Servier and Taiho Oncology Present Overall Survival Data for Trifluridine/Tipiracil (LONSURF®) In Combination With Bevacizumab in Patients With Refractory Metastatic Colorectal Cancer at 2023 ASCO Gastrointestinal Cancers Symposium

- **Patients treated with the investigational combination of trifluridine/tipiracil in combination with bevacizumab in the pivotal Phase 3 SUNLIGHT trial achieved clinically meaningful improvement in overall survival compared to trifluridine/tipiracil alone**

- **Results demonstrate that trifluridine/tipiracil plus bevacizumab may be an effective and well-tolerated therapy for patients with metastatic colorectal cancer following disease progression on two prior chemotherapy regimens**

PARIS, France, and PRINCETON, N.J., January 17, 2023 – Servier and Taiho Oncology, Inc., today announced the release of data from SUNLIGHT, a pivotal Phase 3 global trial evaluating the combination of trifluridine/tipiracil (LONSURF®) and bevacizumab in adults with refractory metastatic colorectal cancer (mCRC), demonstrating that the trial met its primary endpoint of overall survival (OS). These data will be shared during an oral presentation (Abstract #392020) on January 21, 2023 at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI) in San Francisco.

The SUNLIGHT trial investigated the efficacy and safety of trifluridine/tipiracil plus bevacizumab versus trifluridine/tipiracil alone in patients with refractory mCRC following disease progression or intolerance on two prior chemotherapy regimens. Results from the main analysis demonstrated that the investigational combination provided a statistically significant and a clinically meaningful improvement in OS of 3.3 months compared to trifluridine/tipiracil alone (10.8 months vs. 7.5 months, hazard ratio [HR]: 0.61, 95%, confidence interval [CI]: 0.49-0.77, p<0.001). This improvement in OS represents a 39% reduction in the risk of death in patients with refractory mCRC.

Regarding the key secondary endpoint, there was a statistically significant improvement for the trifluridine/tipiracil plus bevacizumab combination versus trifluridine/tipiracil alone in progression-free survival (PFS) (5.6 months vs. 2.4 months, HR: 0.44, 95% CI: 0.36-0.54, p<0.001).

“The prognosis for metastatic colorectal cancer patients who do not respond to chemotherapy remains poor, with median survival times typically ranging from 4 to 8 months,” said Professor Josep Tabernero, MD, PhD, Head of Medical Oncology, Vall d’Hebron University Hospital, Barcelona, Spain, and Principal Investigator for the SUNLIGHT trial. “Coupled with the fact that cases of colorectal

cancer are increasing, there is an urgent need for new treatment options that can extend survival in patients with metastatic colorectal cancer in the later stages of disease. Findings from the SUNLIGHT trial represent an important development, which will be welcomed by the colorectal cancer community."

Side effects were as expected based on the known profile of each treatment and well managed. The percentage of patients who experienced severe adverse events (Grade ≥3) was similar in the trifluridine/tipiracil plus bevacizumab and trifluridine/tipiracil groups: 72.4% versus 69.5%, respectively. The most frequent severe treatment emergent adverse events for trifluridine/tipiracil plus bevacizumab and trifluridine/tipiracil groups were neutropenia (43.1% versus 32.1%) and anemia (6.1% versus 11.0%), respectively.

"We are delighted by the findings from SUNLIGHT which demonstrate trifluridine/tipiracil plus bevacizumab may be an effective and manageable post-progression therapy in metastatic colorectal cancer," said Nadia Caussé-Amellal, MD, Head of Global Development, GI Indications, Oncology and Immuno-Oncology Therapeutic Area, Servier. "In the coming months both Servier and Taiho Oncology plan to submit these data to regulatory authorities with a view to bringing this innovative combination to patients as early as possible."

"Given the typically poor prognosis and limited options for patients with refractory metastatic colorectal cancer, there is a significant need to explore different approaches to treatment that may impact the course of disease for these patients," said Fabio Benedetti, MD, Global Chief Medical Officer for Oncology, Taiho Pharmaceutical Co., Ltd. "The results of this study potentially further validate the utility of trifluridine/tipiracil in this patient population and demonstrate the potential impact of this combination therapy for the management of advanced disease."

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,[1] 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, open-label, active-controlled, two-arm Phase 3 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 plus bevacizumab or trifluridine/tipiracil monotherapy. The primary objective was to demonstrate the superiority of trifluridine/tipiracil plus bevacizumab over trifluridine/tipiracil alone, in terms of OS (primary endpoint). Key secondary objectives were to compare the regimens in terms of progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR) and quality of life (QoL), as well as the safety and tolerability of trifluridine/tipiracil plus bevacizumab in comparison with trifluridine/tipiracil monotherapy.

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

EU
Trifluridine and tipiracil, marketed under the brand name LONSURF, is indicated as monotherapy for the treatment of adult patients with:

- Metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents; and
- Metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease

U.S.
Trifluridine and tipiracil, marketed under the brand name 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 (27% vs 16%), 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 full Prescribing Information for the EU.
https://www.ema.europa.eu/en/documents/product-information/lonsurf-epar-product-information_en.pdf

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

About Servier
Founded to serve health, Servier is a global pharmaceutical 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 21,800 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 €4.7 billion in 2021.

More information on the new Group website: servier.com.

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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 www.taihooncology.com.

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