Pfizer Logo

Pivotal Phase III Data for BAVENCIO® (avelumab) Plus INLYTA® (axitinib) in Advanced Renal Cell Carcinoma Published in The New England Journal of Medicine

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- **JAVELIN Renal 101 shows significant improvement in progression-free survival with a hazard ratio of 0.69 in patients regardless of PD-L1 expression**
- **US FDA has granted Priority Review to BAVENCIO plus INLYTA for patients with advanced renal cell carcinoma**
- **Data at 2019 Genitourinary Cancers Symposium reinforce consistency of PFS and ORR benefits across broad population of patients with advanced RCC, including all prognostic risk groups, and show increased time to progression on next-line therapy**

Darmstadt, Germany and New York, NY, February 16, 2019 – Merck KGaA, Darmstadt, Germany, which operates its biopharmaceutical business as EMD Serono in the US and Canada, and Pfizer Inc. (NYSE: PFE) today announced the publication of results from an interim analysis of the pivotal JAVELIN Renal 101 trial online in the *New England Journal of Medicine.*[1] The combination of BAVENCIO® (avelumab) and INLYTA® (axitinib)* significantly extended median progression-free survival (PFS) by more than five months compared with SUTENT® (sunitinib) as a first-line treatment for patients with advanced renal cell carcinoma (RCC), irrespective of PD-L1 expression (HR: 0.69 [95% CI: 0.56–0.84]; BAVENCIO+INLYTA: 13.8 months [95% CI: 11.1-NE]; SUTENT: 8.4 months [95% CI: 6.9-11.1]; p<0.001). Further, the objective response rate (ORR) was doubled with BAVENCIO+INLYTA versus SUTENT in this population (51.4% [95% CI: 46.6-56.1] vs. 25.7% [95% CI: 21.7-30.0]). The study is continuing for the other primary endpoint of overall survival (OS).

“There is a significant need for patients with advanced RCC to prolong the time until the disease worsens beyond what tyrosine kinase inhibitors alone offer,” said Robert J. Motzer, M.D., Jack and Dorothy Byrne Chair in Clinical Oncology, Memorial Sloan Kettering Cancer Center, New York, US, and principal investigator for JAVELIN Renal 101. “The magnitude and consistency of PFS and response rates seen thus far across populations in the JAVELIN Renal 101 study suggest that many different types of patients, including those with a favorable prognosis, could potentially derive benefit from this particular combination.”

Additional data presented today at the 2019 Genitourinary Cancers Symposium reinforce the consistency of the PFS and ORR results across patient subgroups, including patients with favorable, intermediate and poor prognoses as well as those with PD-L1-positive or negative tumors. In subgroup analyses, approximately two-thirds of patients with favorable risk (66% of patients using the Memorial Sloan Kettering Cancer Center risk model and 68% with the International Metastatic Renal Cell Carcinoma Database Consortium risk model) achieved a complete or partial response with BAVENCIO+INLYTA. Median PFS for these patients is not yet estimable. BAVENCIO+INLYTA also extended median PFS2, defined as the time from randomization to disease progression on next-line therapy (HR: 0.56 [95% CI: 0.42-0.74]; NE [95% CI: 19.9-NE] vs. 18.4 months

[95% CI: 15.7-23.6]) and increased median duration of response by more than four months (95% CI: 2.9-5.1) in the overall population.

“In this study, the combination of avelumab plus axitinib not only prolonged the initial response in treated patients compared to sunitinib, but for patients who went on to subsequent therapy, reduced the risk of disease progression or death on the next treatment,” said Toni K. Choueiri, M.D., Director of the Lank Center for Genitourinary Oncology at Dana-Farber, Boston, US, senior and co-corresponding author of JAVELIN Renal 101, and presenter. “Together with the progression-free survival results and objective response rates, these findings show the potential of this combination regimen to be an important new treatment option for patients with advanced RCC.”

