Exelixis and Bristol-Myers Squibb Initiate Phase 3 Trial of Opdivo® in Combination with CABOMETYX™ or Opdivo and Yervoy® in Combination with CABOMETYX, Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma

July 10, 2017

– First phase 3 trial in a global clinical development program to explore the combination of these agents –

– Exelixis, Bristol-Myers Squibb and Ipsen to co-fund this trial –

SOUTH SAN FRANCISCO, Calif. & NEW YORK--(BUSINESS WIRE)--Jul. 10, 2017-- Exelixis, Inc. (NASDAQ:EXEL) and Bristol-Myers Squibb Company (NYSE:BMY) today announced the initiation of the phase 3 CheckMate 9ER trial to evaluate Opdivo® (nivolumab) in combination with CABOMETYX™ (cabozantinib) tablets, a small molecule inhibitor of receptor tyrosine kinases, or Opdivo and Yervoy® (ipilimumab) in combination with CABOMETYX versus sunitinib in patients with previously untreated, advanced or metastatic renal cell carcinoma (RCC). The primary endpoint for the trial is progression-free survival (PFS).

This Smart News Release features multimedia. View the full release here: http://www.businesswire.com/news/home/20170710005351/en/

“There is strong scientific evidence showing that CABOMETYX results in a more immune permissive tumor environment, and we are eager to determine if combining these active agents with complementary and potentially cooperative mechanisms of action has the potential to further improve patient outcomes,” said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. “We are excited to initiate this first clinical trial from our broad development program with Bristol-Myers Squibb looking at the potential of Opdivo in combination with CABOMETYX, with or without Yervoy, in a variety of tumor types.”

“While existing therapies have improved outcomes for some patients with advanced or metastatic kidney cancer, high rates of relapse and disease progression demonstrate a need for additional therapeutic options, especially among poor and intermediate risk patients,” said Fouad Namouni, M.D., Head of Development, Oncology, Bristol-Myers Squibb. “Combination therapy with agents that target different and complementary pathways—in this case, the combination of immune checkpoint inhibitors and tyrosine kinase inhibitors—may be a potential new approach for these patients.”

CheckMate 9ER is an open-label, randomized, multi-national phase 3 trial that aims to enroll approximately 1,014 patients with previously untreated advanced or metastatic RCC. Patients will be randomized 1:1:1 to one of three arms: CABOMETYX and Opdivo; CABOMETYX, Opdivo and Yervoy; or sunitinib. The primary efficacy analysis will compare the doublet combination versus sunitinib and the triplet combination versus sunitinib in intermediate/poor risk patients with RCC.

More information about this trial is available at ClinicalTrials.gov.

About Advanced Renal Cell Carcinoma

The American Cancer Society’s 2017 statistics cite kidney cancer as among the top ten most commonly diagnosed forms of cancer among both men and women in the U.S.[1] Clear cell RCC is the most common type of kidney cancer in adults.[2] If detected in its early stages, the five-year survival rate for RCC is high; for patients with advanced or late-stage metastatic RCC, however, the five-year survival rate is only 12 percent, with no identified cure for the disease.[3] Approximately 30,000 patients in the U.S. and 68,000 globally require treatment.[4]

The majority of clear cell RCC tumors have lower than normal levels of a protein called von Hippel-Lindau, which leads to higher levels of MET, AXL and VEGF.[5,6] These proteins promote tumor angiogenesis (blood vessel growth), growth, invasiveness and metastasis.[7-10] MET and AXL may provide escape pathways that drive resistance to VEGF receptor inhibitors.[6,7]

About CABOMETYX

CABOMETYX is the tablet formulation of cabozantinib. Its targets include MET, AXL and VEGFR-1, -2 and -3. In preclinical models, cabozantinib has been shown to inhibit the activity of these receptors, which are involved in normal cellular function and pathologic processes such as tumor angiogenesis, invasiveness, metastasis and drug resistance.

CABOMETYX is available in 20 mg, 40 mg or 60 mg doses. The recommended dose is 60 mg orally, once daily.

On April 25, 2016, the FDA approved CABOMETYX tablets for the treatment of patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy. On September 9, 2016, the European Commission approved CABOMETYX tablets for the treatment of advanced renal cell carcinoma in adults who have received prior vascular endothelial growth factor (VEGF)-targeted therapy in the European Union, Norway and Iceland.

