ABBREVIATED CLINICAL STUDY REPORT: PROTOCOL TPU-S1303

AN OPEN-LABEL, MULTICENTER, RANDOMIZED, PHASE 3 STUDY OF S-1 AND CISPLATIN COMPARED WITH 5-FU AND CISPLATIN IN PATIENTS WITH METASTATIC DIFFUSE GASTRIC CANCER PREVIOUSLY UNTREATED WITH CHEMOTHERPY

S-1

Indication: Metastatic Diffuse Gastric Cancer

Report No.: TPU-S1303

IND No.: 53,765

EudraCT No. 2009-016019-39

Phase: 3

First patient randomized: 14 April 2011

Last patient randomized: 25 February 2014

Data cut-off dates: 07 March 2014 (all clinical data except overall survival)

: 15 August 2014 (overall survival)

FINAL REPORT: 23 January 2015

SPONSOR:

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This clinical study was conducted in accordance with International Conference on Harmonisation Good Clinical Practise Guidelines.

2. SYNOPSIS

Name of company: Taiho Oncology, Inc.	**Synopsis for Study Referring to:**	**(For National Authority use only)**
Name of finished product: S-1	**Volume:**	
Name of active ingredient: Tegafur, Gimeracil, Oteracil Potassium	**Page:**	

Title of Report: An Open-Label, Multicenter, Randomized, Phase 3 Study of S-1 and Cisplatin Compared with 5-FU and Cisplatin in Patients with Metastatic Diffuse Gastric Cancer Previously Untreated with Chemotherapy

Report Number: TPU-S1303	**Phase:** Phase 3; Efficacy and Safety

Indication: Metastatic diffuse gastric cancer including carcinoma of the gastro-esophageal junction.

Investigators/Study Centers: Jaffer Ajani, Texas, USA. Patients were randomized at a total of 75 study centers in 20 countries; North America (Mexico [3], United States [3]); Eastern Europe (Bulgaria [2], Croatia [1], Estonia [2], Hungary [6], Poland [2], Russia [7], Ukraine [12], Romania [4]); Western Europe (Belgium [1], Germany [1], Italy [5], Portugal [2], Spain [9], United Kingdom [2]); and rest of world (Argentina [1], Brazil [8], Israel [1], South Africa [3]).

Study Period:
First patient randomized: 14 April 2011
Data cut-off dates: All clinical data except overall survival: 07 March 2014
Overall survival data: 15 August 2014

Publications: None

Objectives:

To compare the following endpoints for the S-1/cisplatin regimen (CS) (experimental group) with the 5 FU/cisplatin regimen (CF) (control group) in patients with metastatic diffuse gastric cancer

Primary:

- overall survival (OS)

Key Secondary:

- Progression-free survival (PFS)
- Time to treatment failure (TTF)
- Safety and tolerability

Other Secondary:

- Antitumor activity: Overall Response Rate (ORR)

Study Design: This was an open-label, international, multicenter, 2-group, parallel, randomized, Phase 3 study evaluating the efficacy and safety of the CS versus the CF regimen in chemotherapy-naïve patients with metastatic diffuse gastric carcinoma including carcinoma of the gastro-esophageal junction. Patients were randomly assigned (2:1) to CS (experimental regimen, Group A) or CF (control regimen, Group B). Patients were stratified by: histologic subtype (adenocarcinoma, diffuse type or signet ring cell adenocarcinoma); extent of metastasis (1 versus more than 1 metastatic site); Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1); and Region (North America/Western Europe/Eastern Europe/Rest of World [ROW]).

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Study Population and Main Criteria for Inclusion: The study enrolled male and female patients ≥18 years of age with histologically confirmed by Central Pathology Review, unresectable (at the time of screening for study eligibility), metastatic diffuse gastric cancer including carcinoma of the gastro-esophageal junction who had no prior chemotherapy for gastric cancer (adjuvant and/or neo-adjuvant chemotherapy was permitted if >12 months had elapsed between the end of adjuvant or neo-adjuvant therapy and first recurrence). Patients must have been at least 4 weeks post radiotherapy, and at least 3 weeks post major surgery. Patients had ECOG performance status of 0 or 1, and met minimum laboratory test requirements.