The Phase III JAVELIN Renal 101 study is evaluating the combination of BAVENCIO+INLYTA compared with SUTENT in 886 patients with previously untreated advanced RCC. BAVENCIO+INLYTA significantly reduced the risk of disease progression or death by 39% in patients with PD-L1-positive (?1%) tumors, a primary endpoint (HR: 0.61 [95% CI: 0.47–0.79], p<0.001; median PFS: 13.8 months [95% CI: 11.1-NE] vs. 7.2 months [95% CI: 5.7-9.7]). In the overall population, which was tested after achieving statistical significance for the primary endpoint, the risk was reduced by 31%. The confirmed ORR in patients with PD-L1-positive tumors was 55.2% (95% CI: 49.0-61.2) with BAVENCIO+INLYTA vs. 25.5% (95% CI: 20.6-30.9) with SUTENT.

In the BAVENCIO+INLYTA arm, 20.8% of patients received subsequent anticancer drug therapies, compared with 39.2% in the SUTENT arm. In the SUTENT arm, about two-thirds (66.7%) of patients who received subsequent anticancer therapy were known to have been treated with an anti–PD-1/PD-L1 agent.

Adverse events of grade 3 or higher during treatment (treatment-emergent adverse events [TEAEs]) occurred in 71.2% of patients in the BAVENCIO+INLYTA arm and 71.5% in the SUTENT arm); grade 3 or higher TEAEs that occurred in more than 5% of patients receiving the combination were hypertension (25.6%), diarrhea (6.7%), increased alanine aminotransferase level (6.0%) and hand–foot syndrome (5.8%). In the combination arm, 9.0% of patients experienced grade 3 or higher immune-related adverse events. Grade 5 events occurred in three patients in the BAVENCIO+INLYTA arm (myocarditis, necrotizing pancreatitis, sudden death; n=1 each); and in one patient in the SUTENT arm (intestinal perforation). There were fewer discontinuations due to adverse events that occurred during treatment with BAVENCIO+INLYTA, compared with SUTENT (7.6% vs. 13.4%).

On February 11, 2019, the alliance announced that the US Food and Drug Administration (FDA) accepted for Priority Review the supplemental Biologics License Application (sBLA) for BAVENCIO in combination with INLYTA for patients with advanced RCC. The application has been given a target action date in June 2019. A supplemental application for BAVENCIO+INLYTA in unresectable or metastatic RCC was submitted in Japan on January 30, 2019. In December 2017, the FDA granted Breakthrough Therapy Designation for BAVENCIO in combination with INLYTA for treatment-naïve patients with advanced RCC. Despite available therapies, the outlook for patients with advanced RCC remains poor.[2]

*The combination of BAVENCIO and INLYTA is under clinical investigation for advanced RCC, and there is no guarantee this combination will be approved for advanced RCC by any health authority worldwide. In the US, INLYTA is approved as monotherapy for the treatment of advanced RCC after failure of one prior systemic therapy. INLYTA is also approved by the European Medicines Agency (EMA) for use in the EU in adult patients with advanced RCC after failure of prior treatment with SUTENT or a cytokine.

About Renal Cell Carcinoma

RCC is the most common form of kidney cancer, accounting for about 2% to 3% of all cancers in adults.[3,4] The most common type of RCC is clear cell carcinoma, accounting for approximately 70% of all cases.[3] In 2019, an estimated 73,820 new cases of kidney cancer will be diagnosed in the US, and approximately 14,770 people will die from the disease.[5] Approximately 20% to 30% of patients are first diagnosed at the metastatic stage.[6] The five-year survival rate for patients with metastatic RCC is approximately 12%.[2]

About the JAVELIN Clinical Development Program

The clinical development program for avelumab, known as JAVELIN, involves at least 30 clinical programs and more than 9,000 patients evaluated across more than 15 different tumor types. In addition to RCC, these tumor types include breast, gastric/gastro-esophageal junction, and head and neck cancers, Merkel cell carcinoma, non-small cell lung cancer, and urothelial carcinoma.

