U.S. Food and Drug Administration Approves Opdivo® (nivolumab) + Yervoy® (ipilimumab) Combination as First-Line Treatment for Patients with Intermediate- and Poor-Risk Advanced Renal Cell Carcinoma

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Terms:

- **CheckMate**: A global, multi-center, open-label, randomized, phase III clinical trial to evaluate the efficacy and safety of Opdivo and Ipilimumab as first-line therapy for advanced renal cell carcinoma.
- **PD-L1**: Programmed death-ligand 1.
- **ORR**: Objective Response Rate.
- **CI**: Confidence Interval.
- **HR**: Hazard Ratio.
- **CI**: Confidence Interval.

**Dateline City:** PRINCETON, N.J.

**BMS Newsroom**

**Background:**

Physicians treating advanced RCC have had few options to help patients achieve improved survival and overall survival (OS) compared to the current standard of care, sunitinib. An estimated 13,000 patients are diagnosed with advanced RCC each year in the U.S. and approximately 7,000 die from the disease. The most common risk factors for advanced RCC are age over 70 years, smoking, and a family history of the disease. In the U.S., only 8% will live beyond 5 years. Among those with advanced RCC, 75% to 80% have one or more risk factors and are considered intermediate- and poor-risk patients according to International Metastatic Renal Cell Carcinoma Database Consortium criteria. These patients historically had a poor prognosis, and although there have been a number of treatment advances over the past decade, overall survival improvement remains a significant unmet need.

**Objective:**

The primary efficacy outcome measures of the trial were OS, ORR, and PFS as determined by an independent radiographic review committee (IRRC) in intermediate- and poor-risk patients. Patients were included regardless of their PD-L1 status. 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.

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

- **W&Ps:** The most common (≥2%) adverse reactions are listed below, including those that are related to immune-mediated adverse reactions.
- **ORR:** The median OS in the Opdivo + Yervoy group was 19.6 months versus 11.6 months for the sunitinib group (HR 0.63; 99.8% CI: 0.44 to 0.89; p < 0.0001).
- **PFS:** Progression-free survival (PFS) was significantly prolonged in the Opdivo + Yervoy group compared to sunitinib (95% CI: 0.44 to 0.89; p < 0.0001).
- **Dose:** The recommended dose for the combination is 3 mg/kg of Opdivo (nivolumab) 2 mg/kg (injections for 4 doses) followed by 3 mg/kg every 2 weeks, and 1 mg/kg of Yervoy (ipilimumab) 10 mg/kg (injections for 4 doses) followed by 10 mg/kg every 6 weeks.

**Key Findings:**

- **ORR:** The ORR for the Opdivo + Yervoy combination was 41.6% (95% CI: 36.9 to 46.5; p < 0.0001) versus 26.5% for sunitinib (95% CI: 22.4 to 31.0; p < 0.0001). The median duration of response was 13.6 months for the Opdivo + Yervoy combination compared to 8.4 months for sunitinib (HR 0.64; 95% CI: 0.46 to 0.84; p = 0.0034).
- **OS:** The median OS in the Opdivo + Yervoy group was 19.6 months versus 11.6 months for the sunitinib group (HR 0.63; 99.8% CI: 0.44 to 0.89; p < 0.0001).
- **PFS:** Progression-free survival (PFS) was significantly prolonged in the Opdivo + Yervoy group compared to sunitinib (95% CI: 0.44 to 0.89; p < 0.0001).

**Conclusion:**

"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 John V. Thayer, Jr., M.D., Ph.D., and Beatrice T. Mann, M.D., F.A.C.P., president, KCCure. "Today's approval of Opdivo + Yervoy for the treatment of intermediate- and poor-risk advanced RCC represents hope for a longer life."
The most frequent serious adverse reactions reported in at least 2% of patients receiving Opdivo + Yervoy were diarrhea, pyrexia, pruritus, rash, and hypothyroidism. The most common adverse reactions reported in patients receiving Opdivo were fatigue (48%), constipation (30%), pyrexia (25%), nausea (20%), hypertension (15%), pruritus (13%), rash (10%), hyperglycemia (9%), diarrhea (7%), and decreased appetite (6%). The most common adverse reactions reported in patients receiving Yervoy were fatigue (45%), pruritus (39%), nausea (30%), rash (28%), decreased appetite (25%), hypertension (24%), and anorexia (21%).

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.11,12 Clear cell RCC is the most prevalent type of RCC and constitutes 70% to 80% of all patients.11,12 Renal cell carcinoma is approximately twice as common in men as women.22 In the United States, the five-year survival rate for those diagnosed with metastatic, or advanced, kidney cancer is 8%.1,2

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/kg) and Yervoy (5 mg/kg) 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, endocrinopathies, in some cases requiring treatment with steroids or other immunosuppressants, and death. If severe, immune-mediated reactions may be fatal. Hypophysitis can cause other immune-mediated endocrinopathies such as endocrine insufficiency and hypophysitis. Advise women to discontinue breastfeeding during treatment with Opdivo or Yervoy because 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 3 months following the final dose of Opdivo or Yervoy.

Assess patients for signs and symptoms of enterocolitis, dermatitis, endocrinopathies, and endomyocarditis and evaluate clinic chemistry 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 and symptoms of pneumonitis, administer corticosteroids for Grade 2 or more severe pneumonitis, permanently discontinue for Grade 3 or 4 pneumonitis. In patients receiving Opdivo 3 mg/kg with Yervoy 1 mg/kg, immune-mediated pneumonitis occurred in 6.4% (24/369) of patients.

