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Sponsor / Company: Sanofi	**Study Identifiers:** NCT00811447
Drug substance(s): Docetaxel	**Study code:** DOCET_L_02195

Title of the study: Open label, randomized, multicenter phase III study of Docetaxel (Taxotere ®) in combination with 5-fluorouracil and cisplatin compared to the combination of cisplatin and 5-fluorouracil in patients with metastatic or locally recurrent gastric cancer previously untreated with chemotherapy for advanced disease.

Study center(s): 15 Active sites in China

Study period:

Date first patient enrolled: 11-Nov-2008

Date last patient completed: 30-Jun-2011

Phase of development: III

Objectives:

Primary objective:

To compare the progression-free-survival (PFS) for the investigational group Docetaxel+Cisplatin+5-fluorouracil (TPF) relatively to the control group Cisplatin+5-fluorouracil (PF).

Note: PFS was analyzed as the primary endpoint instead of time to progression (TTP).

Secondary objectives:

To compare overall survival (OS) for the investigational group relative to the control group.

Other secondary objectives:

To compare response rate (RR), time to treatment failure (TTF), duration of responses, safety profiles, quality of life (QOL), and disease-related symptoms.

Methodology:

This study was a prospective, open-label, multicenter, parallel-group, randomized comparative trial conducted in patients with metastatic or locally recurrent gastric cancer previously untreated with chemotherapy for advanced disease.

Patients were centrally randomized (1:1) to either TPF or PF using a biased-coin minimization method with the following stratification factors: liver metastasis (yes/no), prior gastrectomy (yes/no), Karnofsky performance status (KPS) ≥80 (yes vs. no), weight loss in prior 3 months (≤5% vs. >5%) and investigational centre

Number of patients**:**	Planned: 240
	Randomized: 243
	Treated: 234
Evaluated:	Per protocol: 189
	Safety: 234

Diagnosis and criteria for inclusion:

Inclusion criteria:

- Patient's consent form obtained before beginning specific protocol procedures.
- Gastric adenocarcinoma including adenocarcinoma of the esophageal gastro (EG) junction, histologically proven.
- At least 1 measurable lesion (e.g., lymph node) by RECIST criteria.

- Age ≥18 years.
- Karnofsky performance status (KPS) ≥70.
- Life expectancy of more than 3 months.
- Adequate hematologic parameters (hemoglobin [Hgb] ≥9 g/dL; absolute neutrophil count [ANC] ≥2.0 x 10^9/L; platelets ≥100 x 10^9/L).
- Creatinine ≤1.25 x upper normal limit (UNL) or a calculated creatinine clearance (CrCl) ≥55 mL/min. Serum magnesium to be within the normal value.
- Total bilirubin ≤1 x UNL; alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) ≤2.5 x UNL; alkaline phosphatase ≤5 x UNL, (except in case of bone metastasis without any liver disease).
- No prior palliative treatment (palliative chemotherapy and palliative radiotherapy). Previous adjuvant (neo-adjuvant) chemotherapy was allowed if more than a period of 6 months had elapsed between the end of adjuvant (neoadjuvant) therapy and the first relapse.
- At least 2 weeks from surgery.
- Complete initial work-up within 2 weeks prior to first infusion for imaging and within 8 days prior to first infusion for clinical evaluation and biological work-up. Abdominal enhanced Computer Tomography (CT) scan and chest X-rays were mandatory.
- Able to comply with scheduled follow-up and with the management of toxicity.
- QOL baseline questionnaire completed before the date of randomization.