About BAVENCIO® (avelumab)

BAVENCIO is a human anti-programmed death ligand-1 (PD-L1) antibody. BAVENCIO has been shown in preclinical models to engage both the adaptive and innate immune functions. By blocking the interaction of PD-L1 with PD-1 receptors, BAVENCIO has been shown to release the suppression of the T cell-mediated antitumor immune response in preclinical models.[7-9] BAVENCIO has also been shown to induce NK cell-mediated direct tumor cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro.[9-11] In November 2014, Merck KGaA, Darmstadt, Germany, and Pfizer announced a strategic alliance to co-develop and co-commercialize BAVENCIO.

Approved Indications in the US

In the US, the FDA granted accelerated approval for BAVENCIO for the treatment of (i) adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (mMCC) and (ii) patients with locally advanced or metastatic urothelial carcinoma (mUC) who have disease progression during or following platinum-containing chemotherapy, or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. These indications are approved under accelerated approval based on tumor response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

BAVENCIO is currently approved for patients with MCC in more than 45 countries globally, with the majority of these approvals in a broad indication that is not limited to a specific line of treatment.

Important Safety Information from the US FDA-Approved Label

BAVENCIO can cause **immune-mediated pneumonitis**, including fatal cases. Monitor patients for signs and symptoms of pneumonitis, and evaluate suspected cases with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold BAVENCIO for moderate (Grade 2) and permanently discontinue for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis. Pneumonitis occurred in 1.2% (21/1738) of patients, including one (0.1%) patient with Grade 5, one (0.1%) with Grade 4, and

five (0.3%) with Grade 3.

BAVENCIO can cause **immune-mediated hepatitis**, including fatal cases. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater hepatitis. Withhold BAVENCIO for moderate (Grade 2) immune-mediated hepatitis until resolution and permanently discontinue for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis. Immune-mediated hepatitis was reported in 0.9% (16/1738) of patients, including two (0.1%) patients with Grade 5, and 11 (0.6%) with Grade 3.

BAVENCIO can cause **immune-mediated colitis**. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold BAVENCIO until resolution for moderate or severe (Grade 2 or 3) colitis, and permanently discontinue for life-threatening (Grade 4) or recurrent (Grade 3) colitis upon reinitiation of BAVENCIO. Immune-mediated colitis occurred in 1.5% (26/1738) of patients, including seven (0.4%) with Grade 3.

BAVENCIO can cause **immune-mediated endocrinopathies**, including adrenal insufficiency, thyroid disorders, and type 1 diabetes mellitus.

Monitor patients for signs and symptoms of **adrenal insufficiency** during and after treatment, and administer corticosteroids as appropriate. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Adrenal insufficiency was reported in 0.5% (8/1738) of patients, including one (0.1%) with Grade 3.

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation. Manage hypothyroidism with hormone replacement therapy and hyperthyroidism with medical management. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) thyroid disorders. Thyroid disorders, including hypothyroidism, hyperthyroidism, and thyroiditis, were reported in 6% (98/1738) of patients, including three (0.2%) with Grade 3.

Type 1 diabetes mellitus including diabetic ketoacidosis: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Withhold BAVENCIO and administer antihyperglycemics or insulin in patients with severe or life-threatening (Grade ? 3) hyperglycemia, and resume treatment when metabolic control is achieved. Type 1 diabetes mellitus without an alternative etiology occurred in 0.1% (2/1738) of patients, including two cases of Grade 3 hyperglycemia.

BAVENCIO can cause **immune-mediated nephritis and renal dysfunction**. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater nephritis. Withhold BAVENCIO for moderate (Grade 2) or severe (Grade 3) nephritis until resolution to Grade 1 or lower. Permanently discontinue BAVENCIO for life-threatening (Grade 4) nephritis. Immune-mediated nephritis occurred in 0.1% (1/1738) of patients.

