.0123	1.333	[1.064-1.671]
All randomized	Unstratified	0.0539	1.233	[0.996-1.527]
All randomized	Stratified[b]	0.0320	1.275	[1.021-1.593]

a Value > 1 favors TCF.
b Stratified on liver metastasis (yes, no), prior gastrectomy (yes, no), disease measurability (measurable, evaluable-only) and weight loss in prior 3 months (≤ 5%, > 5%) as specified at randomization.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population; OS = Overall survival; CI = Confidence interval

Tumor Response Rate was higher in the TCF group compared to the CF group (36.7% versus 25.4%, respectively) in the evaluable population. However, there was no statistically significant difference noted in the duration of response between the two arms. Please see table 9.

Table 8: Best overall response

Responses	Number (%) of subjects			
	FAP		PPP	
	TCF	CF	TCF	CF
N	**221 (100)**	**224 (100)**	**170 (100)**	**178 (100)**
Overall RR (CR+PR)	**81 (36.7)**	**57 (25.4)**	**78 (45.9)**	**55 (30.9)**
95% CI for overall response rate	[30.3%-43.4%]	[19.9%-31.7%]	[38.2%-53.7%]	[24.2%-38.2%]
P-value (Chi square test)	0.0106		0.0040	
Complete response	4 (1.8)	3 (1.3)	3 (1.8)	2 (1.1)
Partial response	77 (34.8)	54 (24.1)	75 (44.1)	53 (29.8)
No change/stable disease	67 (30.3)	69 (30.8)	63 (37.1)	68 (38.2)
Progressive disease	37 (16.7)	58 (25.9)	29 (17.1)	55 (30.9)
Not evaluable	36 (16.3)	40 (17.9)	NA	NA

TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population; PPP = Per-protocol population; RR = Response rate; CR = Complete response; PR = Partial response; CI = Confidence interval; NA = Not applicable
Data source: TAX 325a study report, Appendix C. 2.1, Tables 4.40 and 4.41.

3 Safety

The safety population consisted of 445 patients who received treatment; 221 in the Taxotere combination arm and 224 in the control arm (Tables 2 and 3). Baseline signs and symptoms were present in 84 % patients and 26.5% were grade 3 or 4 toxicities. These had a balanced distribution in the two treatment groups. These baseline signs and symptoms were not counted in the treatment-emergent AEs (AEs). Certain toxicities such as neutropenia, infection, diarrhea, and neurosensory toxicity were increased in the TCF arm.

Forty one percent of the TCF-treated subjects and 36% of CF-treated subjects required dose reductions. The median relative dose intensities achieved in both treatment groups was about 90% for all drugs. Total treatment duration tended to be longer in the TCF treatment group (median 19 weeks) compared to the CF treatment group (16 weeks).

Treatment emergent AEs (AEs), regardless of relationship to study medication, were observed in all TCF-treated subjects and in all but 3 CF-treated subjects, and in most treatment cycles for both treatment groups. Among the most frequent AEs (frequency > 10%) regardless of relationship to study medication, diarrhea, neurosensory, infection and fever in the absence of infection, and alopecia, were greater in the TCF treatment group than the CF treatment group.

NCIC-CTC grade 3-4 AEs, regardless of relationship to study medication, were experienced by 81.4% of TCF-treated subjects and 75.4% of CF-treated subjects. The

most frequently (> 10%) observed grade 3-4 AEs in the TCF treatment group, regardless of relationship to study medication, were cancer pain (37.1%), first cycle neutropenia (27.3%), lethargy (21.7%), stomatitis (20.4%), diarrhea (20.4%), nausea (16.3%), anorexia (15.8%), vomiting (14.9%), infection (14.9%). The most frequent (>10%) grades 3-4 AEs observed in the CF treatment group, regardless of relationship to study medication, were cancer pain (36.2%), stomatitis (26.8%), nausea (19.2%), vomiting (19.2%), lethargy (18.3%), and anorexia (13.4%).

