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Sponsor / Company: Sanofi	Study Identifiers: NCT00411229
Drug substances: SR96669 (Capecitabine/Oxaliplatin)	Study code: L_9570 (M017527)

Title of the study: A Phase III Study Comparing Adjuvant Chemotherapy Consisting of Capecitabine/Oxaliplatin Versus Surgery Alone in Patients with Stage II (T1N2, T2N1, T3N0), IIIa (T2N2, T3N1, T4N0), and IIIb (T3N2) Gastric Adenocarcinoma

Study center(s): 35 centers in 3 Asian countries (South Korea, China, and Taiwan)

Study period:

Date first patient enrolled: 13/Jun/2006

Date last patient completed: 24/Sep/2010 (data cut-off date used for all analyses in this report)

Date of follow-up report: 22/Nov/2012 (follow-up data collected from all 3 countries)

Phase of development: Phase 3

Objectives:

Primary Objective

- 3-year disease-free survival (DFS) rate.

Secondary Objective

- To compare overall survival (OS) time in the capecitabine/oxaliplatin arm with the control arm.
- To evaluate the safety profile of capecitabine/oxaliplatin adjuvant therapy using the Common Terminology Criteria (CTC) for adverse events (AEs).

Methodology:

All patients with gastric cancer (GC) who had surgery within 6 weeks prior to randomization and met all other conditions for eligibility was randomized to Arm A (capecitabine/oxaliplatin) or Arm B (observation only) in a 1:1 ratio. The randomization was centralized by Interactive Voice Response system (IVRS) and stratified by country (China, Taiwan, and South Korea) and stage of disease (II or IIIa or IIIb). Following randomization, patients received a 3-week cycle of capecitabine/oxaliplatin or observation only for 8 cycles (24 weeks). Patients were scheduled to be followed up for relapse and survival until the date of death or the last date the patient was known to be alive, or until 2 years after the primary efficacy analysis had taken place.

Demographic data, medical history, GC treatment history, and general physical examination were all assessed at baseline. A pregnancy test, electrocardiogram (ECG), chest X-ray, concomitant diseases and treatments, and tumor assessment were conducted within 14 days prior to randomization and as clinically indicated throughout the study treatment/observation phase. Vital signs including Karnofsky performance status (KPS), hematology, and blood chemistry were assessed within 7 days prior to randomization and at each visit from Cycle 2 during the study treatment/observation phase. Adverse events (AEs) were assessed during the study treatment/observation phase and up to 28 days after last study treatment for patients in Arm A and until 190 days after randomization for patients in Arm B. During the follow-up phase, a chest X-ray and survival information was obtained at each visit, additional cancer therapy was recorded as it occurred, and tumor assessment was obtained every 6 months after randomization until 3 years and then yearly thereafter.

An Independent Data Monitoring Committee (IDMC) was set up to review safety during the study. The IDMC also reviewed the efficacy data at the time of the interim analysis. As the interim data showed efficacy in patients treated with capecitabine and oxaliplatin, the IDMC recommended full evaluation and reporting of the results. Therefore, this report includes full reporting of the interim analysis, which was undertaken after 266 disease-free survival (DFS) events at the time of clinical cutoff on 24 September 2010.

Number of patients: A total 1035 patients were randomized (520 to capecitabine/oxaliplatin and 515 to observation only).

Randomized: 1035

Treated: 775

Evaluated:

Efficacy analysis (in the intent-to-treat population): 1035

Safety: 972

Summary of Intent-to-Treat, Per Protocol and Safety Populations by Trial Treatment
Analysis: Intent-to-Treat Population

	OBSERVATION ONLY	XELOX
No. of Patients Randomized	515	520
No. Included in ITT	515	520
No. Excluded from ITT	-	-
No. of Included in PPP	477	494
No. Excluded from PPP	38	26
No follow-up information	38	18
Randomized to the XELOX arm and did not receive at least one dose of Capecitabine or Oxaliplatin	-	22
Patient exhibiting metastatic disease (including presence of tumour cells in the ascites)	1	-
Patient received previous cytotoxic chemotherapy, radiotherapy, or immunotherapy except corticosteroids, for the currently treated gastric cancer	-	1
Patient with macroscopic or microscopic evidence of remaining tumor after surgery	1	-
Patient without histologically confirmed gastric adenocarcinoma staged pathologically, AJCC/UICC stage II, IIIa, or IIIb	1	-
No. Included in SP	477	495
No. Excluded from SP	38	25
No follow-up information	38	18
Randomized to the XELOX arm and did not receive at least one dose of Capecitabine or Oxaliplatin	-	22

Diagnosis and criteria for inclusion:

Chemotherapy-naïve and radiotherapy-naïve males or females aged ≥18 years with stage II (T2N1, T1N2, T3N0), IIIa (T3N1, T2N2, T4N0), or IIIb (T3N2) following D2 lymphadenectomy resection within 6 weeks prior to randomization. Patients were also required to have a KPS of ≥70% and provide written informed consent.

