European Medicines Agency

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Product name: **TAXOTERE**
Procedure No. **EMEA/H/C/073/II/67**

SCIENTIFIC DISCUSSION

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Following a change of policy the EMEA now publishes the full scientific discussion for Extension of Indication procedures (after removal of any commercially confidential information). For that reason, the information published for recent applications for a particular medicinal product may now be more detailed than what was published for applications in the past.

Introduction

Taxotere 20 and 80 mg concentrate and solvent for solution for infusion (INN: docetaxel) were first granted a Marketing Authorisation (MA) under exceptional circumstances for a restricted indication (second line monotherapeutic treatment of patients with advanced breast cancer after anthracycline failure) in the EU in 1995. Docetaxel is, besides paclitaxel, an important taxane, which displays its cytotoxic/antineoplastic activity by promoting the assembly of free tubulin into stable microtubles.

Meanwhile, after the granting of the full MA and several amendments of the indication, the licensed therapeutic indications are:

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

TAXOTERE (docetaxel) in combination with doxorubicin is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition.

TAXOTERE (docetaxel) monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent.

TAXOTERE (docetaxel) in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress HER2 and who previously have not received chemotherapy for metastatic disease.

TAXOTERE (docetaxel) in combination with capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline.

Non-small cell lung cancer
TAXOTERE (docetaxel) is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.

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

Prostate cancer
TAXOTERE (docetaxel) in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer."

The MAH now applied for an extension of the indication to include also treatment of patients with metastatic gastric adenocarcinoma (in combination with cisplatin and 5-fluorouracil), including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease.

Gastric cancer is the second most common cause of cancer death worldwide (after lung), despite a declining incidence in the west during the 20th century. The incidence of gastric cancer is particularly high in Asia, South America and many Eastern European countries. In Japan, gastric neoplasms are the most common cause of cancer death.

Gastric cancer is defined as any malignant tumour arising from the region extending between the gastroesophageal junction and the pylorus. Adenocarcinoma is the predominant histological form, accounting for approximately 95% of cases, and is classified as intestinal type, diffuse type or linitis plastica, the latter representing only 7% to 10% of the gastric adenocarcinomas.

While the precise etiology is unknown, acknowledged risk factors for gastric cancer include:
Helicobacter pylori gastric infection, Advanced age, Male gender, Diet low in fruits and vegetables, Diet high in salted, smoked, or preserved foods, Chronic atrophic gastritis, Intestinal metaplasia, Pernicious anemia, Gastric adenomatous polyps, Family history of gastric cancer, Cigarette smoking, Menetrier's disease (giant hypertrophic gastritis), Familial adenomatous polyposis.

Radical surgery represents the standard form of therapy having curative intent for early-stage disease. However, many patients are diagnosed at an advanced stage disease, and unfortunately 35% to 80% of the patients with gastric surgery develop recurrences.
The relative 5-year survival rate for gastric cancer of all stages is only 22%. Patients with advanced gastric cancer treated with best supportive care (BSC) alone have a median survival from 3 to 5 months.

A few chemotherapy agents (5-FU, cisplatin, doxorubicin, mitomycin-C, and etoposide) have shown activity in gastric cancer. These compounds were not tested as single agent versus BSC, and were mostly tested using different combinations, regimens, and modalities. Only drug combinations (as opposed to single agent administration) demonstrated survival advantages in comparison to BSC.

The efficacy of several chemotherapy regimens and mainly cisplatin and 5-fluorouracil (5-FU) based regimens were compared through randomized trials. A survival advantage of one regimen over another was demonstrated in very few studies (see table 1).

In 4 randomized trials with more than 100 patients treated with cisplatin plus 5-FU (CF) in each study, the median time to progression (TTP) or progression-free survival (PFS) was 5, 4.1, 3.9, and 4.2 months and the median OS was 8.5, 7.2, 7.3, and 8.7 months, respectively.
The benefit of the addition of cisplatin to 5-FU is demonstrated in 2 phase III studies (Kim et al and Ohtsu et al in which the TTP was significantly longer when cisplatin was added to 5-FU alone. This benefit is counterbalanced with a higher toxicity profile of the combined regimen (see table 1).

Table 1 - Phase III randomized studies in advanced gastric cancer: efficacy results

Author (year)	Regimens	Number of patients	Response rate	Median progression-free survival or time to progression (95% CI)	Median survival (95% CI)
Wils (1991)	FAMTX FAM	81 79	41% 9% (*P*<0.001)	NP NP	9.6 months 6.7 months (*P*=0.004)
Kelsen (1992)	FAMTX EAP	30 30	33% 20%	NP NP	7.3 months 6.1 months (ns)
KRGCGC (1992)	CF CFE	21 22	24% 27%	NP NP	6 months/1 year 34%/13% 6 months/1 year 55%/27% (ns)
Kim (1993)	CF FAM F	103 98 94	51% 25% (P<0.01)[a] 26% (P<0.01)[a]	5 months 2.8 months (P<0.05)[a] 2.1 months (P<0.05)[a]	8.5 months 6.7 months (ns)[a] 7 months (ns)[a]

Author (year)	Regimens	Number of patients	Response rate	Median progression-free survival or time to progression (95% CI)	Median survival (95% CI)
Webb/Waters (1997/1999)	FAMTX ECF	130 126	21% 46% (*P*<0.00003)	3.3 months[b] 7.4 months[b] (P=0.00006)	6.1 months 8.7 months (*P*=0.0005)
Roth (1999)	FE CFE	56 54	28.6% 42.6% (ns)	NP NP	7.1 months 9.6 months (*P*<0.05)
Vanhoefer (2000)	ELF CF FAMTX	128 132 130	9% (ns)[c] 20% (ns)[c] 12%	3.3 months (2.9-4.1) (ns)[c] 4.1 months (3.8-5.4) (ns)[c] 3.3 months (2.3-4.3)	7.2 months (6.0-8.3) (ns)[c] 7.2 months (6.3-9.0) (ns)[c] 6.7 months (5.1-7.6)
Ohtsu (2003)	F CF UFTM	105 105 70	11% 34% (*P*<0.0001)[d] 9% (ns)[d]	1.9 months (1.3-2.7) 3.9 months (3.1-4.8) (*P*<0.001)[d] 2.4 months (1.3-3.2) (ns)[d]	7.1 months 7.3 months (ns)[d] 6.0 months (ns)[d]
Dank (2005)	IF CF	170 163	31.8% 25.8%	5.0 months (3.8-5.8) 4.2 months (3.7-5.5)	9.0 months (8.31-10.15) (ns) 8.7 months (7.75-9.79)

[a] versus CF

[b] failure-free survival

[c] versus FAMTX

[d] versus F.

CI = confidence interval; NP = not provided; ns = not significant; CF = cisplatin + fluorouracil; F = fluorouracil; FAM = fluorouracil + doxorubicin + mitomycin; FAMTX = fluorouracil + doxorubicin + methotrexate; EAP = etoposide + doxorubicin + cisplatin; ELF = etoposide + leucovorin + fluorouracil; ECF and CFE = epirubicin + cisplatin + fluorouracil; UFTM = uracil + tegafur + mitomycin; IF = irinotecan + 5-fluorouracil

The safety profile of the CF regimen was not homogeneously assessed and reported across studies. However, in the 2 most recent studies, where hematology was to be assessed weekly, the incidence of main toxicities were similar and included severe neutropenia in at least half of the patients (54% and 52%) and neutropenic fever or infection in 10% of patients for the most recent trial; other main grade 3-4 side-effects were digestive toxicities (stomatitis and diarrhea).

Although no standard treatment is recognized worldwide, the cisplatin + 5-FU combination (CF) remains one of the most widely assessed, with the most consistent and reproducible efficacy results. This clinical benefit should however take into account a higher toxicity profile as expected.

The application was based on efficacy and safety data generated by **one pivotal randomised phase II-III study, XRP6979E/325**, including two substudies:

-**TAX 325**, the phase II part including 158 patients randomized between docetaxel + cisplatin (TC) or docetaxel + cisplatin + 5-FU (TCF).

-**TAX 325A**, the phase III part including 457 patients randomized between docetaxel plus cisplatin and 5-FU (TCF) or cisplatin plus 5-FU (CF).

In addition, the application contained **one randomized pharmacokinetic interaction study, XRP6976E/1001** that included 15 patients who received either TCF at cycle 1 then TC at cycle 2, or TC at cycle 1 then TCF at cycle 2.

Clinical aspects

Clinical pharmacology - Study XRP6976E/1001

The pharmacokinetics of docetaxel in combination with 5-fluorouracil and/or cisplatin have been assessed in three Phase I studies in patients with several tumour types and compared to that in monotherapy.

The pharmacokinetics of docetaxel and 5-fluorouracil in combination were investigated in 32 metastatic breast cancer patients. The pharmacokinetics of both docetaxel and 5-fluorouracil were not modified.
The pharmacokinetics of docetaxel and cisplatin in combination were investigated in 2 Phase I trials in 58 patients with different solid tumors and in 23 patients with non-small cell lung cancer.
The pharmacokinetics of both docetaxel and cisplatin were not modified by their co-administration in the 2 studies.

One new pharmacokinetic interaction study, XRP6976E/1001, was initiated to determine if there was any clinically significant pharmacokinetic interaction between docetaxel (75 mg/m²), cisplatin (75 mg/m²), and 5-FU (750 mg/m²/day for 5 days) after a triple combination treatment.
This was a single-center, open-label, randomized, cross-over (each patient being his own control), pharmacokinetic study of docetaxel in combination with cisplatin, with or without 5-FU, in the treatment of subjects with solid tumors.

The study consisted of 2 treatment arms that each underwent 2 cycles of treatment.
- In arm A, subjects were treated with the double combination docetaxel (Taxotere) + cisplatin (TC) in Cycle 1 followed by the triple combination docetaxel (Taxotere) + cisplatin + 5-FU (TCF) in Cycle 2.
- In arm B, the opposite sequence was employed so that subjects were treated with the triple combination at Cycle 1 followed by the double combination in Cycle 2. Treatment cycles were repeated every 21 days.
A total of 12 subjects were to be enrolled and treated in this study, 6 in each of the 2 treatment arms.

The main inclusion criteria were: Subjects ≥18 years of age with a recurrent or metastatic, progressive solid tumor that was histologically or cytologically confirmed. Histological or cytological findings had to indicate that a combination of docetaxel and cisplatin, or docetaxel, cisplatin, and 5-FU, were appropriate treatment for the tumor. Subjects were to have no serious concomitant medical conditions, including serious complications secondary to the malignant condition of their disease.

RESULTS

A total of 15 subjects with recurrent or metastatic solid tumors (7 male, 8 female) were randomized to 1 of the 2 treatment arms (8 subjects to arm A, 7 subjects to arm B). Subjects' ages ranged from 23 to 63 years (median = 54.0 years). All randomized subjects received study medication. One subject discontinued treatment due to a serious adverse event (SAE) of myocardial infarction and did not receive TC treatment in Cycle 2.

A total of 12 subjects were available for the PK (6 subjects in arm A, 6 subjects in arm B).
All 15 subjects who received study medication (i.e., treated at Cycle 1) were analyzed for safety.

PK results

- Docetaxel

The compartmental analysis yielded mean docetaxel CL of 20.6 ± 6.7 L/h/m2 and 22.4 ± 6.8 L/h/m2 for TC and TCF treatments, respectively. No statistical difference was observed between the two CL. The geometric mean of the Bayesian CL (19.6 ± 6.7 TC treatment; 21.6 ± 6.8 TCF treatment) were used to generate 90% confidence intervals for the ratio of docetaxel CL from TCF treatment (test) vs. the docetaxel CL from TC treatment (reference). This ANOVA yielded a point estimate of 110.0% and 90% confidence limits of 98.3 – 123.1%.

Table 2 – Docetaxel treatment comparison across study arms

Drug	Parameter ($L/h/m^2$)	Treatment	N	Geom. Mean	CV (%)	Pair[a]	Ratio (%)[b]	90% Confidence Interval[b]
Docetaxel	CL	TCF	12	21.58	30.4			
						TCF/TC	110.0	(98.3; 123.1)
		TC	12	19.62	32.6			

[a] Natural-log transformed results for the ANOVA were transformed to the original scale by exponentiation to obtain the ratio and 90% confidence interval.

[b] Treatment TCF (Docetaxel + Cisplatin + 5-FU) is test and treatment TC (Docetaxel + Cisplatin) is reference.

- Cisplatin

Total platinum analyses are not described in detail, but the ultrafilterable platinum the active moiety relevant for this study. However, concentrations of total platinum were measured and PK parameters estimated via non-compartmental analysis methods were similar across the 2 study treatments.

Total body CL values were similar for the 2 treatments with mean values of 32.3L/h ± 7.9 and 34.2L/h ± 9.0 for TC and TCF treatments, respectively. No statistically significant difference was detected between ultrafilterable platinum clearances between treatments; the ANOVA comparing the ultrafilterable platinum clearance in treatment TCF versus treatment TC yielded a p-value of 0.5990. The point estimate was 105.3%, with a 90% confidence interval ranging from 88.7–125.1%. A summary of these results is presented in the table below.

Table 3 – Ultrafilterable platinum treatment comparison across study arms

Drug	Parameter (mL/h)	Treat-ment	N	Geom. Mean	CV (%)	Pair[a]	Ratio (%)[b]	90% Confidence Interval[b]
Ultrafilterable Platinum	CL	TCF	12	33175.6	26.3			
						TCF/TC	105.3	(88.7; 125.1)
		TC	12	31500.3	24.3			

[a] Natural-log transformed results for the ANOVA were transformed to the original scale by exponentiation to obtain the ratio and 90% confidence interval.

[b] Treatment TCF (Docetaxel + Cisplatin + 5-FU) is test and treatment TC (Docetaxel + Cisplatin) is reference.

- 5-Fluorouracil

Descriptive statistics for the 5-FU PK parameters are given in Table 4 below.

Table 4 – Mean 5-FU PK parameters

Treatment	Statistic	C_{SS} (ng/mL)	CL (L/h)	V_{SS} (L)
TCF	n	12	12	12
	Mean	265.2	234.2	1505.5
	Range	158.2-402.6	140.0-418.8	235.4-4655.2
	SD	60.8	75.8	1147.5
	CV%	22.9	32.4%	76.2

TCF: Docetaxel + Cisplatin + 5-FU.

C_{SS} = Plasma concentration at steady state.

Safety Results

In general, treatment with docetaxel in combination therapy was well tolerated. Only 1 subject discontinued treatment due to a SAE of myocardial ischemia, which later resolved.

Adverse events were reported by all subjects during both TC and TCF treatments. Gastrointestinal (NCIC classification) treatment-emergent adverse events (TEAEs) were the most commonly reported. In general, numbers of subjects with TEAEs suggest that 5-FU was associated with increased numbers of TEAEs, especially gastrointestinal TEAEs, which was consistent with the nature of the underlying disease and the known adverse event profiles for docetaxel, cisplatin, and 5-FU.
No deaths were reported during the study period. Serious adverse events were reported in 2/14 subjects during TC treatment, and in 6/15 subjects during TCF treatment and were classified as either cardiovascular, flu-like symptoms, or gastrointestinal. All but 2 serious adverse events of lethargy had resolved by the end of the study.
Frequencies of hematology and biochemistry toxicities on treatment were consistent with the known safety profile for docetaxel, cisplatin, and 5-FU.