About OPDIVO

Opdivo is a programmed death-1 (PD-1) immune checkpoint inhibitor that is designed to uniquely harness the body’s own immune system to help restore anti-tumor immune response. By harnessing the body’s own immune system to fight cancer, Opdivo has become an important treatment option

across multiple cancers.

Opdivo's leading global development program is based on Bristol-Myers Squibb's scientific expertise in the field of Immuno-Oncology and includes a broad range of clinical trials across all phases, including Phase 3, in a variety of tumor types. To date, the Opdivo clinical development program has enrolled more than 25,000 patients. The Opdivo trials have contributed to gaining a deeper understanding of the potential role of biomarkers in patient care, particularly regarding how patients may benefit from Opdivo across the continuum of PD-L1 expression.

In July 2014, Opdivo was the first PD-1 immune checkpoint inhibitor to receive regulatory approval anywhere in the world. Opdivo is currently approved in more than 60 countries, including the United States, the European Union and Japan. In October 2015, the company's Opdivo and Yervoy combination regimen was the first Immuno-Oncology combination to receive regulatory approval for the treatment of metastatic melanoma and is currently approved in more than 50 countries, including the United States and the European Union.

CABOMETYX U.S. Important Safety Information

Hemorrhage: Severe hemorrhage occurred with CABOMETYX. The incidence of Grade ≥3 hemorrhagic events was 2.1% in CABOMETYX-treated patients and 1.6% in everolimus-treated patients. Fatal hemorrhages also occurred in the cabozantinib clinical program. Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.

Gastrointestinal (GI) Perforations and Fistulas: Fistulas were reported in 1.2% (including 0.6% anal fistula) of CABOMETYX-treated patients and 0% of everolimus-treated patients. GI perforations were reported in 0.9% of CABOMETYX-treated patients and 0.6% of everolimus-treated patients. Fatal perforations occurred in the cabozantinib clinical program. Monitor patients for symptoms of fistulas and perforations. Discontinue CABOMETYX in patients who experience a fistula that cannot be appropriately managed or a GI perforation.

Thrombotic Events: CABOMETYX treatment results in an increased incidence of thrombotic events. Venous thromboembolism was reported in 7.3% of CABOMETYX-treated patients and 2.5% of everolimus-treated patients. Pulmonary embolism occurred in 3.9% of CABOMETYX-treated patients and 0.3% of everolimus-treated patients. Events of arterial thromboembolism were reported in 0.9% of CABOMETYX-treated patients and 0.3% of everolimus-treated patients. Fatal thrombotic events occurred in the cabozantinib clinical program. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication.

Hypertension and Hypertensive Crisis: CABOMETYX treatment results in an increased incidence of treatment-emergent hypertension. Hypertension was reported in 37% (15% Grade ≥3) of CABOMETYX-treated patients and 7.1% (3.1% Grade ≥3) of everolimus-treated patients. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy. Discontinue CABOMETYX if there is evidence of hypertensive crisis or severe hypertension despite optimal medical management.

Diarrhea: Diarrhea occurred in 74% of patients treated with CABOMETYX and in 28% of patients treated with everolimus. Grade 3 diarrhea occurred in 11% of CABOMETYX-treated patients and in 2% of everolimus-treated patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard antidiarrheal treatments until improvement to Grade 1; resume CABOMETYX at a reduced dose. Dose modification due to diarrhea occurred in 26% of patients.

Palmar-Plantar Erythrodysesthesia Syndrome (PPES): Palmar-plantar erythrodysesthesia syndrome (PPES) occurred in 42% of patients treated with CABOMETYX and in 6% of patients treated with everolimus. Grade 3 PPES occurred in 8.2% of CABOMETYX-treated patients and in <1% of everolimus-treated patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPES or Grade 3 PPES until improvement to Grade 1; resume CABOMETYX at a reduced dose. Dose modification due to PPES occurred in 16% of patients.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the cabozantinib clinical program. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Embryo-fetal Toxicity: CABOMETYX can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose.