BAVENCIO can result in **other severe and fatal immune-mediated adverse reactions** involving any organ system during treatment or after treatment discontinuation. For suspected immune-mediated adverse reactions, evaluate to confirm or rule out an immune-mediated adverse reaction and to exclude other causes. Depending on the severity of the adverse reaction, withhold or permanently discontinue BAVENCIO, administer high-dose corticosteroids, and initiate hormone replacement therapy, if appropriate. Resume BAVENCIO when the immune-mediated adverse reaction remains at Grade 1 or lower following a corticosteroid taper. Permanently discontinue BAVENCIO for any severe (Grade 3) immune-mediated adverse reaction that recurs and for any life-threatening (Grade 4) immune-mediated adverse reaction. The following clinically significant immune-

mediated adverse reactions occurred in less than 1% of 1738 patients treated with BAVENCIO: myocarditis with fatal cases, myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, and systemic inflammatory response.

BAVENCIO can cause severe (Grade 3) or life-threatening (Grade 4) **infusion-related reactions**. Patients should be premedicated with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent doses based upon clinical judgment and presence/severity of prior infusion reactions. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for mild (Grade 1) or moderate (Grade 2) infusion-related reactions. Permanently discontinue BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Infusion-related reactions occurred in 25% (439/1738) of patients, including three (0.2%) patients with Grade 4 and nine (0.5%) with Grade 3.

BAVENCIO can cause **fetal harm** when administered to a pregnant woman. Advise patients of the potential risk to a fetus including the risk of fetal death. Advise females of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO. It is not known whether BAVENCIO is excreted in human milk. Advise a lactating woman **not to breastfeed** during treatment and for at least 1 month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants.

The most common adverse reactions (all grades, ? 20%) in patients with **metastatic Merkel cell carcinoma (MCC)** were fatigue (50%), musculoskeletal pain (32%), diarrhea (23%), nausea (22%), infusion-related reaction (22%), rash (22%), decreased appetite (20%), and peripheral edema (20%).

Selected treatment-emergent laboratory abnormalities (all grades, ? 20%) in patients with **metastatic MCC** were lymphopenia (49%), anemia (35%), increased aspartate aminotransferase (34%), thrombocytopenia (27%), and increased alanine aminotransferase (20%).

The most common adverse reactions (all grades, ? 20%) in patients with **locally advanced or metastatic urothelial carcinoma (UC)** were fatigue (41%), infusion-related reaction (30%), musculoskeletal pain (25%), nausea (24%), decreased appetite/hypophagia (21%), and urinary tract infection (21%).

Selected laboratory abnormalities (Grades 3-4, ? 3%) in patients with **locally advanced or metastatic UC** were hyponatremia (16%), increased gamma-glutamyltransferase (12%), lymphopenia (11%), hyperglycemia (9%), increased alkaline phosphatase (7%), anemia (6%), increased lipase (6%), hyperkalemia (3%), and increased aspartate aminotransferase (3%).

Please see full US Prescribing Information and Medication Guide available at http://www.BAVENCIO.com.

About INLYTA® (axitinib)

INLYTA is an oral therapy that is designed to inhibit tyrosine kinases, including vascular endothelial growth factor (VEGF) receptors 1, 2 and 3; these receptors can influence tumor growth, vascular angiogenesis and progression of cancer (the spread of tumors). In the US, INLYTA is approved for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy. INLYTA is also approved by the European Medicines Agency (EMA) for use in the EU in adult patients with advanced RCC after failure of prior treatment with sunitinib or a cytokine.

INLYTA Important Safety Information

Hypertension including **hypertensive crisis** has been observed. Blood pressure should be well controlled prior to initiating INLYTA. Monitor for hypertension and treat as needed. For persistent hypertension, despite use of antihypertensive medications, reduce the dose. Discontinue INLYTA if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis.

Arterial and venous thrombotic events have been observed and can be fatal. Use with caution in patients who are at increased risk or who have a history of these events.

Hemorrhagic events, including fatal events, have been reported. INLYTA has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose.

Cardiac failure has been observed and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

Gastrointestinal perforation and fistula, including death, have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment.

Hypothyroidism requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment.

No formal studies of the effect of INLYTA on **wound healing** have been conducted. Stop INLYTA at least 24 hours prior to scheduled surgery.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed. If signs or symptoms occur, permanently discontinue treatment.

