SYNOPSIS

Title of the study: A Multicenter, Open-Label, Randomized Study Comparing the Efficacy and Safety of S-1 as a Single Agent at 30 mg/m^2 BID versus 5-FU Bolus for the Treatment of Patients with Metastatic Pancreatic Cancer Previously Treated with a Gemcitabine-Based Regimen (EFC10203)
Sponsor's Responsible Medical Officer: [redacted]
Study center(s): Planned number of sites: approximately 80; initiated centers: 64
Publications (reference): None
Study period: Date first patient enrolled: 21 February 2008 Date last patient completed: 22 March 2010 (First database lock on 19 November 2009, with 2 patients, one each in Israel and South Africa remaining on study treatment. Final database lock on 30 March 2010 following all patients withdrawn from treatment and completion of 30-day follow-up period)
Phase of development: 3
Objectives: Primary objective: To determine whether S-1 increases overall survival when compared to 5-Fluorouracil (5-FU) in patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy. Secondary objectives: To compare: Progression Free Survival (PFS), Overall Response Rate (ORR) as assessed by investigators according to RECIST criteria, Clinical Benefit assessed by Time to Symptoms Worsening and improvement in tumor related symptoms To assess: Overall Safety, Pharmacokinetics of S-1 Exploratory (Optional): Genotyping of CYP2A6 in the population of S-1 treatment arm population (Amendment 1).
Methodology: This was a prospective, multicenter, multinational, open-label, randomized (1:1), 2 parallel arms study comparing S-1 (Arm B) administered at 30 mg/m^2 BID, orally, for 14 days, every 3 weeks, to 5-FU (Arm A) administered at 425 mg/m^2/day via intravenous (IV) bolus (<30 minutes) for 5 consecutive days every 4 weeks, in patients with metastatic pancreatic cancer who have progressed on gemcitabine based-therapy.

Number of patients:	Planned: Approximately 400 (approximately 200 in each arm) Randomized: 61 Treated: 59 Efficacy/pharmacodynamic: 59 Safety: 59

Diagnosis and criteria for inclusion: The main inclusion criteria were cytologically or histologically confirmed evidence of adenocarcinoma of the exocrine pancreas and metastatic disease previously treated with a gemcitabine-based regimen (gemcitabine-based regimens which included erlotinib were permitted) as adjuvant chemotherapy or progression on a gemcitabine-based regimen for metastatic disease. Patients treated in addition with prior chemo-radiation to the primary pancreatic tumor, in which the chemotherapeutic agent was used as a radio-sensitizing agent, were eligible. Patients must have been at least 18 years old.

Investigational product: S-1(tegafur/gimeracil/oteracil)
S-1 contained tegafur (5-fluoro-1-(tetrahydro-2-furanyl)-2,4(1H,3H)-pyrimidinedione, FT; a prodrug of 5-FU), gimeracil ([5-chloro-2,4-dihydroxypyrimidine], CDHP; an inhibitor of dihydropyrimidine dehydrogenase), and oteracil potassium (monopotassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine 6-carboxylate, Oxo; a blocker of phosphorylation of 5-FU) at a molar ratio of 1:0.4:1.
S-1 was supplied as 15mg and 20mg oral capsules that contained 15mg and 20mg of tegafur (FT), respectively.

Dose: 30 mg/m^2 BID, Day 1 to Day 14, every 3 weeks

Administration: Oral

Batch number(s): 15mg: [redacted] 20mg: [redacted]

Duration of treatment: Patients were treated as long as they were benefiting from study treatment and did not meet withdrawal criteria (including a patient's request, disease progression, unacceptable toxicity, need for another anticancer treatment or pregnancy).

Duration of observation: All patients were followed up for adverse events (AEs) for 30 days following the last administration of study drug or >30 days if assessed to be study drug-related. Study drug-related AEs and all serious adverse events (SAEs) were followed up until resolution or stabilization. All patients were followed up for efficacy at 6-week intervals until death or the study cut-off date (the date of the 331st death event required for the final overall survival [OS] analysis), whichever came first.

Reference therapy: 5-FU
5-FU was supplied as an IV solution of 500 mg/mL in single-use vials (Adrucil® Injection, SICOR Pharmaceuticals, Inc.).

Dose: 425 mg/m^2/day, Day 1 to Day 5, every 4 weeks

Administration: IV bolus (<30 minutes)

Batch number(s): [redacted]

Criteria for evaluation: The current report is a synopsis report, and as such, only safety results are being presented. The following safety criteria were evaluated and analyzed using descriptive statistics: vital signs (blood pressure and heart rate), laboratory data (hematology and blood chemistry), 12-lead electrocardiography (ECG), and adverse events (AEs). Vital signs, laboratory and ECG abnormalities were recorded as AEs only if they were medically relevant (symptomatic, requiring corrective treatment or leading to discontinuation or to dose delay, reduction, or interruption and/or satisfying a seriousness criterion). The National Cancer Institute Common Toxicity Criteria (NCI CTCAE) version 3.0 were used to grade clinical AEs and laboratory data.