Adverse Reactions: The most commonly reported (≥25%) adverse reactions are: diarrhea, fatigue, nausea, decreased appetite, PPES, hypertension, vomiting, weight decreased, and constipation.

Drug Interactions: Strong CYP3A4 inhibitors and inducers: Reduce the dosage of CABOMETYX if concomitant use with strong CYP3A4 inhibitors cannot be avoided. Increase the dosage of CABOMETYX if concomitant use with strong CYP3A4 inducers cannot be avoided.

Lactation: Advise a lactating woman not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

Reproductive Potential: Contraception—Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose. **Infertility—**CABOMETYX may impair fertility in females and males of reproductive potential.

Hepatic Impairment: Reduce the CABOMETYX dose in patients with mild (Child-Pugh score [C-P] A) or moderate (C-P B) hepatic impairment. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

Please see full Prescribing Information at https://cabometyx.com/downloads/cabometyxuspi.pdf.

OPDIVO AND YERVOY INDICATIONS & IMPORTANT SAFETY INFORMATION

INDICATIONS

OPDIVO® (nivolumab) as a single agent is indicated for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be

contingent upon verification and description of clinical benefit in the confirmatory trials.

OPDIVO® (nivolumab) as a single agent is indicated for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma.

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of patients with unresectable or metastatic melanoma. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

OPDIVO® (nivolumab) is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.

OPDIVO® (nivolumab) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

OPDIVO® (nivolumab) is indicated for the treatment of patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin or after 3 or more lines of systemic therapy that includes autologous HSCT. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

OPDIVO® (nivolumab) is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

OPDIVO® (nivolumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma 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. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

YERVOY can result in severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.

Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests (LFTs), adrenocorticotropic hormone (ACTH) level, and thyroid function tests at baseline and before each dose.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

Immune-Mediated Pneumonitis

OPDIVO can cause immune-mediated pneumonitis. Fatal cases have been reported. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids for Grade 2 or more severe pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In patients receiving OPDIVO monotherapy, fatal cases of immune-mediated pneumonitis have occurred. Immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated pneumonitis occurred in 6% (25/407) of patients.

In Checkmate 205 and 039, pneumonitis, including interstitial lung disease, occurred in 6.0% (16/266) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in 4.9% (13/266) of patients receiving OPDIVO: Grade 3 (n=1) and Grade 2 (n=12).

Immune-Mediated Colitis

OPDIVO can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO monotherapy for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon re-initiation of OPDIVO. When administered with YERVOY, withhold OPDIVO and YERVOY for Grade 2 and permanently discontinue for Grade 3 or 4 or recurrent colitis. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated colitis occurred in 26% (107/407) of patients including three fatal cases.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe, life-threatening, or fatal (diarrhea of ≥7 stools above baseline, fever, ileus, peritoneal signs; Grade 3-5) immune-mediated enterocolitis occurred in 34 (7%) patients. Across all YERVOY-treated patients in that study (n=511), 5 (1%) developed intestinal perforation, 4 (0.8%) died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis.

Immune-Mediated Hepatitis

OPDIVO can cause immune-mediated hepatitis. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. Withhold for Grade 2 and permanently discontinue for Grade 3 or 4 immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated hepatitis occurred in 13% (51/407) of patients.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations >5x the ULN or total bilirubin elevations >3x the ULN; Grade 3-5) occurred in 8 (2%) patients, with fatal hepatic failure in 0.2% and hospitalization in 0.4%.

Immune-Mediated Neuropathies

In a separate Phase 3 study of YERVOY 3 mg/kg, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported.

Immune-Mediated Endocrinopathies

OPDIVO can cause immune-mediated hypophysitis, immune-mediated adrenal insufficiency, autoimmune thyroid disorders, and Type 1 diabetes mellitus. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency, thyroid function prior to and periodically during treatment, and hyperglycemia. Administer hormone replacement as clinically indicated and corticosteroids for Grade 2 or greater hypophysitis. Withhold for Grade 2 or 3 and permanently discontinue for Grade 4 hypophysitis. Administer corticosteroids for Grade 3 or 4 adrenal insufficiency. Withhold for Grade 2 and permanently discontinue for Grade 3 or 4 adrenal insufficiency. Administer hormone-replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 hyperglycemia.

