The Opdivo + low-dose Yervoy combination is the first and only treatment to show significantly superior overall survival versus sunitinib in intermediate- and poor-risk advanced renal cell carcinoma, including a survival benefit regardless of PD-L1 expression.1,2

In the CheckMate -214 trial, which used dosing optimized for advanced renal cell carcinoma, Opdivo + Yervoy was associated with fewer overall 3 or 4 adverse reactions than sunitinib.1,2

PRINCETON, N.J. – BUSINESS WIRE – Bristol-Myers Squibb Company (NYSE: BMY) today announced that Opdivo (nivolumab) 3 mg/kg plus Yervoy (ipilimumab) 1 mg/kg (injections for intravenous use) was approved by the U.S. Food and Drug Administration (FDA) as the first Immuno-Oncology combination therapy for previously untreated patients with intermediate- and poor-risk advanced renal cell carcinoma (RCC).1,3 In the Phase 3 CheckMate -214 clinical trial, the Opdivo + Yervoy combination demonstrated a significant and unprecedented increase in overall survival (OS) in this patient population compared with a current standard of care, sunitinib. An OS benefit was observed regardless of PD-L1 expression level.1,2 Opdivo + Yervoy also delivered durable response, with a higher objective response rate (ORR) compared to sunitinib.1,2 Patients in the CheckMate -214 trial received four cycles of the Opdivo + low-dose Yervoy combination, followed by Opdivo maintenance therapy.1,2 In the combination arm of the trial, 79% of patients received all four doses of Opdivo + Yervoy and went on to the Opdivo monotherapy phase. Flexible dosing options are available during the Opdivo maintenance phase (480 mg infused every four weeks or 240 mg infused every two weeks).

Our goal is to provide cancer patients with medicines that have the potential to extend their lives. As the first treatment option to increase overall survival for subgroups of patients with advanced RCC compared to sunitinib, the Opdivo plus low-dose Yervoy combination helps deliver on that promise,” said Johanna Merckier, head, U.S. Commercial, Bristol-Myers Squibb. “This approval demonstrates our commitment to bringing Immuno-Oncology treatments that may improve outcomes to a broader range of RCC patients.”

Opdivo is associated with the following Warnings and Precautions: Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin adverse reactions, endophthalmitis, other adverse reactions, infusion reactions; and embryofetal toxicity. Please see the Important Safety Information section below, including Boxed WARNING for Yervoy regarding immune-mediated adverse reactions.1,2

Results from the CheckMate -214 trial in patients with previously untreated intermediate- and poor-risk advanced RCC include:

- **Overall Survival:** Opdivo + Yervoy reduced the risk of death by 37% versus sunitinib (hazard ratio [HR] 0.63; 99.8% confidence interval [CI]: 0.44 to 0.89; p<0.0001).1,2 The median OS was not yet reached for Opdivo + Yervoy (95% CI: 28.2 to not estimable [NE]) and was 25.9 months for sunitinib (95% CI: 22.1 to NE).1,2
- **Objective Response Rate:** Opdivo + Yervoy was associated with a 41.6% ORR (95% CI: 36.9 to 46.5; p<0.0001; n=177/425) versus 26.5% for sunitinib (95% CI: 22.4 to 31.0; n=112/422).1,2
- **Complete and Partial Response Rates:** The complete response rate (CR) was 9.4% for Opdivo + Yervoy (n=46/425) and 1.2% for sunitinib (n=5/422), and the partial response (PR) rate was 32.2% for Opdivo + Yervoy (n=137/425) and 25.4% for sunitinib (n=107/422).1,2
- **Duration of Response:** Among patients who responded, median duration of response (durable) for Opdivo + Yervoy was not yet reached (95% CI: 21.8 to NE), compared to 18.2 months for sunitinib (95% CI: 14.8 to NE).1,2
- **Progression-Free Survival:** Progression-free survival (PFS) was 11.6 months for the Opdivo + Yervoy combination, compared to 8.4 months for sunitinib (HR 0.82; 99.1% CI: 0.64 to 1.05; p=not significant), which did not reach statistical significance.1,2

Among those with advanced RCC, 75% to 80% of patients have one or more risk factors and are considered intermediate- and poor-risk patients according to International Metastatic RCC Database Consortium criteria.3,4 These patients historically have had poor prognosis, and although there have been a number of treatment advances over the past decade, additional options to improve overall survival are still needed.2,5,6 Currently, only 36% of patients with advanced RCC survive beyond one year, and only 8% will live past five years.3,7,8 “Physicians treating advanced RCC have had few options to help achieve the goal of improved survival,” said Robert J. Motzer, M.D., medical oncologist, Jack and Dorothy Byrne chair in clinical oncology, Memorial Sloan Kettering Cancer Center. “Data from the CheckMate -214 trial demonstrated superior overall survival with Opdivo + Yervoy, showing the potential for the combination to become a new standard of care for patients with intermediate- and poor-risk advanced RCC. What’s more, the combination resulted in fewer overall Grade 3 and 4 adverse reactions compared to sunitinib. Because of these encouraging results, we now have a new treatment option for newly diagnosed advanced RCC patients across PD-L1 expression levels.”