Number of Patients Enrolled and Analyzed:		CS	CF
	Intent-to-treat (All Randomized)	239	122
	As Treated Population (Safety)	230	118
	Intent-to-treat, Measurable Disease	193	91

Dose and Mode of Administration, Batch Number of Experimental Treatment:

In Group A, S-1 25 mg/m² was administered orally twice daily (BID) every 12 hours from Day 1 through Day 21 followed by a 7 day rest period on Days 22 to 28. This regimen was repeated every 28 days. S-1 was administered 1 hour before or 1 hour after a meal with a glass of water. Lot numbers were: 15-mg capsules, 0183, 2188, and 8G86; 20-mg capsules, 9E81, 1I91, and 13L8820.

Cisplatin 75 mg/m^2 was administered intravenously (IV) as a 1- to 3-hour infusion on Day 1 following the morning dose of S-1. This regimen was repeated every 28 days for a maximum of 8 cycles. Cisplatin used in the study was the commercially available product.

Dose and Mode of Administration, Batch Number of Control Treatment:

In Group B, 5-FU 800 mg/m^2/24 hours was administered IV by continuous infusion over 120 hours (on Days 1 through 5) followed by a 16-day rest period on Days 6 through 21. This regimen was repeated every 3 weeks.

The 5-FU used in the study was the commercially available product.

Cisplatin 80 mg/m^2 was administered IV as a 1- to 3-hour infusion on Day 1 prior to the start of the 5-FU infusion on Day 1 for a maximum of 8 cycles. This regimen was repeated every 21 days.

Cisplatin used in the study was the commercially available product.

Duration of Treatment: Patients received study treatment until progression of disease (PD), adverse event (AE), withdrawal of consent, or other reason for discontinuation. (Cisplatin treatment in both study groups was limited to 8 cycles.) Primary analysis took place on survival data collected up to 6 months after the last patient was randomized.

Evaluation Parameters:

Efficacy: Tumor assessments were performed throughout the study based on Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1, 2009). Computed tomography (CT) scans were performed every 8 weeks during study treatment. After discontinuation of treatment, patients were followed for PD, subsequent antitumor therapies, treatment-related serious adverse events (SAEs), and survival. During follow-up, CT scans were performed every 8 weeks until the occurrence of radiologic progression or the start of a new antitumor therapy. Patients were followed for survival status every 8 weeks until death or until 2 years after the last patient was randomized in the study.

Safety: Patients were monitored for safety using AE information and laboratory evaluations. Adverse events were graded using National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 4.0.

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Statistical Methods:

The study analysis populations were defined as follows:

- All Randomized: all patients randomized including those not dosed according to their randomization
- Intent-to-Treat (ITT) population includes all randomized patients. This population is the primary population for all efficacy parameters. All analyses using this population were based on the treatment assigned by interactive voice/web randomization system (IVRS).
- As Treated (AT) Population: all patients who initiated treatment with either of the 2 regimens with treatment assignment designated according to actual treatment received. This was the primary population for evaluation of safety endpoints.
- Intent-to-Treat, Measurable Disease Population: a subset of the ITT population of those patients with measurable disease (at least 1 target lesion) at baseline and was in the analysis of tumor response.

Efficacy: The primary efficacy endpoint for the study was OS (defined as the time from randomization to the date of death for the ITT population). Patients who did not die as of the OS cut-off date were censored at the date last known to be alive. The difference in OS between the 2 treatment groups was assessed using the unstratified log-rank test (Score statistic from PHREG and ties=Breslow). Survival for each group was summarized using Kaplan Meier curves and was further characterized in terms of the median and survival probability at 3, 6, 9 and 12 months, along with the corresponding 2-sided 95% confidence intervals for the estimates. Confidence intervals (CIs) for median survival were based upon the methods of Brookmeyer and Crowley. The influence of stratification factors and other baseline characteristics was assessed using the stratified log-rank test and Cox's regression approach.

Secondary time-to-event endpoints of PFS and TTF were analyzed using the same methods as for OS.

The treatment comparison for ORR was based on the Fisher's Exact test at the 2-sided alpha=0.05 level. Treatment estimates and differences are presented along with the associated 95% CIs constructed using Clopper-Pearson approximation to the exact binomial proportion for individual estimates within group, and the normal approximation for the difference between groups.

Safety: Study medication exposure and safety data ([AEs and clinical laboratory results) were summarized descriptively. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, Version 14.0, and were categorized by system organ class (SOC) and preferred term (PT).

