Analysis of Patients with Prior Gastrectomy Treated with LONSURF® (trifluridine and tipiracil) Published in *JAMA Oncology*

– Data from pivotal study demonstrate safety and efficacy regardless of prior gastrectomy in previously treated patients with metastatic gastric cancer (mGC) and gastroesophageal junction (GEJ) adenocarcinoma

PRINCETON, N.J., October 14, 2019 – Taiho Oncology, Inc. announced today that detailed results from the analysis of patients with prior gastrectomy enrolled in the Phase 3 **TA**S-102 **G**astric **S**tudy (TAGS) evaluating LONSURF® (trifluridine and tipiracil) in 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, were published in the October 10, 2019 issue of *JAMA Oncology*.

The U.S. Food and Drug Administration (FDA) approved LONSURF in previously treated mGC and GEJ adenocarcinoma in February 2019, based on data from the global, randomized, double-blind, placebo-controlled TAGS trial, which demonstrated clinically meaningful and statistically significant improvement in overall survival (OS) and progression-free survival (PFS) when compared with placebo in these patients. The safety profile of LONSURF was consistent with studies of the drug in metastatic colorectal cancer (mCRC), and no new safety concerns were reported.

“The outcome of the Phase 3 TAGS trial in this patient population is extremely significant, as nearly half of all patients with metastatic gastric cancer and gastroesophageal junction adenocarcinoma have undergone a previous gastrectomy and are prone to more complications than those without gastrectomy,”[1,2,3,4,5] said Memorial Sloan Kettering Cancer Center Medical Oncologist David H. Ilson, MD, PhD. “These data provide further evidence of the safety and efficacy of LONSURF and its utility in patients who may have limited treatment options.”

In the preplanned subgroup analysis, 221 of 507 patients with mGC or GEJ adenocarcinoma with prior gastrectomy were enrolled and randomized to receive LONSURF 35 mg/m^2 (n=147) or placebo (n=74) on days 1-5 and 8-12 of each 28-day treatment cycle. Results showed that treatment with LONSURF was tolerable and prolonged survival versus placebo regardless of prior gastrectomy. Further, the overall safety profile of the drug, including the incidence of severe AEs in this heavily pretreated patient population, was similar in patients with or without gastrectomy.

“Metastatic gastric cancer and gastroesophageal junction adenocarcinoma are debilitating diseases that generally have a very poor prognosis,” said Taiho Oncology,

Inc. Senior Vice President and Chief Medical Officer Martin J. Birkhofer, MD. “Given the unmet treatment need and sense of urgency once earlier rounds of therapy have failed, we are pleased with the results of the subgroup analysis of the TAGS trial, which provide further evidence for the clinical benefit of LONSURF in these vulnerable patients with gastrectomy.”

Data from the subgroup analysis were previously announced as an oral presentation during the 2019 American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO-GI) in San Francisco, CA.

The FDA approval of LONSURF in mGC and GEJ adenocarcinoma builds on the initial U.S. approval of LONSURF in 2015 for the treatment of adult 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.[6]

About TAGS
TAGS (***TA***S-102 ***G***astric ***S***tudy) is a Taiho-sponsored, global, randomized, double-blind, placebo controlled, Phase 3 study evaluating the efficacy and safety of LONSURF in 507 adult patients with previously treated mGC or mGEJ adenocarcinoma. The primary endpoint was OS, and key secondary endpoints included PFS, safety and tolerability, as well as quality of life. LONSURF demonstrated statistically significant improvement in OS and PFS compared with placebo. The median OS improved from 3.6 months with placebo to 5.7 months with LONSURF, HR 0.69 (95% confidence interval [CI], 0·56-0·85; P=0.00058).

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

About LONSURF[6]
LONSURF is an oral nucleoside antitumor agent discovered and developed by Taiho Pharmaceutical Co., Ltd. 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.

Since 2015, Taiho Pharmaceutical and Servier have been 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.

Indications and Use[6]
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

- 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.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Severe Myelosuppression: LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of neutropenia (38%), anemia (18%), 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/mm3, or platelets less than 50,000/mm3. 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 (46% vs 32%), 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

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 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/us/

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

For more information about Otsuka Holdings Co., Ltd., please visit:
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For more information about Servier, please visit:
https://servier.com/en/

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[2] 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. *Lancet Oncol.* 2018;19(11):1437-1448.
[3] Orditura M, Galizia G, Sforza V, et al. Treatment of gastric cancer. *World J Gastroenterol.* 2014;20(7):1635-1649.
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[6] LONSURF [US prescribing information]; Princeton, NJ: Taiho Oncology, Inc.; 2019. 2019.