Exclusion criteria

- Pregnant or lactating women.
- Patients (male/female) with reproductive potential not implementing adequate contraceptive measures.
- Tumor type other than adenocarcinoma (leiomyosarcoma, lymphoma).
- Any prior palliative chemotherapy. Prior adjuvant (and/or neo-adjuvant) chemotherapy with a first relapse within 6 months from the end of adjuvant (or neo-adjuvant).
- Prior treatment with taxanes. Prior cisplatin as adjuvant (and/or neo-adjuvant) chemotherapy with cumulative dose >300 mg/m2, or ≥2 prior adjuvant or neoadjuvant treatment regimens.
- Previous or current malignancies other than gastric carcinoma, with the exception of adequately treated in situ carcinoma of the cervix uteri or non-melanoma skin cancer.
- Patients with known brain or leptomeningeal metastasis.
- Symptomatic peripheral neuropathy of at least grade 2 (National Cancer Institute of Canada Clinical Trial Group Expanded Common Toxicity Criteria [NCIC-CTC]).
- Other serious illness or medical conditions:
- − Unstable cardiac disease despite treatment, myocardial infarction within 6 months prior to study entry
- − History of significant neurologic or psychiatric disorders including dementia or seizures
- − Active uncontrolled infection
- − Active disseminated intravascular coagulation
- − Other serious underlying medical conditions which could impair the ability of the patient to participate in the study.
- Concurrent treatment with corticosteroids (or equivalent) except when used for the prophylactic medication regimen, treatment of acute hypersensitivity reactions (HSR) or unless chronic treatment (initiated >6 months prior to study entry) at low doses (≤20 mg methyl prednisolone or equivalent).
- Definite contraindications for the use of corticosteroids.
- Hypercalcemia not controlled by bisphosphonates and >12 mg/100 mL.
- Liver impairment with ALAT and/or ASAT >1.5 x UNL associated with alkaline phosphatase >2.5 x UNL.
- Concurrent or within a 4-week period administration of any other experimental drugs.
- Concurrent treatment with any other anti-cancer therapy.
- Patients clearly intending to withdraw from the study if not randomized to a given treatment group.

Study treatments

Investigational product and Reference therapy:

TPF: Taxotere (60mg/m2) i.v. for 1 hour
Cisplatin (60mg/m2) i.v. for 1-3 hours
600 mg/m2/day of 5-FU 24 hours c.i.v from Day 1 to Day 5.
Three weeks were taken as one treatment cycle.

PF: Cisplatin (75mg/m2) i.v. for 1-3 hours
600 mg/m2/day of 5-FU 24 hours c.i.v from Day 1 to Day 5.
Three weeks were taken as one treatment cycle.

If serious hematological toxicity and/or non-hematological toxicity occur, dosage could be down-titrated and / or administration delayed according to protocol.

Both groups needed to receive antiemetic and hyperhydration regimen. Corticosteroids must be applied to TPF group.

Duration of treatment:	Before disease progression patient had been receiving investigational product for treatment. No cross-treatment within study was allowed.
Duration of observation:	Patients who had been discontinued from study due to disease progression were followed-up every 3 months until death. If patients experienced unacceptable toxicity or withdrew Informed Consent Form, early termination was commenced. Early-discontinued patients before Progression Disease (PD) were followed-up every 6 weeks post-treatment, until PD, and once every 3 months after PD. Death was recorded when experienced

Criteria for evaluation:

Efficacy: The PFS and OS were assessed in both treatment groups to evaluate efficacy. Patient response was assessed once every 6 weeks. Tumor response was assessed in a patient who had had received at least 2 cycles of treatment, with minimally 1 complete tumor assessment at least 6 weeks after first dose administration with the same imaging procedures as at baseline for each lesion, unless early progression occurred. Tumor response was defined as complete response, partial response, stable disease, and progressive disease. Progression free survival and best response rate were analyzed using Full analysis set (FAS) and Per Protocol set (PPS). Duration of response was calculated in responders. Overall survival, clinical benefit and quality of life measures were analyzed using FAS.

Safety: Clinical and laboratory toxicity/symptom would be graded according to NCI-CTC toxicity standard. Prior to dose administration of every cycle, adverse event, disease symptom/signs, and blood chemistry were assessed once. Blood routine was assessed once weekly. Safety set was used for safety analysis.

Statistical methods:

The primary objective is to detect any significant difference in PFS between the investigational group and control group using an unstratified log-rank test. Testing at two-sided 5% significance level was performed. The Kaplan-Meier curve and life tables were used to describe survival data. Non-parametric confidence intervals (CIs) were calculated for the medians. Hazard ratios and corresponding 95% CIs were also calculated.

