Taiho Oncology Announces Positive Topline Results from Pivotal Phase 3 Trial of LONSURF® (trifluridine/tipiracil) in Metastatic Gastric Cancer

PRINCETON, N.J., May 9, 2018 – Taiho Oncology, Inc. (U.S.), a subsidiary of Taiho Pharmaceutical Co., Ltd. (Japan), and Servier, announced today that the pivotal Phase 3 (TAGS) trial evaluating LONSURF® (trifluridine and tipiracil) plus best supportive care (BSC) versus placebo plus BSC in patients with previously treated metastatic gastric cancer, met its primary endpoint of prolonged overall survival (OS). These results will be presented at an upcoming medical conference and will be submitted to a peer-reviewed journal for publication.

“We are delighted by these positive results in the TAGS study, which further underscore the activity of LONSURF in prolonging survival and as a potential treatment option for patients with metastatic gastric cancer who have failed prior treatments,” said Martin J. Birkhofer, M.D., Senior Vice President, Chief Medical Officer, Taiho Oncology, Inc. “This is particularly important given that these patients currently have limited approved standard third-line treatment options available to them after first and second line therapies have failed. We look forward to including these data in an sNDA submission to the U.S. Food and Drug Administration (FDA) for consideration as a third-line treatment option for appropriate patients with metastatic gastric cancer.”

LONSURF is currently indicated in the United States for the treatment of patients with metastatic colorectal cancer 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.

About TAGS

The TAGS (***TA***S-102 ***G***astric ***S***tudy) trial is a Taiho-sponsored 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 overall survival (OS), and secondary endpoint measures include progression-free survival (PFS), and safety and tolerability, as well as quality of life.

The TAGS trial enrolled 507 adults 18 years and older with metastatic gastric cancer who had previously received at least two prior regimens for advanced disease. The TAGS trial 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 Metastatic Gastric Cancer

Gastric cancer, also known as stomach cancer, is a disease in which malignant cells form in the lining of the stomach. It 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]. Approximately 50 percent of patients with gastric cancer have advanced disease at the time of diagnosis [2].

Standard chemotherapy regimens for advanced gastric cancer include fluoropyrimidines, platinum derivatives, and taxanes (with Ramucirumab), or irinotecan. The addition of trastuzumab to chemotherapy is standard of care for patients with HER2-neu-positive advanced gastric cancer. However, after failure of first- and second-line therapies, standard third line treatments are limited.

About LONSURF

LONSURF is an oral combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, anticancer drug indicated in United States for the treatment of patients with metastatic colorectal cancer (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.[3-4] LONSURF is also available in EU, [3] Japan, and other countries.

In June 2015, Taiho Pharmaceutical Co., Ltd. entered into an exclusive license agreement with Servier for the co-development and commercialization of LONSURF®. Under the terms of the agreement, Taiho Pharmaceutical Co., Ltd. granted Servier the right to co-develop and commercialize LONSURF® in Europe and other countries outside of the United States, Canada, Mexico and Asia. Taiho Pharmaceutical Co., Ltd. retains the right to develop and commercialize LONSURF® in the United States, Canada, Mexico, and Asia and to manufacture and supply the product.

Important Safety Information [4]

WARNINGS AND PRECAUTIONS

Severe Myelosuppression: In RECOURSE Study, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%), and febrile neutropenia (3.8%). One patient (0.2%) died due to neutropenic infection. In Study 1, 9.4% of LONSURF-treated patients received granulocyte-colony stimulating factors.

Obtain complete blood counts prior to and on day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for febrile neutropenia, Grade 4 neutropenia, or platelets less than 50,000/mm^3. Upon recovery, resume LONSURF at a reduced dose as clinically indicated.

Embryo-Fetal Toxicity: LONSURF can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF.

USE IN SPECIFIC POPULATIONS

Lactation: It is not known whether LONSURF or its metabolites are present in human milk. There are no data to assess the effects of LONSURF or its metabolites on the breast-fed infant or the effects on milk production. Because of the potential for serious adverse reactions in breast-fed infants, advise women not to breastfeed during treatment with LONSURF and for 1 day following the final dose.

Male Contraception: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose.

Geriatric Use: Patients 65 years of age or over who received LONSURF had a higher incidence of the following compared to patients younger than 65 years: Grade 3 or 4 neutropenia (48% vs 30%), Grade 3 anemia (26% vs 12%), and Grade 3 or 4 thrombocytopenia (9% vs 2%).

Hepatic Impairment: Patients with severe hepatic impairment (total bilirubin greater than 3 times ULN and any AST) were not studied. No adjustment to the starting dose of LONSURF is recommended for patients with mild hepatic impairment. Do not initiate LONSURF in patients with baseline moderate or severe (total bilirubin greater than 1.5 times ULN and any AST) hepatic impairment.

