Pfizer Provides Topline Results From Phase 3 Study Of Torisel® As Second-Line Treatment In Advanced Renal Cell Carcinoma (RCC)

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(BUSINESS WIRE)--Pfizer Inc announced today that the Phase 3 INTORSECT (B1771003) study, evaluating TORISEL® (temsirolimus) in patients with advanced renal cell carcinoma (RCC) whose disease had progressed on or after SUTENT® (sunitinib malate) therapy, did not meet the primary endpoint of prolonging progression free survival (PFS) when compared to sorafenib. Although PFS was numerically higher in patients treated with temsirolimus, the difference was not statistically significant. Overall survival, a secondary endpoint in the study, showed statistical significance favoring patients randomized to the sorafenib arm. Adverse events in this study were consistent with the known safety profiles for both drugs. Full efficacy and safety data from this study will be presented at an upcoming major medical congress.

Approximately 270,000 people worldwide are diagnosed with renal cell cancer every year with about 20 percent having advanced disease at the time of diagnosis.1 Between 40 and 65 percent of patients in the U.S. who progress following first-line therapy go on to receive a second-line treatment.2,3,4

“This trial advances our knowledge about TORISEL in RCC. TORISEL remains an important drug for treatment of advanced kidney cancer based on its pivotal study in first-line patients with poor prognostic risk,” said Dr. Mace Rothenberg, senior vice president of

clinical development and medical affairs for Pfizer’s Oncology Business Unit. “TORISEL continues to be an important part of Pfizer’s portfolio of therapies for advanced kidney cancer.”

About TORISEL® (temsirolimus)

TORISEL is approved in the US and other countries for the treatment of advanced RCC. TORISEL is approved in the European Union for the first-line treatment of patients with advanced renal cell carcinoma (RCC) who have at least three of six prognostic risk factors. In a pivotal Phase 3 study, TORISEL demonstrated median overall survival (OS) in previously untreated patients of 10.9 months in patients with advanced RCC with poor prognostic risk, compared with 7.3 months for interferon-alpha (IFN-α).

TORISEL is the only intravenous mammalian target of rapamycin (mTOR) inhibitor approved for the treatment of advanced RCC. TORISEL remains the only treatment to show a significant improvement in OS in treatment-naïve poor risk patients with advanced RCC.5

Based on preclinical studies, TORISEL inhibits the activity of mTOR, an intracellular protein implicated in multiple growth-related cellular functions including proliferation, growth and survival. The inhibition of mTOR also reduces levels of certain growth factors, such as vascular endothelial growth factor (VEGF), which are overexpressed in solid tumors like kidney cancer and are thought to play a crucial role in angiogenesis, the process by which tumors acquire blood vessels, nutrients and oxygen needed for growth.

Important TORISEL® (temsirolimus) Safety Information

TORISEL is contraindicated in patients with bilirubin >1.5 x ULN and should be used with caution when treating patients with mild hepatic impairment (bilirubin >1 – 1.5 x ULN or AST > ULN but bilirubin ≤ ULN). If TORISEL must be given to patients with mild hepatic impairment, reduce the dose of TORISEL to 15 mg/week. In a phase 1 study, the overall frequency of ≥ grade 3 adverse reactions and deaths, including deaths due to progressive disease, was greater in patients with baseline bilirubin > 1.5 x ULN.

Hypersensitivity/infusion reactions, including flushing, chest pain, dyspnea, hypotension, apnea, loss of consciousness, hypersensitivity and anaphylaxis, may occur very early in the first infusion or with subsequent infusions. Pretreat with an H1 antihistamine. TORISEL infusion should be interrupted in patients with infusion reactions and appropriate therapy given.

Serum glucose, serum cholesterol, and triglycerides should be tested before and during TORISEL treatment. TORISEL is likely to result in hyperglycemia and hyperlipemia. This may result in the need for an increase in the dose of, or initiation of, insulin and/or oral hypoglycemic agent therapy and/or lipid-lowering agents, respectively.