Results:

Disposition: At the time of the cut-off date of 07 March 2014, 690 patients had been screened (signed informed consent) and 361 patients had been randomized in the study: 239 patients to the S-1 + cisplatin (CS) group and 122 patients to the 5-FU + cisplatin (CF) group (ITT Population). Of the 361 patients randomized, 2 patients (1 in the CS group, 1 in the CF group) discontinued study prior to receiving study drug. A total of 359 patients received at least one dose of study treatment including 11 patients who had not completed their first cycle of treatment at the time of the clinical data cut-off; as these 11 patients did not have a complete full cycle of safety assessments, the safety analysis was performed based on 348 patients. A total of 284 patients had measurable disease (at least 1 target lesion) at baseline and with at least one tumor evaluation while on study treatments (Tumor Response Population). The primary reasons for study treatment discontinuation for the 361 randomized patients was radiologic progression (186 patients, 51.5%), followed by clinical disease progression (69 patients, 19.1%), discontinuation due to an AE/SAE (32 patients, 8.9%), and withdrawal of consent (27 patients, 7.5%). As of 15 August 2014, 29 patients (19 in CS group, 10 in CF group) were continuing on study treatments.

Demographics and Baseline Characteristics: Demographic and baseline characteristics were similar for the 2 treatment groups. Approximately one-half of the patients (ITT Population) were male (51.0%) and the majority was White (95.0%). The median age was 56.0 years (range: 25 to 86 years) with 19.1% of patients ≥65 years of age. The ECOG performance status was 0 for 31.0% of patients and 1 for 68.7% of patients. The 2 groups were similar with respect to baseline disease characteristics and prior cancer therapies.

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Efficacy Results:

Primary Efficacy (data cut-off 15 August 2014):

Overall survival: The 2 treatment groups were comparable with respect to the primary efficacy endpoint. As of 15 August 2014, consistent with the slow accrual in the study, the median follow-up survival time for patients in the ITT population was 18.4 months. There were 174 patients (72.8%) in the CS group and 90 (73.8%) patients in the CF group who had died. The median OS was 7.5 months for the CS group (95% CI: 6.7, 9.3) and 6.6 months for the CF group (95% CI: 5.7, 8.1). The difference between the 2 treatment groups was not statistically significant (unstratified log-rank p value = 0.9312) with a hazard ratio (HR) of 0.99 (95% CI: 0.76, 1.28).

Secondary Efficacy (data cut-off 07 March 2014):

Progression-free survival: 152 (63.6%) of patients in the CS group and 71 (58.2%) in the CF group had radiologic disease progression. The median time to progression was 4.4 months in the CS group and 3.9 months in the CF group. The difference between the 2 treatment groups was not statistically significant (log-rank p value = 0.3039) with a HR of 0.86 (95% CI: 0.65, 1.14). The results for PFS analysis including clinical progression were similar.

Time to Treatment Failure: The median time to treatment failure was 4.2 months in the CS group and 3.8 months in the CF group. The difference between the 2 treatment groups was not statistically significant (log-rank p value = 0.1683) with a HR of 0.84 (95% CI: 0.66, 1.08).

Overall Response Rate: An overall response of complete response (CR) or partial response (PR) was observed in 67/193 (34.7%) evaluable patients in the CS group and 18/91 (19.8%) evaluable patients in the CF group. The difference between the 2 treatment groups of 14.9% was statistically significant (Fisher's exact test p-value = 0.0122; 95% CI: 4.3, 25.5) in favor of the CS group.

Safety Results:

Exposure: The median duration of cycles was 3.7 months in the CS group and 3.4 months in the CF group. The median relative dose intensities of S-1 and 5-FU were 0.965 and 0.995 for the CS and CF treatment groups, respectively; and the median relative dose intensities of cisplatin was the same, 0.990, for both groups, indicating that treatments were received at the planned dosages in the majority of patients in both treatment groups. However, dose reductions (of either S-1/5 FU or cisplatin) were less frequent in the CS group (42.2%) than in the CF group (61.0%).

Treatment-emergent Adverse events (*AEs):* The percentages of patients with at least one AE, with at least one Grade 3 or higher AE, and with at least 1 SAE, regardless of relationship to study medication, were similar for the 2 treatment groups. However, the percentage of patients with at least one treatment-related AE Grade 3 or higher was lower in the CS group than in the CF group (45.2%, CS; 55.9%, CF), and the percentage of patients with at least one AE resulting in discontinuation of study medication was lower in the CS group than in the CF group (23.9%, CS; 27.1%, CF). The percentage of patients with at least one fatal AE regardless of relationship to study medication was higher in the CS group than in the CF group (7.4%, CS; 4.2% CF).