Monitor for **proteinuria** before initiation of, and periodically throughout, treatment. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment.

Liver enzyme elevation has been observed during treatment with INLYTA. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout, treatment.

For patients with moderate **hepatic impairment**, the starting dose should be decreased. INLYTA has not been studied in patients with severe hepatic impairment.

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

Avoid strong **CYP3A4/5 inhibitors**. If unavoidable, reduce the dose. Grapefruit or grapefruit juice may also increase INLYTA plasma concentrations and should be avoided.

Avoid strong **CYP3A4/5 inducers** and, if possible, avoid moderate CYP3A4/5 inducers.

The **most common (?20%) adverse events (AEs)** occurring in patients receiving INLYTA (all grades, vs sorafenib) were diarrhea (55% vs 53%), hypertension (40% vs 29%), fatigue (39% vs 32%), decreased appetite (34% vs 29%), nausea (32% vs 22%), dysphonia (31% vs 14%), hand-foot syndrome (27% vs 51%), weight decreased (25% vs 21%), vomiting (24% vs 17%), asthenia (21% vs 14%), and constipation (20% vs 20%).

The **most common (?10%) grade 3/4 AEs** occurring in patients receiving INLYTA (vs sorafenib) were hypertension (16% vs 11%), diarrhea (11% vs 7%), and fatigue (11% vs 5%).

The **most common (?20%) lab abnormalities** occurring in patients receiving INLYTA (all grades, vs sorafenib) included increased creatinine (55% vs 41%), decreased bicarbonate (44% vs 43%), hypocalcemia (39% vs 59%), decreased hemoglobin (35% vs 52%), decreased lymphocytes (absolute) (33% vs 36%), increased ALP (30% vs 34%), hyperglycemia (28% vs 23%), increased lipase (27% vs 46%), increased amylase (25% vs 33%), increased ALT (22% vs 22%), and increased AST (20% vs 25%).

For more information and full Prescribing Information, visit www.INLYTA.com.

About SUTENT® (sunitinib malate)

Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases, some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was evaluated for its inhibitory activity against a variety of kinases (>80 kinases) and was identified as an inhibitor of platelet-derived growth factor receptors (PDGFR? and PDGFR?), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET).

SUTENT is indicated in the US for the treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate; the treatment of advanced RCC; the adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy; and the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease.

SUTENT Important Safety Information

Boxed Warning/Hepatotoxicity has been observed in clinical trials and postmarketing experience. Hepatotoxicity may be severe, and in some cases fatal. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. Fatal liver failure has been observed. Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. Interrupt SUTENT for Grade 3 or 4 drug-related hepatic adverse reactions and discontinue if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have signs and symptoms of liver failure.

Cardiovascular events, including myocardial ischemia, myocardial infarction, left ventricular ejection fraction declines to below the lower limit of normal and cardiac failure including death have occurred. Monitor patients for signs and symptoms of congestive heart failure. Discontinue SUTENT for clinical manifestations of congestive heart failure. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered. Baseline and periodic evaluations of left ventricular ejection fraction should also be considered

while these patients are receiving SUTENT.

SUTENT can cause **QT Prolongation** 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. Monitor patients that are at a higher risk for developing QT interval prolongation, including those with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Consider monitoring of electrocardiograms and electrolytes. Concomitant treatment with strong CYP3A4 inhibitors may increase sunitinib plasma concentrations and dose reduction of SUTENT 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.

Hemorrhagic events, including tumor-related hemorrhage, and viscus perforation (both with fatal events) have occurred. These events may occur suddenly, and in the case of pulmonary tumors, may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. Perform serial complete blood counts (CBCs) and physical examinations.

Cases of **tumor lysis syndrome (TLS)** (some fatal) have been reported. Patients generally at risk of TLS are those with high tumor burden prior to treatment. Monitor these patients closely and treat as clinically indicated.

Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in patients who received SUTENT as monotherapy and in combination with bevacizumab. Discontinue SUTENT in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued.