Discussion on Clinical Pharmacology

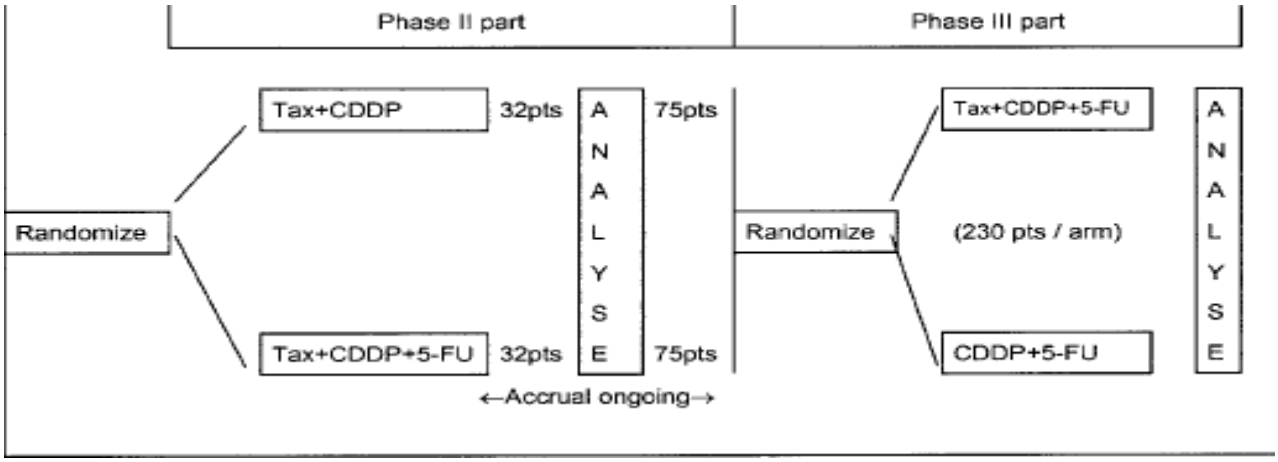
Blood sampling procedure as well as analytical methods were adequate.
Pharmacokinetics interaction between docetaxel and 5-fluorouracil or cisplatin could be reasonably excluded due to the respective way of elimination for each drug:
- docetaxel metabolised by CytP450 3A
- cisplatin : mainly urinary elimination, and nearly irreversible binding to plasma proteins
- 5-fluorouracil catabolised by the dihydropyrimidine dehydrogenase,

Thus, the addition of Taxotere to cisplatin and 5-fluorouracil is unlikely to result in a pharmacokinetic interaction. This was also reported in the literature for the cisplatin and 5-fluorouracil combination.

Clinical Efficacy - Pivotal Study XRP6979E/325

TAX325 is an open label, randomized multicenter phase II/III study of docetaxel in combination with cisplatin (**TC – Arm A**) or docetaxel in combination with 5-fluorouracil and cisplatin (**TCF – Arm B**) compared to the combination of cisplatin and 5-fluorouracil (**CF - Arm C**) in patients with metastatic or locally recurrent gastric cancer previously untreated with chemotherapy for advanced disease.
The study was divided in a phase II part (TAX 325) to select one test arm, and a phase III part (TAX 325A) to assess efficacy of the selected test arm (TCF) compared to the reference treatment (CF).
No patient included in the phase II part of the study was treated in the phase III part of it.

The study design was as follows:



Tax= docetaxel CDDP= cisplatin 5-FU=5-fluorouracil

The inclusion/exclusion criteria of the study were shared by both Part II and Part III. The main inclusion criteria were the following: subjects were to be ≥18 years of age with histologically proven gastric adenocarcinoma, including adenocarcinoma of the esophagogastric (EG) junction and were to have a Karnofsky Performance Status (KPS) of >70. They were to have measurable and/or evaluable metastatic disease, or locally recurrent disease with a measurable lesion, and no prior palliative chemotherapy. Adjuvant chemotherapy was allowed if ended more than 12 months before first relapse. Radiotherapy had to have been completed more than 6 weeks prior to the first infusion, and surgery more than 3 weeks prior to the first infusion.

The Clinical Study Protocol and SAP defined 3 populations for analysis, the FAP, the PPP, and the SP:
-FAP: Full analysis population (all treated subjects analyzed in the treatment group to which they were assigned by randomization);
-PPP Per Protocol Population: (a subset of the FAP, consisted of subjects eligible and evaluable for response without a major protocol deviation during the study);
-SP: Safety population consisted of all subjects treated with at least 1 dose of study therapy and analyzed according to the study medication actually received.

Phase II part - TAX 325

The phase II part (TAX 325) of the study, was conducted to select 1 of 2 test treatments (Taxotere combined with cisplatin [TC], or Taxotere combined with cisplatin and 5-fluorouracil [TCF]), based primarily on complete tumor responses, to be used in a phase III trial comparison against a control group (cisplatin combined with 5-FU [CF]).

Patients were assessed for tumor response (defined according to standard World Health Organization [WHO] criteria) every 8 weeks plus or minus 1 week (regardless of intervening cycle lengths or day of cycle). They were considered as evaluable for tumor response after having received at least 2 cycles of study treatment (unless early progression occurred), with the same imaging procedures as at baseline for each lesion.

Based on the response rate obtained in the first 69 subjects (60 PPP), the IDMC recommended that TCF be selected.

The final analysis of the phase II part of the study based on a total of 155 subjects (124 PPP), confirmed this decision. Indeed, the overall RR (PPP) tended to be higher in the TCF-treated group (33 of 60 subjects, 55.0% [95% CI: 41.6-67.9]), than in the TC-treated group (20 of 64 subjects, 31.3% [95% CI: 20.2-44.1]).

The median TTP was 5.9 months in TCF-treated subjects and 5.0 months in TC-treated subjects and the median overall survival was 9.6 months in TCF-treated subjects and 10.5 months in TC treated subjects, with 95% CIs overlapping. The phase II part of the study was not adequately powered to show a statistical difference on these endpoints.

The safety profiles of both treatment groups were similar, with the exception of grade 3-4 stomatitis, nausea, and diarrhea, which were more frequent in TCF-treated patients.

Taking into account the similar overall safety profile for both arms, and the higher ORR in the TCF arm, the choice of TCF as test arm for the phase III part, is acceptable.

Phase III Part - TAX325 A

The *primary objective* of the phase III part was to detect a statistically significant increase in time to progression (TTP) for TCF relative to CF.
The time to progression, was calculated from the day of randomization to the date of the first TTP event. A TTP event was defined as disease progression (DP), or death from any cause.

Only deaths within 12 weeks (corresponding to 1.5 times the planned period between 2 tumor assessments) 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.

Secondary objectives included:
- detecting a statistically significant increase in overall survival (OS) for TCF compared to CF,
- and comparing response rate (RR), time to treatment failure (TTF), duration of response, safety, quality of life (QOL). Other endpoint associated with clinical benefit were assessed (time to definitive worsening of KPS by at least 1 category compared to baseline; time to definitive weight loss by 5% and 10% from baseline and time to definitive worsening of appetite; Curative analgesic consumption).

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 ±1 week on therapy until the documentation of the progression. All tumor assessments were to be reviewed by an External Response Review Committee (ERRC). Response was defined according the World Health Organization (WHO) criteria.

TREATMENT REGIMEN

The 2 treatment arms were as follows:

TCF:
-docetaxel 75 mg/m^2 (1 hour i.v. infusion) on D1,
-cisplatin 75 mg/m^2 (1 to 3 hours i.v. infusion) on D1 after the end of the docetaxel infusion,
-and 5-FU 750 mg/m^2 per day (24-hour continuous i.v. infusion over 5 days) on D1 to D5 after the end of the cisplatin infusion.
This schedule was administered **every 3 weeks** (1 cycle).

CF:
- cisplatin 100 mg/m^2 (1 to 3 hours i.v. infusion) on D1
- and 5-FU 1000 mg/m^2 per day (24-hour continuous i.v. infusion over 5 days) on D1 to D5 after the end of the cisplatin infusion.
This schedule was administered **every 4 weeks** (1 cycle).

Treatment was to be administered up to disease progression, unacceptable toxicities, or consent withdrawal. Crossover was not allowed. After progression, further chemotherapy treatment with taxanes or camptothecins was not recommended.

The same planned dose intensity of both cisplatin and 5-FU in each treatment arm (25 mg/m2/week for cisplatin and 1250 mg/m2/week c.i. for 5-FU).

Sample size
The sample size was calculated to ensure 95% power to detect a hazard ratio (HR) for TTP of 1.5 (e.g. corresponding to an improvement in median TTP from 4 months to 6 months in favour of TCF over CF) and to ensure 95% power to detect a HR of 1.5 (from 8 months to 12 months) for OS (main secondary endpoint.) A total of 460 subjects (230 per group) were planned for the phase III part.

The statistical analysis plan specified that TTP and OS analyses, respectively, would be completed when 325 TTP and death events had occurred.
The number of TTP and death events exceeded 325 in the database at the cut-off date The analysis was performed with exactly the number of protocol pre-specified events (“325 events” analysis) and was also performed to include all events in the database (“end-of-study” analysis).

Statistical methods

- Primary efficacy analysis

Superiority
The Phase III primary analysis will be a comparison of the time to progression in the full analysis population (FAP) to demonstrate superiority of the test arm relative to the control.

Non-inferiority
In the event that the test arm prolongs the time to progression (TTP) relative to the control, but the difference is not statistically significant, then attention will be focused on whether TTP in the test arm is statistically non-inferior to TTP in the CDDP + 5-FU arm.
Considering TTP and OS data described by Kim *et al.*, and requiring that at least 50% of the smallest (TTP or OS) treatment effect of CDDP + 5-FU over 5-FU alone should be retained by the test treatment, a hazard ratio of 0.91 (control / test) was to preferred for the null hypothesis for the non-inferiority test. 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 HR CF/TCF (control / test) exceeded 0.91.

Since the study reached the superiority objective, no non-inferiority analysis was performed and presented in the study report appendix. Thus, these results will not be presented within this report.

- Secondary efficacy analyses

OS was to be compared using the same statistical methods (unstratified log-rank test in the FAP) as defined for TTP0.

- Supportive analyses
Sensitivity 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.

- 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, 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]).

- Subgroup analyses were performed according to gender, age (< 65 v. ≥ 65 and < 70 v. ≥ 70), race (Caucasian, non-caucasian), region (North America, South America, Western Europe, Eastern Europe, Asia), prior gastrectomy (no, yes), measurable disease (no, yes), liver involvement (no, yes), weight loss (≤ 5% v. > 5%), KPS (100 v. ≤ 90), and anatomical site (distal v. proximal).

- The study 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. Consequently, it was assesses if the actual tumor assessment pattern was similar across treatment arms, and if it was different, to determine the extent of the difference. 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.

Randomisation

Subjects were centrally randomized (1:1) to either TCF or CF with the following stratification factors: liver metastasis (yes versus no), prior gastrectomy (yes versus no), disease measurability (measurable versus evaluable-only lesions), weight loss in prior 3 months (≤5% versus >5%), and investigational center.

Interim analysis

A single interim analysis was planned when 162 TTP events or approximately 50% of the total expected number of events to be included in the final analysis had occurred.
Tumor response rate, TTP and OS were the main endpoints analyzed. Given 50% of the total expected events at the time of the interim analysis, the nominal significance levels for the interim and final analysis of TTP would be 0.36% and 4.87%, respectively.
The following interim analysis data, with a 15 September 2001 cut-off date, were presented at IDMC in August 2002 and at the American Society of Clinical Oncology Annual Meeting in Chicago, IL, in June 2003: the results of 115 TCF-treated subjects and 117 CF-treated subjects were reported. Among treated subjects (96%), the median age was 54 years; the site of the primary tumor was in the gastric body in 68% of subjects, and 98% had metastatic disease.
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 met the pre-specified boundary (0.0053).
The RR of TCF (38.7%) was also higher than that of CF (23.2%) (chi-square test, *P*=0.012). Grade 3-4 AEs were reported in 82% of TCF-treated subjects and 81% of CF-treated subjects. The death rate from all causes within 30 days of last infusion was 11.7% in TCF and 8.0% in CF.

These results were extensively reviewed by the IDMC (Independent Data Monitoring Committee) and the SC (Steering Committee). Because the difference in OS was not statistically significant, it was decided not to stop the study at this point.

Follow up

After the end of treatment, 30 days after the last infusion:
- Subjects who had progressed were followed every 3 months until death.
- Subjects who had ended treatment but who had not yet progressed were followed every 8 weeks, calculated from the first administration of study medication, until documented occurrence of progression, and then every 3 months thereafter.
- QOL assessment was performed every 8 weeks, calculated from the first administration of study medication until the documentation of the progression and then every 3 months until death.
- Any AE that was considered to be possibly or probably related to study medication had to be recorded and reported immediately.
- Socio-economic parameters every 3 months: hospital admissions were to be collected until a second line treatment was administered if any.

Efficacy results

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 in various populations:

Table 5 - 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)

Populations	Number (%) of subjects		
	TCF	CF	Total
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)

TCF = Taxotere + cisplatin + 5-fluorouracil; SP = Safety population;
FAP = Full analysis population; PPP = Per-protocol population;
CF = Cisplatin + 5-fluorouracil

Baseline data

Table 6 - Summary of patient and disease characteristics at baseline (FAP)

	Number (%) of patients		
	TCF (N=221)	CF (N=224)	Total (N=445)
Male	159 (71.9)	158 (70.5)	317 (71.2)
Median age (range)	55 (26-79)	55 (25-76)	55 (25-79)
≥65 years	54 (24.4)	55 (24.6)	109 (24.5)
Median KPS before first infusion (range)	90 (70-100)	90 (70-100)	90 (70-100)
≥90	141 (63.8)	143 (63.8)	284 (63.8)
Weight loss >5%	126 (57.0)	127 (56.7)	253 (56.9)
At least one sign and symptom (any grade)	188 (85.1)	186 (83.0)	374 (84.0)
Histological 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 [a]	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[b]			
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)
Number of organs involved[b]			
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)

	Number (%) of patients		
	TCF (N=221)	CF (N=224)	Total (N=445)
No organs	2 (0.9)	1 (0.4)	3 (0.7)
Organ involvement[b, c]			
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)
Prior surgery	68 (30.8)	71 (31.7)	139 (31.2)
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] Includes 6 patients with adenocarcinoma, one patient with stromal tumor, and one patient with squamous cell carcinoma

[b] As determined by External Response Review Committee

[c] Only organs in at least 15% of patients are given

FAP = full analysis population; TCF = docetaxel + cisplatin + 5-fluorouracil; CF = cisplatin + 5-fluorouracil; KPS = Karnofsky Performance Status; CSR = clinical study report

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)

[a]As determined by ERRC

There was no difference in the distribution of baseline patients and disease characteristics between both treatment arms: median age 55 years; median Karnofsky performance status of 90.
Imbalance in some tumour characteristics differences could have disadvantaged the control arm (CF) based on the clinical knowledge:
- more patients in the control arm, had an esogastric junction tumor localisation (25% vs 19%) and a peritoneal involvement (28% vs 23%),
- more patients in the tested arm, TCF, had an evaluable only disease for whom the progression could be establish less easily.
However, these differences were not likely to impact on efficacy results. Indeed, in all 4 anatomical sites the point estimate of the hazard ratio was in favour of the TCF arm for both TTP and OS, and similar to the overall estimate in the full analysis population.
In the end-of study analysis, the only covariate that was statistically significant in a multivariate analysis was primary tumour site, where a distal site (i.e., body and antrum) was shown to be an adverse prognostic factor for TTP. This observation was not confirmed by subgroup and treatment interaction analyses.
However, since the sample size per each sub-group is limited, it is difficult to draw any conclusion per sub-group.