Although a higher incidence of grade 3-4 AE and SAE was seen in the TCF treatment group, the AE related mortality rate were similar in the treatment groups, with 20 (9%) for TCF-treated subjects and 26 (12%) for CF-treated subjects. The leading cause of AE related death were infection, which was fairly balanced between the two arms (3% for both arm in SP). In addition, the death within 60 days of randomization was 6.8% for TCF-treated subjects and 8.9% of CF-treated subjects. The frequency of deaths within 30 days of last administration of study medication was similar to the death due to AES, with 23 (10.4%) deaths in the TCF treatment group, and 19 (8.5%) deaths in the CF treatment group. In contrast, deaths occurring beyond 30 days of the last administration of study medication were more frequent in the CF treatment group (154/224, 68.8%), and were usually attributed to malignant disease (64.7%, n = 224), comparing to TCF arm (140/221, 63.3%) and 129 death due to PD (58.4%, n=221).

More treatment cycles on the TCF arm than that of CF arm were interrupted (10.8% vs. 4.5%), discontinued (26.7% vs 19%), dose reduction (40.7% vs 35.7%), treatment delay (40.7% vs 27.1%), or had treatment delays with dose reduction (9.5% vs 5.4%). There were no treatment modifications due to myelosupression. The most frequent causes for treatment discontinuation were GI toxicities, flu-like symptoms and neurosensory toxicity.

Within the TCF treatment group, infection, fever in the absence of infection, GI toxicities, and neurosensory toxicity were key AEs impacting the incidence of TE-SAE, discontinuation, or non-malignant death.

Although neutropenia observed at any given cycles were 95% (all grade) and 82.3% (grade 3/4) for TCF arm vs. 83.3% (all grade) and 56.8% (grade 3/4) for CF arm, secondary GCSF prophylaxis were used in less than 20% of subjects (18.6 for TCF and 8.9 for CF) and 10.0% of TCF cycles and 3.3% of CF cycles.

Table 9: Febrile neutropenia and neutropenic infection in evaluable subjects (SP)

	Number (%) of subjects					
	Regardless of G-CSF		With prophylactic G-CSF		Without prophylactic G-CSF	
	TCF	CF	TCF	CF	TCF	CF
Evaluable subjects	**220 (99.5)**	**222 (99.1)**	**41 (18.6)**	**20 (8.9)**	**219 (99.1)**	**222 (99.1)**
Regardless of relationship						
Febrile neutropenia	36 (16.4)	10 (4.5)	4 (9.8)	0 (0)	33 (15.1)	10 (4.5)
Neutropenic infection	35 (15.9)	23 (10.4)	1 (2.4)	3 (15.0)	34 (15.5)	21 (9.5)
Febrile neutropenia or neutropenic infection	66 (30.0)	30 (13.5)	5 (12.2)	3 (15.0)	62 (28.3)	29 (13.1)
Related to study medication						
Febrile neutropenia	35 (15.9)	8 (3.6)	4 (9.8)	0 (0)	32 (14.6)	8 (3.6)
Neutropenic infection	31 (14.1)	20 (9.0)	1 (2.4)	3 (15.0)	30 (13.7)	18 (8.1)
Febrile neutropenia or neutropenic infection	63 (28.6)	27 (12.2)	5 (12.2)	3 (15.0)	59 (26.9)	25 (11.3)
Death from febrile neutropenia[a] or neutropenic infection[a]	5 (2.3)	7 (3.2)	0 (0)	1 (5.0)	5 (2.3)	6 (2.7)

a Regardless of relationship to study medication.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population; G-CSF = Granulocyte colony-stimulating factor
Data source: Appendix C.3.1, Tables 7.01, 7.02, and 7.03.
Note: evaluable subjects: denominator is safety population

Table 10: First Cycle Neutropenia, Neutropenic Fever, and Infection (Evaluable Population)