TORISEL may result in immunosuppression. Patients should be carefully observed for the occurrence of infections, including opportunistic infections.

Cases of interstitial lung disease, some resulting in death, have occurred. Some patients were asymptomatic or had minimal symptoms. Patients should undergo baseline radiography prior to TORISEL therapy and periodically thereafter, even in the absence of clinical respiratory symptoms. Follow patients closely and, if clinically significant respiratory symptoms develop, consider withholding TORISEL until recovery of symptoms and radiographic improvement of pneumonitis findings. Some patients required TORISEL discontinuation and/or treatment with corticosteroids and/or antibiotics.

Cases of fatal bowel perforation occurred with TORISEL. These patients presented with fever, abdominal pain, metabolic acidosis, bloody stools, diarrhea, and/or acute abdomen.

Cases of rapidly progressive and sometimes fatal acute renal failure not clearly related to disease progression occurred in patients who received TORISEL.

Due to abnormal wound healing, use TORISEL with caution in the perioperative period.

Patients with central nervous system tumors (primary CNS tumor or metastases) and/or receiving anticoagulation therapy may be at an increased risk of developing intracerebral bleeding (including fatal outcomes) while receiving TORISEL.

Live vaccinations and close contact with those who received live vaccines should be avoided.

TORISEL may cause fetal harm. Patients and their partners should be advised to avoid pregnancy throughout treatment and for 3 months after TORISEL therapy has stopped.

Elderly patients may be more likely to experience certain adverse reactions including diarrhea, edema and pneumonia.

The most common (incidence ≥30%) adverse reactions observed with TORISEL are: rash (47%), asthenia (51%), mucositis (41%), nausea (37%), edema (35%), and anorexia (32%). The most common laboratory abnormalities (incidence ≥30%) are anemia (94%),

hyperglycemia (89%), hyperlipemia (87%), hypertriglyceridemia (83%), elevated alkaline phosphatase (68%), elevated serum creatinine (57%), lymphopenia (53%), hypophosphatemia (49%), thrombocytopenia (40%), elevated AST (38%), and leukopenia (32%).

Most common grades 3/4 adverse events and laboratory abnormalities included asthenia (11%), dyspnea (9%), hemoglobin decreased (20%), lymphocytes decreased (16%), glucose increased (16%), phosphorus decreased (18%), and triglycerides increased (44%).

Pleural effusion, hemodynamically significant pericardial effusions requiring intervention, convulsions, rhabdomyolysis, Stevens-Johnson Syndrome, complex regional pain syndrome and extravasations have been reported during postmarketing use.

Strong inducers of CYP3A4/5 (eg, dexamethasone, rifampin) and strong inhibitors of CYP3A4 (eg, ketoconazole, atazanavir) may decrease and increase concentrations of the major metabolite of TORISEL, respectively. If alternatives cannot be used, dose modifications of TORISEL are recommended.

Avoid St. John’s Wort which may decrease TORISEL plasma concentrations, and grapefruit juice which may increase plasma concentrations of the major metabolite of TORISEL.

The combination of TORISEL and sunitinib resulted in dose-limiting toxicity (Grade 3/4 erythematous maculopapular rash, and gout/cellulitis requiring hospitalization).

For more information on TORISEL, including full prescribing information for TORISEL (temsirolimus), please visit www.pfizer.com.

About SUTENT(®) (sunitinib malate)

SUTENT is an oral multi-kinase inhibitor approved for the treatment of advanced renal cell carcinoma (RCC), gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate and progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease. SUTENT works by blocking multiple molecular targets implicated in the growth, proliferation and spread of cancer. Two important SUTENT targets, vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) are expressed by many types of solid tumors and are thought to play a crucial role in angiogenesis, the process by which tumors acquire blood vessels, oxygen and nutrients needed for growth. SUTENT also inhibits other targets important to tumor

growth, including KIT, FLT3 and RET.