Primary efficacy endpoint

In the end of study analysis, 341 of 445 (76.6%) subjects had an event. 104 of 445 (23.4%) subjects were censored: 54 in the TCF arm and 50 in CF arm. The median follow-up was 13.6 months ([95% CI: 11.30-22.28].

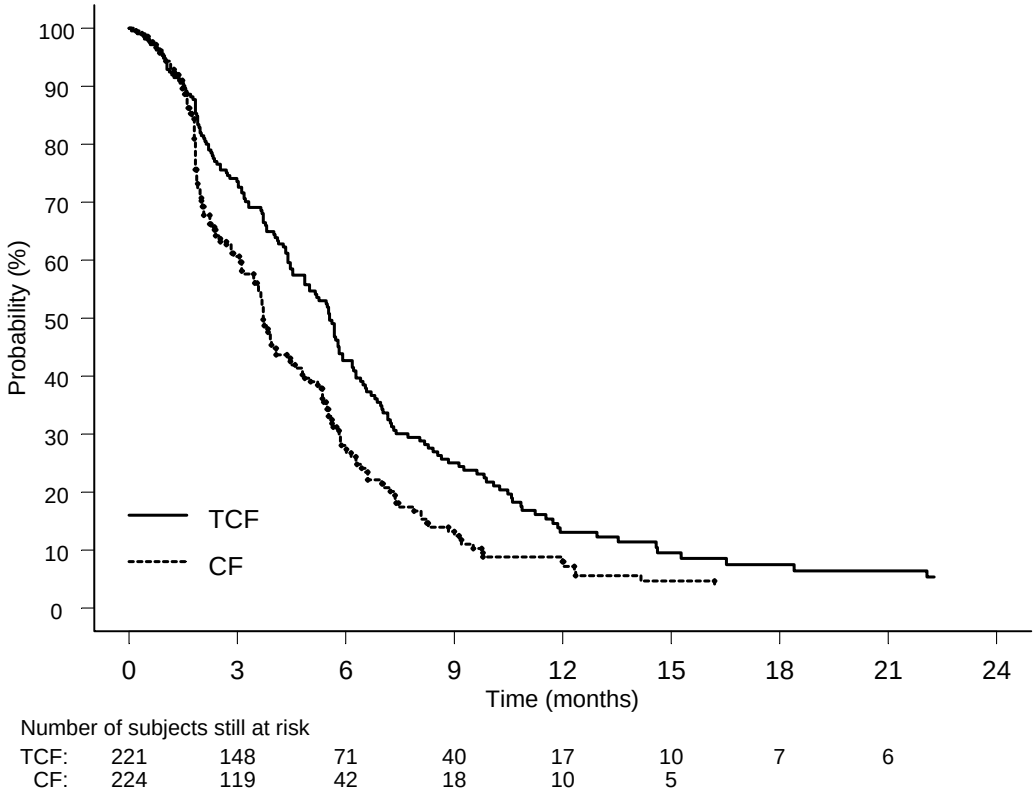
The observed median TTP was 5.6 months in the TCF group [95% CI: 4.86-5.91] and 3.7 months [95% CI: 3.45-4.47] in the CF group as shown in Table 7 and Figure 1.
The difference between the 2 treatments was statistically significant (log-rank test, *P*=0.0004) with an HR of 1.473 [95% CI: 1.189-1.825] and a risk reduction of 32.1%.
At 6 months, 42.7% of the TCF-treated subjects had not progressed compared with 27.4% of the CF-treated subjects.

Table 7 - 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]	
Risk reduction	32.1%	

[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

Figure 1 – Time to progression – Kaplan-Meier curve – end of study (FAP)



TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; FAP = Full analysis population

- Supportive analysis for the primary endpoint of TTP

Table 8 - 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

-The study 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.

The median times from randomization to first, second, and third tumor assessment were similar between the groups, and none of the log-rank tests comparing treatments was significant at the 5% level (although the time from randomization to first tumor assessment was borderline [*P*=0.0729]).

-In the multivariate analysis, the only covariate that was statistically significant was primary tumor site, where a distal site (i.e., body and antrum) was shown to be an adverse prognostic factor for TTP.

-The HR for TTP according to the age, gender and race subgroups showed extensive overlap of the respective 95% CIs, thus indicating the lack of any influence of these factors on the results. The analysis of TTP by age group showed that the treatment difference seen for all subjects was the same for both elderly (≥65 years of age) and non-elderly (<65 years of age).

Secondary efficacy endpoints

Overall Survival

Pre-specified end-of-study analysis: A total of 334 of 445 (75.1%) subjects had an event, and 111 of 445 (24.9%) subjects were censored.

Table 9 - 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

In January 2005, after post-study follow-up, 416 deaths (93.5%) had been recorded among the 445 patients in the full analysis population (FAP): 206 in the TCF arm, 210 in the CF arm. The median follow-up time in this update is 41.6 months (compared to 23.4 months in the end-of-study analysis). Of the 29 censored patients, 3 only (all in TCF arm) were considered lost to follow-up.

Table 10 – Overall survival – End-of study analysis (FAP)

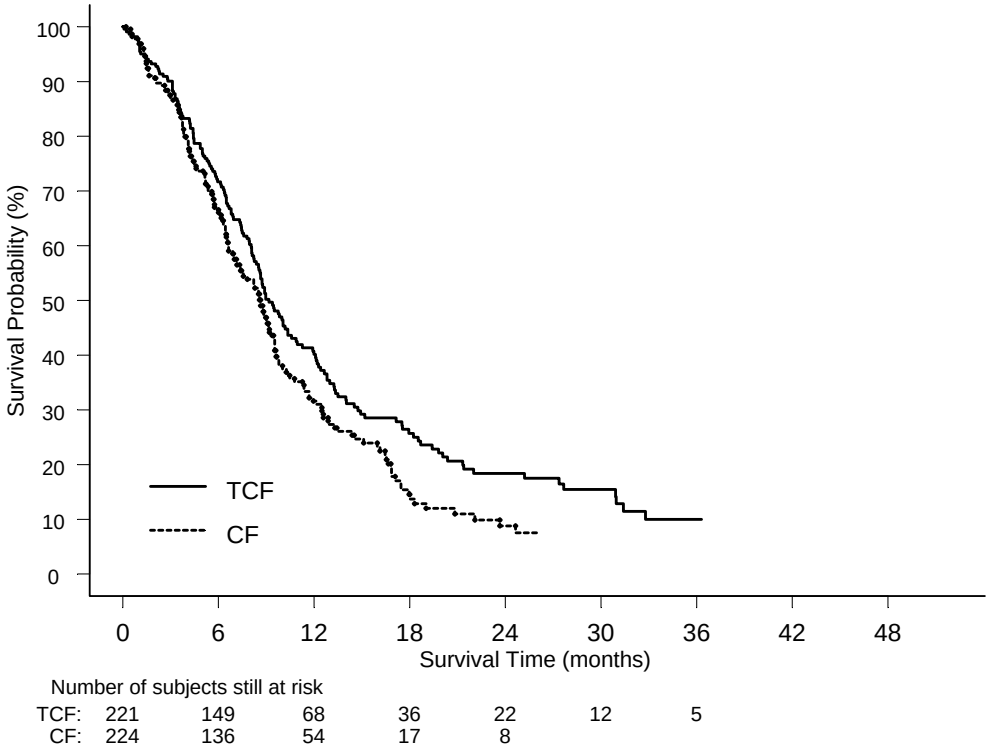
Event/parameter	Number (%) of patients	
	End of study analysis	
	TCF (N=221)	CF (N=224)
Survival event (deaths)	162 (73.3)	172 (76.8)
Censored patients	59 (26.7)	52 (23.2)

Event/parameter	Number (%) of patients	
	End of study analysis	
	TCF (N=221)	CF (N=224)
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.

The Kaplan-Meier plot of the end-of-study overall survival is presented below (see Figure 2).

Figure 2 - Overall Survival – End-of-Study May 2003 (FAP)



A summary of updated OS analyses is presented in Table 11 below in the FAP (primary presentation of OS) and ITT (exploratory analysis). Analyses are presented as either unstratified or stratified by the binary factors used in randomization (prior gastrectomy, disease measurability, liver metastasis and >5% weight loss in prior 3 months) and are summarized in the table below. For comparison, the end-of-study OS results are also given for both the FAP and ITT.

Table 11 – Summary of OS Analyses

Population	Analysis	Stratified	Hazard ratio [a] (95% CI)
FAP	**End-of-Study**	**No**	**1.293 (1.041 – 1.606)**
FAP	End-of-Study	Yes	1.333 (1.064 – 1.671)
FAP	**Update**	**No**	**1.169 (0.964 – 1.418)**

Population	Analysis	Stratified	Hazard ratio [a] (95% CI)
FAP	Update	Yes	1.213 (0.993 – 1.481)
ITT	**End-of-Study**	**No**	**1.233 (0.996 – 1.527)**
ITT	End-of-Study	Yes	1.275 (1.021 – 1.593)
ITT	**Update**	**No**	**1.131 (0.935 – 1.369)**
ITT	Update	Yes	1.178 (0.966 – 1.435)

a Value >1 favors TCF

The survival update analysis conducted with a median follow-up time of 41.6 months no longer showed a statistically significant difference although all planned (end-of-study) and unplanned ("update") analyses for OS were always in favour of the TCF regimen and showed that the benefit of TCF over CF is clearly observed between 18 and 30 months of follow up. The updated OS analysis was performed without a pre-defined hypothesis and the statistical interpretation of the results is limited, having previously met the nominal boundary set for OS in the end-of-study analysis.

Response

The best overall RRs for the FAP and the PPP are shown in Table 12.

Table 12 - 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

Quality of Life

- The primary QOL analysis, time to 5% definitive deterioration of global health status scale of the QLC-C30 questionnaire was significantly in favor of TCF (HR 1.445 [95% CI: 1.082-1.929], log rank test *P*=0.0121).
Secondary analyses of QLC-C30 functional subscales (physical and social) and symptoms (nausea/vomiting, pain, and appetite loss) as well as the EQ-5D thermometer were
all consistent and in favor of TCF.
- The primary clinical benefit analysis, time to definitive worsening of KPS was significantly longer in TCF (6.1 months) compared to CF (4.8 months) (HR 1.379 [95%CI: 1.083-1.756], log-rank test, *P*=0.0088).
Secondary clinical benefit analyses of time to definitive weight loss worsening of appetite, were consistently in favour of TCF but did not reach statistical significance. Pain-free survival and time to first cancer pain-related opioid intake, did not show a difference between TCF and CF.

Post-study anti-cancer chemotherapy treatments

Post-study anticancer chemotherapies are summarized in Table 13.
Of the 445 subjects, 163 (36.6%) received subsequent chemotherapeutic agents (as monotherapy or in combination chemotherapy) after discontinuation from study treatment.
The number of subjects who received post-study chemotherapy was higher in the CF treatment group (92 [41.1%] subjects) than in the TCF treatment group (71 [32.1%] subjects). 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 (CF: 9.8%; TCF: 10.0%).

Table 13 - 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

Discussion on Clinical Efficacy

The primary efficacy endpoint of the pivotal study was changed from survival to TTP. This endpoint is acceptable compared to ORR as the study allows inclusion of patients with evaluable-only lesions.
In addition, prolongation of TTP interval could be considered as a clinical benefit. However, overall survival was a secondary endpoint of the study.

The phase III part of the pivotal trial presented in this application, used CF as a control arm. The data submitted by the MAH supporting the comparator choice, summarise the difficulty to establish a reference treatment. Although no standard treatment is recognized worldwide, the cisplatin + 5-FU combination (CF) remains one of the most widely assessed, with consistent and reproducible efficacy results and appears to be a valid option for patients with preserved Performance Status. The combination of cisplatin and 5-FU at the dose of 100 and 1000 mg/ m^2 was a valid comparator for the phase III study TAX 325 A. Indeed this regimen has shown consistent and reproducible efficacy results.

Doses were modified in the case of severe hematologic and/or non-hematologic toxicities (cutaneous reactions, diarrhea, stomatitis, impaired liver function, peripheral neuropathy).
Dose adjustments are in accordance with the SPC recommendations.

Prophylactic anti-emetic treatment and hydratation for cisplatin, and oral dexamethasone pre-medication regimen for docetaxel, were well planned and are in accordance with the SPC.

The primary superiority objective of the phase III part was met. The study primary endpoint, TTP analyzed in the FAP, was significantly in favour of TCF compared to CF (unstratified log-rank test, P=0.0004). The risk reduction of progression, 32.1%, was associated with a 2-month improvement in the median TTP (3.7 months for the CF group to5.6 months for the TCF group). Results were consistent across PPP analysis and also confirmed the interim analysis results.

Supportive sensitivity analysis on PPP, and multivariate analysis taking into account possible prognostic factors (only primary tumor site was statistically significant), were in accordance with the primary analysis.

Although survival assumptions considered during sample size calculation were not reached, statistical significance have been reached in favour of TCF.

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 results are in accordance with similar literature data.

In comparison with the May 2003 cut-off analysis, the main changes observed in the updated January 2005 analysis, are "late" deaths in both arms. These deaths were not unexpected in view of the known outcome of metastatic gastric cancers (OS expected about 8 months). The observed differences between control and test arm are clearly identifiable between 18 and 30 months follow-up.

Sensitivity analysis reported statistical difference in favor of TCF in the PPP. The analysis of OS by agegroup 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).
This confirms the clinical benefit associated with the use of TCF.

In the FAP, the overall RR (CR + PR) was higher in the TCF group (36.7% [95% CI: 30.3%-43.4%]) than in the CF group (25.4% [95% CI: 19.9%-31.7%]). The difference between the 2 treatment groups was statistically significant (Chi square test, P=0.0106). The number and percentage of subjects with PD was lower in the TCF group (37 [16.7%]) than in the CF group (58 [25.9%]). Similar trends were reported in the PPP analysis.

RRs in the FAP were also calculated in subgroups defined by several baseline parameters such as age (<70 vs. ≥70), PS (100 versus <100), weight loss, measurability of disease, liver involvement, anatomic site of cancer, histological type, and prior surgery.
In each case except "no measurable disease," the overall RR was greater in TCF subjects than in CF but the cut off value for age was different from the use for TTP and OS.

Globally, the results of QOL and clinical benefit were consistent and support the benefit of TCF.

In conclusion, the MAH has provided statistically significant efficacy results as measured through the primary endpoint (TTP) and the secondary endpoint (OS) that are associated with improved QoL and longer preservation of PS.

Clinical Safety

Safety data are based on the findings of a phase II-III study: the phase II part XRP6976E/325 (TAX 325) and the pivotal phase III part, XRP6976E/325A (TAX 325A) in subjects with advanced gastric cancer, including adenocarcinoma of the gastroesophageal junction, and a pharmacokinetic interaction study (XRP6976E/1001) of TCF in subjects with recurrent or metastatic solid tumors.