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients. In patients receiving OPDIVO with YERVOY, hypophysitis occurred in 9% (36/407) of patients. In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994) of patients. In patients receiving OPDIVO with YERVOY, adrenal insufficiency occurred in 5% (21/407) of patients. In patients receiving OPDIVO monotherapy, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 9% (171/1994) of patients. Hyperthyroidism occurred in 2.7% (54/1994) of patients receiving OPDIVO monotherapy. In patients receiving OPDIVO with YERVOY, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (89/407) of patients. Hyperthyroidism occurred in 8% (34/407) of patients receiving OPDIVO with YERVOY. In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients. In patients receiving OPDIVO with YERVOY, diabetes occurred in 1.5% (6/407) of patients.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3-4) occurred in 9 (1.8%) patients. All 9 patients had hypopituitarism, and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. 6 of the 9 patients were hospitalized for severe endocrinopathies.

Immune-Mediated Nephritis and Renal Dysfunction

OPDIVO can cause immune-mediated nephritis. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grades 2-4 increased serum creatinine. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 increased serum creatinine. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients.

Immune-Mediated Skin Adverse Reactions and Dermatitis

OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. Administer corticosteroids for Grade 3 or 4 rash. Withhold for Grade 3 and permanently discontinue for Grade 4 rash. For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment; if confirmed, permanently discontinue. In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated rash occurred in 22.6% (92/407) of patients.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe, life-threatening, or fatal immune-mediated dermatitis (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3-5) occurred in 13 (2.5%) patients. 1 (0.2%) patient died as a result of toxic epidermal necrolysis. 1 additional patient required hospitalization for severe dermatitis.

Immune-Mediated Encephalitis

OPDIVO can cause immune-mediated encephalitis. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out other causes. If other etiologies are ruled out, administer corticosteroids and permanently discontinue OPDIVO for immune-mediated encephalitis. In patients receiving OPDIVO monotherapy, encephalitis occurred in 0.2% (3/1994) of patients. Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation of OPDIVO and administration of corticosteroids. Encephalitis occurred in one patient receiving OPDIVO with YERVOY (0.2%) after 1.7 months of exposure.

Other Immune-Mediated Adverse Reactions

Based on the severity of adverse reaction, permanently discontinue or withhold treatment, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO the following clinically significant immune-mediated adverse reactions occurred in <1.0% of patients receiving OPDIVO: uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), myositis, myocarditis, rhabdomyolysis, motor dysfunction, vasculitis, and myasthenic syndrome.

Infusion Reactions

OPDIVO can cause severe infusion reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. In patients receiving OPDIVO monotherapy, infusion-related reactions occurred in 6.4% (127/1994) of patients. In patients receiving OPDIVO with YERVOY, infusion-related reactions occurred in 2.5% (10/407) of patients.

Complications of Allogeneic HSCT after OPDIVO

Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO. Outcomes were evaluated in 17 patients from Checkmate 205 and 039, who underwent allogeneic HSCT after discontinuing OPDIVO (15 with reduced-intensity conditioning, 2 with myeloablative conditioning). Thirty-five percent (6/17) of patients died from complications of allogeneic HSCT after OPDIVO. Five deaths occurred in the setting of severe or refractory GVHD. Grade 3 or higher acute GVHD was reported in 29% (5/17) of patients. Hyperacute GVHD was reported in 20% (n=2) of patients. A

steroid-requiring febrile syndrome, without an identified infectious cause, was reported in 35% (n=6) of patients. Two cases of encephalitis were reported: Grade 3 (n=1) lymphocytic encephalitis without an identified infectious cause, and Grade 3 (n=1) suspected viral encephalitis. Hepatic veno-occlusive disease (VOD) occurred in one patient, who received reduced-intensity conditioned allogeneic HSCT and died of GVHD and multi-organ failure. Other cases of hepatic VOD after reduced-intensity conditioned allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. Cases of fatal hyperacute GVHD have also been reported. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT.

Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immune-mediated adverse reactions, and intervene promptly.

Embryo-Fetal Toxicity

Based on their mechanisms of action, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with an OPDIVO- or YERVOY-containing regimen and for at least 5 months after the last dose of OPDIVO.