	CS (N=230)	**CF (N=118)**
Total number of adverse events (AEs)	2864	1341
Number (%) of patients with:		
At least 1 AE regardless of relationship to study medication	214 (93.0)	111 (94.1)
At least 1 AE related to study medication	200 (87.0)	107 (90.7)
At least 1 ≥Grade 3 AE regardless of relationship to study medication	157 (68.3)	78 (66.1)
At least 1 ≥Grade 3 AE related to study medication	104 (45.2)	66 (55.9)

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At least 1 SAE regardless of relationship to study medication		63 (27.4)	31 (26.3)
At least 1 AE resulting in discontinuation of study medication regardless of relationship to study medication		55 (23.9)	32 (27.1)
At least 1 fatal AE regardless of relationship to study medication		17 (7.4)	5 (4.2)

Safety Results (continued):

The most frequently (≥25%) reported AEs (all grades) in the CS group were: nausea (54.3%), decreased appetite (41.7%), vomiting (36.1%), anaemia (45.2%), fatigue (25.7%), and neutropenia (30.0%). The most frequently reported AEs (all grades) in the CF group were: nausea (52.5%), anaemia (44.1%), neutropenia (36.4%), decreased appetite (34.7%), and vomiting (29.7%). Adverse events reported more frequently (≥ 5% difference) in the CS group compared with the CF group were abdominal pain and decreased appetite, while AEs of neutropenia, stomatitis, asthenia, mucosal inflammation, decreased appetite, hypokalaemia and alopecia were reported more frequently in the CF group compared with the CS group.

The most frequently (≥5%) reported Grade ≥3 AEs in the CS group were: neutropenia (20.9%), anaemia (16.5%), fatigue (10.4%), abdominal pain (5.7%), and asthenia (5.7%). In the CF group, the most frequently reported Grade ≥3 AEs were: neutropenia (27.1%), anaemia (11.0%), asthenia (10.2%), decreased appetite (5.9%), and hypokalaemia (5.9%). Grade ≥3 anemia and fatigue were reported more frequently (≥5% difference) in the CS group compared with the CF group, while Grade ≥3 neutropenia and asthenia were reported more frequently in the CF group compared with the CS group.

Treatment-emergent AEs resulting in Treatment Discontinuation: A total of 87 patients, 55 (23.9%) in the CS group and 32 (27.1%) in the CF group, had AEs resulting to treatment discontinuation. In the CS group, the most frequently reported AEs leading to treatment discontinuation (≥5 patients) were fatigue (6, 2.6%) and vomiting (6, 2.6%). In the CF group, the most frequent AE (≥5 patients) leading to discontinuation was asthenia (5, 4.2%).

Treatment-emergent serious adverse events (SAEs)/Deaths: SAEs were reported for 63 (27.4%) of patients in the CS group and 31 (26.3%) of patients in the CF group. The most frequently (≥2%) reported SAEs in the CS group regardless of relationship were anaemia (11, 4.8%), dehydration (6, 2.6%), vomiting (5, 2.2%), and acute renal failure (5, 2.2%). The most frequently reported SAEs in the CF group were anaemia (5, 4.2%), and vomiting, gastric haemorrhage, dehydration and hypokalaemia (each 4, 3.4%). A notable difference (≥3.0%) between the 2 treatment groups was observed for hypokalaemia (CS, 0%; CF, 3.4%).

Of the 348 treated patients, 169 patients (73.5%) in the CS group and 89 patients (75.4%) in the CF group had a death documented in the database. Two patients (011034 in the CS group; 582001 in the CF group) were reported to have died due to drug toxicity within 30 days after the last dose of study drug. In addition, there were 3 patients whose primary cause of death was due to radiologic disease progression (268001 in the CS group) or clinical disease progression (323002 and 534009 both in the CF group) for whom the Investigator also reported that the patients had died due to drug toxicity within 30 days after the last dose of study drug.

Clinical laboratory results: Across all cycles, the most frequently observed Grade 3 or 4 hematology abnormality in both groups was neutropenia (CS, 27.3%; CF, 28.3%). Across all cycles, the most frequently (≥5%) observed Grade 3 or 4 serum chemistry abnormalities in the CS group were alkaline phosphatase increased (5.5%) and hyponatraemia (7.7%). In the CF group, the most frequently (≥5%) observed Grade 3 or 4 serum chemistry abnormalities were hypokalaemia (7.0%), hyperkalaemia (5.0%), hyponatraemia (10.0%), and hypophosphataemia (7.9%).

Conclusions: The study was closed early by the Sponsor due to slow accrual. Nevertheless, the available data, obtained during accrual and follow-up, suggest that the 2 treatment groups were comparable with respect to efficacy and safety.

Final Report Date: 23 January 2015