No previous study investigated this TCF combination and schedule in gastric cancer. One study in the literature reported results on a TCF combination with a different 5-FU administration schedule (300 mg/m2 per day continuous infusion over 2 weeks, rather than 750 mg/m2 per day over 5 days).
See below an overview table of the submitted studies.

Table 14 - Overview of studies

Study	Title	No. of randomized/ treated subjects	Dosage/ combination
TAX 325	Open label, randomized, multicenter phase II-III study of docetaxel in combination with cisplatin or docetaxel in combination with 5-FU and cisplatin compared to the combination of cisplatin and 5-FU in patients with metastatic or locally recurrent gastric cancer previously untreated with chemotherapy for advanced disease.	158 / 155	Docetaxel: 85 mg/m^2, i.v., D1; Cisplatin: 75 mg/m^2, i.v., D1; every 3 weeks Docetaxel: 75 mg/m^2, i.v. D1; Cisplatin: 75 mg/m^2, i.v., D1; 5-FU: 750 mg/m^2 per day, c.i. D1 to D5; every 3 weeks
TAX 325A	Open label, randomized multicenter phase II-III study of docetaxel in combination with cisplatin or docetaxel in combination with 5-FU and cisplatin compared to the combination of cisplatin and 5-FU in patients with metastatic or locally recurrent gastric cancer previously untreated with chemotherapy for advanced disease.	457 / 445	Docetaxel: 75 mg/m^2, i.v., D1; Cisplatin: 75 mg/m^2, i.v., D1; 5-FU: 750 mg/m^2 per day, c.i., D1 to D5; every 3 weeks Cisplatin: 100 mg/m^2, D1; 5-FU: 1,000 mg/m^2 per day, c.i., D1 to D5; every 4 weeks
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 per day for 5 days) in the treatment of patients with recurrent or metastatic solid tumors.	15 / 15	Docetaxel: 75 mg/m^2, i.v., D1; Cisplatin: 75 mg/m^2, i.v., D1; every 3 weeks Docetaxel: 75 mg/m^2, i.v., D1; Cisplatin: 75 mg/m^2, i.v., D1; 5-FU: 750 mg/m^2 per day, c.i. D1 to D5; every 3 weeks

D = day; c.i. = continuous infusion; 5-FU = 5-fluorouracil

Phase III, TAX 325A

Analysis of Adverse Events

Overview of Treatment-emergent adverse events (TEAEs)

Table 15 - Overview of subjects and cycles with TEAEs

Type of TEAE	Number (%)			
	TAX 325 phase II		TAX 325A phase III	
	TCF	**TC**	**TCF**	**TC**
Total number of subjects	**79 (100.0)**	**76 (100.0)**	**221 (100.0)**	**224 (100.0)**
At least 1 TEAE regardless of relationship to study medication	78 (98.7)	75 (98.7)	221 (100.0)	221 (98.7)
At least 1 TEAE possibly or probably related to study medication	77 (97.5)	74 (97.4)	214 (96.8)	212 (94.6)
At least 1 grade 3-4 TEAE regardless of relationship to study medication	61 (77.2)	52 (68.4)	180 (81.4)	169 (75.4)
At least 1 grade 3-4 TEAE possibly or probably related to study medication	50 (63.3)	38 (50.0)	152 (68.8)	132 (58.9)
Total number of cycles	**438 (100.0)**	**428 (100)**	**1186 (100.0)**	**906 (100.0)**
At least 1 TEAE regardless of relationship to study medication	432 (98.6)	411(96.0)	1153 (97.2)	864 (95.4)
At least 1 TEAE possibly or probably related to study medication	423 (96.6)	401 (93.7)	1117 (94.2)	824 (90.9)
At least 1 grade 3-4 TEAE regardless of	161 (36.8)	113 (26.4)	478 (40.3)	360 (39.7)

relationship to study medication At least 1 grade 3-4 TEAE possibly or probably related to study medication	115 (26.3)	86 (20.1)	332 (28.0)	255 (28.1)
SP = safety population; TEAE = treatment-emergent adverse event; TCF = docetaxel + cisplatin + 5-fluorouracil; CF = cisplatin + 5-fluorouracil.				

445 subjects in TAX 325A phase III, 79 subjects in TAX 325 phase II and 15 subjects in XRP6976E/1001 were evaluable for safety analysis.

In the TCF arm of the 325A phase III part, 1186 cycles were administered to 221 subjects. The median duration of study chemotherapy was 19 weeks. The median number of cycles by subjects was 6 (range 1- 16). The number of subjects with at least 1 dose reduction was 91 (41.2 %). The number of subjects with at least 1 cycle delay was 141 (63.8 %). The median Relative Dose Intensity of docetaxel, cisplatin and 5-FU was 0.92, 0.91 and 0.89 respectively.
In the CF arm, 906 cycles were administered to 224 subjects. The median duration of study chemotherapy was 16 weeks. The median number of cycles by subjects was 4 (range 1- 12). The number of subjects with at least 1 dose reduction was 81 (36.2 %). The number of subjects with at least 1 cycle delay was 95 (42.4 %). The median Relative Dose Intensity of cisplatin and 5-FU was 0.96 and 0.95 respectively.

TEAEs any grade were observed in all subjects except 1 in the TCF phase II part and 3 in the CF phase III part. Incidence of TEAEs by subject, both regardless of relationship to and related to the study medication as well as grade 3-4 were similar for the TCF treatment group in the phase II and III parts, while the percentages of grade 3-4 TEAEs were slightly lower in the CF treatment group in the phase III part. The TEAEs by cycle were similar across the phase II and III parts and treatment groups.

Treatment-emergent adverse events (TEAEs)

The main differences in grade 3-4 TEAEs between the TCF and CF treatment groups in the phase III part, regardless of relationship to and related to the study medication, were more diarrhea, fever in absence of infection and infection in the TCF treatment group, and more stomatitis in the CF treatment group.
The TCF treatment group had a similar safety profile between the phase II and III parts, except for stomatitis, which was more common in the phase II part, probably due to the fact that guidelines for dose modifications of 5-FU were adjusted between the phase II and the phase III part of the study.
In all treatment groups, gastrointestinal TEAEs were the most common TEAEs, both regardless of relationship to the study medication and related to the study medication.

Table 16 - Subjects with TEAEs by NCIC-CTC category related to study medication (SP)

NCIC-CTC category	Number (%) of subjects			
	TAX 325A Phase III			
	TCF		CF	
	Grade 3-4	Any grade	Grade 3-4	Any grade
By Subject (Total)I	221 (100.0)		224 (100.0)	
Gastrointestinal	108 (48.9)	205 (92.8)	106 (47.3)	204 (91.1)
Flu-like symptoms	45 (20.4)	148 (67.0)	35 (15.6)	116 (51.8)
Neurologic	33 (14.9)	114 (51.6)	20 (8.9)	100 (44.6)
Infection	28 (12.7)	37 (16.7)	16 (7.1)	27 (12.1)
Skin	12 (5.4)	154 (69.7)	7 (3.1)	113 (50.4)
Cardiovascular	6 (2.7)	49 (22.2)	15 (6.7)	28 (12.5)
Genitourinary	4 (1.8)	14 (6.3)	5 (2.2)	12 (5.4)

NCIC-CTC category	Number (%) of subjects			
	TAX 325A Phase III			
	TCF		CF	
	Grade 3-4	Any grade	Grade 3-4	Any grade
Hypersensitivity	4 (1.8)	21 (9.5)	0 (0)	6 (2.7)
Hepatic	1 (0.5)	1 (0.5)	0 (0)	0 (0)
Pulmonary	1 (0.5)	28 (12.7)	4 (1.8)	22 (9.8)
Other	1 (0.5)	11 (5.0)	1 (0.4)	6 (2.7)
Blood bone marrow	0 (0)	1 (0.5)	0 (0)	1 (0.4)
Ocular	0 (0)	20 (9.0)	2 (0.9)	7 (3.1)
Dentition	0 (0)	0 (0)	0 (0)	1 (0.4)
Osseous	0 (0)	1 (0.5)	0 (0)	0 (0)
Endocrine	0 (0)	3 (1.4)	0 (0)	0 (0)

Data are ordered by frequency of grade 3-4 TEAEs in the TCF treatment group.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population; TEAE = Treatment-emergent adverse event

Table 17 - Subjects with TEAEs by NCIC-CTC category regardless of relationship to study medication (SP)

NCIC-CTC category	Number (%) of subjects			
	TAX 325A Phase III			
	TCF		CF	
	Grade 3-4	Any grade	Grade 3-4	Any grade
By Subject (Total)I	221 (100.0)		224 (100.0)	
Gastrointestinal	122 (55.2)	214 (96.8)	119 (53.1)	212 (94.6)
Flu-like symptoms	51 (23.1)	167 (75.6)	45 (20.1)	155 (69.2)
Neurologic	50 (22.6)	149 (67.4)	37 (16.5)	144 (64.3)
Cancer-related symptoms	40 (18.1)	74 (33.5)	45 (20.1)	73 (32.6)
Cardiovascular	39 (17.6)	95 (43.0)	37 (16.5)	78 (34.8)
Infection	36 (16.3)	65 (29.4)	23 (10.3)	51 (22.8)
Skin	15 (6.8)	158 (71.5)	8 (3.6)	119 (53.1)
Pulmonary	7 (3.2)	59 (26.7)	14 (6.3)	54 (24.1)
Genitourinary	7 (3.2)	31 (14.0)	8 (3.6)	28 (12.5)
Hypersensitivity	4 (1.8)	24 (10.9)	0 (0)	13 (5.8)
Other	4 (1.8)	33 (14.9)	2 (0.9)	24 (10.7)
Osseous	4 (1.8)	15 (6.8)	0 (0)	3 (1.3)
Hepatic	2 (0.9)	3 (1.4)	2 (0.9)	2 (0.9)
Ocular	1 (0.5)	23 (10.4)	2 (0.9)	10 (4.5)
Blood bone marrow	0 (0)	1 (0.5)	0 (0)	1 (0.4)
Dentition	0 (0)	5 (2.3)	1 (0.4)	4 (1.8)
Endocrine	0 (0)	4 (1.8)	1 (0.4)	1 (0.4)
Metabolic	0 (0)	0 (0)	1 (0.4)	2 (0.9)

Data are ordered by frequency of grade 3-4 TEAEs in the TCF treatment group.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population; TEAE = Treatment-emergent adverse event

Analysis of specific adverse events

Analysis of TAX 325A phase III safety data

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).

TEAEs, 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. The frequency of specific AEs was generally similar between the two groups, although some notable differences were apparent within the safety profiles of each group. In particular, among any grade TEAE regardless of relationship to study medication, diarrhea, neurosensory, 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.

Table 18 - TE-SAEs by NCIC-CTC term in at least 2 subjects, by relationship to study medication (SP)

NCIC-CTC term	Number (%) of subjects			
TAX325A phase III	TCF (N=221)		CF (N=224)	
	Related	Regardless	Related	Regardless
Infection	33 (14.9)	41 (18.6)	17 (7.6)	28 (12.5)
Fever in Absence of Infection	37 (16.7)	37 (16.7)	9 (4.0)	10 (4.5)
Diarrhea	23 (10.4)	25 (11.3)	10 (4.5)	11 (4.9)
Vomiting	22 (10.0)	24 (10.9)	20 (8.9)	24 (10.7)
Granulocytes	23 (10.4)	23 (10.4)	6 (2.7)	6 (2.7)
Stomatitis	18 (8.1)	18 (8.1)	23 (10.3)	23 (10.3)
Nausea	15 (6.8)	17 (7.7)	9 (4.0)	10 (4.5)
Gastrointestinal bleeding	3 (1.4)	11 (5.0)	1 (0.4)	8 (3.6)
Venous	1 (0.5)	11 (5.0)	1 (0.4)	9 (4.0)
Anorexia	8 (3.6)	9 (4.1)	2 (0.9)	4 (1.8)
Lethargy	7 (3.2)	8 (3.6)	4 (1.8)	4 (1.8)
Hemoglobin	7 (3.2)	7 (3.2)	8 (3.6)	9 (4.0)
Cortical, somnolence	1 (0.5)	6 (2.7)	0 (0)	1 (0.4)
Small Bowel Obstruction	0 (0)	5 (2.3)	0 (0)	3 (1.3)
Hypotension	1 (0.5)	5 (2.3)	3 (1.3)	4 (1.8)
Platelets	5 (2.3)	5 (2.3)	9 (4.0)	9 (4.0)
Creatinine	5 (2.3)	5 (2.3)	10 (4.5)	10 (4.5)
Cancer pain	0 (0)	4 (1.8)	0 (0)	4 (1.8)
Dysrhythmias	1 (0.5)	4 (1.8)	0 (0)	1 (0.4)
Other: dehydration	1 (0.5)	4 (1.8)	0 (0)	1 (0.4)
Gastrointestinal pain/cramping	2 (0.9)	3 (1.4)	0 (0)	4 (1.8)
Fistula	0 (0)	3 (1.4)	0 (0)	0 (0)
Hyponatremia	1 (0.5)	3 (1.4)	0 (0)	2 (0.9)
Shortness of breath	0 (0)	3 (1.4)	3 (1.3)	6 (2.7)
Other: kidney failure	1 (0.5)	2 (0.9)	2 (0.9)	3 (1.3)
Constipation	2 (0.9)	2 (0.9)	0 (0)	0 (0)
Other: accidental injury (osseous)	0 (0)	2 (0.9)	0 (0)	0 (0)
Other: electrolyte abnormality	2 (0.9)	2 (0.9)	0 (0)	0 (0)
Dizziness	1 (0.5)	2 (0.9)	0 (0)	0 (0)

NCIC-CTC term	Number (%) of subjects			
TAX325A phase III	TCF (N=221)		CF (N=224)	
	Related	Regardless	Related	Regardless
Neuromotor	0 (0)	2 (0.9)	0 (0)	0 (0)
Other: reaction unevaluable	0 (0)	2 (0.9)	0 (0)	0 (0)
Prothrombin time	1 (0.5)	2 (0.9)	1 (0.4)	1 (0.4)
Pain chest	1 (0.5)	2 (0.9)	0 (0)	1 (0.4)
Arterial non myocardial	0 (0)	2 (0.9)	0 (0)	2 (0.9)
Esophagitis/dysphagia/ odynophagia	1 (0.5)	1 (0.5)	2 (0.9)	4 (1.8)
Other: apnea	0 (0)	1 (0.5)	1 (0.4)	2 (0.9)
Other: pneumothorax	0 (0)	1 (0.5)	0 (0)	2 (0.9)
Other: pancreatitis	0 (0)	0 (0)	1 (0.4)	2 (0.9)
Other: gastrointestinal disorder	0 (0)	0 (0)	0 (0)	2 (0.9)
Altered hearing	0 (0)	0 (0)	2 (0.9)	2 (0.9)
Hyperglycemia	0 (0)	0 (0)	0 (0)	2 (0.9)
Ischemia myocardial	0 (0)	0 (0)	3 (1.3)	4 (1.8)

Data are ordered by the regardless column of the TCF treatment group.
TCF = Taxotere + cisplatin + 5-fluorouracil; CF = Cisplatin + 5-fluorouracil; SP = Safety population; TE-SAE = Treatment-emergent serious adverse event

NCIC-CTC grade 3-4 TEAEs, regardless of relationship to study medication, were experienced by 81.4% of TCF-treated subjects and 75.4% of CF-treated subjects. Among grade 3-4 TEAEs, the 5 most frequently observed TEAEs in the TCF treatment group, regardless of relationship to study medication, were lethargy (21.3%), stomatitis (20.8%), diarrhea (20.4%), cancer pain (18.1%), and infection (16.3%). The 5 most frequent grade 3-4 TEAEs observed in the CF treatment group, regardless of relationship to study medication, were stomatitis (27.2%), cancer pain (19.6%), nausea (18.8%), vomiting (18.8%), and lethargy (17.9%). TE-SAEs, regardless of relationship, were also greater in the TCF treatment group (62.0% of TCF-treated subjects and 45.1% of CF-treated subjects). However, the incidence of grade 3-4 TE-SAE (regardless of relationship) by cycle was comparable across treatment groups (13.2% of TCF cycles and 12.5% of CF cycles).