Important SUTENT(®) (sunitinib malate) Safety Information

Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported. Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.

Given the potential for serious adverse reactions (ARs) in nursing infants, a decision should be made whether to discontinue nursing or SUTENT.

Cardiovascular events, including heart failure, myocardial disorders, and cardiomyopathy, some of which were fatal, have been reported. Monitor patients for signs and symptoms of congestive heart failure (CHF) and, in the presence of clinical manifestations, discontinuation is recommended. Patients who presented with cardiac events, pulmonary embolism, or cerebrovascular events within the previous 12 months were excluded from clinical studies.

SUTENT has been shown to prolong QT interval in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias including torsades de pointes, which has been seen in <0.1% of patients. Monitoring with on-treatment electrocardiograms and electrolytes should be considered.

Hypertension may occur. Monitor blood pressure and treat as needed with standard antihypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.

There have been rare (<1%) nonfatal reports of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS).

Hemorrhagic events, including tumor-related hemorrhage such as pulmonary hemorrhage, have occurred. Some of these events were fatal. Perform serial complete blood counts (CBCs) and physical examinations.

Osteonecrosis of the jaw (ONJ) has been reported. Consider preventive dentistry prior to treatment with SUTENT. If possible, avoid invasive dental procedures, particularly in patients receiving bisphosphonates.

Cases of tumor lysis syndrome (TLS) have been reported primarily in patients with high tumor burden. Monitor these patients closely and treat as clinically indicated.

Thyroid dysfunction may occur. Monitor thyroid function in patients with signs and/or symptoms of hypothyroidism or hyperthyroidism and treat per standard medical practice.

Cases of impaired wound healing have been reported. Temporary interruption of therapy with SUTENT is recommended in patients undergoing major surgical procedures.

Adrenal hemorrhage was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma, or severe infection.

CBCs with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

Dose adjustments are recommended when administered with CYP3A4 inhibitors or inducers.

The most common ARs occurring in ≥20% of patients receiving SUTENT for treatment-naïve metastatic RCC (all grades, vs IFNα) were diarrhea, fatigue, nausea, anorexia, altered taste, mucositis/stomatitis, pain in extremity/limb discomfort, vomiting, bleeding, all sites, hypertension, dyspepsia, arthralgia, abdominal pain, rash, hand-foot syndrome, back pain, cough, asthenia, dyspnea, skin discoloration/yellow skin, peripheral edema, headache, constipation, dry skin, fever, and hair color changes. The most common grade 3/4 ARs (occurring in ≥5% of patients with RCC receiving SUTENT vs IFNα) were fatigue, hypertension, asthenia, diarrhea, hand-foot syndrome, dyspnea, nausea, back pain, pain in extremity/limb discomfort, vomiting, and abdominal pain.

The most common grade 3/4 lab abnormalities (occurring in ≥5% of patients with RCC receiving SUTENT vs IFNα) included lymphocytes, lipase, neutrophils, uric acid, platelets, hemoglobin, sodium decreased, leukocytes, glucose increased, phosphorus, and amylase.

For more information on SUTENT, including full prescribing information for SUTENT (sunitinib malate), please visit www.pfizer.com.

About Pfizer Oncology

Pfizer Oncology is committed to the discovery, investigation and development of innovative treatment options to improve the outlook for cancer patients worldwide.

As a leader in the treatment of advanced RCC, Pfizer Oncology is dedicated to offering multiple treatments and investigating new agents in different populations and stages of disease. Pfizer Oncology has helped transform treatment expectations for advanced kidney cancer, providing confidence and options to physicians, allowing them to better tailor treatment for different patient populations.

For more information please visit www.Pfizer.com.

1 Pfizer data on file.

2 D. Y. Heng et al. Ann. Onc., November 5, 2011; (2011) mdr533v1.

3 Pfizer data on file.

4 Pfizer data on file.

5 Hudes G, Carducci M, Tomczak P, et al. Global ARCC Trial. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007; 356: 2271-81.

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