PRESS RELEASE

Phase 3 Data Demonstrate TIBSOVO® (ivosidenib tablets) in Combination with Azacitidine Significantly Improves Event-Free Survival and Overall Survival in Patients with Previously Untreated IDH1-mutated Acute Myeloid Leukemia

TIBSOVO in combination with azacitidine compared to placebo plus azacitidine also demonstrated significant improvements in complete remission rate, complete remission and complete remission with partial hematologic recovery rate and objective response rate

Safety profile was favorable and consistent with previously published data

Data from the Phase 3 AGILE trial of patients with previously untreated IDH1-mutated acute myeloid leukemia will be presented in an oral session on Monday, December 13, 2021, and featured in the official press program of the 63rd American Society of Hematology Annual Meeting

PARIS and BOSTON, December 11, 2021 – Servier, a growing leader in oncology committed to bringing the promise of tomorrow to the patients we serve, today announced Phase 3 data demonstrating that TIBSOVO® (ivosidenib tablets) in combination with the chemotherapy azacitidine significantly improved event-free survival (EFS) and overall survival (OS) compared to azacitidine plus placebo in adults with previously untreated IDH1-mutated acute myeloid leukemia (AML) who are not candidates for intensive chemotherapy. These data from the global AGILE study will be presented in an oral session on Monday, December 13, 2021 from 2:45 - 4:15 PM ET, Abstract #697 and featured in the official press program during the 63rd American Society of Hematology Annual Meeting and Exposition.

Treatment with TIBSOVO in combination with azacitidine demonstrated a statistically significant improvement in EFS (hazard ratio [HR] = 0.33, 95% CI 0.16, 0.69, 1-sided P = 0.0011 [1,2]). In addition, the combination of TIBSOVO with azacitidine showed a statistically significant improvement in OS (HR = 0.44 [95% CI 0.27, 0.73]; 1-sided P = 0.0005), with a median OS of 24.0 months in the ivosidenib + azacitidine arm vs 7.9 months in the placebo + azacitidine arm.

“These significant findings from the AGILE Phase 3 study for TIBSOVO bolster our growing body of evidence supporting the rationale to target IDH1 mutations early in blood cancers like acute myeloid leukemia,” said Susan Pandya, M.D., Vice President Clinical Development & Head of Cancer Metabolism Global Development Oncology & Immuno-Oncology, Servier Pharmaceuticals. “Up to 10 percent of patients with AML have mutations in the IDH1 enzyme, and current treatment options are limited, especially for those who are newly diagnosed and are not eligible for intensive chemotherapy.”

Additional Study Results

Investigators reported on results of key secondary endpoints of the AGILE trial including:

- Complete remission (CR) rate was 47.2% (n=34/72) for TIBSOVO in combination with azacitidine vs. 14.9% (n=11/74) for placebo plus azacitidine ($p < 0.0001$).
- CR + complete remission with partial hematologic recovery rate (CR + CRh rate) was 52.8% (n=38/72) for TIBSOVO in combination with azacitidine vs. 17.6% (n=13/74) for placebo plus azacitidine ($p < 0.0001$).
- Objective response rate (ORR) was 62.5% (n=45/72) for TIBSOVO in combination with azacitidine vs. 18.9% (n=14/74) for placebo plus azacitidine ($p < 0.0001$).

“We are excited about the potential to bring a new treatment option to patients with previously untreated IDH1-mutated AML. This further extends the significant clinical benefit for patients with acute myeloid

leukemia and IDH1 mutations," said Patrick Therasse, M.D., Ph.D., Vice President, Head of Late Stage and Life Cycle Management in Oncology and Immuno-Oncology Therapeutic Area, Servier Group.

Acute myeloid leukemia is a rapidly progressing type of cancer, and the prognosis is often poor," said Stephane De Botton, M.D. Ph.D., Principle Investigator and Head of Multidisciplinary Hematology Committee at the Institut Gustave Roussy, Villejuif, France. "Our goal with treatment is to prolong overall survival, and the impressive clinical benefit following treatment with TIBSOVO in combination with azacitidine is incredibly promising for these patients with previously untreated IDH1-mutated acute myeloid leukemia."

Common all-grade adverse events (AEs) occurring in more than 20 percent of patients receiving TIBSOVO in combination with azacitidine vs. placebo plus azacitidine were nausea (42.3% vs. 38.4%), vomiting (40.8% vs 26.0%), diarrhea (35.2% vs 35.6%), pyrexia (33.8% vs 39.7%), anemia (31.0% vs 28.8%), febrile neutropenia (28.2% vs 34.2%), thrombocytopenia (28.2% vs 20.5%), neutropenia (28.2% vs 16.4%), constipation (26.8% vs 52.1%) and pneumonia (23.9% vs 31.5%).

The AGILE study has halted further enrollment due to compelling efficacy data for TIBSOVO.