Although a higher incidence of grade 3-4 TEAE and TE-SAE was seen in the TCF treatment group, the 60-day all-cause mortality rate was comparable between treatment groups, with 6.8% of TCF-treated subjects and 8.9% of CF-treated subjects dying within 60 days of randomization. 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.

AEs leading to treatment discontinuation, regardless of relationship, were also comparable between both treatment groups, occurring in 27.1% of subjects in the TCF treatment group and in 25.0% of subjects in the CF treatment group. Of note, AEs leading to treatment discontinuation often occurred in later cycles. Among TCF-treated subjects, 10.0% had AEs leading to treatment discontinuation within the first 4 cycles, while 11.6% of CF-treated subjects had AEs leading to treatment discontinuation within the first 3 cycles.

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

Infections occurred with increased frequency in the TCF treatment group, 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. In particular, 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.

Hematological abnormalities were frequent in this study, and grade 3-4 neutropenia was more frequent in the TCF treatment group, occurring in 82.3% of TCF-treated subjects and 56.8% of CF-treated subjects. Neutropenic infections were similarly more frequent in the TCF treatment group, with 15.9% of the TCF treatment group and 10.4% of the CF treatment group having neutropenic infections. In addition, febrile neutropenia occurred in 16.4% of TCF-treated subjects compared to 4.5% of CF-treated subjects. Neutropenic infection comprised 31 (68.9%) of 45 cycles with infection TE-SAE in the TCF treatment group, and 16 (53.3%) of 30 cycles with infection TE-SAE in the CF treatment group. Of 7 deaths in the TCF group and 6 of the deaths in the CF group that occurred within 30 days of the last administration of study medication, in which infection or moniliasis led to death, all but two had concurrent grade 3-4 neutropenia. Of note, in this study prophylactic G-CSF was used in a minority of evaluable cycles (TCF: 10.0%; CF: 3.3%). In the TCF treatment group, grade 3-4 neutropenia was reported in 52.3% of evaluable cycles without G-CSF compared to 37.0% of evaluable cycles with prophylactic G-CSF.

Strategies that mitigate the risk of neutropenic infection (for example, more proactive use of GCSF) might enhance the safety profile of TCF in patients with metastatic gastric cancer. 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. In the TCF treatment group, 12.2% of subjects receiving prophylactic G-CSF experienced febrile neutropenia or neutropenic infection, while 28.3% of subjects without prophylactic G-CSF experienced febrile neutropenia or neutropenic infection.

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 frequently 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 TEAEs 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 TEAEs, compared to 3.6% of subjects in the CF treatment group. However, discontinuation of treatment due to neurosensory TEAEs occurred in later cycles, with no TCF subject discontinuing treatment due to neurosensory TEAEs prior to the fourth cycle.

Analysis of Serious adverse events

Deaths

Overall, 336 of 445 (75.5%) treated subjects died: 163 (73.8%) TCF-treated subjects and 173 (77.2%) CF-treated subjects. Of these, 15 (6.8%) TCF-treated subjects and 20 (8.9%) CF-treated subjects died within 60 days from the randomization date. There were 42 deaths (9.4%) during study treatment (within 30 days of the last administration of study medication): 23 (10.4%) of the TCF-treated subjects and 19 (8.5%) of the CF-treated subjects. There were 294 (66.1%) deaths more than 30 days after last administration of study medication: 140 (63.3%) of the TCF-treated subjects and 154 (68.8%) of the CF-treated subjects.

Table 19 - Summary of deaths (SP)

TAX 325A Phase III	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

Infection was the most common AE leading to a non-malignant cause of death within 30 days of the last administration of study medication, with 6 subjects in the TCF treatment group and 6 subjects in the CF treatment group who had infection-associated deaths. In all of these cases the infection was considered by the investigator to be related to study medication. In addition, a seventh subject in the TCF-treatment group had grade 4 moniliasis leading to death, considered by the investigator to be unlikely related to study medication but possibly related by the sponsor. In 3 TCF-treated subjects and 3 CF-treated subjects the infection-associated death occurred following a single cycle of treatment. Frequently, the fatal infection or fatal moniliasis was concurrent with grade 3-4 neutropenia, being so in 5 of the 7 TCF-treated subjects who had infection or moniliasis leading to death within 30 days of the last administration of study medication, and in all 6 CF-treated subjects who had infection leading to death within 30 days of the last administration of study medication.

Overall, 5 of 16 (31.3%) non-malignant deaths that occurred within 30 days of the last administration of study medication in the TCF treatment group, and 6 of 15 (40%) non-malignant deaths that occurred within 30 days of the last administration of study medication in the CF treatment group, were due to infections/moniliasis occurring with grade 3-4 neutropenia. Overall, 11 of the 13 (84.6%) infections or moniliasis leading to death within 30 days of the last administration of study medication in this study were in association with grade 3-4 neutropenia.

Other frequent AEs leading to non-malignant death within 30 days of the last administration of study medication, included GI bleeding (2 TCF-treated subjects and 2 CF-treated subjects), and venous events (pulmonary embolism) (3 TCF-treated subjects and 2 CF-treated subjects). There were no cases of diarrhea, vomiting, or nausea reported as the AE leading to death, while one subject (CF-treated) was reported with stomatitis as the AE leading to death within 30 days of the last administration of study medication.

Of the 294 subjects (66.1%) who died more than 30 days after their last i.v. infusion, all but 20 died of their malignant disease: 11 in the TCF treatment group and 9 in the CF treatment group. There were 5 deaths related to study medication more than 30 days after the last administration of study medication: 2 in TCF-treated subjects and 3 in CF-treated subjects. These included one infection and one hepatic failure in TCF-treated subjects, and two infections and one renal failure in CF-treated subjects.

Of the 11 subjects in the TCF treatment group and 9 subjects in the CF treatment group having non-malignant deaths more than 30 days after the last administration of study medication, 10 subjects (3 TCF-treated subjects and 7 CF-treated subjects) died from infection or an infectious complication (peritonitis, sepsis, or septic shock). However, the fatal infection was considered to be study drug related in one TCF subject, and 2 CF treated subjects. In 2 of these subjects, the infections were concomitant with grade 3-4 neutropenia.

Other serious adverse events (treatment emergent serious adverse events)

Incidences of TE-SAEs of both any grade and grade 3-4, both treatment-related and regardless of relationship to the study medication, were more common in the TCF treatment groups than in the CF treatment group in the phase III part.
Incidences were similar for TE-SAEs per cycle in the phase II and III parts for the TCF treatment group.

The incidence of TE-SAEs was similar for TCF in the phase II and III parts, except for granulocytes, which was more frequently serious for TCF in phase III.
The incidence of fever in absence of infection, infection, diarrhea and granulocytes, related to and regardless of relationship to the study medication, were more frequent in the TCF treatment groups than in CF, and explained the higher incidence of subjects with at least one TE-SAE in TCF.
Results by cycle tended to reflect those by subject, except infection per cycle which was similar in the TCF and CF treatment groups.

Table 20 - Overview of subjects and cycles with TE-SAEs (SP)

	Number (%)	
	TAX 325A phase III	
	TCF	CF
Total subjects	221 (100.0)	224 (100.0)
At least 1 TE-SAE regardless of relationship to study medication	137 (62.0)	101 (45.1)
At least 1 TE-SAE possibly or probably related to study medication	103 (46.6)	65 (29.0)
At least 1 grade 3-4 TE-SAE regardless of relationship to study medication	117 (52.9)	92 (41.1)
At least 1 grade 3-4 TE-SAE possibly or probably related to study medication	85 (38.5)	60 (26.8)
Total cycles	1186 (100.0)	906 (100.0)
At least 1 TE-SAE regardless of relationship to study medication	204 (17.2)	128 (14.1)
At least 1 TE-SAE possibly or probably related to study medication	146 (12.3)	79 (8.7)
At least 1 grade 3-4 TE-SAE regardless of relationship to study medication	156 (13.2)	113 (12.5)
At least 1 grade 3-4 TE-SAE possibly or probably related to study medication	108 (9.1)	70 (7.7)

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

	Number (%)	
	TAX 325A phase III	
	TCF	CF

TE-SAE = Treatment-emergent serious adverse event

The following Table presents a summary of the most common TE SAEs (in ≥5% of subjects or ≥2% of cycles):

Table 21 - TE-SAEs by NCIC-CTC term, regardless of relationship to study medication and related to study medication, in at least 5% of subjects or at least 2% of cycles

	Number (%)			
	TAX 325A phase III			
	TCF		CF	
	Related	Regardless	Related	Regardless
Total number of subjects with at least one TE-SAE	**103 (46.6)**	**137 (62.0)**	**65 (29.0)**	**101 (45.1)**
Fever in absence of infection	37 (16.7)	37 (16.7)	9 (4.0)	10 (4.5)
Infection	33 (14.9)	41 (18.6)	17 (7.6)	28 (12.5)
Diarrhea	23 (10.4)	25 (11.3)	10 (4.5)	11 (4.9)
Granulocytes	23 (10.4)	23 (10.4)	6 (2.7)	6 (2.7)
Vomiting	22 (10.0)	24 (10.9)	20 (8.9)	24 (10.7)
Stomatitis	18 (8.1)	18 (8.1)	23 (10.3)	23 (10.3)
Nausea	15 (6.8)	17 (7.7)	9 (4.0)	10 (4.5)
Hemoglobin	7 (3.2)	7 (3.2)	8 (3.6)	9 (4.0)
Lethargy	7 (3.2)	8 (3.6)	4 (1.8)	4 (1.8)
Gastrointestinal bleeding	3 (1.4)	11 (5.0)	1 (0.4)	8 (3.6)
Venous	1 (0.5)	11 (5.0)	1 (0.4)	9 (4.0)
Hypotension	1 (0.5)	5 (2.3)	3 (1.3)	4 (1.8)
Small bowel obstruction	0 (0)	5 (2.3)	0 (0)	3 (1.3)
Fever in absence of infection	NP	48 (4.0)	NP	10 (1.1)
Infection	NP	45 (3.8)	NP	30 (3.3)
Diarrhea	NP	27 (2.3)	NP	11 (1.2)
Vomiting	NP	25 (2.1)	NP	24 (2.6)
Granulocytes	NP	24 (2.0)	NP	6 (0.7)
Stomatitis	NP	21 (1.8)	NP	26 (2.9)

Note: Data for subjects are ordered by frequency of related TE-SAEs in the TCF treatment group from the TAX 325A phase III study, data
for cycles by frequency in the TCF treatment group from the TAX 325A phase III study.
SP = safety population; TCF = docetaxel + cisplatin + 5-fluorouracil; CF = cisplatin + 5-fluorouracil; NCIC= National Cancer Institute of Canada; TE-SAE = treatment-emergent serious adverse event; NP = not provided

Adverse events leading to study discontinuation

Table 22 - Reason for treatment discontinuation (FAP)

Primary reason for discontinuation	Number (%) TAX 325A phase III	
	TCF (N=221)	CF (N=224)
Total discontinued	216 (97.7)	214 (95.5)
Progressive disease	66 (29.9)	98 (43.8)
Adverse event	60 (27.1)	56 (25.0)
Related AE (i.e., toxicity)[a]	52 (23.5)	47 (21.0)
Not related AE	8 (3.6)	9 (4.0)

Consent withdrawn	48 (21.7)	26 (11.6)
Death	23 (10.4)	21 (9.4)
Malignant disease	7 (3.2)	5 (2.2)
Toxicity from study medication	6 (2.7)	10 (4.5)
Other	10 (4.5)	6 (2.7)
Other	14 (6.3)	11 (4.9)
Other major protocol violation	2 (0.9)	2 (0.9)
Lost to follow-up	3 (1.4)	0 (0)

FAP = full analysis population; TCF = docetaxel + cisplatin + 5-fluorouracil; CF = cisplatin + 5-fluorouracil; AE = adverse event

[a] Five subjects were discontinued for related AE and for not related AE but were counted only as related AE.

In the phase III part, the main reason for study treatment discontinuation was also progressive disease, but the incidence was higher in CF than in TCF. A similar rate of subjects discontinued study treatment due to AE and death in both groups, while a higher rate discontinued study treatment due to consent withdrawn in TCF than in the CF treatment group. In the phase III part, the 3 most common AEs leading to discontinuation in the TCF treatment group were neurosensory, infection, and lethargy. In the CF treatment group, the 3 most common AEs leading to treatment discontinuation were neurosensory, altered hearing, and creatinine. Discontinuation from study treatment due to neurosensory TEAEs occurred in later cycles, with no phase III TCF subject discontinuing treatment due to neurosensory TEAEs prior to the fourth cycle.

Safety in special groups

Age

Table 23 - Overview of subjects with TEAEs and TE-SAEs by age (SP)

	Number (%) of subjects			
	<65 years		≥65 years	
Type of event	**TCF**	**CF**	**TCF**	**CF**
Total number of subjects	167 (100.0)	169 (100.0)	54 (100.0)	55 (100.0)
At least 1 TEAE regardless of relationship to study medication	167 (100.0)	166 (98.2)	54 (100.0)	55 (100.0)
At least 1 TEAE possibly or probably related to study medication	161 (96.4)	160 (94.7)	53 (98.1)	52 (94.5)
At least 1 grade 3-4 TEAE regardless of relationship to study medication	138 (82.6)	127 (75.1)	42 (77.8)	42 (76.4)
At least 1 grade 3-4 TEAE possibly or probably related to study medication	115 (68.9)	98 (58.0)	37 (68.5)	34 (61.8)
At least 1 TE-SAE regardless of relationship to study medication	98 (58.7)	71 (42.0)	39 (72.2)	30 (54.5)
At least 1 TE-SAE possibly or probably related to study medication	74 (44.3)	43 (25.4)	29 (53.7)	22 (40.0)

SP = safety population; TEAE = treatment-emergent adverse event; TE-SAE = treatment-emergent serious adverse event; TCF = docetaxel + cisplatin + 5-fluorouracil; CF = cisplatin + 5-fluorouracil

No data on the TCF combination is available for pediatric population.
Safety data by age groups (elderly, ≥65 years of age; younger, <65 years of age) were only analyzed in the phase III part. There were 336 younger subjects and 109 elderly subjects.

