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TAIHO ONCOLOGY

FDA Approves Taiho Oncology's LONSURF® (trifluridine/tipiracil) for Adult Patients with Previously Treated Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

PRINCETON, N.J., February 25, 2019 – Taiho Oncology, Inc. today announced that the United States Food and Drug Administration (FDA) has approved LONSURF® as a treatment for adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

"The approval of LONSURF represents a significant milestone for patients living with advanced gastric or GEJ adenocarcinoma who have limited effective treatment options after standard treatment options have failed," said Timothy Whitten, President and Chief Executive Officer, Taiho Oncology, Inc. "We thank all the patients and physicians who helped make this possible through their participation in LONSURF clinical trials."

The approval for LONSURF follows an FDA Priority Review designation and is based on data from a global, randomized, Phase III TAGS trial evaluating LONSURF plus best supportive care (BSC) versus placebo plus BSC in patients with previously treated advanced gastric cancer or GEJ adenocarcinoma following progression or intolerance to previous lines of standard therapy. The trial met its primary and secondary endpoints demonstrating prolonged overall survival (OS) with LONSURF versus placebo, and a safety profile consistent with prior experience with this drug. Full results from the TAGS trial were presented at the European Society of Medical Oncology (ESMO) 2018 Congress with a simultaneous publication in *The Lancet Oncology*.[1]

"Effective treatments for patients with heavily pretreated advanced gastric and GEJ cancer are limited," said Martin Birkhofer, MD, Senior Vice President and Chief Medical Officer, Taiho Oncology, Inc. "By improving survival, LONSURF may provide a significant impact on the lives of these patients."

This approval expands the current indication for LONSURF in the United States, where it is currently approved for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with standard chemotherapy, based on results obtained in the RECOURSE trial.[2,3]

About TAGS

TAGS (***TA***S-102 ***G***astric ***S***tudy) is a Taiho-sponsored, global, randomized, double-blind Phase III study evaluating trifluridine/tipiracil (TAS-102) plus BSC versus placebo plus BSC in patients with metastatic gastric or GEJ cancer, refractory to standard treatments. The primary endpoint in the TAGS trial was OS, and the main secondary

endpoint measures included progression-free survival (PFS), safety and tolerability, as well as quality of life. The study enrolled 507 adult patients with metastatic gastric or GEJ cancer who had previously received at least two prior regimens for advanced disease and was conducted in 17 countries and 110 sites around the world.

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

About RECOURSE
The RECOURSE trial was a global, randomized, double-blind, placebo-controlled Phase III comparison trial evaluating the efficacy and safety of orally administered TAS-102 in patients with previously treated mCRC. The trial enrolled 800 patients in North America, Japan, Europe and Australia. Patients were randomized (2:1) to receive TAS-102 (35 mg/m^2) or placebo, plus best supportive care, twice daily. The study met its primary and secondary endpoint of OS and PFS versus placebo.

About Gastric Cancer
Gastric cancer is the fifteenth most commonly diagnosed cancer in the United States (U.S.).[4] In 2018, there were an estimated 26,240 new cases and 10,800 deaths in the U.S.[4] Approximately 35 percent of U.S. patients with gastric cancer are diagnosed at the distant or metastasized stage.[4] Metastatic gastric cancer (mGC) is associated with a five-year survival rate of about 5 percent.[4]

Standard chemotherapy regimens for advanced gastric cancer include fluoropyrimidines, platinum derivatives, and taxanes (with ramucirumab), or irinotecan. After failure of first- and second-line therapies, subsequent treatment options are limited.

About LONSURF[2]
LONSURF consists of a thymidine-based nucleoside analog, trifluridine, and the thymidine phosphorylase (TP) inhibitor, tipiracil, which increases trifluridine exposure by inhibiting its metabolism by TP. Trifluridine is incorporated into DNA, resulting in DNA dysfunction and inhibition of cell proliferation.

In Japan, Taiho Pharmaceutical Co., Ltd. has been marketing LONSURF for the treatment of unresectable advanced or recurrent colorectal cancer since 2014. Taiho Oncology, Inc., a U.S. subsidiary of Taiho Pharmaceutical, has been marketing LONSURF in the United States for metastatic CRC refractory to prior therapy, since receiving FDA approval in 2015. Taiho Pharmaceutical and Servier* are in an exclusive license agreement for the co-development and commercialization of LONSURF in Europe and other countries outside of the United States, Canada, Mexico, and Asia.

As of February 2019, LONSURF has been approved as a treatment option for advanced mCRC in 66 countries and regions worldwide.

*Servier is an international pharmaceutical company governed by a non-profit foundation, headquartered in France (Suresnes).

Important Safety Information

WARNINGS AND PRECAUTIONS

Severe Myelosuppression:

LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%), and febrile neutropenia (3%). Two patients (0.2%) died due to neutropenic infection. A total of 12% 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, absolute neutrophil count less than 500/mm^3, 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 and for at least 6 months after the final dose.

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 (22% vs 16%), and Grade 3 or 4 thrombocytopenia (7% vs 4%).

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. 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.

Renal Impairment: No adjustment to the starting dosage of LONSURF is recommended in patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min). Patients with severe renal impairment (CLcr < 30 mL/min) 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 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%), infections (27% vs 16%), abdominal pain (21% vs 18%), pyrexia (19% vs 14%), stomatitis (8% vs 6%), dysgeusia (7% vs 2%), and alopecia (7% vs 1%). In metastatic gastric cancer or gastroesophageal junction (GEJ), the most common adverse drug reactions, respectively were, nausea (37% vs 32%), decreased appetite (34 vs 31%), vomiting (25% vs 20%), infections (23% vs 16%) and diarrhea (23% vs 14%).

Pulmonary emboli occurred more frequently in LONSURF-treated patients compared to placebo: (2% vs 0%) in mCRC and (3% vs 2%) in metastatic Gastric Cancer and GEJ.

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 mCRC, respectively, were anemia (77% vs 33%), neutropenia (67% vs 1%), and thrombocytopenia (42% vs 8%). In metastatic Gastric Cancer or GEJ, the test abnormalities, respectively, were neutropenia (66% vs 4%), anemia (63% vs 38%), and thrombocytopenia (34% vs 9%).

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

Indications and Use[2]
LONSURF is indicated for the treatment of adult patients with metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

LONSURF is indicated for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

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 has built a commercial business in the U.S. Taiho has an oral oncology pipeline consisting of both 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 the 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*1 business to support the maintenance and promotion of everyday health. Our 47,000*2 employees across 189 companies in 30 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/.

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*1. Nutraceuticals: nutrition + pharmaceuticals *2. As of end of December 2018

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[1] Shitara, K., Doi, T., Dvorkin, M., et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology.* 2018;19(11): 1437-1438. https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30739-3/fulltext. Accessed December 2018.

[2] LONSURF [US prescribing information]; Princeton, NJ: Taiho Oncology, Inc.; 2019. 2019.

[3] Mayer, RJ., Van Cutsem, E., Falcone, A., et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015;372(20):1909-19.

[4] National Cancer Institute Surveillance Epidemiology and End Results Program. Cancer Stat Facts: Stomach Cancer. https://seer.cancer.gov/statfacts/html/stomach.html. Accessed January 3, 2019.