Renal Impairment: In RECOURSE Study, patients with moderate renal impairment (CLcr=30 to 59 mL/min, n=47) had a higher incidence (difference of at least 5%) of ≥Grade 3 adverse events, serious adverse events, and dose delays and reductions compared to patients with normal renal function (CLcr ≥90 mL/min, n=306) or patients with mild renal impairment (CLcr=60 to 89 mL/min, n=178).

Patients with moderate renal impairment may require dose modifications for increased toxicity. Patients with severe renal impairment were not studied.

ADVERSE REACTIONS

Most Common Adverse Drug Reactions in Patients Treated With LONSURF

(≥5%): The most common adverse drug reactions in LONSURF-treated patients vs placebo-treated patients with refractory mCRC, respectively, were asthenia/fatigue (52% vs 35%), nausea (48% vs 24%), decreased appetite (39% vs 29%), diarrhea (32% vs 12%), vomiting (28% vs 14%), abdominal pain (21% vs 18%), pyrexia (19% vs 14%), stomatitis (8% vs 6%), dysgeusia (7% vs 2%), and alopecia (7% vs 1%).

Additional Important Adverse Drug Reactions: The following occurred more frequently in LONSURF-treated patients compared to placebo: infections (27% vs 15%) and pulmonary emboli (2% vs 0%).

The most commonly reported infections which occurred more frequently in LONSURF-treated patients were nasopharyngitis (4% vs 2%) and urinary tract infections (4% vs 2%).

Interstitial lung disease (0.2%), including fatalities, has been reported in clinical studies and clinical practice settings in Asia.

Laboratory Test Abnormalities in Patients Treated With LONSURF: Laboratory test abnormalities in LONSURF-treated patients vs placebo-treated patients with refractory mCRC, respectively, were anemia (77% vs 33%), neutropenia (67% vs 1%), and thrombocytopenia (42% vs 8%).

Please see full US Prescribing Information.
www.taihooncology.com/us/prescribing-information.pdf.

About Taiho Oncology, Inc. (U.S.)
Taiho Oncology, Inc., a subsidiary of Taiho Pharmaceutical Co., Ltd. and Otsuka Holdings Co., Ltd., has established a world class clinical development organization that works urgently to develop innovative cancer treatments and with a strong commercial business in the U.S. dedicated to bringing the company's approved medical innovations to patients. Taiho has an oral oncology pipeline consisting of both novel antimetabolic agents and selectively targeted agents. Advanced technology, dedicated researchers, and state of the art facilities are helping us to define the way the world treats cancer. It's our work; it's our passion; it's our legacy.

For more information about Taiho Oncology, please visit:
https://www.taihooncology.com.

About Taiho Pharmaceutical Co., Ltd. (Japan)
Taiho Pharmaceutical, a subsidiary of Otsuka Holdings Co., Ltd., is an R&D-driven specialty pharma focusing on the three fields of oncology, allergy and immunology, and urology. Its corporate philosophy takes the form of a pledge: “We strive to improve human health and contribute to a society enriched by smiles.” In the field of oncology, in particular, Taiho Pharmaceutical is known as a leading company in Japan for developing innovative medicines for the treatment of cancer, a reputation that is rapidly expanding through their extensive global R&D efforts. In areas other than oncology, as well, the company creates and markets quality products that effectively treat medical conditions and can help improve people's quality of life. Always putting customers first, Taiho Pharmaceutical also aims to offer consumer healthcare products that support people's efforts to lead fulfilling and rewarding lives.

For more information about Taiho Pharmaceutical, please visit: https://www.taiho.co.jp/en/.

About Otsuka Holdings Co., Ltd. (Japan)
The Otsuka group of companies is a total-healthcare enterprise that aims to contribute to the health of people around world under the corporate philosophy, “Otsuka-people creating new products for better health worldwide.”

Healthcare is broadly and holistically addressed through the two main pillars – the pharmaceutical business for the diagnosis and treatment of diseases and the nutraceutical [5] business to support the maintenance and promotion of everyday health. Our 46,000 [6] employees across 183 companies in 28 countries and regions take on challenges across various fields and themes to help fulfill the universal wish of people to be healthy. Our pursuit of these challenges is motivated by the Otsuka’ s corporate culture, articulated as “Ryukan-godo” (by sweat we recognize the way), “Jissho” (actualization) and “Sozosei” (creativity), and fostered by successive generations of Otsuka leaders. By striving to provide unique products and services, we seek to achieve sustainable growth and be an indispensable contributor to the world.

For more information, please visit the company's website at https://www.otsuka.com/en/.

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 percent 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.

For more information about Servier, please visit www.servier.com and www.servier-oncology.com

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[1] Ferlay J, Soerjomataram I, Dikshit R, et al. Int J Cancer. 2015;136:E359-86.
[2] National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Gastric cancer. Version 1.2018. http://www.nccn.org
[3] Lonsurf EU Summary of Product Characteristics (SmPC); August 2017: http://www.ema.europa.eu/ema/
[4] Full Prescribing Information available at: www.taihooncology.com/us/prescribing-information.pdf
[5] Nutraceuticals: nutrition + pharmaceuticals
[6] As of end of December 2017