Table 24 - TEAEs by NCIC-CTC term, regardless of relationship to study medication by age in at least 10% of subjects with any grade or in at least 5% of subjects with grade 3-4 (SP)

	Number (%) of subjects							
	Age <65 years				Age ≥65 years			
	TCF (N=167)		CF (N=169)		TCF (N=54)		CF (N=55)	
NCIC-CTC term	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade
Subject with at least one TEAE	138 (82.6)	167 (100.0)	127 (75.1)	166 (98.2)	42 (77.8)	54 (100.0)	42 (76.4)	55 (100.0)
Lethargy	35 (21.0)	98 (58.7)	30 (17.8)	95 (56.2)	12 (22.2)	41 (75.9)	10 (18.2)	35 (63.6)
Stomatitis	34 (20.4)	93 (55.7)	47 (27.8)	101 (59.8)	12 (22.2)	38 (70.4)	14 (25.5)	36 (65.5)
Diarrhea	32 (19.2)	124 (74.3)	11 (6.5)	82 (48.5)	13 (24.1)	48 (88.9)	7 (12.7)	29 (52.7)
Cancer pain	32 (19.2)	61 (36.5)	38 (22.5)	61 (36.1)	8 (14.8)	13 (24.1)	6 (10.9)	12 (21.8)
Nausea	26 (15.6)	122 (73.1)	35 (20.7)	134 (79.3)	9 (16.7)	40 (74.1)	7 (12.7)	37 (67.3)
Vomiting	25 (15.0)	110 (65.9)	32 (18.9)	127 (75.1)	8 (14.8)	37 (68.5)	10 (18.2)	37 (67.3)
Infection	24 (14.4)	46 (27.5)	15 (8.9)	36 (21.3)	12 (22.2)	19 (35.2)	8 (14.5)	15 (27.3)
Anorexia	22 (13.2)	82 (49.1)	21 (12.4)	93 (55.0)	7 (13.0)	30 (55.6)	5 (9.1)	28 (50.9)
Neurosensory	13 (7.8)	67 (40.1)	4 (2.4)	43 (25.4)	4 (7.4)	17 (31.5)	3 (5.5)	12 (21.8)
Venous	13 (7.8)	16 (9.6)	9 (5.3)	9 (5.3)	4 (7.4)	4 (7.4)	4 (7.3)	5 (9.1)
Alopecia	10 (6.0)	116 (69.5)	3 (1.8)	78 (46.2)	1 (1.9)	31 (57.4)	0 (0)	14 (25.5)
Dizziness	6 (3.6)	22 (13.2)	3 (1.8)	15 (8.9)	4 (7.4)	13 (24.1)	1 (1.8)	3 (5.5)
Constipation	4 (2.4)	39 (23.4)	4 (2.4)	54 (32.0)	0 (0)	17 (31.5)	3 (5.5)	22 (40.0)
Fever in absence of infection	4 (2.4)	57 (34.1)	2 (1.2)	39 (23.1)	0 (0)	22 (40.7)	1 (1.8)	12 (21.8)
Mood	4 (2.4)	25 (15.0)	1 (0.6)	17 (10.1)	1 (1.9)	6 (11.1)	0 (0)	6 (10.9)
Myalgia	4 (2.4)	24 (14.4)	3 (1.8)	18 (10.7)	0 (0)	4 (7.4)	0 (0)	3 (5.5)
Hypersensitivity, other: allergic reaction	4 (2.4)	20 (12.0)	0 (0)	7 (4.1)	0 (0)	3 (5.6)	0 (0)	6 (10.9)
Hypotension	4 (2.4)	20 (12.0)	4 (2.4)	14 (8.3)	1 (1.9)	7 (13.0)	0 (0)	3 (5.5)
Neuromotor	4 (2.4)	14 (8.4)	3 (1.8)	10 (5.9)	3 (5.6)	5 (9.3)	3 (5.5)	7 (12.7)
Gastrointestinal bleeding	4 (2.4)	16 (9.6)	6 (3.6)	12 (7.1)	3 (5.6)	5 (9.3)	1 (1.8)	3 (5.5)
Esophagitis/ dysphagia/ odynophagia	3 (1.8)	33 (19.8)	9 (5.3)	25 (14.8)	1 (1.9)	3 (5.6)	2 (3.6)	6 (10.9)
Gastrointestinal pain/ cramping	3 (1.8)	20 (12.0)	4 (2.4)	9 (5.3)	1 (1.9)	5 (9.3)	2 (3.6)	7 (12.7)
Shortness of breath	3 (1.8)	10 (6.0)	8 (4.7)	19 (11.2)	1 (1.9)	7 (13.0)	3 (5.5)	5 (9.1)
Edema	2 (1.2)	26 (15.6)	1 (0.6)	20 (11.8)	0 (0)	14 (25.9)	1 (1.8)	12 (21.8)
Insomnia	1 (0.6)	34 (20.4)	1 (0.6)	23 (13.6)	0 (0)	14 (25.9)	1 (1.8)	10 (18.2)
Headache	1 (0.6)	18 (10.8)	0 (0)	21 (12.4)	0 (0)	4 (7.4)	0 (0)	5 (9.1)
Heartburn	1 (0.6)	18 (10.8)	0 (0)	7 (4.1)	0 (0)	5 (9.3)	0 (0)	6 (10.9)
Rash/itch	1 (0.6)	18 (10.8)	0 (0)	15 (8.9)	1 (1.9)	8 (14.8)	0 (0)	4 (7.3)

	Number (%) of subjects							
	Age <65 years				Age ≥65 years			
	TCF (N=167)		CF (N=169)		TCF (N=54)		CF (N=55)	
NCIC-CTC term	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade
Local toxicity	0 (0)	28 (16.8)	2 (1.2)	14 (8.3)	0 (0)	4 (7.4)	1 (1.8)	5 (9.1)
Hiccough	0 (0)	16 (9.6)	0 (0)	12 (7.1)	0 (0)	7 (13.0)	1 (1.8)	7 (12.7)
Cough	0 (0)	12 (7.2)	0 (0)	13 (7.7)	0 (0)	8 (14.8)	0 (0)	7 (12.7)
Taste, sense of smell altered	0 (0)	12 (7.2)	0 (0)	7 (4.1)	0 (0)	8 (14.8)	0 (0)	3 (5.5)
Altered hearing	0 (0)	11 (6.6)	3 (1.8)	23 (13.6)	0 (0)	3 (5.6)	1 (1.8)	5 (9.1)
Dry skin	0 (0)	11 (6.6)	0 (0)	9 (5.3)	0 (0)	7 (13.0)	0 (0)	1 (1.8)
Nail changes	0 (0)	11 (6.6)	0 (0)	0 (0)	0 (0)	7 (13.0)	0 (0)	0 (0)

Note: Data are ordered by the grade 3-4 column of the TCF treatment group, age <65 years
SP = safety population; TEAE = treatment-emergent adverse event; TCF = docetaxel + cisplatin + 5-fluorouracil; CF = cisplatin + 5-fluorouracil; NCIC-CTC = National Cancer Institute of Canada – common toxicity criteria

In the TCF treatment group, elderly (≥65 years old) and younger (<65 years old) subjects experienced a similar rate of TEAEs, any grade and grade 3-4, but more elderly subjects experienced TE-SAEs, both regardless of relationship to the study medication and related to the study medication. In the CF treatment group, elderly and younger subjects experienced a similar rate of TEAEs, any grade and grade 3-4, but more elderly subjects experienced TE-SAEs, both regardless of relationship to the study medication and related to the study medication. The differences observed in the overall population are also observed in the age sub-group populations.

The main difference for grade 3-4 TEAEs between elderly and younger subjects is infection, which was more common in elderly subjects. There was a difference between diarrhea any grade, however, this difference was less obvious for grade 3-4. Incidence of stomatitis was similar. The differences between the TCF and CF treatment groups observed in the overall population were also observed within elderly and younger sub-populations.

The frequency of infections, of any grade or grades 3 or 4, treatment-related or regardless of relationship to the study medication, by cycle or subject, was higher in elderly compared to younger subjects within the TCF treatment group. Incidences are similar within the CF treatment group, except for infections any grade and regardless of relationship to the study medication. Infection by subject in the elderly sub-group, regardless of relationship, tended to occur at a higher frequency in the TCF treatment group compared to the CF treatment group. However, a similar rate of fatal study treatment-related infection occurred in elderly TCF-treated subjects and in elderly CF-treated subjects. Among the 7 and 8 fatal treatment-related infections in the TCF and CF treatment groups, 3 occurred in elderly TCF-treated subjects, and 2 occurred in elderly CF-treated.

Febrile neutropenia and neutropenic infection, treatment-related and regardless of relationship to the study medication, occurred at higher frequencies in the elderly in the TCF treatment group, whereas the frequencies were comparable for the 2 age groups in the CF treatment group. The frequencies were higher in the TCF treatment group compared to the CF treatment group. However, the incidence of death from febrile neutropenia or neutropenic infection was similar.

Gender and race

Safety data by gender (male; female) were only analyzed in the phase III part. There were 317 men and 128 women. TEAEs were generally comparable between male and female subjects in both treatment groups. However, in the TCF treatment group notable differences (≥10%) were seen in the incidences of TEAEs (any grade, regardless of relationship to the study medication) of hypotension,

nausea, headache, hiccough, skin local toxicity, and rash/itch. All except hiccough were seen more frequently in females (62 TCF-treated subjects) than in males (159 TCF-treated subjects). In the CF treatment group, no notable differences were seen in the incidences of TEAEs between female and male subjects.

Safety data by race (Caucasian subjects; non-Caucasian) were only analyzed in the phase III part. There were 315 Caucasian subjects and 130 non-Caucasian subjects. TEAEs were generally comparable between Caucasian and non-Caucasian subjects in both treatment groups. However, in the TCF treatment group, notable differences (≥10%) were seen in the incidences of TEAEs (any grade, regardless of relationship to the study medication) including: cancer pain, anorexia, vomiting, dizziness, and insomnia with a higher frequency in non-Caucasians (64 TCF-treated subjects), and fever in absence of infection, lethargy, stomatitis, skin local toxicity, venous disorder, and heartburn with a higher frequency in Caucasians (157 TCF-treated subjects). In CF arm cancer pain, anorexia, infection, insomnia, alopecia, and neuromotor TEAEs (any grade, regardless of relationship to the study medication) were more frequent (difference ≥10%) in non-Caucasian and lethargy was more frequent in Caucasian.

Pregnancy and Lactation

No pregnant or lactating women were randomized in these studies as these were exclusion criteria since pregnancy and lactation are contra-indicated for the use of docetaxel.

Overdose

In the study TAX 325A phase III, any administered dose of docetaxel above 110% of the dose calculated from the subject's body surface area was considered as an overdose. For cisplatin and 5-FU, the limit was 120%. There were 5 subjects (4 TCF, 1 CF) in the 2 studies who received doses of study chemotherapy that were considered "high." All were slightly above the definition of overdose and none gave any indication of associated safety concerns.
In the phase III study, 4 TCF-treated subjects received a dose higher than the limit, 3 TCF-treated subjects (dose of docetaxel between 83.1 mg/m² and 84.1 mg/m² instead of 75 mg/m², 2 at cycle 1 and 1 at cycle 2) and 1 CF-treated subject (dose of cisplatin at 120.3 mg/m² and 5-FU 6012.6 mg/m² at cycle 4, instead of 100 mg/m² and 5000 mg/m², respectively). One of these subjects (74 years old) experienced grade 4 hepatic failure at cycle 1, went-off study for toxicity and died on D49 from hepatic failure, considered as related to the study medication. Liver function was normal at baseline. Other subjects did not experience unexpected related AEs, and the nature and severity of the AEs reported during this cycle were not any different from what the subjects experienced during other cycles of chemotherapy.

Phase II, TAX 325

Patient exposure
438 cycles TCF were administered to 79 subjects. The median duration of study chemotherapy was 19 weeks. The median number of cycles by subjects was 6 (range 1- 13). The number of subjects with at least 1 dose reduction was 32 (40.5 %). The number of subjects with at least 1 cycle delay was 45 (57 %). The median Relative Dose Intensity of docetaxel, cisplatin and 5-FU was 0.93, 0.92 and 0.92 respectively.

Treatment-emergent adverse events (TEAEs)

Table 25 - Overview of subjects and cycles with TEAEs

Type of TEAE	Number (%)			
	TC		TCF	
Total subjects	76	(100)	79	(100)
At least 1 TEAE regardless of relationship to study treatment	75	(98.7)	78	(98.7)
At least 1 TEAE related to study treatment	74	(97.4)	77	(97.5)
At least 1 NCIC grade 3-4 TEAE regardless of relationship to study treatment	52	(68.4)	61	(77.2)
At least 1 NCIC grade 3-4 TEAE related to study treatment	38	(50.0)	50	(63.3)
Total cycles	428	(100)	438	(100)
At least 1 TEAE regardless of relationship to study treatment	411	(96.0)	432	(98.6)
At least 1 TEAE related to study treatment	401	(93.7)	423	(96.6)
At least 1 NCIC grade 3-4 TEAE regardless of relationship to study treatment	113	(26.4)	161	(36.8)
At least 1 NCIC grade 3-4 TEAE related to study treatment	86	(20.1)	115	(26.3)

There were slightly more TCF-treated subjects (77.2%) than TC-treated subjects (68.4%) who experienced at least 1 NCIC grade 3-4 TEAE regardless of relationship to the study indication. More TCF-treated subjects (63.3%) than TC-treated subjects (50.0%) experienced at least 1 possibly or probably study-drug related NCIC grade 3-4 TEAE.

Notable (>10%) differences were observed, for any grade, in the skin category (higher in TC-treated subjects), cardiovascular and cancer-related symptoms categories (higher in TCF-treated subjects) and, for grade 3-4, in the gastrointestinal and cardiovascular categories (higher in TCF-treated subjects).
The cardiovascular NCIC category includes edema.

Table 26 - TEAEs by NCIC category regardless of relationship to study drug (SP)

NCIC Category	Number of subjects (%)			
	TC (N = 76)		TCF (N = 79)	
	Grade 3-4	Any grade	Grade 3-4	Any grade
Total subjects with TEAE	52 (68.4)	75 (98.7)	61 (77.2)	78 (98.7)
Gastrointestinal	33 (43.4)	72 (94.7)	51 (64.6)	76 (96.2)
Flu-like symptoms	22 (28.9)	66 (86.8)	23 (29.1)	68 (86.1)
Neurologic	19 (25.0)	55 (72.4)	18 (22.8)	61 (77.2)
Skin	8 (10.5)	66 (86.8)	6 (7.6)	60 (75.9)
Cardiovascular	7 (9.2)	31 (40.8)	18 (22.8)	47 (59.5)
Infection	4 (5.3)	22 (28.9)	7 (8.9)	28 (35.4)
Pulmonary	3 (3.9)	34 (44.7)	5 (6.3)	28 (35.4)
Cancer-related symptoms	6 (7.9)	17 (22.4)	11 (13.9)	27 (34.2)
Hypersensitivity	2 (2.6)	18 (23.7)	2 (2.5)	14 (17.7)
Other[a]	3 (3.9)	11 (14.5)	0 (0)	14 (17.7)
Ocular	1 (1.3)	13 (17.1)	0 (0)	12 (15.2)
Genitourinary	1 (1.3)	7 (9.2)	0 (0)	11 (13.9)
Dentition	0 (0)	2 (2.6)	0 (0)	3 (3.8)
Osseous	1 (1.3)	4 (5.3)	1 (1.3)	2 (2.5)
Endocrine	0 (0)	1 (1.3)	0 (0)	1 (1.3)
Hepatic	0 (0)	1 (1.3)	0 (0)	0 (0)

[a] The "Other" TEAEs were: abdominal pain, accidental injury, asthenia, breast pain, dehydration, epistaxis, herpes simplex, herpes zoster, hypertonia, lymphadenopathy, nail disorder, otitis media, pain, rhinitis and sinusitis.
Note: Ordered by decreasing frequency in the TCF-treated group.

