June 25, 2018
Taiho Pharmaceutical Co., Ltd.

Taiho and Servier Present Promising Data on LONSURF® (trifluridine and tipiracil) at ESMO 20th World Congress on Gastrointestinal Cancer 2018

Taiho Pharmaceutical Co., Ltd. and Servier announced that promising clinical data for LONSURF® (trifluridine and tipiracil) from the pivotal Phase III TAGS trial and Phase II TASCO-1 trial were presented at the ESMO 20th World Congress on Gastrointestinal Cancer 2018 (ESMO-GI) in Barcelona, Spain, June 20 to 23.

The TAGS trial was conducted to evaluate the safety and efficacy of trifluridine and tipiracil plus best supportive care (BSC) versus placebo plus BSC in patients with previously treated metastatic gastric cancer refractory to standard therapies. The primary endpoint was overall survival (OS).

In the trial, patients treated with trifluridine and tipiracil had a 31% risk reduction of death and a prolongation of their median survival by 2.1 months compared to patients treated with placebo (OS of 5.7 vs. 3.6 months) (hazard ratio [HR]: 0.69). At 12-months, OS rates were 21% in the trifluridine and tipiracil group and 13% in the placebo group. In addition, the risk for disease progression as measured by PFS, a key secondary endpoint, was reduced by 43% (HR: 0.57).

Any Grade 3 or higher adverse events (AEs) occurred in 80% of treated patients who received trifluridine and tipiracil and in 58% of treated patients who received placebo. Grade 3/4 hematological AEs in patients treated with trifluridine and tipiracil included neutropenia (38%), leucopenia (21%), anemia (19%) and lymphocytopenia (19%). Of the 38% of patients who experienced grade 3/4 neutropenia when treated with trifluridine and tipiracil, six (2%) experienced febrile neutropenia. No new safety signals were observed for trifluridine and tipiracil in the TAGS study.

The abstract for this presentation is available on the ESMO-GI website at https://academic.oup.com/annonc/article/29/suppl_5/mdy208.001/5043314?searchresult=1.

The TASCO-1 trial evaluated efficacy of trifluridine and tipiracil in combination with bevacizumab and the current standard of care (capecitabine and bevacizumab) for patients with untreated metastatic colorectal cancer, who are not suitable for intensive therapy.

The trial demonstrated a median PFS of 9.2 months. The median PFS of the capecitabine with bevacizumab arm was 7.8 months. The combination of trifluridine/tipiracil and bevacizumab was manageable, with the most frequently observed toxicities being gastrointestinal and hematologic. There was a 3.9% serious febrile neutropenia event rate reported in both arms of the trial.

The abstract for this presentation is available on the ESMO-GI website at https://academic.oup.com/annonc/article/29/suppl_5/mdy149.021/5039386?searchresult=1.

Taiho Pharmaceutical and Servier remain committed to making further contributions to patients and to medical practitioners engaged in the treatment of cancer.

About TAGS

The TAGS (***TA***S-102 ***G***astric ***S***tudy) trial is a pivotal Phase III multinational, randomized, double-blind study evaluating LONSURF® (trifluridine and tipiracil), also known as TAS-102, plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic gastric cancer refractory to standard treatments. The primary endpoint in the TAGS trial is OS, and secondary endpoint measures include PFS, and safety and tolerability, as well as quality of life.

The TAGS trial aimed to enroll 500 adults 18 years and older with metastatic gastric cancer who had previously received at least two prior regimens for advanced disease. The trial enrolled 507 subjects and was conducted in Japan, North America, Europe, Russia and Turkey, among other locations.

For more information on the TAGS trial, please visit www.ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT02500043). The ClinicalTrials.gov Identifier is NCT02500043.

About TASCO-1

TASCO-1 trial is an international, randomized Phase II trial designed to evaluate efficacy of LONSURF® (trifluridine and tipiracil) in combination with bevacizumab and the current standard of care (capecitabine and bevacizumab) for patients with untreated metastatic colorectal cancer, who are not suitable for intensive therapy. The primary endpoint in the

TASCO-1 trial is PFS, and secondary endpoints include OS and disease control rate.

The TASCO-1 trial enrolled 150 adults 18 years and older with untreated metastatic colorectal cancer. The TASCO-1 trial was conducted in Europe, Russia, Australia, and Brazil.

For more information on the TASCO-1 trial, please visit www.ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT02743221). The ClinicalTrials.gov Identifier is NCT02743221.