Servier is in discussions with regulatory health authorities regarding submissions to expand the currently approved indications for TIBSOVO.

TIBSOVO[*] is currently approved in the U.S. as monotherapy for the treatment of adults with IDH1-mutant relapsed or refractory acute myeloid leukemia (AML), and for adults with newly diagnosed IDH1-mutant AML who are ≥75 years old or who have comorbidities that preclude the use of intensive induction chemotherapy. Recently, TIBSOVO was approved as a first and only targeted therapy for patients with previously treated IDH1-mutated cholangiocarcinoma.

About NCT03173248 AGILE Phase 3 AML Trial
The AGILE trial is a global, Phase 3, multicenter, double-blind, randomized, placebo-controlled clinical trial designed to evaluate the efficacy and safety of TIBSOVO in combination with azacitidine compared with placebo in combination with azacitidine, in adults with previously untreated IDH1-mutated acute myeloid leukemia (AML) who are not candidates for intensive chemotherapy (≥75 years old or who have comorbidities that preclude the use of intensive induction chemotherapy). The study's primary endpoint is EFS, defined as the time from randomization until treatment failure, relapse from remission, or death from any cause, whichever occurs first. Treatment failure is defined as failure to achieve complete remission (CR) by Week 24.

Other key secondary endpoints included complete remission rate (CR rate), defined as the proportion of participants who achieve a CR; overall survival (OS), defined as the time from date of randomization to the date of death due to any cause; CR and complete remission with partial hematologic recovery (CRh) rate, defined as the proportion of participants who achieve a CR or CRh; and objective response rate (ORR), defined as the rate of CR, CR with incomplete hematologic recovery (CRi) (including CR with incomplete platelet recovery [CRp]), partial remission (PR), and morphologic leukemia-free state (MLFS).

[*] Servier has an exclusive license agreement with CStone for the development and commercialization of TIBSOVO (ivosidenib tablets) in Mainland China, Taiwan, Hong Kong, Macau and Singapore.

About Acute Myeloid Leukemia
Acute myeloid leukemia (AML) is a cancer of the blood and bone marrow marked by rapid disease progression and is the most common acute leukemia affecting adults with approximately 20,000 new cases in the U.S., and 43,000 cases in Europe each year[3,4]. The majority of patients with AML eventually relapse. Relapsed or refractory AML has a poor prognosis[5]. The five-year survival rate is approximately 27%[3]. For 6 to 10 percent of AML patients, the mutated IDH1 enzyme blocks normal blood stem cell differentiation, contributing to the genesis of acute leukemia[6].

About Servier Pharmaceuticals
Servier Pharmaceuticals, LLC is a commercial-stage company with a passion for innovation and improving the lives of patients, their families and caregivers. A privately held company, Servier has the unique freedom to devote its time and energy toward putting those who require our treatment and care first, with future growth driven by innovation in areas of unmet medical need.

As a growing leader in oncology, Servier is committed to finding solutions that will address today's challenges. The company's oncology portfolio of innovative medicines is designed to bring more life-saving treatments to a greater number of patients, across the entire spectrum of disease and in a variety of tumor types.

Servier believes co-creation is fundamental to driving innovation and is actively building alliances, acquisitions, licensing deals and partnerships that bring solutions and accelerate access to therapies. With our commercial expertise, global reach, scientific expertise and commitment to clinical excellence, Servier Pharmaceuticals is dedicated to bringing the promise of tomorrow to the patients that we serve.

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About Servier Group
Servier is a global pharmaceutical group governed by a Foundation. With a strong international presence in 150 countries and a total revenue of 4.7 billion euros in 2020, Servier employs 22,500 people worldwide. Servier is an independent group that invests over 20% of its brand-name revenue in Research and Development every year. To accelerate therapeutic innovation for the benefit of patients, the Group is committed to open and collaborative innovation with academic partners, pharmaceutical groups, and biotech companies. It also integrates the patient's voice at the heart of its activities.

A leader in cardiology, the ambition of the Servier Group is to become a renowned and innovative player in oncology. Its growth is based on a sustained commitment to cardiovascular and metabolic diseases, oncology, neuroscience and immuno-inflammatory diseases. To promote access to healthcare for all, the Servier Group also offers a range of quality generic drugs covering most pathologies.

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About TIBSOVO® (ivosidenib tablets)

TIBSOVO is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for the treatment of adult patients with a susceptible IDH1 mutation as detected by an FDA-approved test with:

Acute Myeloid Leukemia (AML)

- Newly-diagnosed AML who are ≥ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.
- Relapsed or refractory AML.

Locally Advanced or Metastatic Cholangiocarcinoma

- Locally advanced or metastatic cholangiocarcinoma who have been previously treated.