Analysis of specific adverse events

Analysis of TAX 325 phase II safety data

The safety analysis of this trial shows that the tolerability and overall safety of TCF and TC are comparable, with some exceptions. The Safety Population consisted of 155 subjects having received at least one dose of study medication. A total of 438 TCF cycles and 428 TC cycles were administered. The median number of cycles administered (6) was the same in both treatment groups (range of 1-13 for TCF and 1-14 for TC). The median duration of treatment was 19 weeks for the TCF group (range: 3-43) and 18 weeks for the TC group (range: 3-56).
The frequency of TEAEs was identical for both treatment groups, with 98.7% of subjects experiencing at least 1 TEAE in each group. Grade 3-4 TEAEs tended to be more frequent in TCF-treated subjects (77.2%) than TC-treated subjects (68.4%). The 5 most frequent grade 3-4 TEAEs among TCF-treated subjects, regardless of the relationship to study medication, were stomatitis (31.6%), lethargy (24.1%), nausea (22.8%), diarrhea (20.3%), and anorexia (20.3%). The 5 most frequent grade 3-4 TEAEs among TC-treated subjects, regardless of the relationship to study medication were lethargy (25.0%), vomiting (14.5%), anorexia (14.5%), nausea (11.8%), and neuro-sensory (10.5%).

49 TCF-treated subjects (62.0%) and 38 TC-treated subjects (50.0%) had at least 1 TE-SAE, regardless of the relationship to study treatment.

The incidence of hematologic toxicities in both treatment groups was very similar. Grade 3-4 neutropenia, regardless of the use of G-CSF, was observed in 85.7% of the TCF-treated subjects and

86.7% of the TC-treated subjects. Grade 3-4 anemia was observed in 28.6% of the TCF treated subjects and 32.0% of the TC-treated subjects. These hematologic toxicities rarely resulted in dose delays or reductions. Thrombocytopenia was infrequent in this study. Both treatments were similar with regard to the incidence of febrile neutropenia (20.8% in TCF-treated subjects and 20.0% in TC-treated subjects).

Fluid retention, mostly evidenced by grade 1 peripheral edema, was observed in 29.1% of the TCF-treated subjects and 25.0% of the TC-treated subjects. No unanticipated AEs were observed in either treatment groups.
Stomatitis, nausea, and diarrhea occured more frequently in TCF treated subjects.

Table 27 - TEAEs by NCIC term related to the study medication in greater than or equal to 5% of subjects (SP)

NCIC term	Number (%) of subjects			
	TC (N = 76)		TCF (N = 79)	
	Grade 3-4	All grade	Grade 3-4	All grade
Total subjects with related TEAE	38 (50.0)	74 (97.4)	50 (63.3)	77 (97.5)
Nausea	8 (10.5)	52 (68.4)	16 (20.3)	61 (77.2)
Diarrhea	4 (5.3)	48 (63.2)	16 (20.3)	61 (77.2)
Alopecia	3 (3.9)	65 (85.5)	1 (1.3)	59 (74.7)
Stomatitis	0 (0)	22 (28.9)	25 (31.6)	57 (72.2)
Vomiting	9 (11.8)	44 (57.9)	11 (13.9)	52 (65.8)
Lethargy	14 (18.4)	44 (57.9)	16 (20.3)	49 (62.0)
Anorexia	8 (10.5)	41 (53.9)	12 (15.2)	42 (53.2)
Neuro-sensory	8 (10.5)	33 (43.4)	9 (11.4)	29 (36.7)
Fever	3 (3.9)	25 (32.9)	3 (3.8)	28 (35.4)
Edema	2 (2.6)	19 (25.0)	2 (2.5)	21 (26.6)
Infection	2 (2.6)	12 (15.8)	7 (8.9)	14 (17.7)
Myalgia	5 (6.6)	22 (28.9)	1 (1.3)	11 (13.9)
Rigors/chills	1 (1.3)	10 (13.2)	1 (1.3)	11 (13.9)
Allergic reaction	2 (2.6)	16 (21.1)	1 (1.3)	11 (13.9)
Taste, sense of smell altered	1 (1.3)	11 (14.5)	1 (1.3)	11 (13.9)
Local toxicity (reaction at i.v. site)	0 (0)	2 (2.6)	1 (1.3)	11 (13.9)
Rash/itch	1 (1.3)	13 (17.1)	1 (1.3)	10 (12.7)
Nail changes	3 (3.9)	13 (17.1)	2 (2.5)	10 (12.7)
Dizziness	2 (2.6)	8 (10.5)	1 (1.3)	8 (10.1)
Gastrointestinal pain/cramping	0 (0)	7 (9.2)	0 (0)	8 (10.1)
Constipation	1 (1.3)	6 (7.9)	1 (1.3)	7 (8.9)
Tearing	1 (1.3)	7 (9.2)	0 (0)	7 (8.9)
Altered hearing	0 (0)	7 (9.2)	0 (0)	6 (7.6)
Headache	0 (0)	4 (5.3)	0 (0)	6 (7.6)
Hiccough	1 (1.3)	9 (11.8)	1 (1.3)	6 (7.6)
Hypotension	1 (1.3)	3 (3.9)	3 (3.8)	5 (6.3)
Neuro-motor	2 (2.6)	7 (9.2)	0 (0)	5 (6.3)
Cough	1 (1.3)	2 (2.6)	1 (1.3)	5 (6.3)
Shortness of breath	0 (0)	4 (5.3)	0 (0)	4 (5.1)
Dry skin	0 (0)	3 (3.9)	0 (0)	4 (5.1)
Skin changes	0 (0)	0 (0)	0 (0)	4 (5.1)
Esophagitis/dysphagia/odynophagia	0 (0)	2 (2.6)	0 (0)	4 (5.1)
Heartburn	0 (0)	5 (6.6)	0 (0)	2 (2.5)
Arthralgia	0 (0)	4 (5.3)	0 (0)	1 (1.3)

Note: Ordered by decreasing frequency in the TCF-treated group.

Adverse events leading to study discontinuation

Twenty six TCF-treated subjects (32.9%) and 24 TC-treated subjects (31.6%) had adverse events resulting in discontinuation of treatment or death, regardless of the relationship to study medication. The most frequent AE resulting in discontinuation was neuro-sensory.
Thirty-nine subjects (25.2%) experienced at least 1 AE related to study medication resulting in the discontinuation of treatment or death. Both treatment groups were similar in this respect for the number of subjects.
Only in the TCF-treated subjects did diarrhea (4 subjects), and stomatitis, vomiting, dysrhythmias, hypotension, venous, and local toxicity (1 subject each) resulted in discontinuation.
Discontinuation due to decreased creatinine clearance (2 subjects), nail changes, skin pain, nausea, granulocytes, and otitis media (1 subject each) occurred only in the TC-treated subjects.

Table 28 - Toxicity that led to discontinuation or death (SP)

NCIC category/term	Number of subjects (%)					
	TC (N = 76)		TCF (N = 79)		Total (N = 155)	
Total with AE related to study medication leading to discontinuation or death[a]	18	(23.7)	21	(26.6)	39	(25.2)
Neurologic:	10	(13.2)	8	(10.1)	18	(11.6)
Neuro-sensory	10	(13.2)	8	(10.1)	18	(11.6)
Flu-like symptoms:	3	(3.9)	6	(7.6)	9	(5.8)
Lethargy	3	(3.9)	6	(7.6)	9	(5.8)
Gastrointestinal:	2	(2.6)	6	(7.6)	8	(5.2)
Anorexia	1	(1.3)	1	(1.3)	2	(1.3)
Diarrhea	0	(0)	4	(5.1)	4	(2.6)
Nausea	1	(1.3)	0	(0)	1	(0.6)
Stomatitis	0	(0)	1	(1.3)	1	(0.6)
Vomiting	0	(0)	1	(1.3)	1	(0.6)
Cardiovascular:	2	(2.6)	4	(5.1)	6	(3.9)
Dysrhythmias	0	(0)	1	(1.3)	1	(0.6)
Edema	2	(2.6)	1	(1.3)	3	(1.9)
Hypotension	0	(0)	1	(1.3)	1	(0.6)
Venous	0	(0)	1	(1.3)	1	(0.6)
Genitourinary:	3	(3.9)	2	(2.5)	5	(3.2)
Creatinine	1	(1.3)	2	(2.5)	3	(1.9)
Other: CrCl decreased	2	(2.6)	0	(0)	2	(1.3)
Infection:	2	(2.6)	1	(1.3)	3	(1.9)
Infection	2	(2.6)	1	(1.3)	3	(1.9)
Skin:	2	(2.6)	1	(1.3)	3	(1.9)
Local toxicity	0	(0)	1	(1.3)	1	(0.6)
Nail changes	1	(1.3)	0	(0)	1	(0.6)
Skin pain	2	(2.6)	0	(0)	2	(1.3)
Blood bone marrow:	1	(1.3)	0	(0)	1	(0.6)
Granulocytes	1	(1.3)	0	(0)	1	(0.6)
Other:	1	(1.3)	0	(0)	1	(0.6)
Other: Otitis media	1	(1.3)	0	(0)	1	(0.6)

[a] A subject could be discontinued for more than 1 toxicity.

Deaths

Thirteen of the 155 (8.4%) treated subjects died during study treatment (within 30 days of the last administration of study medication regardless of relationship to study medication), and 125 (80.6%) subjects died more than 30 days after the last administration of study medication.

Table 29 - Summary of deaths (SP)

Death	Number of subjects (%)					
	TC (N=76)		TCF (N=79)		Total (N=155)	
Total deaths	68	(89.5)	70	(88.6)	138	(89.0)
Within 30 days of last administration of study medication	5	(6.6)	8	(10.1)	13	(8.4)
Malignant disease	1	(1.3)	2	(2.5)	3	(1.9)
Toxicity from study medication	0	(0)	3	(3.8)	3	(1.9)
Other causes	4	(5.3)	3	(3.8)	7	(4.5)
More than 30 days after end of last administration of study medication	63	(82.9)	62	(78.5)	125	(80.6)
Malignant disease	61	(80.3)	59	(74.7)	120	(77.4)
Drug-related toxicity from study medication	1	(1.3)	0	(0)	1	(0.6)
Other causes	1	(1.3)	3	(3.8)	4	(2.6)

There were 3 treatment-related deaths within 30 days of the last administration of study medication. All subjects received TCF and related AE leading to death were infection for 1 subject, diarrhea for 1 subject and diarrhea plus vomiting and dysrhythmia for 1 subject.

There was 1 treatment-related death more than 30 days after the last administration of study medication, TC-treated and the subject died from creatinine clearance decrease.

There were 8 (10.1%) and 6 (8.0%) deaths (within 30 days of the last infusion of study medication or after 30 days) considered by the investigators to be treatment related in the TCF and TC groups, respectively.

Global Analysis by SOC (Phase III, Pivotal TAX 325 A and Phase II, TAX325)

Gastrointestinal disorders

Gastrointestinal TEAEs were generally comparable across the phase II and III parts and treatment groups with the following notable exceptions:
- The frequencies of grade 3-4 stomatitis, both treatment-related and regardless of relationship, were lower for TCF in the phase III part than in the phase II part. In the phase III part, incidence was higher in the CF treatment group than in the TCF treatment group.

- The frequencies of grade 3-4 diarrhea, both treatment-related and regardless of relationship, were similar for the TCF treatment groups in the phase II and III parts but lower for the CF treatment group in the phase III part.
Results by cycle reflected those by subject. Of note, less than 5% of cycles were reported with grade 3-4 diarrhea in the TCF groups of both the phase II and phase III parts.

Flu-like symptom and infection

Flu-like symptom and infection TEAEs were varied across the phase II and III parts and treatment groups as follows:

- For TCF in the phase II and III parts, the frequencies of fever in absence of infection any grade and regardless of relationship was higher in the phase II part, and similar when considered as related. It was higher in the TCF treatment group than in CF in the phase III part.
- For TCF, globally, the incidence of infections any grade were similar in the phase II and III parts. However, a tendency of higher severity for grade 3-4 was observed for TCF in the phase III part compared to the phase II part. During the phase III part, infections were more common in the TCF treatment group than in the CF treatment group.
Results by cycle reflected those by subject, except fever in absence of infection grade 3-4 and regardless of relationship to the study medication, which was similar to TCF in the phase II and III parts.

Febrile neutropenia and neutropenic infection

Granulocyte-colony stimulating factor (G-CSF) was allowed only as secondary prophylaxis. The incidence of febrile neutropenia and/or neutropenic infection, regardless of the use of G-CSF, was comparable for the TCF treatment groups in the phase II and III parts and lower for the CF treatment group in the phase III part. Few subjects received secondary prophylaxis with G-CSF and few cycles were administered with G-CSF, however, in the TCF treatment group in the phase III part, the incidence of febrile neutropenia and/or neutropenic infection was lower when subjects received secondary prophylaxis with G-CSF than when subjects did not receive secondary prophylaxis.
Similar rates of subjects died from febrile neutropenia and/or infection in the TCF and CF treatment groups in the phase III part, and in the TCF treatment group all occurred during cycles without G-CSF. One subject died from febrile neutropenia and/or neutropenic infection in TCF in the phase II part.
Results by cycle were comparable across phase II and III and treatment groups.

Neutropenia

The frequencies of neutropenia of any grade or grade 3-4 were comparable in the TCF treatment groups in the phase II and III parts and lower in the CF treatment group, independent of the use of G-CSF. Secondary prophylactic G-CSF was used in a minority of subjects and cycles, but was used more frequently in the TCF treatment groups in the phase II and III parts than in the CF treatment group. A similar rate of subjects and cycles received secondary prophylaxis of G-CSF in TCF in the phase II and III parts. Incidence by subject and cycle of grade 3-4 neutropenia was smaller when TCF-treated subjects received secondary prophylaxis of G-CSF in the phase II and III parts. Results by cycle reflected those observed by subject.

(other) Blood and the lymphatic system disorders

Anemia of any grade occurred at similar incidence in all treatment groups, but grade 3-4 anemia occurred more commonly for TCF in the phase II part than in the phase III part. Incidence of grade 3-4 anemia was more frequent in CF than in TCF in the phase III part.
Incidence of leukopenia, any grade and grade 3-4, was similar for TCF in the phase II and III parts, but was lower in CF compared to TCF in the phase III part.
Incidence of thrombocytopenia any grade was higher for TCF in phase II than in the phase III part, and was higher in CF compared to TCF in the phase III part.

Neoplasms benign and malignant (including cysts and polyps)

Cancer-related TEAEs were generally comparable across studies and treatment groups, by subject and by cycle.

Nervous system disorders

Neurosensory AEs are a known toxicity for both docetaxel and cisplatin. Neurologic TEAEs were generally comparable across phase II and III parts and treatment groups with the following notable exceptions. The frequency of neurosensory of any grade, both treatment-related and regardless of relationship, was comparable for the TCF treatment group in the phase II and III parts and lower in the

CF treatment group in the phase III part. Altered hearing, either regardless of relationship to or related to the study medication, was more frequent in the CF treatment group compared to TCF in the phase III part.
Results by cycle reflected those by subject.

