SYNOPSIS

Name of Sponsor/Company	Yakult Honsha Co., Ltd., and Daiichi Sankyo Co., Ltd.
Name of Finished Product	CAMPTO®/Topotecin® TS-1 capsule®
Name of Active Ingredient	Irinotecan Hydrochloride Hydrate (CPT-11) Tegafur/Gimeracil/Oteracil Potassium (S-1)
Title of Study	Randomized phase III study of S-1 plus CPT-11 versus S-1 alone as first line treatment for advanced gastric cancer (GC0301/TOP-002).
Study centre(s)	54 sites, 56 branches
Publication (reference)	2008 ASCO Gastrointestinal Cancers Symposium (H.Imamura, et al, Abstract#5)
Studied Period	From Jun 24, 2004 to May 9, 2007
Phase of development	Phase III
Objectives	This study was conducted to demonstrate the superiority of S-1 plus CPT-11 (Arm B) over S-1 alone (Arm A) in terms of overall survival, for unresectable or recurrent gastric cancer.
Methodology	Randomized open-label multi-center phase III clinical study
Number of patients (planned and analyzed)	Planned : 150 pts per Arm, Total 300 pts. Analyzed : Enrolled : 326 pts (Arm A;162 pts, Arm B;164 pts) With drug administration : 319 pts (Arm A;161 pts, Arm B;158 pts) Full Analysis Set (FAS) : 315 pts (Arm A;160 pts, Arm B;155 pts) Safety Analysis Set : 315 pts (Arm A;160 pts、Arm B;155 pts)
Diagnosis and main criteria for inclusion	Diagnosis : Unresectable or recurrent gastric cancer Inclusion criteria : ① Histologically and/or cytologically confirmed gastric cancer ② Ability to take oral medication ③ Unresectable or recurrent gastric cancer ④ No prior radiotherapy or chemotherapy ⑤ Age ranging between 20 and 75 years ⑥ An expected survival duration of ≥12 weeks ⑦ ECOG performance status 0–2 ⑧ Adequate organ function ⑨ Written informed consent
Test product, dose and mode of administration, batch number	Arm A : S-1 ; Oral S-1 80 mg/m²/day from Day 1 to 28, q6w. Arm B : S-1 ; Oral S-1 80 mg/m²/day from Day 1 to 21. CPT-11 ; Intravenous irinotecan 80 mg/m² on Days 1 and 15, q5w. Batch numbers of CPT-11 and S-1 were uncontrolled, because of post-marketing drugs.

Duration of treatment	Treatment was discontinued in the event of documented disease progression, unacceptable toxicity, or consent withdrawal.
Criteria for evaluation	Primary endpoint ： Overall survival Secondary endpoint ：(1) Time to treatment failure (TTF) (2) 1-year survival rate (3) Response rate(RR) (4) Safety
Statistical method	Efficacy ： The difference of overall survival was analyzed using the stratified log-rank test. Probability of survival, median-TTF and 1-year survival rate was estimated using the Kaplan-Meier method. Response rate was evaluated on the basis of RECIST guidelines, the difference was analyzed using the chi-square test. Safety ： In safety analysis set, the incidence of adverse event and side effect were Estimated, and the frequencies of those were compiled according to grade.
Summary - Conclusion	Efficacy ： Although the median survival time (MST) of Arm A was 318 days and of Arm B was 389 days, Arm B didn't show statistically significant superiority to Arm A (log-rank test p=0.234). The median-TTF were 111 days in Arm A and 138 days, Arm B didn't show statistically significant superiority to Arm A (log-rank test p=0.157). The 1-year survival rates were 44.9% in Arm A and 52.0% in Arm B. RR was statistically significant different (Arm A/B, 26.9%/41.5%; chi-square test p=0.035) in 187 RECIST evaluable pts. Safety ： Grade 3/4 adverse events over 3 percent in Arm A were anorexia 18.8%, hemoglobin 11.9%, neutrophils 10.6%, fatigue 7.5%, hyponatremia 6.9%, diarrhea 5.6%, nausea 5.6%, bilirubin 5.6%, AST (SGOT) 5.0%, hypocalcemia 5.0%, platelets 3.8%, hypoalbuminemia 3.8%, infection/febrile neutropenia 3.8%, pain 3.8%, leukocytes 3.1%, ileus 3.1%, those of in Arm B were neutrophils 27.1%, anorexia 17.4%, diarrhea 16.1%, hemoglobin 15.5%, leukocytes 11.6%, hyponatremia 7.7%, nausea 7.1%, fatigue 6.5%, hypokalemia 4.5%, dehydration 3.2%, vomiting 3.2%, bilirubin 3.2%, AST (SGOT) 3.2%, febrile neutropenia 3.2%. Treatment-related death was documented 2 patients in Arm B. Conclusion ： Although S-1 plus CPT-11 didn't show statistically significant superiority to S-1 alone in overall survival of primary endpoint, RR and MST were not inferior to those of phase III clinical study reported recently both domestically and internationally. In safety, S-1 alone and S-1 plus CPT-11 were well tolerable.
Date of report	Sept 30, 2009

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