Taiho Oncology and Servier Announce Publication in the *New England Journal of Medicine* of Pivotal Phase 3 Data for Trifluridine/Tipiracil (LONSURF®) in Combination With Bevacizumab in Patients With Refractory Metastatic Colorectal Cancer

PRINCETON, N.J., and Paris, France [May 3, 2023] – Taiho Oncology, Inc. and Servier today announced the publication of results from the pivotal Phase 3 SUNLIGHT* clinical trial of trifluridine/tipiracil (LONSURF®), alone or in combination with bevacizumab, in refractory metastatic colorectal cancer (mCRC) in the May 4, 2023, issue of the *New England Journal of Medicine* (NEJM).

Results of this multinational trial, led by Professor Josep Tabernero, MD, PhD, Head of Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, showed that treatment with the investigational combination of trifluridine/tipiracil and bevacizumab resulted in statistically significant and clinically meaningful improvements in overall survival and progression-free survival for patients with refractory mCRC following disease progression or intolerance on two prior chemotherapy regimens compared to trifluridine/tipiracil alone. In addition, the median time to worsening of ECOG (Eastern Cooperative Oncology Group) performance-status score was significantly delayed in patients receiving the investigational combination of trifluridine/tipiracil and bevacizumab. The safety profile of the investigational combination was consistent with that of each agent.

"Individuals living with metastatic colorectal cancer and who have progressed following fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and anti-Epidermal Growth Factor Receptor (EGFR) antibodies – if RAS wild-type – have limited treatment options. There is a growing need for new approaches that improve survival in this population," said Marwan Fakih, MD, Professor, Medical Oncology and Therapeutics Research, City of Hope, and lead U.S. investigator for the SUNLIGHT trial. "The publication of the SUNLIGHT results in the *New England Journal of Medicine* speaks to the quality of the science and potential impact of this investigational combination on the treatment of metastatic colorectal cancer."

Added Professor Tabernero: "Trifluridine/tipiracil plus bevacizumab may represent a meaningful new treatment option in patients with mCRC who have progressed after two lines of therapy."

Based on results of the SUNLIGHT trial, Servier and Taiho Oncology submitted respectively a type II variation for approval to the European Medicines Agency (EMA) and a supplemental new drug application (sNDA) to the U.S. Food and Drug Administration (FDA) for trifluridine/tipiracil in combination with bevacizumab for the treatment of adult 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. Taiho Oncology announced on April 18, 2023, that the FDA accepted the sNDA for Priority Review and

set an anticipated Prescription Drug User Fee Act (PDUFA) action date of August 13, 2023.

Please click here for the Original Article, "Trifluridine–Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer."

Please click here for a NEJM "Quick Take" video summarizing the article findings.

About Colorectal Cancer
Colorectal cancer is the third most common cancer worldwide[1] with nearly 1.4 million people diagnosed with colorectal cancer (CRC) each year equating to 10% of the global cancer cases.[1] CRC is the second most common cause of cancer mortality, accounting for 881,000 deaths globally in 2018.[2] The worldwide incidence of colorectal cancer is expected to exceed 3 million cases annually by 2040,[3] and the number of deaths is predicted to increase by more than 70% to 1.6 million per year.[3]

About the SUNLIGHT Trial
SUNLIGHT is a multinational, randomized, active-controlled, open-label, two-arm Phase 3 clinical trial to investigate the efficacy and safety of trifluridine/tipiracil plus bevacizumab versus trifluridine/tipiracil alone, in patients with refractory mCRC following two chemotherapy regimens. A total of 492 patients were randomly allocated (in a 1:1 ratio) to receive trifluridine/tipiracil in combination with bevacizumab or trifluridine/tipiracil monotherapy. The primary objective was to assess trifluridine/tipiracil plus bevacizumab versus trifluridine/tipiracil alone, in terms of OS (primary endpoint). Key secondary endpoints were PFS, overall response rate (ORR), disease control rate (DCR) and quality of life (QoL), as well as the safety and tolerability of trifluridine/tipiracil used in combination with bevacizumab in comparison with trifluridine/tipiracil monotherapy.

The SUNLIGHT trial was conducted by Servier and Taiho Oncology, Inc. For more information on SUNLIGHT, please visit: https://clinicaltrials.gov/ct2/show/NCT04737187.