Lactation

It is not known whether OPDIVO or YERVOY is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from an OPDIVO-containing regimen, advise women to discontinue breastfeeding during treatment. Advise women to discontinue nursing during treatment with YERVOY and for 3 months following the final dose.

Serious Adverse Reactions

In Checkmate 037, serious adverse reactions occurred in 41% of patients receiving OPDIVO (n=268). Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse drug reactions reported in 2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. In Checkmate 066, serious adverse reactions occurred in 36% of patients receiving OPDIVO (n=206). Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%). In Checkmate 067, serious adverse reactions (73% and 37%), adverse reactions leading to permanent discontinuation (43% and 14%) or to dosing delays (55% and 28%), and Grade 3 or 4 adverse reactions (72% and 44%) all occurred more frequently in the OPDIVO plus YERVOY arm (n=313) relative to the OPDIVO arm (n=313). The most frequent (≥10%) serious adverse reactions in the OPDIVO plus YERVOY arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.6%), colitis (10% and 1.6%), and pyrexia (10% and 0.6%). In Checkmate 017 and 057, serious adverse reactions occurred in 46% of patients receiving OPDIVO (n=418). The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO (n=406). The most frequent serious adverse reactions reported in ≥2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. In Checkmate 205 and 039, adverse reactions leading to discontinuation occurred in 7% and dose delays due to adverse reactions occurred in 34% of patients (n=266). Serious adverse reactions occurred in 26% of patients. The most frequent serious adverse reactions reported in ≥1% of patients were pneumonia, infusion-related reaction, pyrexia, colitis or diarrhea, pleural effusion, pneumonitis, and rash. Eleven patients died from causes other than disease progression: 3 from adverse reactions within 30 days of the last OPDIVO dose, 2 from infection 8 to 9 months after completing OPDIVO, and 6 from complications of allogeneic HSCT.

In Checkmate 141, serious adverse reactions occurred in 49% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infections, and sepsis. In Checkmate 275, serious adverse reactions occurred in 54% of patients receiving OPDIVO (n=270). The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration.

Common Adverse Reactions

In Checkmate 037, the most common adverse reaction (≥20%) reported with OPDIVO (n=268) was rash (21%). In Checkmate 066, the most common adverse reactions (≥20%) reported with OPDIVO (n=206) vs dacarbazine (n=205) were fatigue (49% vs 39%), musculoskeletal pain (32% vs 25%), rash (28% vs 12%), and pruritus (23% vs 12%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO plus YERVOY arm (n=313) were fatigue (59%), rash (53%), diarrhea (52%), nausea (40%), pyrexia (37%), vomiting (28%), and dyspnea (20%). The most common (≥20%) adverse reactions in the OPDIVO (n=313) arm were fatigue (53%), rash (40%), diarrhea (31%), and nausea (28%). In Checkmate 017 and 057, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=418) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite. In Checkmate 025, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=406) vs everolimus (n=397) were asthenic conditions (56% vs 57%), cough (34% vs 38%), nausea (28% vs 29%), rash (28% vs 36%), dyspnea (27% vs 31%), diarrhea (25% vs 32%), constipation (23% vs 18%), decreased appetite (23% vs 30%), back pain (21% vs 16%), and arthralgia (20% vs 14%). In Checkmate 205 and 039, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=266) were upper respiratory tract infection (44%), fatigue (39%), cough (36%), diarrhea (33%), pyrexia (29%), musculoskeletal pain (26%), rash (24%), nausea (20%) and pruritus (20%). In Checkmate 141, the most common adverse reactions (≥10%) in patients receiving OPDIVO were cough and dyspnea at a higher incidence than investigator's choice. In Checkmate 275, the most common adverse reactions (≥ 20%) reported in patients receiving OPDIVO (n=270) were fatigue (46%), musculoskeletal pain (30%), nausea (22%), and decreased appetite (22%).

In a separate Phase 3 study of YERVOY 3 mg/kg, the most common adverse reactions (≥5%) in patients who received YERVOY at 3 mg/kg were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%).