Cardiac and vascular disorders

Frequencies of cardiovascular TEAEs either regardless of relationship to or related to the study medication were generally similar, except edema which was more frequent for TCF in the phase II part than in the phase III part, and which was also more common with TCF compared to CF in the phase III part. Results by cycle reflected those by subject.
Knowing the safety profile of 5-FU, cardiac dysrhythmia and myocardial ischemia are 2 clinically relevant TEAEs. They occurred in less than 5% of subjects in both treatment groups of the phase III part, and incidence was comparable for TCF in the phase II and III parts.

Renal impairment

Any grade abnormal creatinine laboratory value was more common in the CF than in the TCF treatment group in the phase III part, and was similar for the TCF treatment groups in the phase II and III parts. In the phase II part, no TCF-treated patient had creatinemia or renal failure reported as serious. No obvious difference was observed between TCF and CF in the phase III part regarding the low incidence of serious creatinemia and renal failure in both treatment groups, even if the number of patients was always greater in the CF than in the TCF treatment group.

Fluid retention

Fluid retention was defined as any edema, ascites, pericardial effusion, pleural effusion, and weight gain. More subjects experienced fluid retention in the TCF treatment group compared to the CF treatment group in the phase III part. Fluid retention was more frequent for TCF in the phase II part than in the phase III part.

Hepato-bilary disorders

The frequencies of ASAT, ALAT, and alkaline phosphatase abnormalities of any grade were highest in the TCF treatment group in the phase III part, and comparable in the TCF phase II part and the CF treatment group. There were no differences between the treatment groups with respect to grade 3-4 abnormalities for ASAT, ALAT, and alkaline phosphatase. There were no obvious differences between the incidence of total bilirubin abnormalities in all treatment groups, in particular, incidence of any grade and grade 3-4 in the phase III part which were similar between the TCF and CF treatment groups.

Skin and subcutaneous tissue disorders

Frequencies of skin TEAEs any grade and grade 3-4, regardless of relationship to and related to the study medication, were generally similar for TCF in the phase II and III parts, except alopecia which was more frequent in the phase II part. In the phase III part, skin TEAEs any grade and both related to and regardless of relationship to the study medication, were more common in the TCF treatment group than in CF. However, grade 3-4 skin TEAEs were similar between both treatment groups. Results by cycle reflected those by subject.
Knowing the safety profile of 5-FU, skin desquamation is a clinically relevant TEAE, which occurred, any grade and regardless of relationship to the study medication, in 2.5%, 1.8% and 0.4% of subjects in TCF in the phase II part, TCF in the phase III part and CF, respectively. No grade 3-4 skin desquamation occurred in any treatment groups

Respiratory, thoracic and mediastinal disorders

Pulmonary TEAEs were generally comparable across studies and treatment groups. The frequencies of cough of any grade, regardless of relationship, were comparable for the TCF and CF treatment groups in the phase III part but higher for TCF in the phase II part. No pulmonary TEAEs occurred in 10% or more of cycles.

Immune system disorders and Eye disorders

Frequencies of hypersensitivity and ocular TEAEs, regardless of relationship to and related to the study medication, were ranged from 9.5% to 17.7% of patients for the TCF in phase II and III parts, and incidence was lower in the CF treatment group in the phase III part. However, grade 3-4 hypersensitivity and ocular TEAEs were similar between both treatment groups in the phase III part.

Others

Frequencies of hypokalemia and hypomagnesemia any grade were highest in the phase II part, followed by the TCF treatment group, and the lowest being the CF treatment group.

Phase I, XRP6976E /1001

Safety evaluation plan and narratives of safety studies

This was a single-center, open-label, randomized, cross-over, pharmacokinetic study of docetaxel (RP56976, Taxotere) in combination with cisplatin, with or without 5-FU, in the treatment of subjects with recurrent or metastatic solid tumors.
The primary objective of this study was to determine in a randomized, cross-over setting (each patient being his own control), if there was any clinically significant pharmacokinetic interaction between docetaxel (Taxotere) 75 mg/m2, cisplatin 75 mg/m2, and 5-fluorouracil (5-FU) 750 mg/m2/day for 5 days. The secondary objective of this study was to confirm safety.
The study consisted of 2 treatment arms that each underwent 2 cycles of treatment. In arm A, subjects were treated with the double combination docetaxel (Taxotere) 75 mg/m2 + cisplatin (TC) 75 mg/m2 in Cycle 1 followed by the triple combination docetaxel (Taxotere) 75 mg/m2 + cisplatin 75 mg/m2 + 5-FU (TCF) 750 mg/m2/day in Cycle 2. In arm B, the opposite sequence was employed so that subjects were treated with the triple combination at Cycle 1 followed by the double combination in Cycle 2. Treatment cycles were repeated every 21 days.

No pharmacokinetic interaction between docetaxel, cisplatin, and 5-FU used in combination were noted in study XRP6976E /1001. Mean pharmacokinetic parameters of all agents were within the ranges for previously reported monotherapy treatment. In addition, mean clearance values for cisplatin and docetaxel showed no statistically significant difference across triple and double combination treatments and docetaxel clearance values were not statistically different from historical monotherapy docetaxel data. No other drug interaction was studied.
XRP6976E /1001 Results – Safety:

In general, treatment with docetaxel in combination therapy was well tolerated. Only 1 subject (00009) discontinued treatment due to a SAE of myocardial ischemia, which later resolved.
Adverse events were reported by all 15 subjects during both TC and TCF treatments. Gastrointestinal (NCIC classification) treatment-emergent adverse events (TEAEs) were the most commonly reported. In general, numbers of subjects with TEAEs suggest that 5-FU was associated with increased numbers of TEAEs, especially gastrointestinal TEAEs, which was consistent with the nature of the underlying disease and the known adverse event profiles for docetaxel, cisplatin, and 5-FU.

No deaths were reported during the study period. Serious adverse events were reported in 2/14 subjects during TC treatment, and in 6/15 subjects during TCF treatment and were classified as either cardiovascular, flu-like symptoms, or gastrointestinal. Regardless of relationship to the study medication, no grade 4 TEAEs occurred during the study. Grade 3 diarrhea and cancer pain were each

reported in 2 subjects, and grade 3 vascular disorder, lethargy, anorexia, nausea, vomiting, stomatitis, gastrointestinal pain, constipation, and cortical somnolence each occurred in 1 subject. All but 2 serious adverse events of lethargy had resolved by the end of the study. A total of 8 subjects experienced grade 3-4 neutropenia during the TCF cycle. No grade 3-4 thrombocytopenia or anemia were reported. Frequencies of hematology and biochemistry toxicities on treatment were consistent with the known safety profile for docetaxel, cisplatin, and 5-FU.

Discussion on Clinical Safety

Phase III, Pivotal TAX 325 A

The extent of exposure was slightly inferior (median number of cycles, median duration of treatment) in the CF arm versus the TCF arm. Despite the fact the median actual dose intensity for all study medications was close to the planed dose intensity, the addition of Taxotere (docetaxel) to the CF combination provides the occurrence of frequent and/or severe adverse events.

More patients had at least one cycle delay in the TCF arm compared to CF arm with a difference of 21%. In addition, a dose reduction was noticed in 41 % of TCF-treated subjects and was due to TEAEs related to the study medication (37.9 %).

The safety profile is in accordance with what was expected in both treatment arms:
The 5 most frequently observed grade 3-4 TEAEs in the TCF treatment group, regardless of relationship to study medication, were lethargy (21.3%), stomatitis (20.8%), diarrhea (20.4%), cancer pain (18.1%), and infection (16.3%).
The 5 most frequent grade 3-4 TEAEs observed in the CF treatment group, regardless of relationship to study medication, were stomatitis (27.2%), cancer pain (19.6%), nausea (18.8%), vomiting (18.8%), and lethargy (17.9%).
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 frequently in the TCF treatment group (20.4%) compared to the CF treatment group (8.0%).
In both treatment groups, related gastrointestinal TEAE was the most common NCIC-CTC category, and was the predominant reason for dose reductions (26.7% in TCF and 22.3% in CF).

Neurosensory AEs are a known toxicity for both Taxotere and cisplatin and occurred (any grade) in 38.0% of subjects receiving TCF and 24.6% of subjects receiving CF.
This was the most frequently reported AE leading to treatment discontinuation among TCF-treated subjects. However, no TCF-treated subjects discontinued due to neurosensory AE prior to cycle number 4.

Infections frequency increased in the TCF treatment group with grade 3-4 infections regardless of relationship 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.
Seven of the 16 non-malignant deaths occurring within 30 days after the last administration of study medication in the TCF treatment group were attributed to infections or moniliasis (1 case), as were 6 of the 15 non-malignant deaths in the CF treatment group, all but one being considered related to study medication.
In addition, 1 subject in the TCF treatment group and 2 subjects in the CF treatment group died beyond 30 days of the last administration of study medication from infection considered related to study medication. Thus a similar rate of subjects died from infection (or moniliasis) in each treatment group.

Haematological abnormalities occurred frequently in the study. Grade 3-4 neutropenia was more frequent in the TCF treatment group, occurring in 82.3% of TCF-treated subjects and 56.8% of CF-treated subjects. Similarly, occurrences of neutropenic infection and/or febrile neutropenia were more frequent in the TCF treatment group, occurring in 30.0% of the TCF treatment group and in 13.5% of the CF treatment group. Five of the deaths in the TCF group and 7 of the deaths in the CF group were

attributed to neutropenic infection or febrile neutropenia. In this study, prophylactic G-CSF was used in a minority of cycles (TCF: 10.0%; CF: 3.3%). 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.
A recommendation for use of prophylactic GCSF to mitigate the risk of complicated neutropenia in patients treated with TCF has been added in section 4.4 of the SPC.

TESAEs (regardless of relationship to study medication) occurred in 62.0% of TCF-treated subjects compared to 45.1% of CF-treated subjects, with fever in absence of infection, neutropenia, infection, and diarrhea contributing to a higher incidence of TE-SAE in TCF-treated subjects.
Grade 3-4 TESAEs including flu-like syndrome (20.4 %), nervous system disorders (14.9 %), infections (12.7 %), skin disorders (5.4 %), hypersensitivity reactions (1.8 %) were more frequently observed in TCF arm. Similarly cardiac disorders and severe stomatitis occured more frequently in the CF arm.
TEAEs leading to discontinuation (regardless of relationship to study medication) were comparable between treatment groups (TCF: 27.1%; CF: 25.0%), with the majority of AE discontinuations occurring in later cycles.

Deaths within 30 days after the last administration of study medication were comparable, occurring in 23 (10.4%) TCF-treated subjects and in 19 (8.5%) CF-treated subjects.
A similar rate of deaths within 30 days after the last administration of study medication attributed to non-malignant cause was observed in both treatment groups (16 TCF-treated subjects and 15 CF-treated subjects). Infection was the most frequent cause of death in both treatment groups, as mentioned above.

Phase II, TAX 325

The safety data reported in study TAX 325 Phase II do not present strong differences between TC and TCF treated groups. It has to be noted that SAEs occurred in 62 % of the patients in the TCF arm compared to 50 % in the TC arm. Haematologic toxicity was similar in both groups. However, the TCF group developed more gastrointestinal disorders such as stomatitis, nausea and diarrhea. Neurosensory events were the most frequent events leading to dose discontinuation in both treatment groups.

Phase I, XRP6976E /1001

No deaths were reported during the study period. Serious adverse events were reported in 2/14 subjects during TC treatment, and in 6/15 subjects during TCF treatment and were classified as either cardiovascular (a patient discontinued the treatment due to a SAE of myocardial ischemia), flu-like symptoms, or gastrointestinal. No pharmacokinetic interaction between docetaxel, cisplatin, and 5-FU used in combination were noted in study, but it is of interest to note in the Taxotere SPC the mention of a possible pharmacokinetic interaction between docetaxel and carboplatin. When combined to docetaxel, the clearance of carboplatin was about 50% higher than values previously reported for carboplatin monotherapy.

In conclusion, the addition of Taxotere to the CF combination has not introduced any new types of treatment-emergent adverse events outside those expected with a standard-dose CF combination in the population of subjects with advanced gastric cancer.
The new proposed extended indication does not require additional risk minimisation measures beyond the Product Information. The proposed SPC and PL, were updated accordingly to TCF regimen for the new indication, particularly in terms of dosage recommendation and undesirable effects, and reflect the known safety profile of Taxotere

Benefit Risk assessment

The application to extend the indications of TAXOTERE in the “advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction”, was supported by study XRP6979E/325

a well-managed and well-analysed phase II-III trial. The study was divided in a phase II part (TAX 325) to select one test arm (TCF or TC), and a phase III part (TAX 325A) to assess efficacy of the selected test arm (TCF) compared to the reference treatment (CF). No patient included in the phase II took part in the study was treated in the phase III part of it.

There was no difference in the distribution of baseline patients and disease characteristics between both treatment arms: median age 55 years; median Karnofsky performance status of 90.
The median follow-up time at end-of-study analysis was 24 months. Clinical efficacy results of study TAX325 A were convincing in terms of significantly decrease of the risk of time to disease progression - TTP (primary criterion) and Overall Survival (OS) benefit (secondary criterion).
The results were clinically relevant and reached statistical significance:

- The 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 (log-rank test, P=0.0004), an HR of 1.473 [95% CI: 1.189-1.825] and a risk reduction of 32.1%.
- The 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] (log-rank test, P=0.0201); an HR of 1.293 [95% CI: 1.041-1.606] and a risk reduction of 22.7%. 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.

The robustness of this benefit was confirmed using sensitive and multivariate Cox model adjusted analyses for prognostic covariates. Analyses by pre-specified sub-group analyses (age, gender, race) did not suggest a plausible differential treatment effect. The results of QOL and clinical benefit were globally consistent and support the benefit of TCF with a longer preservation of PS.
A survival update analysis conducted with a median follow-up time of 41.6 months reported a no more significant difference although always in favour of the TCF regimen. The “late” deaths reported in both arms were not unexpected in view of the known outcome of metastatic gastric cancers (OS expected to be about 8 months). The Kaplan-Meier plot of the “updated” overall survival curve showed that the benefit of TCF over CF is clearly observed between 18 and 30 months of follow up.

From the safety point of view, the addition of Taxotere to the CF combination has not introduced any new types of treatment-emergent adverse events outside those expected with a standard-dose CF combination in the population of subjects with advanced gastric cancer.
The new proposed extended indication did not require additional risk minimisation measures beyond the Product Information. The proposed SPC and PL, were updated according to TCF regimen for the new indication, particularly in terms of dosage recommendation and undesirable effects, and reflect the known safety profile of Taxotere.

In addition, the application contained one randomized pharmacokinetic interaction study, XRP6976E/1001, that included 15 patients with solid tumors who received either TCF at cycle 1 and TC at cycle 2, or TC at cycle 1 and TCF at cycle 2.
Blood sampling procedures as well as analytical methods were adequate. The results suggested no interaction between drugs.

In conclusion, the CHMP considers that the Benefit/Risk ratio of docetaxel in combination with cisplatin and 5-fluorouracil for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease, is positive.

CONCLUSION

- On 23 March 2006 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.