Proteinuria and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Monitor patients for the development or worsening of proteinuria. Perform baseline and periodic urinalysis during treatment, with follow-up measurement of 24-hour urine protein as clinically indicated. Interrupt treatment for 24-hour urine protein ?3 grams. Discontinue for repeat episodes of protein ?3 grams despite dose reductions or nephrotic syndrome.

Dermatologic toxicities: Severe cutaneous reactions have been reported, including cases of necrotizing fasciitis, erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of EM, SJS, or TEN are present, discontinue SUTENT treatment. If a diagnosis of SJS or TEN is suspected, treatment must not be restarted.

Necrotizing fasciitis, including fatal cases, has been reported, including of the perineum and secondary to fistula formation. Discontinue SUTENT in patients who develop necrotizing fasciitis.

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

Hypoglycemia may occur. SUTENT can result in symptomatic hypoglycemia, which may lead to a loss of consciousness or require hospitalization. Reductions in blood glucose levels may be worse in patients with diabetes. Check blood glucose levels regularly during and after discontinuation of treatment with SUTENT. Assess if antidiabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

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 intravenous bisphosphonate therapy.

Impaired wound healing has occurred with SUTENT. Temporary interruption of therapy with SUTENT is recommended in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume SUTENT therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

Embryo fetal toxicity and reproductive potential

Females - SUTENT can cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with SUTENT and for 4 weeks following the final dose.

Males - Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment with SUTENT and for 7 weeks after the last dose.

Male and female infertility - based on findings in animals, male and female fertility may be compromised by treatment with SUTENT

Lactation: Because of the potential for serious adverse reactions in breastfed infants from SUTENT, advise a lactating woman not to breastfeed during treatment with SUTENT and for at least 4 weeks after the last dose.

Venous thromboembolic events: In patients treated with SUTENT (N=7527) for GIST, advanced RCC, adjuvant treatment of RCC and pNET, 3.5% of patients experienced a venous thromboembolic event; 2.2% Grade 3-4.

There have been (<1%) reports, some fatal, of subjects presenting with seizures and radiological evidence of **reversible posterior leukoencephalopathy syndrome (RPLS).** Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning, and visual loss, including cortical blindness, should be controlled with medical management including control of hypertension. Temporary suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating healthcare provider.

Pancreatic function: In a trial of patients receiving adjuvant treatment for RCC, 1 patient (<1%) on SUTENT and none on placebo experienced pancreatitis.

CYP3A4 inhibitors and inducers: Dose adjustments are recommended when SUTENT is administered with CYP3A4 inhibitors or inducers. During treatment with SUTENT, patients should not drink grapefruit juice, eat grapefruit, or take St. John’s Wort.

Most common ARs & most common grade 3/4 ARs (adjuvant RCC): The **most common ARs** reported in ? 20% of patients receiving SUTENT for adjuvant treatment of RCC and more commonly than in patients given placebo (all grades, vs placebo) were mucositis/stomatitis (61% vs 15%), diarrhea (57% vs 22%), fatigue/asthenia (57% vs 34%), hand-foot syndrome (50% vs 10%), hypertension (39% vs 14%), altered taste (38% vs 6%), nausea (34% vs 15%), dyspepsia (27% vs 7%), abdominal pain (25% vs 9%), hypothyroidism/TSH increased (24% vs 4%), rash (24% vs 12%), hair color changes (22% vs 2%). The **most**

common grade 3/4 ARs reported in ?5% of patients receiving SUTENT for adjuvant treatment of RCC and more commonly than in patients given placebo (vs placebo) were hand-foot syndrome (16% vs <1%), fatigue/asthenia (8% vs 2%), hypertension (8% vs 1%), and mucositis/stomatitis (6% vs 0%).

Most common grade 3/4 lab abnormalities (adjuvant RCC): The **most common grade 3/4 lab abnormalities** (occurring in ? 2% of patients receiving SUTENT) included neutropenia (13%), thrombocytopenia (5%), leukopenia (3%), lymphopenia (3%), elevated alanine aminotransferase (2%), elevated aspartate aminotransferase (2%), hyperglycemia (2%), and hyperkalemia (2%).

