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FDA Approves LONSURF® (trifluridine/tipiracil) in Combination With Bevacizumab for Adult Patients With Metastatic Colorectal Cancer (mCRC)

- *Approval is based on data from a pivotal clinical trial showing that treatment with LONSURF plus bevacizumab resulted in statistically significant and clinically meaningful improvements in overall survival in patients with previously treated mCRC compared to LONSURF as a single agent*

PRINCETON, N.J., August 2, 2023 – Taiho Oncology, Inc. and Taiho Pharmaceutical Co., Ltd. announced today that the U.S. Food and Drug Administration (FDA) has approved LONSURF® (trifluridine/tipiracil) as a single agent or in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

“The FDA approval of this combination provides patients with mCRC an important new treatment option, one that has been shown to extend life in addition to other benefits and which I believe will change the treatment landscape for this patient population,” said Marwan Fakih, MD, Professor, Medical Oncology and Therapeutics Research, City of Hope, Duarte, Calif., and lead U.S. investigator for the pivotal Phase 3 SUNLIGHT trial that evaluated this combination. “Notably, the use of LONSURF plus bevacizumab in these patients did not result in an increase in potentially intolerable side effects that might limit the utility of this combination.”

The results from the Phase 3 SUNLIGHT trial, which were published in the *New England Journal of Medicine* in May 2023, demonstrated that the combination of LONSURF plus bevacizumab provided statistically significant and clinically meaningful improvements in overall survival (OS) and progression-free survival (PFS) for patients with mCRC following disease progression or intolerance on two prior chemotherapy regimens compared to LONSURF alone.[1] This was the first Phase 3 study against an active control in third-line mCRC that demonstrated statistically significant efficacy and safety. Key results include:

- Median OS was 10.8 months in the LONSURF plus bevacizumab arm versus 7.5 months in the LONSURF arm (hazard ratio [HR]: 0.61, 95% confidence interval [CI]: 0.49-0.77, p<0.001).[1] This improvement in OS represented a 39% reduction in the risk of death in patients with mCRC.[1]
- The median PFS was 5.6 months in the LONSURF plus bevacizumab arm versus 2.4 months in the LONSURF arm (HR: 0.44, 95% CI: 0.36-0.54, p<0.001), indicating a 56% relative risk reduction of disease progression.[1]
- Results were consistent across subgroups regardless of age, sex, location of primary disease, number of metastatic sites, KRAS mutation status, and prior bevacizumab treatment.[1]
- Median time to worsening of the ECOG performance status score from 0 or 1 to 2 or more was 9.3 months (95% CI: 8.3-10.6) in the LONSURF plus bevacizumab arm versus 6.3 months (95% CI: 5.6-7.2) in the LONSURF arm (HR: 0.54, 95% CI: 0.43-0.67).[1]
- The OS and PFS benefits of LONSURF plus bevacizumab were associated with maintenance of quality of life from baseline to cycle 6 and no clinically relevant changes in mean scores were observed in any subdomains for EORTC QLQ-C30 and EuroQol EQ-5D-5L health-related quality of life questionnaires.[2]
- The combination of LONSURF plus bevacizumab had a manageable safety profile as was expected based on the known profile of each agent.[1] The most frequent severe treatment emergent adverse events for LONSURF plus bevacizumab versus LONSURF alone were neutropenia (43.1% vs 32.1%) and anemia (6.1% vs 11.0%), respectively.[1]

“The treatment of advanced colorectal cancer has been a core focus of our work at Taiho Oncology since our inception and with good reason: approximately 22% of patients[3] with colorectal cancer in the U.S. are diagnosed after the cancer has metastasized,” said Timothy Whitten, President and Chief Executive Officer, Taiho Oncology, Inc. “The FDA approval of LONSURF in combination with bevacizumab is another example of how we are continuing to advance care in this disease and provide new hope to patients and their families.”

In 2023, the National Comprehensive Cancer Network® (NCCN®) Drugs and Biologics Compendium (NCCN Compendium®) for Colon Cancer and Rectal Cancer was updated to include a Category 2A recommendation for trifluridine/tipiracil as subsequent therapy, either single agent or in combination with bevacizumab (preferred) (per NCCN®, an FDA-approved biosimilar is an appropriate substitute for bevacizumab),[a] as treatment options for patients who have progressed through all available regimens besides regorafenib or trifluridine/tipiracil with or without bevacizumab.[3,4]

“From Taiho Pharmaceutical’s initial discovery of LONSURF to this latest regulatory milestone, we are appreciative of the investigators and patients who helped to contribute to our growing body of knowledge of this important therapeutic through their participation in our clinical development programs,” said Fabio Benedetti, MD, Global Chief Medical Officer for Oncology, Taiho Pharmaceutical Co., Ltd. “And now we look forward to supporting healthcare professionals in the treatment of patients with mCRC who may be candidates for treatment with LONSURF in combination with bevacizumab.”

On July 31, 2023, Servier, which conducted the SUNLIGHT trial with Taiho Oncology, received approval from the European Commission for LONSURF in combination with bevacizumab for the treatment of adult patients with mCRC who have received two prior anti-cancer treatment regimens, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents. The Marketing Authorization covers the 27 countries of the European Union as well as Iceland, Northern Ireland, Liechtenstein and Norway.