Immune-Mediated Colitis
Opdivo can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or more than 5 days duration, 1, 4, or 6 patients. Without Opdivo monotherapy for Grade 2 or 3 and permanently discontinue for Grade 4 or neutrophil count <0.5 × 10^9/L upon initiation of Opdivo. If administered with Yervoy, withhold Opdivo and Yervoy for Grade 2 and permanently discontinue for Grade 3 or 4 or neutrophil count <0.5 × 10^9/L. When administered with Opdivo 3 mg/kg with Yervoy 1 mg/kg, immune-mediated colitis occurred in 12% (66/547) of patients.

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. Without Opdivo for Grade 2 and permanently discontinue Opdivo 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.

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, sign and symptoms of adrenal insufficiency, thyroid dysfunction prior to and periodically during treatment, and hyperglycemia. Administer hormone replacement as clinically indicated and corticosteroids for Grade 2 or greater hypophysitis. Without Grade 2 or 3 and permanently discontinue for Grade 4 hypophysitis. Administer corticosteroids for Grade 2 or adrenal insufficiency. Without Grade 2 or 3 and permanently discontinue for Grade 4 adrenal insufficiency. Without corticosteroids for Grade 2 and permanently discontinue for Grade 4 hypophysitis.

In patients receiving Opdivo 3 mg/kg with Yervoy 1 mg/kg, hypophysitis occurred in 4.4% (24/547) of patients. In patients receiving Opdivo 3 mg/kg with Yervoy 1 mg/kg, adrenal insufficiency occurred in 3% (15/481) of patients. In patients receiving Opdivo 3 mg/kg with Yervoy 1 mg/kg, hypophysitis or myelitis resulting in hypophysitis occurred in 12% (66/547) of patients. Hypophysitis occurred in 0.0% (3/547) of patients receiving this dose of Opdivo with Yervoy. In patients receiving Opdivo 3 mg/kg with Yervoy 1 mg/kg, diabetes occurred in 1.7% (15/547) of patients.

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 Grade 2 or greater transaminase elevations. Without Opdivo for Grade 2 and permanently discontinue Opdivo for Grade 3 or 4. In patients receiving Opdivo 3 mg/kg with Yervoy 1 mg/kg, immune-mediated nephritis and renal dysfunction occurred in 0.5% (2/368) 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), in some cases with fatal outcome. Monitor patients for signs and symptoms of rash or TEN. Without corticosteroids for Grade 3 and permanently discontinue for Grade 4 rash. For symptoms of SJS or TEN, without Opdivo and refer the patient for special care and assessment of treatment if confirmed, permanently discontinue. In patients receiving Opdivo 3 mg/kg with Yervoy 1 mg/kg, immune-mediated rash occurred in 16.6% (93/547) of patients.

Immune-Mediated Esophagitis
Opdivo can cause immune-mediated esophagitis. Evaluation of patients with neuropsychiatric symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Without corticosteroids for Grade 3 or 4 or recurrent symptoms and evaluate to rule out other causes for the symptoms, effectively treat esophagitis without corticosteroids. In patients receiving Opdivo 3 mg/kg with Yervoy 1 mg/kg, immune-mediated esophagitis occurred in 1.5% (8/547) of patients.

Other Immune-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 monotherapy or in combination with Yervoy, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving Opdivo: myocarditis, mabbledyphiosis, hepatitis, uveitis, iritis, pancreatitis, facial and abducens nerve palsy, myositis, rash, pancytopenia, myopathy, pericarditis, and myocarditis.

If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada (VKH) syndrome, which has been observed in patients receiving Opdivo and may require administration of high-dose corticosteroids to control the acute inflammation. Prior to and at periodic intervals during treatment, obtain serum electrolyte levels and liver function tests (LFTs), adrenocorticotropic hormone (ACTH) level, and thyroid function tests at baseline and before each dose. Permanently discontinue for Grade 3 or 4 hyperglycemia.

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 a separate study in which patients received Opdivo monotherapy at a 60-minute infusion or 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/368) of patients, respectively. Additionally, 0.6% (3/547) and 1.4% (5/368) of patients reported Grade 3 or 4 infusion reactions, respectively, experienced adverse reactions within 24 hours of infusion that led to dose delay, discontinuation, or death, respectively. In patients receiving Opdivo 3 mg/kg with Yervoy 1 mg/kg, infusion-related reactions occurred in 2.3% (66/2862) of patients.

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 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 and in 33% of patients receiving sunitinib. The most frequent serious adverse reactions reported in both Opdivo plus Yervoy and sunitinib arms were fatigue (28% vs 43%), dyspnea (23% vs 19%), cough (26% vs 19%), nausea (19% vs 33%), pyrexia (17% vs 14%), diarrhea (17% vs 14%), pruritus (17% vs 12%), vomiting (14% vs 7%), anorexia (12% vs 14%), and decreased appetite (13% vs 12%).

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=369) were fatigue (56% vs 69%), rash (28% vs 25%), diarrhea (28% vs 58%), mucositis/stomatitis (31% vs 45%), pruritus (33% vs 31%), nausea (36% vs 43%), cough (29% vs 19%), pyrexia (23% vs 37%), arthralgia (0.2% vs 18%), and decreased appetite (21% vs 29%).
Bristol-Myers Squibb & Immuno-Oncology: Advancing Oncology Research

All Bristol-Myers Squibb, patients are at the center of everything we do. Our vision for the future of cancer care is focused on research and developing transformative 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 programs 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 designs position us as a leader in I-O. Our research, development and commercialization of I-O agents is focused on identifying a number of potentially predictive biomarkers, including PD-L1, TMB, MHC-HELBR and LAG-3, advancing the possibility of precision medicine for more patients with cancer.

We understand 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 commitment to excellence, innovation and our partnerships support our promise to deliver innovative medicines that help patients prevail over serious diseases.

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, Facebook and YouTube.

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References


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