Most common ARs & most common grade 3/4 ARs (advanced RCC): The **most common ARs** reported in ? 20% of patients receiving SUTENT for treatment-naïve metastatic RCC (all grades, vs IFN?) were diarrhea (66% vs 21%), fatigue (62% vs 56%), nausea (58% vs 41%), anorexia (48% vs 42%), altered taste (47% vs 15%), mucositis/stomatitis (47% vs 5%), pain in extremity/limb discomfort (40% vs 30%), vomiting (39% vs 17%), bleeding, all sites (37% vs 10%), hypertension (34% vs 4%), dyspepsia (34% vs 4%), arthralgia (30% vs 19%), abdominal pain (30% vs 12%), rash (29% vs 11%), hand-foot syndrome (29% vs 1%), back pain (28% vs 14%), cough (27% vs 14%), asthenia (26% vs 22%), dyspnea (26% vs 20%), skin discoloration/yellow skin (25% vs 0%), peripheral edema (24% vs 5%), headache (23% vs 19%), constipation (23% vs 14%), dry skin (23% vs 7%), fever (22% vs 37%), and hair color changes (20% vs <1%). The **most common grade 3/4 ARs** reported in ?5% of patients with RCC receiving SUTENT (vs IFN?) were fatigue (15% vs 15%), hypertension (13% vs <1%), asthenia (11% vs 6%), diarrhea (10% vs <1%), hand-foot syndrome (8% vs 0%), dyspnea (6% vs 4%), nausea (6% vs 2%), back pain (5% vs 2%), pain in extremity/limb discomfort (5% vs 2%), vomiting (5% vs 1%), and abdominal pain (5% vs 1%).

Most common grade 3/4 lab abnormalities (advanced RCC): The **most common grade 3/4 lab abnormalities** (occurring in ?5% of patients with RCC receiving SUTENT vs IFN?) included lymphocytes (18% vs 26%), lipase (18% vs 8%), neutrophils (17% vs 9%), uric acid (14% vs 8%), platelets (9% vs 1%), hemoglobin (8% vs 5%), sodium decreased (8% vs 4%), leukocytes (8% vs 2%), glucose increased (6% vs 6%), phosphorus (6% vs 6%), and amylase (6% vs 3%).

Most common ARs & most common grade 3/4 ARs (imatinib-resistant or -intolerant GIST): The **most common ARs** reported in ?20% of patients with GIST and more commonly with SUTENT than placebo (all grades, vs placebo) were diarrhea (40% vs 27%), anorexia (33% vs 29%), skin discoloration (30% vs 23%), mucositis/stomatitis (29% vs 18%), asthenia (22% vs 11%), altered taste (21% vs 12%), and constipation (20% vs 14%). The **most common grade 3/4 ARs** reported in ?4% of patients with GIST receiving SUTENT (vs placebo) were asthenia (5% vs 3%), hand-foot syndrome (4% vs 3%), diarrhea (4% vs 0%), and hypertension (4% vs0%).

Most common grade 3/4 lab abnormalities (imatinib-resistant or - intolerant GIST): The **most common grade 3/4 lab abnormalities** (occurring in ?5% of patients with GIST receiving SUTENT vs placebo) included lipase (10% vs 7%), neutrophils (10% vs 0%), amylase (5% vs 3%), and platelets (5% vs 0%).