The survival data including PFS and OS were also compared between groups with the stratified log-rank test and the Cox proportional hazards model. For multivariate analyses, the following baseline parameters were considered for inclusion in the model as covariates: liver metastasis, weight loss, prior gastrectomy, Karnofsky performance status (KPS), age, and primary tumor site. Pre-specified subgroup analysis about PFS and OS were conducted to check consistency of treatment effect. Best RR was analyzed using the chi-square test or Fisher's exact test.

QOL and clinical benefit time-to-event endpoints were analyzed similarly to secondary efficacy endpoints.

All adverse events were summarized with counts and percentage. The selected safety endpoints profile was analyzed using Fisher's exact test.

Summary:

Population characteristics:

Both treatment groups were comparable for demographics at baseline. Most patients were male (72.2%). The median age of patients was 56.1 years (range: 19 to 80 years) with 16.6% of patients ≥65 years. At baseline, a weight loss of >5% was noted in 42.3% of the patients, most of patients 217(92.7%) were with baseline KPS score of 80-90.

A total of 45 (19.2%) patients had previous chemotherapy as adjuvant or neo adjuvant treatment. A total of 85 (36.3%) patients had previous surgery, which was curative in 57 patients (67.1%).

Both treatment groups were comparable for tumor characteristics at baseline. Majority of patients (226 (96.6%)) had American Joint Committee on Cancer (AJCC) stage IV disease. Antrum (85 (36.3%)), body (80 (34.2%)) and esogastric junction (49 (20.9%)) were most common anatomical sites in this population. A total of 100 (42.7%) patients had liver metastasis.

A total of 91.5% of patients presented with one or more clinical signs or symptoms at baseline with a balanced distribution across treatment groups, which reflecting the advanced stage of the disease in these patients.

Therefore, based on the demographics and baseline characteristics, the study population was representative of advanced gastric cancer patients who could be considered for treatment with combination chemotherapy.

Efficacy results:

Efficacy results of this study demonstrate that the addition of Docetaxel (Taxotere ®) to PF resulted in statistically significant and consistent improvements over PF patients on the 3 relevant endpoints that are universally used to establish the effectiveness (efficacy) of anticancer drugs (PFS, RR and TTF), and patients in TPF group have numerically longer survival time in PF group.

The study primary endpoint, PFS analyzed in the FAS, was significantly in favor of TPF compared to PF (HR =0.63, 95% CI: 0.48-0.85, unstratified log-rank test, P=0.0018). The risk reduction of progression, 36.6%, was associated with a 2-month improvement in the median PFS (4.9 months for the PF group to 7.2 months for the TPF group), also with improvement of 6 months PFS rate (40.50% in PF group to 57.34% in TPF group).

The difference was not statistically significant but numerically longer for OS in TPF group compared with PF group with unstratified log-rank test (HR=0.78, 95% CI: 0.58-1.05, P=0.0985), the result suggested survival advantage in TPF group with the risk reduction of mortality of 22.1%. The supportive stratified log-rank test was statistical significant (HR= 0.71, 95% CI: 0.52-0.97), P=0.0319). This effect on mortality was associated with a median survival of 10.2 months in the TPF group, compared with 8.5 months in the PF group. 12 months OS rate was 40.9% in TPF group and 28.7% in PF group.

Sensitivity analyses for both PFS and survival endpoints demonstrated the robustness, significance and magnitude of the treatment effect. These included multivariate analyses taking into account possible prognostic factors, PPS and separate analyses in per-protocol analysis population. Pre-specified subgroup analyses did not suggest a plausible differential treatment effect.

Tumor RR was higher in the TPF group compared to the PF group (48.7% versus 33.9%, respectively, P<0.05), with fewer refractory patients (patients with best overall response as PD).

Regarding TTF, an endpoint that integrates efficacy and safety parameters, there was a statistically significant benefit in favor of TPF (HR=0.67, 95% CI: 0.52-0.88, P=0.0027). The median time to treatment failure (TTF) was 3.4 months in the TPF group [95% CI: 2.5-3.8] and 2.4 months in the PF group [95% CI: 2.3- 3.2].

