TAIHO ONCOLOGY

U.S. Food and Drug Administration Accepts for Priority Review Taiho Oncology's Supplemental New Drug Application for the Use of Trifluridine/Tipiracil (LONSURF®) in Combination With Bevacizumab for Refractory Metastatic Colorectal Cancer (mCRC)

The sNDA is supported by data from the Phase 3 SUNLIGHT clinical trial, the first to show improved efficacy over an approved comparator in adults with refractory mCRC[1,2,3,4,5,6]

PRINCETON, N.J., April 18, 2023 – Taiho Oncology, Inc. and Taiho Pharmaceutical Co., Ltd. announced today that the U.S. Food and Drug Administration (FDA) has accepted for Priority Review the supplemental new drug application (sNDA) for trifluridine/tipiracil (LONSURF®) as monotherapy or in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (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. A Priority Review designation by the FDA reduces the review period of the sNDA by four months. In this case, the FDA provided an anticipated Prescription Drug User Fee Act (PDUFA) action date of August 13, 2023.

"The poor prognosis for patients with previously treated, late-stage metastatic colorectal cancer has been an ongoing challenge in the oncology community, which has driven our pursuit of a potential new treatment option," said Volker Wacheck, MD, PhD, Vice President, Clinical Development, Taiho Oncology, Inc. "We believe the combination of trifluridine/tipiracil plus bevacizumab may represent a significant advance in the treatment of refractory disease, and we look forward to working with the FDA as it considers this application."

The sNDA is based on data from the pivotal Phase 3 SUNLIGHT trial, which demonstrated that the investigational combination of trifluridine/tipiracil plus bevacizumab provided statistically significant and clinically meaningful improvements in overall survival (OS) and progression-free survival (PFS) for patients with refractory mCRC following disease progression or intolerance on two prior chemotherapy regimens compared to trifluridine/tipiracil alone. Median OS was 10.8 months in the trifluridine/tipiracil plus bevacizumab arm versus 7.5 months in the trifluridine/tipiracil arm (hazard ratio [HR]: 0.61, 95%, confidence interval [CI]: 0.49-0.77, $p<0.001$). This improvement in OS represented a 39% reduction in the risk of death in patients with refractory mCRC. The median PFS was 5.6 months in the trifluridine/tipiracil plus bevacizumab arm versus 2.4 months in the trifluridine/tipiracil arm (HR: 0.44, 95% CI: 0.36-0.54, $p<0.001$), indicating a 56% relative risk reduction of disease progression.

The combination of trifluridine/tipiracil and bevacizumab had a demonstrative manageable safety profile as was expected based on the known profile of each agent. The most frequent severe treatment emergent adverse events for trifluridine/tipiracil plus bevacizumab versus trifluridine/tipiracil alone were neutropenia (43.1% vs 32.1%) and anemia (6.1% vs 11.0%), respectively.

Results from the SUNLIGHT trial were presented by Professor Josep Tabernero, MD, PhD, Head of Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, and Principal Investigator for the SUNLIGHT trial, at the 2023 American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI), held in January in San Francisco.

In 2021, 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 (per NCCN®, an FDA-approved biosimilar is an appropriate substitute for bevacizumab),[a,b] as treatment options for patients who have progressed through all available regimens.[7]

The combination use of trifluridine/tipiracil plus bevacizumab in refractory mCRC is investigational and not currently approved in any country. The approved indications for trifluridine/tipiracil in the U.S. can be found under the "About LONSURF" section of this document.

About Colorectal Cancer

Colorectal cancer is the fourth most commonly diagnosed cancer in the U.S.[8] In 2022, there were an estimated 151,030 new cases and 52,580 deaths in the U.S.[9] Approximately 22% of U.S. patients with colorectal cancer are diagnosed at the distant or metastasized stage.[9] Metastatic colorectal cancer is associated with a poor prognosis, with a five-year survival rate of approximately 15.1%.[9]

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.

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

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

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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

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%).

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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 Taiho Pharmaceutical Co., Ltd.
Taiho Pharmaceutical, a subsidiary of Otsuka Holdings Co., Ltd. (https://www.otsuka.com/en/), is an R&D-driven specialty pharma focusing on the 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/

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

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[1] Grothey A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303-12. https://www.thelancet.com/article/S0140-6736(12)61900-X/fulltext. Last accessed: March 2023.
[2] Li J, et al. Concur: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Regorafenib Monotherapy in Asian Patients with Previously Treated Metastatic Colorectal Cancer (MCRC). *Annals of Oncology*. 2014;25(supplement 2):ii105-ii117. https://www.annalsofoncology.org/article/S0923-7534(19)36333-1/fulltext. Last accessed: March 2023.
[3] Mayer RJ, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015;372(20):1909-19. https://www.nejm.org/doi/full/10.1056/nejmoa1414325. Last accessed: March 2023.
[4] Kim TW, et al. TERRA: a randomized, double-blind, placebo-controlled phase 3 study of TAS-102 in Asian patients with metastatic colorectal cancer. *Annals of Oncology*. 2016;27(supplement 6):vi149-vi206. https://www.annalsofoncology.org/article/S0923-7534(19)44095-7/fulltext. Last accessed: March 2023.
[5] Li J, et al. Effect of Fruquintinib vs Placebo on Overall Survival in Patients With Previously Treated Metastatic Colorectal Cancer: The FRESCO Randomized Clinical Trial. *JAMA*. 2018;319(24):2486-2496. https://jamanetwork.com/journals/jama/fullarticle/2685988. Last accessed: March 2023.
[6] Dasari NA, et al. LBA25 - FRESCO-2: A global phase III multiregional clinical trial (MRCT) evaluating the efficacy and safety of fruquintinib in patients with refractory metastatic colorectal cancer. *Annals of Oncology*. 2022;33(supplement 7):S808-S869. https://oncologypro.esmo.org/meeting-resources/esmo-congress/fresco-2-a-global-phase-iii-multiregional-clinical-trial-mrct-evaluating-the-efficacy-and-safety-of-fruquintinib-in-patients-with-refractory-met. Last accessed: March 2023.
[7] National Comprehensive Cancer Network® Drugs and Biologics Compendium (NCCN Compendium®) for Colon Cancer (Version 2.2021 - January 21, 2021) and Rectal Cancer (Version 1.2021 - December 22, 2020). Available at: http://www.nccn.org/. Last accessed: March 2023.
[8] U.S. Centers for Disease Control and Prevention. Division of Cancer Prevention and Control. Colorectal Cancer Statistics. 2022. https://www.cdc.gov/cancer/colorectal/statistics/index.htm. Last accessed: March 2023.
[9] National Cancer Institute Surveillance Epidemiology and End Results Program. Cancer Stat Facts: Colon and Rectum Cancer. https://seer.cancer.gov/statfacts/html/colorect.html. Last accessed: March 2023.