Most common ARs & most common grade 3/4 ARs (advanced pNET): The **most common ARs** reported in ?20% of patients with advanced pNET and more commonly with SUTENT than placebo (all grades, vs placebo) were diarrhea (59% vs 39%), stomatitis/oral syndromes (48% vs 18%), nausea (45% vs 29%), abdominal pain (39% vs 34%), vomiting (34% vs 31%), asthenia (34% vs 27%), fatigue (33% vs 27%), hair color changes (29% vs 1%), hypertension (27% vs 5%), hand-foot syndrome (23% vs 2%), bleeding events (22% vs 10%), epistaxis (21% vs 5%), and dysgeusia (21% vs 5%). The **most common grade 3/4 ARs** reported in ?5% of patients with advanced pNET receiving SUTENT (vs placebo) were hypertension (10% vs 1%), hand-foot syndrome (6% vs 0%), stomatitis/oral syndromes (6% vs 0%), abdominal pain (5% vs 10%), fatigue (5% vs 9%), asthenia (5% vs 4%), and diarrhea (5% vs 2%).

Most common grade 3/4 lab abnormalities (advanced pNET): The **most common grade 3/4 lab abnormalities** (occurring in ?5% of patients with advanced pNET receiving SUTENT vs placebo) included decreased neutrophils (16% vs 0%), increased glucose (12% vs 18%), increased alkaline phosphatase (10% vs 11%), decreased phosphorus (7% vs 5%), decreased lymphocytes (7% vs 4%), increased creatinine (5% vs 5%), increased lipase (5% vs 4%), increased AST (5% vs 3%), and decreased platelets (5% vs 0%).

Please see full Prescribing Information, including BOXED WARNING and Medication Guide, for SUTENT® (sunitinib malate) at www.SUTENT.com.

Alliance between Merck KGaA, Darmstadt, Germany, and Pfizer Inc., New York, US

Immuno-oncology is a top priority for Merck KGaA, Darmstadt, Germany, and Pfizer. The global strategic alliance between Merck KGaA, Darmstadt, Germany, and Pfizer enables the companies to benefit from each other's strengths and capabilities and further explore the therapeutic potential of BAVENCIO, an anti-PD-L1 antibody initially discovered and developed by Merck KGaA, Darmstadt, Germany. The immuno-oncology alliance is jointly developing and commercializing BAVENCIO. The alliance is focused on developing high-priority international clinical programs to investigate BAVENCIO as a monotherapy as well as combination regimens, and is striving to find new ways to treat cancer.

About Merck KGaA, Darmstadt, Germany

Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and performance materials. Around 51,000 employees work to make a positive difference to millions of people's lives every day by creating more joyful and sustainable ways to live. From advancing gene editing technologies and discovering unique ways to treat the most challenging diseases to enabling the intelligence of devices – the company is everywhere. In 2017, Merck KGaA, Darmstadt, Germany, generated sales of € 15.3 billion in 66 countries.

Pfizer Inc.: Working together for a healthier world®

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer health care products. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.pfizer.com. In addition, to learn more, please visit us on www.pfizer.com and follow us on Twitter at @Pfizer and @Pfizer_News, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.

Pfizer Disclosure Notice

The information contained in this release is as of February 16, 2019. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about BAVENCIO (avelumab), including a potential new indication for BAVENCIO in combination with INLYTA (axitinib) for the treatment of patients with advanced renal cell carcinoma, the alliance between Merck KGaA, Darmstadt, Germany, and Pfizer involving BAVENCIO and clinical development plans, including their potential benefits, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, uncertainties regarding the commercial success of BAVENCIO; the uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for our clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as the possibility of unfavorable further analyses of existing clinical data and uncertainties regarding whether the other primary endpoint of JAVELIN Renal 101 will be met; risks associated with interim data; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; whether and when any drug applications may be filed for BAVENCIO in combination with INLYTA for the potential new indication in any other jurisdictions or in any jurisdictions for any other potential indications for BAVENCIO or combination therapies; whether and when the pending applications in the U.S. and Japan for BAVENCIO in combination with INLYTA for the potential new indication may be approved and whether and when regulatory authorities in any jurisdictions where any other applications are pending or may be submitted for BAVENCIO or combination therapies may approve any such applications, which will depend on myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy, and, if approved, whether they will be commercially successful; decisions by regulatory authorities impacting labeling, manufacturing processes

and/or other matters that could affect the availability or commercial potential of BAVENCIO or combination therapies, including BAVENCIO in combination with INLYTA for the potential new indication; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2017, and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

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