In CheckMate -214, the combination was associated with fewer overall Grade 3 or 4 adverse events than sunitinib (65% versus 76%),1,2 Treatment discontinuation due to adverse events occurred in 31% of patients in the Opdivo + Yervoy arm, compared to 21% in the sunitinib arm. Forty-four percent (54%) of patients receiving Opdivo + Yervoy and 43% of patients receiving sunitinib had a dose delay for an adverse reaction. In the sunitinib group, 53% of patients required a dose reduction, which was not permitted for patients treated with the Opdivo + Yervoy combination. Serious adverse reactions occurred in 59% of patients receiving Opdivo + Yervoy and in 43% of patients receiving sunitinib.1,2

“Kidney cancer is the deadliest of all urological cancers, and too many patients are faced with this grim diagnosis,” said Dena Battle, osteologist, Jack and Dorothy Byrne chair in clinical oncology, Memorial Sloan Kettering Cancer Center. “Patients with metastatic renal cell carcinoma (RCC) are living longer, but they have a long journey ahead of them. The number of treatment options is growing, and we are excited by the results of this trial.”

**Approval Based on CheckMate -214 Trial: Demonstrating Superior Overall Survival and Objective Response Rate vs. Sunitinib**

CheckMate -214 is a Phase 3, randomized, open-label study evaluating the combination of Opdivo + Yervoy versus sunitinib in patients with previously untreated advanced RCC. In the intermediate- and poor-risk study population, 422 patients received Opdivo 3 mg/kg plus Yervoy 1 mg/kg every three weeks for four doses, followed by Opdivo 3 mg/kg every two weeks, and 422 patients received sunitinib 50 mg once daily for four weeks, followed by two weeks off every cycle.1,2 The recommended dosing for the Opdivo + Yervoy combination is Opdivo 3 mg/kg followed by Yervoy 1 mg/kg each infused intravenously over 30 minutes. After completing four doses of the combination, Opdivo should be administered intravenously 240 mg every two weeks and sunitinib every four weeks for up to 36 months, or until disease progression or unacceptable toxicity.1,2

The primary efficacy outcome measures of the trial were OS, ORR (CR+PR) and PFS as determined by an independent radiographic review committee (IRC) in intermediate- and poor-risk patients. Patients were included regardless of their PD-L1 status.1,2 Data from CheckMate -214 were presented at the European Society for Medical Oncology Congress in September 2017 and the Society for Immunotherapy of Cancer Annual Meeting in November 2017 and were published in the *New England Journal of Medicine* in March 2018.2,9,10

**Select Safety Profile for the CheckMate -214 Trial**

The most frequent serious adverse reactions reported in at least 2% of patients receiving Opdivo + Yervoy were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, adult onset Still’s disease, and pneumonitis. The most common adverse reactions (≥20%) reported in patients receiving Opdivo + Yervoy were fatigue (58%), rash (39%), diarrhea (38%), musculoskeletal pain (37%), pruritus (33%), nausea (30%), cough (28%), pyrexia (25%), arthralgia (23%), decreased appetite (21%), dyspnea (20%) and vomiting (20%).1,2

**About Renal Cell Carcinoma**

Renal cell carcinoma is the most common type of kidney cancer in adults, accounting for nearly 15,000 deaths in the United States each year.12,13 Clear-cell RCC is the most prevalent type of RCC and constitutes 70% to 80% of all patients.14 Renal cell carcinoma is approximately twice as common in men as in women.15 In the United States, the five-year survival rate for those diagnosed with metastatic, or advanced, kidney cancer is 8%.1,7

**INDICATION**

Opdivo® (nivolumab), in combination with Yervoy® (ipilimumab), is indicated for the treatment of patients with intermediate or poor-risk, previously untreated advanced renal cell carcinoma (RCC).

Opdivo (10 mg/mL) and Yervoy (5 mg/mL) are injections for intravenous use.

**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
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 and our commitment to advancing oncology, visit www.BristolMyersSquibb.com.

Immuno-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. Permanently discontinue for Grade 3 or more and withhold until resolution for Grade 2. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 4.9% (24/474) of patients.

Immuno-Medicated Coils

OPDIVO can cause immune-mediated coiled. Monitor patients for signs of and symptoms of coiled. Administer corticosteroids for Grade 2 (more than 5 days duration), 3, or 4 coiled. Withhold OPDIVO monotherapy for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent coiled upon re-initiation of OPDIVO. When administered with YERVOY, withhold OPDIVO and YERVOY for 2 and permanently discontinue for Grade 2 or 3 or recurrent coiled. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated coiled occurred in 10% (52/547) of patients.

Immuno-Medicated 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.

OPDIVO for Grade 2 and permanently discontinue for Grade 3 or 4 in patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hepatitis occurred in 7% (38/547) of patients.

Immuno-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 hypoglycemia. Administer hormone replacement as clinically indicated and continued for 1 year after discontinuation of OPDIVO or greater hypophysitis. Withhold for Grade 2 or 3 and permanently discontinue for Grade 4 or adrenal insufficiency. Administer hormone-replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. Withhold for Grade 3 and permanently discontinue for Grade 4 hyperglycemia.