Treatment/ Parameter	Number (%) of patients					
	Total evaluable	Grade 1	Grade 2	Grade 3	Grade 4	Any
TCF						
Neutropenia	220 (100)	23 (10.5)	30 (13.6)	40 (18.2)	60 (27.3)	153 (69.5)
Febrile Neutropenia	220 (100)	-	-	-	15 (6.8)	15 (6.8)
Neutropenic infection	220 (100)	-	-	4 (1.8)	11 (5.0)	15 (6.8)
CF						
Neutropenia	222 (100)	33 (14.9)	44 (19.8)	36 (16.2)	34 (15.3)	147 (66.2)
Febrile Neutropenia	222 (100)	-	-	-	7 (3.2)	7 (3.2)
Neutropenic infection	222 (100)	-	-	3 (1.4)	8 (3.6)	11 (5.0)

Data source: TAX325a data sets

Grade 4 neutropenia, neutropenic fever and neutropenic infection observed on TCF arm during the first cycle are almost two fold to that of CF arm, whereas the grade 1-3 neutropenia and grade 3 neutropenic infection were comparable between the two arms.

4 Special Populations

Subjects at or over the age of 65 years appeared to be more prone to developing infections in this study. In the TCF treatment group, 21.9% of subjects over the age of 65 years developed grade 3-4 infection, regardless of relationship to study drug, compared to 14.4% of subjects under the age of 65 years. The majority of these grade 3-4 infections were observed during neutropenic episodes. The elderly age group may thus particularly benefit from strategies that mitigate the risk of neutropenic infection.

Questions:

1. Do you have any general comments on efficacy or safety of Taxotere in combination with cisplatin and 5FU in the treatment of gastric adenocarcinoma?

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

/s/

Ann Staten

3/17/2006 01:37:03 PM

CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 20-449 Supplement # S-035 SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Taxotere
Generic Name: docetaxel
Strengths: 20mg and 80 mg concentrate

Applicant: Aventis

Date of Application: 9-23-05
Date of Receipt: 9-25-05
Date clock started after UN:
Date of Filing Meeting: 11-14-05
Filing Date: 11-24-05
Action Goal Date (optional): 3-11-05 User Fee Goal Date: 3-25-05

Indication(s) requested: TAXOTERE in combination with cisplatin and 5-fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

Type of Original NDA: (b)(1) _____ (b)(2) _____
OR
Type of Supplement: (b)(1) ____X_____ (b)(2) _____

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

__X__ NDA is a (b)(1) application OR ___ NDA is a (b)(2) application

Therapeutic Classification: S _____ P ____X_____
Resubmission after withdrawal? _____ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) _____
Other (orphan, OTC, etc.) _____

Form 3397 (User Fee Cover Sheet) submitted: X YES NO

User Fee Status: Paid ____ X_____ Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication*

for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application?

  YES NO

  If yes, explain: NDA 20-449 Taxotere (docetaxel)

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

  YES NO

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
  If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO

  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A YES NO

- Is it an electronic CTD? N/A YES NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, ___3____years NO
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? N/A YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: IND 35,555

- End-of-Phase 2 Meeting(s)? Date(s) 1-30-98; 4-8-98 NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _7-8-03;4-4-05 NO
If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? NA YES NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?

  N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?

  YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES
  NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11-14-05

BACKGROUND:

ATTENDEES: Robert Justice, MD; Ramzi Dager, MD also for Qin Ryan, MD; Janet Jiang, PhD; Ling Zhou, PhD; Raji Sridhara, PhD

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Qin Ryan, MD
Secondary Medical:	Amna Ibrahim, MD Acting Team Leader
Statistical:	Shenghui Tang, PhD
Pharmacology:	N/A
Statistical Pharmacology:	N/A
Chemistry:	Liang Zhou, PhD
Environmental Assessment (if needed):	Liang Zhou, PhD
Biopharmaceutical:	Sophia Abraham, PhD
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Lauren Iaconno-Conners/Lloyd Johnson
Regulatory Project Management:	Ann Staten
Other Consults:	SEALD; DDMAC; ODAC consultants; DBOP (Pending)

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE ___X___ REFUSE TO FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known __possible 3/14/05 NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A YES NO

CLINICAL MICROBIOLOGY NA __X_____ FILE _____ REFUSE TO FILE _____

STATISTICS FILE ___X____ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE ___X___ REFUSE TO FILE _____