Statistical methods: The statistical evaluation of safety was descriptive only and focused on treatment-emergent adverse events (TEAEs), defined as AEs that developed or worsened in severity during the on-treatment period (from the first dose to 30 days after the last dose). TEAEs were tabulated (counts and percentages) by exposure drug. Potentially clinically significant abnormalities (PCSAs) were evaluated based on individual values and descriptive statistics. The all-treated (AT) population, which consisted of all randomized patients who took at least a part of one dose of study medication, was used for the analysis of safety parameters, according to the actual treatment received by the patient. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 12.1. A subgroup analysis of safety in the pharmacogenomic population for CYP2A6 genotype using descriptive statistics to support the exploratory objective was optional (Amendment 1). No statistical analyses plan was written.

Summary: This CSR was prepared as synopsized, as sanofi-aventis returned its territory rights for the development and commercialization of S-1 to Taiho Pharmaceutical Co., Ltd, Japan on July 18, 2008. This termination followed the announcement by Taiho Pharmaceutical Co., Ltd of their Phase III study results which evaluated the efficacy and safety of the oral anti-cancer agent S-1 in a multicentric trial in patients with locally advanced gastric cancer (see Press Release dated 18 July 2008). This decision to terminate the development and commercialization of S-1 was made before the interim analysis was conducted (planned for the time when 50% of events required for the OS analysis would have been observed).

Only safety results are being discussed. The efficacy evaluations originally planned were no longer considered to be relevant and were not performed.

All summary results presented in this section were performed on the all-treated population, including 59 patients who received at least one dose of study medication and information available at the date of database lock. Two additional patients (1 patient in France and 1 patient in the USA) were discontinued due to inclusion/exclusion violations and never received IP dosing.

Study population: A total of 61 study participants were randomized; however, 2 patients were immediately determined to be ineligible and discontinued prior to treatment as noted above. A total of 59 patients entered treatment: 28 patients (47%) in S-1-treated group and 31 patients (53%) in 5-FU-treated group. A high percentage of patients discontinued treatment. Disease progression (65%) and AEs (21%) were the most frequent reasons provided for discontinuing treatment in both groups. A total of 34 patients (59%) died while on study.

No significant differences in demographic characteristics were observed between the two treatment groups. Patients ranged in age from 36 to 80 years were on average 64 years old. The majority of patients were Caucasian (91.5%). Near all patients were diagnosed with a location primary site in pancreas (57 patients, 97% of overall patients) except 2 patients in S-1-treated group. All patients in S-1-treated group and 30 patients (97%) in 5-FU-treated group were defined with a hystological type of disease of adenocarcinoma except 1 patient with a carcinoma-papillary pattern. Stage of the diagnosed disease ranged from stage Ib to stage IV with a majority of stage IV (36 patients, 61% of overall patients). A total of 34 patients died while on study.

Safety population: Except for 2 patients (1 patient in France and 1 patient in the USA) who discontinued prior to treatment due to ineligibility, no major protocol violations in this study were reported. A total of 59 patients were included in the safety analyses. On average, patients received study drug for 12 weeks during the study with a range from 3 to 57 weeks of treatment. Twenty-two patients (79%) in S-1-treated group and 25 patients (81%) in 5-FU-treated group completed from 1 to 4 cycles of treatment. Six patients in both groups completed at least 5 cycles of treatment with a maximum of 19 cycles in S-1-treated group and 8 cycles in 5-FU-treated group.

Incidence of TEAEs, grade 3-4 TEAEs, serious TEAEs, and TEAEs leading to permanent discontinuation were similar between the two treatment groups. The percentage of TEAEs with an outcome of death in S-1-treated group (32%) was higher than the percentage in 5-FU-treated group (13%).

More than half the all patients (59%) experienced at least one TEAEs considered as serious. These serious TEAEs were considered as grade 3-4 serious events for all of these patients in S-1-treated group and 15 of these patients (88%) in 5-FU group. Among these serious TEAEs, the most frequent consisted of Gastrointestinal disorders (51%), General disorders and administration site conditions (29%), Infection and infestations (23%), Metabolism and nutrition disorders (20%), Respiratory, thoracic and mediastinal disorders (14%), and Blood and lymphatic system disorders (14%). The most frequent serious TEAEs by preferred term were diarrhea, disease progression, abdominal pain, general physical health deterioration, febrile neutropenia, dehydration, urinary tract infection, nausea, vomiting, and pyrexia.

Sixteen patients (27%) were reported with TEAEs leading to treatment discontinuation. The majority of these TEAEs were defined as grade 3-4 TEAEs. Eight patients in S-1 group and 3 patients in 5-FU group died during the on-treatment period and 11 patients in S-1 group and 12 patients in 5-FU group died after the on-treatment period. The cause of death, in most of cases (26 patients), was the progression of underlying disease.

Conclusion: [redacted]

Date of report: 23-Nov-2010