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**Randomized Phase III Study of S-1 Alone versus S-1 Plus Cisplatin
(SPIRITS: TS-1 Advanced Gastric Cancer Clinical Trial Group)**

**M. Takagi,¹ W. Koizumi,² H. Narahara,³ T. Hara,⁴ A. Takagane,⁵ T. Akiya,⁶
K. Miyashita,⁷ T. Nishizaki,⁸ O. Kobayashi⁹**

¹Department of Surgery
Shizuoka General Hospital
Shizuoka, Japan

²Department of Gastroenterology
Kitasato University East Hospital
Kanagawa, Japan

³Department of Gastroenterology
Osaka Medical Center for Cancer and Cardiovascular Diseases
Osaka, Japan

⁴Department of Surgery
Kouseiren Takaoka Hospital
Toyama, Japan

⁵Department of Surgery
Iwate Medical University
Iwate, Japan

⁶Department of Gastroenterology
Gunma Prefectural Cancer Center
Gunma, Japan

⁷Department of Surgery
National Hospital Organization Nagasaki Medical Center

Nagasaki, Japan

⁸Department of Surgery

Matsuyama Red Cross Hospital

Ehime, Japan

⁹Department of Gastrointestinal Surgery

Kanagawa Cancer Center

Kanagawa, Japan

Background: S-1 (TS-1) has been widely used for advanced gastric cancer in Japan. In addition, it was reported that combination therapies of S-1 with other cytotoxic agents were highly effective and tolerable. Recently, two randomized phase III trials in advanced gastric cancer (SPIRITS [S-1 plus Cisplatin vs. S-1 in RCT in the Treatment of Stomach Cancer] and FLAGS [First-Line Advanced Gastric Cancer Study]), including S-1 + cisplatin combination therapy, were carried out. The SPIRITS study, conducted in Japan, aimed to compare overall survival of advanced gastric cancer patients treated with S-1 + cisplatin combination therapy (arm SP) vs. S-1 monotherapy (arm S). Results of SPIRITS were presented at the 2007 American Society of Clinical Oncology (ASCO) annual meeting.

Methods: Patients were randomized to one of two treatment arms: arm S (S-1 40 mg/m², bid, days 1-28, every 6 weeks) or arm SP (S-1 40 mg/m², bid, days 1-21 and cisplatin 60 mg/m², day 8, every 5 weeks). Patients were required to have unresectable/recurrent advanced gastric cancer, age of 20-74 years, performance status (PS) of 0-2, and no previous chemotherapy for advanced disease. End points were overall survival (OS), response rate, progression-free survival (PFS), time to treatment failure (TTF), and toxicities.

Results: A total of 305 patients (arm S/SP, 152/153) were randomized between March 2002 and November 2004. Of these, 299 (150 S/149 SP) patients were eligible for assessment. Overall survival durations in arms S/SP were 335.5 days (95% confidence interval [CI], 292-402)/396 days (95% CI, 342-471), and the hazard ratio was 0.774 (95%

CI, 0.610-0.982). The 1- and 2 year-survival rates in arms S/SP were 46.7%/54.1% and 15.3%/23.6%, respectively. In both treatment arms, approximately 90% of patients who survived more than 1 year, and more than 2 years, received second-line therapy. Response rates were 31.1% with S-1 alone and 54.0% with S-1 plus cisplatin. Median PFS durations in arms S/SP were 122 days (95% CI, 112-142)/ 183 days (95% CI, 156- 236). Median TTF in arm S was 119 days (95% CI, 91-136), and in arm SP was 145 days (95% CI, 112-162). Common grade 3/4 toxicities were leukopenia (2.0%/11.5%), neutropenia (10.7%/39.9%), anemia (4.0%/25.7%), anorexia (6.0%/30.4%), and nausea (1.3%/11.5%).

Conclusions: Results of the SPIRITS study established the superiority of S-1 + cisplatin combination therapy over S-1 monotherapy. S-1 + cisplatin combination therapy demonstrated high efficacy and tolerability and is considered a standard first-line treatment for advanced gastric cancer.