Checkmate Trials and Patient Populations

Checkmate 067 - advanced melanoma alone or in combination with YERVOY; **Checkmate 037 and 066** - advanced melanoma; **Checkmate 017** - squamous non-small cell lung cancer (NSCLC); **Checkmate 057** - non-squamous NSCLC; **Checkmate 025** - renal cell carcinoma; **Checkmate 205/039** - classical Hodgkin lymphoma; **Checkmate 141** – squamous cell carcinoma of the head and neck; **Checkmate 275** - urothelial carcinoma.

Please see U.S. Full Prescribing Information for OPDIVO and YERVOY, including **Boxed WARNING regarding immune-mediated adverse reactions** for YERVOY.

About Exelixis

Exelixis, Inc. (Nasdaq: EXEL) is a biopharmaceutical company committed to the discovery, development and commercialization of new medicines to improve care and outcomes for people with cancer. Since its founding in 1994, three products discovered at Exelixis have progressed through clinical development, received regulatory approval, and entered the marketplace. Two are derived from cabozantinib, an inhibitor of multiple tyrosine kinases including MET, AXL and VEGF receptors: CABOMETYX™ tablets approved for previously treated advanced kidney cancer and COMETRIQ® capsules approved for progressive, metastatic medullary thyroid cancer. The third product, COTELLIC®, is a formulation of cobimetinib, a selective inhibitor of MEK, is marketed under a collaboration with Genentech (a member of the Roche Group), and is approved as part of a combination regimen to treat advanced melanoma. Both cabozantinib and cobimetinib have shown potential in a variety of forms of cancer and are the subjects of broad clinical development programs. For more information about Exelixis, please visit www.exelixis.com or follow @ExelixisInc on Twitter.

About Exelixis' Collaboration with Ipsen

On February 29, 2016, Exelixis and Ipsen jointly announced an exclusive licensing agreement for the commercialization and further development of cabozantinib indications outside of the United States, Canada and Japan. On December 21, 2016, this agreement was amended to include commercialization rights for Ipsen in Canada. Ipsen, Exelixis' global partner for cabozantinib in all geographies outside the United States and Japan, has opted in to participate in the phase 3 pivotal trial in first-line RCC and will have access to the results to support potential future regulatory submissions. They may also participate in future studies at their choosing.

About Exelixis' Collaboration with Takeda

On January 30, 2017, Exelixis and Takeda jointly announced an exclusive licensing agreement for the commercialization and further development of cabozantinib indications in Japan. Takeda may also participate in this trial and future studies and will have access to the results to support potential future regulatory submissions in their territories, if they opt into their funding obligations under the respective collaboration agreements.

Exelixis holds the exclusive rights to develop and commercialize cabozantinib in the United States.

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube and Facebook.

About the Bristol-Myers Squibb and Ono Pharmaceutical Collaboration

In 2011, through a collaboration agreement with Ono Pharmaceutical Co., Bristol-Myers Squibb expanded its territorial rights to develop and commercialize *Opdivo* globally except in Japan, South Korea and Taiwan, where Ono had retained all rights to the compound at the time. On July 2014, Ono and Bristol-Myers Squibb further expanded the companies' strategic collaboration agreement to jointly develop and commercialize multiple immunotherapies – as single agents and combination regimens – for patients with cancer in Japan, South Korea and Taiwan.