This study successfully achieved the significance level for the primary endpoint of PFS. The statistical tests for the secondary endpoints (RR and TTF) achieved significance; while the test for the OS was not statistically significance but showed numerically longer survival.

Safety results:

More patients in the TPF group experienced Treatment-emergent Adverse Events (TEAEs) or Grade 3 or 4 TEAEs or Serious Adverse Events (SAEs) that were possibly related to study drug compared to the PF group ($p<0.05$);While the number of deaths and discontinuations due to a TEAE in both groups were similar.

The TEAEs, regardless of relationship to study medication, were observed in 99.2% of TPF-treated patients and 98.3% of PF-treated patients, and in most treatment cycles for both treatment groups. The frequency of specific AEs was generally similar between the two groups, despite some notable differences within the safety profiles of each group. In particular, among any grade TEAE regardless of relationship to study medication, leukopenia (TPF: 88.2%; PF: 64.3%), neutropenia (TPF: 79.0%; PF: 58.3%), diarrhea (TPF: 47.9%; PF: 7.8%), alopecia (TPF: 21%; PF: 0%), and mouth ulceration (TPF: 21.8%; PF: 4.3%), were more frequent by nearly 20% differences between the 2 treatment groups. Taxotere DLT, Febrile neutropenia was higher TPF than PF group (TPF: 13.4%; PF: 0.9%). In contrast, the PTs experienced more frequently in the PF group than the TPF group were: nausea (TPF: 71.4%; PF: 77.4%), decreased appetite (TPF: 53.8%; PF: 57.4%), vomiting (TPF: 52.9%; PF: 68.7%), thrombocytopenia (TPF: 21.8%; PF: 32.2%), and dyspepsia (TPF: 8.4%; PF: 11.3%).

Grade 3-4 TEAEs, regardless of relationship to study medication, were experienced by 77.3% of TPF-treated patients and 46.1% of PF-treated patients. Among grade 3-4 TEAEs, the most commonly reported TEAE shared by both groups, regardless of relationship to study medication, was neutropenia (TPF: 60.5%; PF: 9.6%), followed by, in the TFP group leukopenia (52.1%), diarrhea (12.6%), febrile neutropenia (12.6%), and lymphopenia (10.1%);in the PF group, nausea (7.0%), vomiting (11.3%), anaemia (5.2%), and thrombocytopenia (4.3%). The TE-SAEs, regardless of relationship, were also greater in the TPF group (17.6% of TPF-treated patients and 11.3% of PF-treated patients). The incidence of grade 3-4 TE-SAE (regardless of relationship) by cycle was comparable across treatment groups (4.6% of TPF cycles and 2.2% of PF cycles).

The 60-day all-cause mortality events occurred only in PF group, and no TPF-treated patient died within 60 days of randomization. Death within 30 days of the last administration of study medication was rare in both treatment groups: 4 patients in the TPF group and 1 patient in the PF group. Death occurring beyond 30 days of the last administration of study medication was more frequent in the PF group, and was usually attributed to progressive disease.

Adverse Events (AEs) leading to treatment discontinuation, regardless of relationship, were also comparable between both treatment groups.

Overall, as expected, in this population of patients with advanced gastric cancer, the addition of Taxotere to the PF combination has not introduced any previously unreported TEAE other than those expected with a standard-dose PF combination. Compared to PF-treated group, specific adverse safety events such as leukopenia, neutropenia and diarrhea were more frequent with TPF but others, such as nausea, decreased appetite and vomiting, thrombocytopenia and dyspepsia are less frequent.

The safety profile in Chinese advanced gastric cancer patients is similar with that of TAX 325 but less frequent in overall AE summary and specific toxicities, such as neutropenia, febrile neutropenia, and diarrhea, which was aligned with the experience of previous local Phase I and Phase II results of better tolerance with modified TPF.

Health Outcomes:

Predefined primary analysis of quality of life and clinical benefit were both statistically significant in favor of TPF, and all other analyses were also in favor of TPF.

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