In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, hypophysitis occurred in 4.6% (25/547) of patients. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, adrenal insufficiency occurred in 7% (41/547) of patients. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, thyrotoxicosis resulted in hyperthyroidism occurred in 22% (119/547) of patients. Hypothyroidism occurred in 12% (66/547) of patients receiving this dose of OPDIVO with YERVOY. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, diabetes occurred in 2.7% (15/547) of patients.

Immuno-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 increase serum creatinine.

Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 increase serum creatinine. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated nephritis and renal dysfunction occurred in 4.6% (25/547) of patients.

Immuno-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. Permanently discontinue for Grade 4 rash. For signs or symptoms of SJS or TEN, withhold OPDIVO and refer for specialized care for assessment and treatment. If confirmed, permanently discontinue. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated rash occurred in 16.6% (91/547) of patients.

Immuno-Medicated 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 for Grade 2 or more. Encephalitis occurs in one patient receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg (0.2%) after approximately 4 months of exposure.

Other Immuno-Mediated Adverse Reactions

Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO, OPDIVO monotherapy or in combination with YERVOY, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <10% of patients receiving OPDIVO: myasthenia gravis, rheumatoid arthritis, myositis, uveitis, iritis, pancreatitis, facial and abductor nerve paresis, dermelymphoma, polyangiitis rheumatica, autoimmune neurophagia, Guillain-Barré syndrome, hyperthyroidism, antiphospholipid syndrome, ganciclovir, daudennol, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.

If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving OPDIVO and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Infusion Reactions

OPDIVO can cause severe infusion reactions, which have been reported in <1% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion reactions. Interrupt or slow the rate of infusion for Grade 2 reactions. In a separate study in which patients receiving OPDIVO 3 mg/kg in which patients received OPDIVO monotherapy as a 60-minute infusion, infusion related reactions occurred in 2.2% (83/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 5.1% (28/547) of patients.

Embryo-Fetal Toxicity

Based on their mechanisms of action, and 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 breastfeeding during treatment with YERVOY and for 3 months following the final dose.

Serious Adverse Reactions

In CheckMate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY in 43% of patients receiving sunitinib. The most frequent serious adverse reactions reported in at least 2% of patients were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis; in patients treated with sunitinib, they were pneumonia, pleural effusion, and dyspnea.

Common Adverse Reactions

In CheckMate 214, the most common adverse reactions reported in at least 20% of patients treated with OPDIVO plus YERVOY (n=547) vs sunitinib (n=355) were fatigue (58% vs 69%), rash (39% vs 25%), diarrhea (38% vs 58%), musculoskeletal pain (37% vs 48%), pruritus (33% vs 11%), nausea (30% vs 43%), cough (28% vs 25%), pyrexia (25% vs 17%), arthralgia (23% vs 16%), and decreased appetite (21% vs 29%).

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

Bristol-Myers Squibb & Immuno-Oncology: Advancing Oncology Research

At Bristol-Myers Squibb, patients are at the center of everything we do. Our vision for the future of cancer care is focused on researching and developing transformational Immuno-Oncology (I-O) medicines for hard-to-treat cancers that could potentially improve outcomes for these patients.

We are advancing the scientific understanding of I-O through our extensive portfolio of investigational compounds and approved agents. Our differentiated clinical development program is studying broad patient populations across more than 50 types of cancers with 24 clinical-stage molecules designed to target different immune system pathways. Our deep expertise and innovative clinical trial design capabilities are allowing us to advance these I-O medicines across multiple tumors and potentially deliver the next wave of therapies with a sense of urgency.

Through our leading translational capabilities, we are pioneering immune biology research and identifying a number of potentially predictive biomarkers, including PD-L1, TMB, MSI-H/MMR- deficient and alterations in other genes. Patients will receive therapy based on these biomarkers.

We understand that making the promise of I-O a reality for the many patients who may benefit from these therapies requires not only innovation on our part but also close collaboration with leading experts in the field. Our partnerships with academia, government, advocacy and biotech companies support our collective effort of providing new treatment options to advance the standards of clinical practice.

About Bristol-Myers Squibb's Patient Access Support

Bristol-Myers Squibb remains committed to providing assistance so that cancer patients who need our medicines can access them and expedite time to therapy.

BMS Access Support®, the Bristol-Myers Squibb patient access and reimbursement program, is designed to help appropriate patients initiate and maintain access to BMS medicines during their treatment journey. BMS Access Support offers benefit investigation, prior authorization assistance and co-pay assistance for eligible, commercially insured patients. More information about our access and reimbursement support can be obtained by calling BMS Access Support® at 1-866-361-0448 or by visiting www.bmsaccesssupport.com.

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 23, 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.

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

www.bmsaccesssupport.com
# FDA approves BMY combination therapy as first-line treatment for certain patients with advanced Kidney Cancer

**Bristol-Myers Squibb Forward-Looking Statement**

The 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. 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, 2017 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**

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**Ticker Slug:**

Ticker: BMY
Exchange: NYSE

#FDA approves BMY combination therapy as first-line treatment for certain patients with advanced Kidney Cancer