- Biopharm. inspection needed: YES NO

PHARMACOLOGY NA ___X____ FILE _____ REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE __X____ REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:
Any comments: appears fine

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

___X____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

___X____ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Send DBOP consult with questions when ready.
2. Document no filing issues conveyed to applicant by Day 74. (done 11-15-05)

_____
Ann Staten, RD
Regulatory Project Manager, DDOP

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES NO

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES NO

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

   YES NO

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," skip to question 5. Otherwise, answer part (b).*

(b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

***NOTE:** If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES NO

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND # _____ NO

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

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

/s/

Ann Staten
2/1/2006 03:43:15 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 20-449/S-035

Aventis Pharmaceuticals, Inc.
200 Crossing Blvd., Route 202-206
P.O. Box 6890
Bridgewater, PA 08807-0890

Attention: Mark W. Moyer
Vice President
Drug Regulatory Affairs

Dear Mr. Moyer:

Please refer to your September 23, 2005 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Taxotere (docetaxel) concentrate for injection, 20 mg and 80 mg.

We also refer to your submission dated October 31, 2005.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on November 25, 2005 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Ann Staten, Regulatory Project Manager, at (301) 796-1468.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Ann Staten
11/15/2005 10:40:41 AM
Signed for Dotti Pease

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-449/S-035

PRIOR APPROVAL SUPPLEMENT

Aventis Pharmaceuticals, Inc.
200 Crossing Blvd., Route 202-206
P.O. Box 6890
Bridgewater, PA 08807-0890

Attention: Mark W. Moyer
Vice President
Drug Regulatory Affairs

Dear Mr. Moyer:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Taxotere (docetaxel) Concentrate for Injection, 20 mg and 80 mg.

NDA Number: 20-449

Supplement number: 035

Review Priority Classification: Priority (P)

Date of supplement: September 23, 2005

Date of receipt: September 26, 2005

This supplemental application proposes the following change: Taxotere in combination with cisplatin and 5-fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced gastric cancer.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 25, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 25, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a

waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call Ann Staten, Regulatory Project Manager, at (301) 796-1468.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Ann Staten

11/15/2005 10:21:20 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO (*Division/Office*			FROM:	
Raquel Peat, HFD-20			Ann Staten for Qin Ryan	
DATE 11-4-05	IND NO.	NDA NO. 20-449/S-035	TYPE OF DOCUMENT sNDA in the EDR	DATE OF DOCUMENT 9-23-05
DRUG: Taxotere (docetaxel)		PRIORITY CONSIDERATION High	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE If Priority review; PDUFA=3-26-05

NAME OF FIRM: Aventis

REASON FOR REQUEST

I. GENERAL

□NEW PROTOCOL
□ PROGRESS REPORT
□ NEW CORRESPONDENCE
□ DRUG ADVERTISING
□ ADVERSE REACTION REPORT
□ MANUFACTURINGCHANGE/ADDITION
□ MEETING PLANNED BY
□ PRE-NDA MEETING
□ END OF PHASE II MEETING
□ RESUBMISSION
□ SAFETY/EFFICACY
□ PAPER NDA
□ CONTROL SUPPLEMENT
□ RESPONSE TO DEFICIENCY LETTER (fax)
□ FINAL PRINTED LABELING
□ LABELING REVISION
□ ORIGINAL NEW CORRESPONDENCE
□ FORMULATIVE REVIEW
■OTHER *(SPECIFY BELOW)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
□ TYPE A OR B NDA REVIEW □ END OF PHASE II MEETING □ CONTROLLED STUDIES □ PROTOCOL REVIEW □ OTHER	□ CHEMISTRY REVIEW □ PHARMACOLOGY □ BIOPHARMACEUTICS OTHER

III. BIOPHARMACEUTICS

□ DISSOLUTION
□BIOAVAILABILTY STUDIES
□ PHASE IV STUDIES
□ DEFICIENCY LETTER RESPONSE
□PROTOCOL-BIOPHARMACEUTICS
□ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

□ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
□ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
□ CASE REPORTS OF SPECIFIC REACTIONS*(List below)*
□ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
□ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
□ SUMMARY OF ADVERSE EXPERIENCE
□ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

□ CLINICAL
□ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: QOL Endpoint review. Indication: gastric cancer. The submission is in the EDR. Thanks.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)*
Ann Staten	■ MAIL □ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Ann Staten
11/4/2005 11:58:37 AM
Document room - please log out as a consult
to HFD-20, SEALD consult. Thanks

DSI CONSULT: Request for Clinical Inspections

Date: October 26, 2005

To: Leslie Ball, HFD-47

From: Ann Staten, Project Manager, DDOP

Subject: **Request for Clinical Inspections**
NDA 20-449/S-035 (submitted to the Electronic Document Room)
Aventis
Taxotere (docetaxel)

Protocol/Site Identification:

As discussed with you, the following protocol/site essential for approval have been identified for inspection.

This Supplement provides for the following new indication: Taxotere in combination with cisplatin and 5-fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced gastric cancer. For this supplemental NDA which has one large randomized international pivotal trial, we would propose one inspection site at the MD Anderson Cancer Center, which was the largest single accruing site.

Indication	Protocol #	Site (Name and Address)	Number of Subjects
Taxotere in combination with cisplatin and 5-fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced gastric cancer.	325a	University of Texas PI: Jaffer Ajani, MD MD Anderson Cancer Center Dept of GI oncology 1515 Holcome blvd Houston, TX 77030 jajani@mdanderson.org 713-792-2828 Fax: 713-745-1163	55

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **March 5, 2006**. We intend to issue an action letter on this application by (action goal date) **March 26, 2006**.

Should you require any additional information, please contact Ann Staten at 301-796-1468.

Concurrence: Ramzi Dagher, MD, Medical Team Leader
Qin Ryan, MD, Medical Reviewer

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/s/

Robert Justice

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (*Division/Office*)			FROM:	
DDMAC, HFD-42			Ann Staten	
DATE 10-26-05	IND NO.	NDA NO. 20-449/S-035	TYPE OF DOCUMENT New sNDA	DATE OF DOCUMENT 9-23-05
DRUG Taxotere (docetaxel)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE

NAME OF FIRM: Aventis

REASON FOR REQUEST

I. GENERAL

9 NEW PROTOCOL	9 PRE-NDA MEETING	9 RESPONSE TO DEFICIENCY LETTER (fax)
9 PROGRESS REPORT	9 END OF PHASE II MEETING	9 FINAL PRINTED LABELING
9 NEW CORRESPONDENCE	9 RESUBMISSION	9 LABELING REVISION
9 DRUG ADVERTISING	9 SAFETY/EFFICACY	9 ORIGINAL NEW CORRESPONDENCE
9 ADVERSE REACTION REPORT	9 PAPER NDA	9 FORMULATIVE REVIEW
9 MANUFACTURINGCHANGE/ADDITION	9 CONTROL SUPPLEMENT	OTHER *(SPECIFY BELOW)*
9 MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
9 TYPE A OR B NDA REVIEW	9 CHEMISTRY REVIEW
9 END OF PHASE II MEETING	9 PHARMACOLOGY
9 CONTROLLED STUDIES	9 BIOPHARMACEUTICS
9 PROTOCOL REVIEW	9 OTHER
9 OTHER	

III. BIOPHARMACEUTICS

9 DISSOLUTION	9 DEFICIENCY LETTER RESPONSE
9 BIOAVAILABILTY STUDIES	9 PROTOCOL-BIOPHARMACEUTICS
9 PHASE IV STUDIES	9 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

9 PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	9 REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
9 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	9 SUMMARY OF ADVERSE EXPERIENCE
9 CASE REPORTS OF SPECIFIC REACTIONS *(List below)*	9 POISON RISK ANALYSIS
9 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

9 CLINICAL	9 PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This is a new sNDA for gastric cancer. Qin Ryan is the medical reviewer. The submission is in the EDR (S-035).

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)*
Ann Staten	9 MAIL 9 HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Ann Staten

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