Study treatments

Investigational medicinal product: Capacitabine

Dose: 150 mg/500 mg

Route of administration: Oral

Investigational medicinal product: Oxaliplatin

Dose: 50 mg/100 mg

Route of administration: Intravenous

Reference therapy: Observation only

Duration of treatment: 24 weeks

Duration of observation: Patients were scheduled to be followed for relapse and survival until the date of death or the last date the patient was known to be alive, or until 2 years after the primary efficacy analysis had taken place.

Criteria for evaluation:

Efficacy: Disease-free survival rate was defined as the time from randomization to the time of evidence of a recurrence, new GC, or occurrence of death due to any cause. Assessment occurred at predefined intervals during the study treatment phase or if clinically indicated.

Overall survival (OS) was defined as the time from the date of randomization to the date of death from any cause.

Safety was assessed as described below.

Safety: All AEs were graded according to the National Cancer Institute (NCI)-CTC AE criteria (version 3.0).

- AEs and serious AEs (SAEs).
- Laboratory tests.
- Vital signs including KPS.
- ECG.

Statistical methods:

A sample size of 512 patients per arm was planned to observe the 385 DFS events required to provide 80% power at a 5% significance level for the hypothesized 3-year DFS increase from 56.2% to 65% with adjuvant capecitabine/oxaliplatin (hazard ratio [HR] 0.75).

The null hypothesis of no difference between arms was tested using Cox proportional hazards regression stratified by country (South Korea and Taiwan/China) and stage of disease with age, sex, and nodal status included as covariates.

Planned interim analysis was conducted after 257 DFS events (67% of the events for the full analysis) had occurred and was tested using the model specified for the full analysis.

Summary:

Efficacy results:

The primary endpoint for efficacy was met in this study of adjuvant chemotherapy (capecitabine/oxaliplatin) after potentially curative resection in patients with stage II and III GC. A statistically significant benefit for the capecitabine/oxaliplatin arm over the observation only arm for DFS at 3 years was observed: HR=0.56 (95% CI 0.44, 0.72, p<0.0001). At the time of clinical cutoff a greater proportion of patients in the capecitabine/oxaliplatin arm had no event compared to patients in the observation arm: 79.8% versus 68.7%. In the full population, a benefit was observed at patients with disease stage II over patients with stage IIIa and IIIb and at patients with a nodal status of N1/2 over patients with a nodal status of N0.

A statistically significant DFS benefit was observed at patients from South Korea: HR was 0.55 (95% CI 0.43, 0.72; p<0.0001). However, the results from China and Taiwan were mixed and cannot be meaningfully interpreted due to the small sample size.

The HR for OS was 0.74 (95% CI 0.53, 1.03; p=0.0775); however, as only 14% of patients reported an OS event at the time of clinical cutoff the data are relatively immature.

Safety results:

The majority of patients in the capecitabine/oxaliplatin arm (99%) and 52% of patients in the observation only arm had at least 1 AE. During the study treatment period, 75 (14%) patients withdrew from capecitabine/oxaliplatin treatment due to an AE, and 1 (0%) patient withdrew from the observation arm due to an AE. The most commonly reported AEs in the capecitabine/oxaliplatin arm were nausea (325 patients, 66%; observation arm, 20 patients, 4%), neutropenia (296 patients, 60%; observation arm, no patients), and decreased appetite (293 patients, 59%; observation arm, 18 patients, 4%). Majority of

AEs reported were mild or moderate in intensity (NCI-CTC Grade 1 or Grade 2). The number of patients who experienced a severe event (NCI-CTC Grade ≥3) was 263 (15%) in the capecitabine/oxaliplatin arm versus 27 (6%) patients in the observation arm. Nearly all patients (99.6%) in the capecitabine/oxaliplatin arm experienced an AE considered related to the study treatment. Around half of patients (49%) in the capecitabine/oxaliplatin arm experienced a severe AE (Grade ≥3) considered related to the study treatment.

At the time of clinical cutoff, 64 (12%) patients in the capecitabine/oxaliplatin arm and 80 (17%) patients in the observation arm had died (34 patients and 45 patients, respectively, died due to progressive disease). Three patient deaths were considered to be related to study treatment (capecitabine/oxaliplatin): 2 to progressive disease and 1 to sepsis.

Patients in the capecitabine/oxaliplatin arm had a higher rate of SAEs compared with patients in the observation arm: 14% versus 7%. Forty-three patients had an SAE considered related to capecitabine and/or oxaliplatin. Nausea (n=7, 1%), vomiting (n=7, 1%), and asthenia (n=5, 1%) were the only SAEs considered to be related to capecitabine and/or oxaliplatin treatment with an incidence of >1%.

Most of laboratory abnormalities were considered as Grade 1 or 2 in both study arms. The most common key abnormal parameter in the capecitabine/oxaliplatin arm considered Grade ≥3 was neutrophils: 85 patients (17%) had an abnormal neutrophil count at Grade 3/4. Other key Grade 3/4 laboratory abnormalities in the capecitabine/oxaliplatin arm included: platelets (30 patients, 6.0%), hemoglobin (7 patients, 1.4%), and total bilirubin (2 patients, 0.4%). The only key abnormal parameters in the observation arm considered Grade ≥3 were hemoglobin (2 patients, 0.4%) and neutrophils (1 patient, 0.2%).

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