Exelixis Forward-Looking Statement Disclaimer

This press release contains forward-looking statements, including, without limitation, statements related to: the potential of CABOMETYX in combination with Opdivo, with or without Yervoy to improve patient outcomes; Exelixis' commitment to the discovery, development and commercialization of new medicines with the potential to improve care and outcomes for people with cancer; the therapeutic potential and continued development of cabozantinib and cobimetinib; the potential for Ipsen's participation in future studies under the collaboration; and the potential for Takeda's participation in the phase 3 first-line RCC and in future studies under the collaboration and to have access to the results to support potential future regulatory submissions in their territories. Words such as "potential," "committed," "may," or other similar expressions identify forward-looking statements, but the absence of these words does not necessarily mean that a statement is not forward-looking. In addition, any statements that refer to expectations, projections or other characterizations of future events or circumstances are forward-looking statements. These forward-looking statements are based upon Exelixis' current plans, assumptions, beliefs, expectations, estimates and projections. Forward-looking statements involve risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in the forward-looking statements as a result of these risks and uncertainties, which include, without limitation: Exelixis' ability and the ability of its collaborators to conduct clinical trials of CABOMETYX in combination with Opdivo, with or without Yervoy, sufficient to achieve a positive completion; risks related to the potential failure of the combination of these compounds to demonstrate safety and efficacy in clinical testing; Exelixis' dependence on its collaboration partners, including, the level of their investment in the resources necessary to successfully develop CABOMETYX in combination with Opdivo, with or without Yervoy; the complexities and challenges associated with regulatory review and approval processes; the degree of market acceptance of CABOMETYX and the availability of coverage and reimbursement for CABOMETYX; the risk that unanticipated developments could adversely affect the commercialization of CABOMETYX; Exelixis' dependence on third-party vendors; Exelixis' ability to protect the company's intellectual property rights; market competition; changes in economic and business conditions, and other factors discussed under the caption "Risk Factors" in Exelixis' quarterly report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on May 1, 2017, and in Exelixis' future filings with the SEC. The forward-looking statements made in this press release speak only as of the date of this press release. Exelixis expressly disclaims any duty, obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in Exelixis' expectations with regard thereto or any change in events, conditions or circumstances on which any such statements are based.

Bristol-Myers Squibb Company Forward-Looking Statements

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and

involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among other risks, there can be no guarantee that cabozantinib in combination with Opdivo or the Opdivo+Yervoy regimen will be successfully developed or approved for any of the indications described in this release. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb's business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2016, in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

References

1. American Cancer Society. Cancer Facts & Figures 2017. Atlanta: American Cancer Society; 2017.
2. Jonasch E., Gao J., Rathmell W.K., Renal cell carcinoma. BMJ. 2014; 349:g4797.
3. Ko, J. J., Choueiri, T.K., et al. First-, second- third-line therapy for mRCC: benchmarks for trial design from the IMDC. British Journal of Cancer. 2014; 110: 1917-1922.
4. Decision Resources Report: Renal Cell Carcinoma. October 2014 (internal data on file).
5. Harshman, L.C. and Choueiri, T.K., Targeting the hepatocyte growth factor/c-Met signaling pathway in renal cell carcinoma. Cancer J. 2013; 19(4):316-23.
6. Rankin et al., Direct regulation of GAS6/AXL signaling by HIF promotes renal metastasis through SRC and MET. Proc Natl Acad Sci U S A. 2014; 111(37):13373-8.
7. Zhou L, Liu X-D, Sun M, et al. Targeting MET and AXL overcomes resistance to sunitinib therapy in renal cell carcinoma. Oncogene. 2016;35(21):2687–2697.
8. Koochekpour et al.,The von Hippel-Lindau tumor suppressor gene inhibits hepatocyte growth factor/scatter factor-induced invasion and branching morphogenesis in renal carcinoma cells. Mol Cell Biol. 1999; 19(9):5902–5912.
9. Takahashi A, Sasaki H, Kim SJ, et al. Markedly increased amounts of messenger RNAs for vascular endothelial growth factor and placenta growth factor in renal cell carcinoma associated with angiogenesis. Cancer Res. 1994;54:4233-4237.
10. Nakagawa M, Emoto A, Hanada T, Nasu N, Nomura Y. Tubulogenesis by microvascular endothelial cells is mediated by vascular endothelial growth factor (VEGF) in renal cell carcinoma. Br J Urol. 1997;79:681-687.

View source version on businesswire.com: http://www.businesswire.com/news/home/20170710005351/en/

Source: Exelixis, Inc. and Bristol-Myers Squibb Company

Exelixis:
Investors:
Susan Hubbard, 650-837-8194
EVP, Public Affairs & Investor Relations
shubbard@exelixis.com
or
Media:
Lindsay Treadway, 650-837-7522
Director, Public Affairs & Advocacy Relations
ltreadway@exelixis.com
or
Bristol-Myers Squibb:
Media:
Ken Dominski, 609-252-5251
ken.dominski@bms.com
or
Lisa McCormick Lavery, 609-252-7602
lisa.mccormicklavery@bms.com
or
Investors:
Tim Power, 609-252-7509
timothy.power@bms.com
or
Bill Szablewski, 609-252-5894
william.szablewski@bms.com