Patients with Advanced Metastatic Colorectal Cancer in Europe Now Have a New Treatment Option as LONSURF® (trifluridine/tipiracil) Receives EU Approval

Suresnes (France), 27th April 2016 – Servier today announced that the European Commission (EC) has granted marketing authorization for LONSURF® (trifluridine/tipiracil), formerly known as TAS-102, in the European Union (EU) for the treatment of adult patients with metastatic colorectal cancer (mCRC) 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. LONSURF is an oral anticancer drug, comprising the combination of trifluridine (FTD) and tipiracil (TPI), whose dual mechanism of action is designed to maintain clinical activity.

"Data from the pivotal RECOURSE study provides evidence that LONSURF may offer patients with refractory metastatic colorectal cancer extended survival as well as a reduction in risk of death compared to placebo," said Professor Eric Van Cutsem, MD, PhD, Digestive Oncology, University Hospitals Leuven in Belgium. "The combination of trifluridine and tipiracil in LONSURF works by directly attacking the DNA of the tumor cells which reduces the growth of cancer cells. This approach fights the cancer differently to other previously given treatments, allowing us to delay cancer progression rather than cycling back through therapies that have already been used."

"With this approval, we are delivering on a promise to bring a new treatment to patients with advanced metastatic colorectal cancer across Europe," said Dr. U. Marion Schrenk, Head of Global Medical Strategy, Oncology at Servier. "We are excited about this important milestone, which demonstrates Servier's commitment to improving the lives of patients living with cancer. LONSURF has also been shown to prolong progression-free survival and preserve performance status, allowing patients to make time for more moments that matter."

The decision from the EC follows the positive opinion issued by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommending the approval of LONSURF in February 2016.[1] Both the CHMP opinion and the EC decisions were based on data from the international, double-blind, placebo-controlled Phase III RECOURSE study, which investigated the efficacy and safety of LONSURF with best supportive care (BSC) compared to placebo with BSC in 800 patients with previously treated mCRC. The study met the primary endpoint of statistically significant improvement in overall survival (OS).**Erreur ! Signet non défini.**,**Erreur ! Signet non défini.**,[2]

About RECOURSE

RECOURSE is an international, double-blind, placebo-controlled Phase III study, which investigated the efficacy and safety of LONSURF with BSC compared to placebo with BSC in 800 patients with previously treated mCRC, among which 403 were treated in Europe.[3] The study met the primary endpoint of statistically significant improvement in OS. Results demonstrated a 32% reduction in risk of death compared to BSC (HR=0.68; 95% CI: 0.58 to 0.81 p<0.001). An updated OS analysis in 89% of events, presented at ASCO GI 2016, confirmed the clinically meaningful and statistically significant survival benefit of LONSURF with BSC compared to placebo with BSC. This translates into a 31% relative reduction in the risk of death (HR=0.69; 95% CI: 0.59 to 0.81; p<0.0001) and an improvement

of 2 months in the median OS. The median OS was 7.2 months for LONSURF with BSC vs 5.2 months for placebo with BSC, this translated into 1-year survival rates of 27.1% and 16.6%, respectively.**Erreur ! Signet non défini.**,**Erreur ! Signet non défini.**,[2]

The most frequently observed side effects (≥ 30%) in patients receiving LONSURF were neutropenia, nausea, decreased appetite, diarrhea, fatigue, anemia, thrombocytopenia, increase in total bilirubin, alkaline phosphatase and ASAT levels, and leucopenia.**Erreur ! Signet non défini.**,[2]

About Metastatic Colorectal Cancer

There remains a high unmet need in the treatment of colorectal cancer (CRC), which was the second leading cause of cancer-related deaths in Europe in 2012, responsible for 215,000 deaths.[4] Approximately 25% of patients with CRC present with metastases at initial diagnosis and almost 50% of patients with CRC will develop metastases.[5] This contributes to the high mortality rates reported for CRC; the 5-year survival rate of patients diagnosed with stage IV mCRC is about 11%.**Erreur ! Signet non défini.**

About LONSURF

LONSURF is currently available in Japan for the treatment of unresectable advanced or recurrent CRC and in the United States for the treatment of 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.[6,7,8] LONSURF is an oral anticancer drug, comprising the combination of trifluridine (FTD) and tipiracil (TPI), whose dual mechanism of action is designed to maintain clinical activity and differs from fluoropyrimidines. FTD is an antineoplastic nucleoside analog, which is incorporated directly into DNA, thereby interfering with the function of DNA. The blood concentration of FTD is maintained via TPI, which is an inhibitor of the FTD-degrading enzyme, thymidine phosphorylase.**Erreur ! Signet non défini.**,[2,9]

In June 2015, Servier entered into an exclusive license agreement with Taiho Pharmaceutical Co., Ltd. for the co-development and commercialization of LONSURF. Under the terms of the agreement, Servier has the rights to co-develop and commercialize LONSURF in Europe and other countries outside of the United States, Canada, Mexico and Asia. Taiho Pharmaceutical retains the right to develop and commercialize LONSURF in the United States, Canada, Mexico, and Asia and to manufacture and supply the product.

About Servier

Servier is an independent research-based pharmaceutical company headquartered in France. With a strong international presence in 148 countries and 92% of its medicines being prescribed outside of France, Servier employs more than 21,200 people worldwide. In 2015, the company recorded a turnover of 3.9 billion euros of which 24% was reinvested in research and development. Currently, there are nine new molecular entities in clinical development for oncology respectively in breast, lung and other solids tumors as well as various leukemias and lymphomas.

This portfolio of innovative cancer treatments is being developed with various partners worldwide, and covers different hallmarks of cancer including cytotoxics, proapoptotic, targeted, immune and cellular therapies.

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[1] Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 22-25 February 2016. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/02/news_detail_002474.jsp&mid=WC0b01ac058004d5c1 Accessed April 2016

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