About LONSURF
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.

Indications and Use in the United States
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; and
- 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

Indications and Use
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/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 (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). Reduce the starting dose of LONSURF for patients with severe renal impairment (CLcr of 15 to 29 mL/min) to a recommended dosage of 20 mg/m^2.

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: in mCRC (2% vs 0%) and in metastatic gastric cancer and GEJ (3% 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: The most common 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 U.S. full Prescribing Information.
https://www.taihooncology.com/us/prescribing-information.pdf

About Taiho Oncology, Inc.
The mission of Taiho Oncology, Inc. is to improve the lives of patients with cancer, their families and their caregivers. The company specializes in the development of orally administered anti-cancer agents and markets these medicines for a range of tumor types in the U.S. Taiho Oncology's growing pipeline of antimetabolic and selectively targeted anti-cancer agents is led by a world-class clinical development organization. Taiho Oncology is a subsidiary of Taiho Pharmaceutical Co., Ltd. which is part of Otsuka Holdings Co., Ltd. Taiho Oncology is headquartered in Princeton, New Jersey and oversees its parent company's European and Canadian operations, which are located in Zug, Switzerland and Oakville, Ontario, Canada.

For more information, visit http://www.taihooncology.com

About Servier

Founded to serve health, Servier is a global group governed by a Foundation that aspires to have a meaningful social impact, both for patients and for a sustainable world. With its unique governance model, it can fully serve its vocation with a long-term vision: being committed to therapeutic progress to serve patient needs. The 21,400 employees of the Group are committed to this shared vocation, source of inspiration every day.

As a world leader in cardiology, Servier's ambition is to become a renowned, focused and innovative player in oncology by targeting hard-to-treat cancers. That is why the Group allocates over 50% of its R&D budget to developing targeted and innovative therapies in oncology.

Neuroscience and immuno-inflammatory diseases are the future growth drivers. In these areas, Servier is focused on a limited number of diseases in which accurate patient profiling makes it possible to offer a targeted therapeutic response through precision medicine.

To promote access to quality care for all at a lower cost, the Group also offers a range of quality generic drugs covering most pathologies, relying on strong brands in France, Eastern Europe, Brazil and Nigeria.

In all these areas, the Group includes the patient voice at each stage of the life cycle of a medicine.

Headquartered in France, Servier relies on a strong geographical footprint in over 150 countries and achieved a revenue of €4.9 billion in 2022.

More information on the new Group website: servier.com

Follow us on social media: LinkedIn, Facebook, Twitter, Instagram

LONSURF is a registered trademark of Taiho Pharmaceutical Co., Ltd.

*The SUNLIGHT trial is a Phase III **S**tudy of trif**U**ridine/tipiracil in combi**N**ation with bevacizumab vs trif**L**urdine/tip**I**racil sin**G**le agent in patients wit**H** refractory me**T**astatic colorectal cancer

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Taiho Oncology Media Contact:
Judy Kay Moore
Taiho Oncology, Inc.
574-526-2369
jumoore@taihooncology.com
www.taihooncology.com

Servier press contact
Group: presse@servier.com I Tel. +33 (0)1 55 72 40 21
US: Julia.Ferreira@servier.com I +1 857.262.3852

[1] Digestive Cancers Europe. Prevalence of Colorectal Cancer. Available at: https://digestivecancers.eu/colorectal-cancer/prevalence-of-colorectal-cancer-prevalence/?menu_id=13873. Last accessed: May 2023.
[2] Tabernero J., Taieb J., Prager G., et al. Trifluridine/tipiracil plus bevacizumab for third-line management of metastatic colorectal cancer: SUNLIGHT study design. *Future Oncol*. 2021.17(16): 1977–1985. Available at: https://www.futuremedicine.com/doi/full/10.2217/fon-2020-1238. Last accessed: May 2023.
[3] World Health Organization. International Agency for Research on Cancer. Global burden of colorectal cancer in 2020 and 2040: incidence and mortality estimates from GLOBOCAN. Available at: https://www.iarc.who.int/news-events/global-burden-of-colorectal-cancer-in-2020-and-2040-incidence-and-mortality-estimates-from-globocan/#:~:text=The%20authors%20predict%20that%20by,an%20increase%20of%2073%25). Last accessed: May 2023.

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