About Gastric Cancer

Gastric cancer is the fifth most common cancer worldwide and the third most common cause of cancer-related death (after lung and liver cancer), with an estimated 723,000 deaths annually[1]. In Japan, gastric cancer is the most common cancer and the third most common cause of cancer-related death (after lung and colorectal cancer), causing around 45,000 deaths annually[2].

In recent years, the outcome for gastric cancer has improved remarkably, and survival has increased dramatically over the past 10 years. As cancer progresses, however, numerous complications can limit the usable drugs and preclude intensive chemotherapy. Prolonging survival and relieving symptoms in late-stage treatment for metastatic gastric cancer are issues for which it is thought important to increase the options for new therapeutic drugs. At present, nivolumab and irinotecan are recommended in Japan as the standard third line treatment for metastatic gastric cancer.

About Colorectal Cancer

Colorectal cancer is the third most common cancer worldwide with approximately 1.4 million new diagnoses in 2012[3]. Each year there are over 690,000 deaths making it the fourth biggest cancer killer worldwide (after lung, liver and gastric cancer)[4]. In Japan, colorectal cancer is the second most prevalent cancer in terms of both incidence and the number of deaths, with around 50,000 deaths annually[2].

Those with metastatic disease (where the cancer has spread from the primary site) the average five-year survival is approximately 11%[5]. Standard chemotherapy regimens for advanced metastatic colorectal cancer include fluoropyrimidines, oxaliplatin, irinotecan or targeted treatments, such as those that target vascular endothelial growth factors (VEGF) or endothelial growth factor receptors (EGFR).

About LONSURF (trifluridine and tipiracil)

LONSURF is an oral anticancer drug, comprising the combination of trifluridine (FTD) and tipiracil (TPI), whose dual mechanism of action is

designed to maintain clinical activity and differs from conventional fluoropyrimidines.

FTD is an antineoplastic nucleoside analogue, which is incorporated directly into the DNA, thereby interfering with the function of DNA. The blood concentration of FTD is maintained via TPI, which is an inhibitor of the FTD-degrading enzyme, thymidine phosphorylase.

In Japan, Taiho Pharmaceutical markets LONSURF for the treatment of unresectable advanced or recurrent colorectal cancer. In the United States, Taiho Oncology, Inc., a U.S. subsidiary of Taiho Pharmaceutical, markets the drug for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

In June 2015, Taiho Pharmaceutical and Servier entered into an exclusive license agreement for the co-development and commercialization of LONSURF. Under the terms of the agreement, Servier has the rights to co-develop and commercialize LONSURF in Europe and other countries outside of the United States, Canada, Mexico and Asia. In parts of Asia outside Japan, Jeil Pharmaceutical and TTY Biopharm, which are Taiho Pharmaceutical's business partners in South Korea and Taiwan, respectively, are preparing to bring the drug to market.

As of May 2018, the drug has been approved as a treatment for advanced mCRC in 50 countries including Japan, USA, and EU.

About Servier

Servier is an international pharmaceutical company governed by a non-profit foundation, with its headquarters in France (Suresnes). With a strong international presence in 148 countries and a turnover of 4.152 billion euros in 2017, Servier employs 21,600 people worldwide. Entirely independent, the Group reinvests 25% of its turnover (excluding generic drugs) in research and development and uses all its profits for development. Corporate growth is driven by Servier's constant search for innovation in five areas of excellence: cardiovascular, immune-inflammatory and neuropsychiatric diseases, cancer and diabetes, as well as by its activities in high-quality generic drugs.

Becoming a key player in oncology is part of Servier's long-term strategy. Currently, there are nine molecular entities in clinical development in this area, targeting gastric and lung cancers and other solid tumors, as well as different types of leukemia and lymphomas. This portfolio of innovative cancer treatments is being developed with partners worldwide, and covers different cancer hallmarks and modalities, including cytotoxics, proapoptotics, immune, cellular and targeted therapies, to deliver

life-changing medicines to patients. Servier also offers eHealth solutions beyond drug development.

More information: www.servier.com

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Int J Cancer. 2015;136:E359-86.
2. “Latest Cancer Statistics,” a cancer information service of the National Cancer Center Japan (in Japanese). https://ganjoho.jp/reg_stat/statistics/stat/summary.html Last accessed June 2018
3. World Health Organisation. Globocan (2012), colorectal cancer. Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx?cancer=colorectal Last accessed June 2018
4. Cancer Research UK. Worldwide cancer statistics. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/worldwide-cancer/mortality#heading-One Last accessed June 2018
5. American Cancer Society. Survival Rates for Colorectal Cancer, by Stage. Available at: https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/survival-rates.html Last accessed June 2018