About the SUNLIGHT Trial[1]
SUNLIGHT is a multinational, randomized, active-controlled, open-label, two-arm Phase 3 clinical trial to investigate the efficacy and safety of LONSURF plus bevacizumab versus LONSURF alone, in patients with metastatic colorectal cancer following two chemotherapy regimens. A total of 492 patients were randomly allocated (in a 1:1 ratio) to receive LONSURF in combination with bevacizumab or LONSURF monotherapy. The primary objective was to assess LONSURF plus bevacizumab versus LONSURF 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 LONSURF used in combination with bevacizumab in comparison with LONSURF monotherapy.

For more information on SUNLIGHT, please visit: https://clinicaltrials.gov/ct2/show/NCT04737187.

About Colorectal Cancer
Colorectal cancer is the third most commonly diagnosed cancer in the U.S.[5] In 2023, there will be an estimated 153,020 new cases and 52,550 deaths in the U.S.[6] Approximately 22% of U.S. patients are diagnosed after their cancer has metastasized.[3] The relative five-year survival rate for patients with metastatic colorectal cancer is 14%.[3]

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

LONSURF is indicated as a single agent or in combination with bevacizumab 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.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Severe Myelosuppression: In the 1114 patients who received LONSURF as a single agent, LONSURF caused severe or life-threatening myelosuppression (Grade 3-4) consisting of neutropenia (38%), anemia (17%), thrombocytopenia (4%) and febrile neutropenia (3%). Three patients (0.3%) died due to neutropenic infection/sepsis; four other patients (0.5%) died due to septic shock. A total of 14% of patients received granulocyte-colony stimulating factors. In the 246 patients who received LONSURF in combination with bevacizumab, LONSURF caused severe or life-threatening myelosuppression (Grade 3-4) consisting of neutropenia (52%), anemia (5%), thrombocytopenia (4%) and febrile neutropenia (0.4%). One patient (0.4%) died due to abdominal sepsis and two other patients (0.8%) died due to septic shock. A total of 29% of 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 severe myelosuppression and resume at the next lower dosage.

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 breastfed child or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, 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 older who received LONSURF as a single agent had a higher incidence of the following hematologic laboratory abnormalities compared to patients younger than 65 years: Grade 3 or 4 neutropenia (46% vs 32%), Grade 3 anemia (20% vs 14%), and Grade 3 or 4 thrombocytopenia (6% vs 3%). Patients 65 years of age or older who received LONSURF in combination with bevacizumab had a higher incidence of the following hematologic laboratory abnormalities compared to patients younger than 65 years: Grade 3 or 4 neutropenia (60% vs 46%) and Grade 3 or 4 thrombocytopenia (5% vs 4%).

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.

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

ADVERSE REACTIONS

Serious adverse reactions occurred in 25% of patients. The most frequent serious adverse reactions (≥2%) were intestinal obstruction (2.8%), and COVID-19 (2%). Fatal adverse reactions occurred in 1.2% of patients who received LONSURF in combination with bevacizumab, including rectal fistula (0.4%), bowel perforation (0.4%) and atrial fibrillation (0.4%).

The most common adverse reactions or laboratory abnormalities (≥10% in incidence) in patients treated with single-agent LONSURF at a rate that exceeds the rate in patients receiving placebo were anemia (77% vs 33%), neutropenia (67% vs 0.8%), asthenia/fatigue (52% vs 35%), nausea (48% vs 24%), thrombocytopenia (42% vs 8%), decreased appetite (39% vs 29%), diarrhea (32% vs 12%), vomiting (28% vs 14%), abdominal pain (21% vs 19%), and pyrexia (19% vs 14%).

The most common adverse reactions or laboratory abnormalities (≥20% in incidence) in patients treated with LONSURF in combination with bevacizumab vs LONSURF alone were neutropenia (80% vs 68%), anemia (68% vs 73%), thrombocytopenia (54% vs 29%), fatigue (45% vs 37%), nausea (37% vs 27%), increased aspartate aminotransferase (34% vs 28%), increased alanine aminotransferase (33% vs 23%), increased alkaline phosphate (31% vs 36%), decreased sodium (25% vs 20%), diarrhea (21% vs 19%), abdominal pain (20% vs 18%), and decreased appetite (20% vs 15%).

Please see accompanying full Prescribing Information.

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.

About Taiho Pharmaceutical Co., Ltd.
Taiho Pharmaceutical, a subsidiary of Otsuka Holdings Co., Ltd. (www.otsuka.com/en/), is an R&D-driven specialty pharma with a focus on oncology. Taiho Pharmaceutical also has development programs in allergy and immunology, and consumer healthcare products. Our corporate philosophy takes the form of a pledge: "We strive to improve human health and contribute to a society enriched by smiles."

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

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

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

Taiho Pharmaceutical Media Contact:
Junko Onishi
Taiho Pharmaceutical Co., Ltd.

+81-3293-2878
junn-onishi@taiho.co.jp

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[a] Regorafenib or trifluridine + tipiracil with or without bevacizumab are treatment options for patients who have progressed through all available regimens.

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