IMPORTANT SAFETY INFORMATION

WARNING: DIFFERENTIATION SYNDROME IN AML
Patients treated with TIBSOVO have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

WARNINGS AND PRECAUTIONS

Differentiation Syndrome in AML: In the clinical trial, 25% (7/28) of patients with newly diagnosed AML and 19% (34/179) of patients with relapsed or refractory AML treated with TIBSOVO experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with TIBSOVO included noninfectious leukocytosis, peripheral edema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased. Of the 7 patients with newly diagnosed AML who experienced differentiation syndrome, 6 (86%) patients recovered. Of the 34 patients with relapsed or refractory AML who experienced differentiation syndrome, 27 (79%) patients recovered after treatment or after dose interruption of TIBSOVO. Differentiation syndrome occurred as early as 1 day and up to 3 months after TIBSOVO initiation and has been observed with or without concomitant leukocytosis.

If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. If concomitant noninfectious leukocytosis is observed, initiate treatment with hydroxyurea or leukapheresis, as clinically indicated. Taper corticosteroids and hydroxyurea after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxyurea treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt TIBSOVO until signs and symptoms are no longer severe.

QTc Interval Prolongation: Patients treated with TIBSOVO can develop QT (QTc) prolongation and ventricular arrhythmias. Concomitant use of TIBSOVO with drugs known to prolong the QTc interval (e.g., anti-arrhythmic medicines, fluoroquinolones, triazole anti-fungals, 5-HT_3 receptor antagonists) and CYP3A4 inhibitors may increase the risk of QTc interval prolongation. Conduct monitoring of electrocardiograms (ECGs) and electrolytes. In patients with congenital long QTc syndrome, congestive heart failure, or electrolyte abnormalities, or in those who are taking medications known to prolong the QTc interval, more frequent monitoring may be necessary.

Interrupt TIBSOVO if QTc increases to greater than 480 msec and less than 500 msec. Interrupt and reduce TIBSOVO if QTc increases to greater than 500 msec. Permanently discontinue TIBSOVO in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

Guillain-Barré Syndrome: Guillain-Barré syndrome can develop in patients treated with TIBSOVO. Monitor patients taking TIBSOVO for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome.

ADVERSE REACTIONS

- **In patients with AML,** the most common adverse reactions including laboratory abnormalities (≥20%) were hemoglobin decreased (60%), fatigue (43%), arthralgia (39%), calcium decreased (39%), sodium decreased (39%), leukocytosis (38%), diarrhea (37%), magnesium decreased (36%), edema (34%), nausea (33%), dyspnea (32%), uric acid increased (32%), potassium decreased (32%), alkaline phosphatase increased (30%), mucositis (28%), aspartate aminotransferase increased (27%), phosphatase decreased (25%), electrocardiogram QT prolonged (24%), rash (24%), creatinine increased (24%), cough (23%), decreased appetite (22%), myalgia (21%), constipation (20%), and pyrexia (20%).
- **In patients with newly diagnosed AML,** the most frequently reported Grade ≥3 adverse reactions (≥5%) were fatigue (14%), differentiation syndrome (11%), electrocardiogram QT prolonged (11%), diarrhea (7%), nausea (7%), and leukocytosis (7%). Serious adverse reactions (≥5%) were differentiation syndrome (18%), electrocardiogram QT prolonged (7%), and fatigue (7%). There was one case of posterior reversible encephalopathy syndrome (PRES).
- **In patients with relapsed or refractory AML,** the most frequently reported Grade ≥3 adverse reactions (≥5%) were differentiation syndrome (13%), electrocardiogram QT prolonged (10%), dyspnea (9%), leukocytosis (8%), and tumor lysis syndrome (6%). Serious adverse reactions (≥5%) were differentiation syndrome (10%), leukocytosis (10%), and electrocardiogram QT prolonged (7%). There was one case of progressive multifocal leukoencephalopathy (PML).
- **In patients with cholangiocarcinoma,** the most common adverse reactions (≥15%) were fatigue (43%), nausea (41%), abdominal pain (35%), diarrhea (35%), cough (27%), decreased appetite (24%), ascites (23%), vomiting (23%), anemia (18%), and rash (15%). The most common laboratory abnormalities (≥10%) were hemoglobin decreased (40%), aspartate aminotransferase increased (34%), and bilirubin increased (30%).

DRUG INTERACTIONS

Strong or Moderate CYP3A4 Inhibitors: Reduce TIBSOVO dose with strong CYP3A4 inhibitors. Monitor patients for increased risk of QTc interval prolongation.

Strong CYP3A4 Inducers: Avoid concomitant use with TIBSOVO.

Sensitive CYP3A4 Substrates: Avoid concomitant use with TIBSOVO.

QTc Prolonging Drugs: Avoid concomitant use with TIBSOVO. If co-administration is unavoidable, monitor patients for increased risk of QTc interval prolongation.

LACTATION

Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed children, advise women not to breastfeed during treatment with TIBSOVO and for at least 1 month after the last dose.

Please see Full Prescribing Information, including BOXED WARNING for AML patients.

References

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