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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**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.**

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.

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). In the Phase 3 CheckMate -214 trial, the Opdivo + Yervoy combination demonstrated a significant and unprecedented increase in overall survival (OS) in this patient population compared to the current standard of care, sunitinib. An OS benefit was observed regardless of PD-L1 expression level. Opdivo + Yervoy also delivered durable responses, with a higher objective response rate (ORR) compared to sunitinib. Patients in the CheckMate -214 trial received four cycles of the Opdivo + low-dose Yervoy combination, followed by Opdivo maintenance therapy. 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 Johnathan Merck, 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 patients." Opdivo is associated with the following Warnings and Precautions: Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin reactions, endarteritis, other adverse reactions, infusion reactions; and embryo-fetal toxicity. Please see the Important Safety Information section below, including Boxed WARNING for Yervoy regarding immune-mediated adverse reactions.

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). 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).2,3
- **Objective Response Rate:** Opdivo + Yervoy was associated with a 41.6% ORR (95% CI: 36.9 to 46.5; p < 0.0001; median duration of response [DOR]: 177/425 vs. 26.5% for sunitinib (95% CI: 22.4 to 31.0; p = 0.112/422).1,2
- **Complete and Partial Response Rates:** The complete response rate (CR) was 9.4% for Opdivo + Yervoy (n=40/425) 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 (durability) 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% have one or more risk factors and are considered intermediate- and poor-risk patients according to International Metastatic RCC Database Consortium criteria. These patients historically had a poor prognosis; however, for the first time, data from the CheckMate -214 trial demonstrate that there is a treatment option that provides superior overall survival for subgroups of patients with advanced RCC based on PD-L1 expression. In the CheckMate -214 trial, patients were stratified for PD-L1 expression (intensity) of tumor-infiltrating lymphocytes.

In CheckMate -214, the combination was associated with fewer overall Grade 3 or 4 adverse events than sunitinib (65% versus 76%).2,3 Treatment discontinuation due to adverse events occurred in 31% of patients in the Opdivo + Yervoy arm, compared to 21% in the sunitinib arm. Fifty-four percent (54%) of patients receiving Opdivo + Yervoy and 43% of patients receiving sunitinib had a dose delay for an adverse event. Among the PD-L1 positive 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, president, KCCure. "Today's approval of Opdivo + Yervoy for advanced RCC has the potential to transform the first-line treatment landscape for kidney cancer. But for patients, it is more than just a new therapy option - it represents hope for a longer life." 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, 425 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. 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 on the same day for four doses. After completing four doses of the combination, Opdivo should be administered intravenously 240 mg every two weeks on an 80 mg every four weeks for 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. 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 2018.3,10,11 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, acute kidney injury, dyspnea, arterial thrombosis, and cramps. 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.10 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 areenterocolitis, 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 symptoms 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 greater pneumonitis.

Permanent discontinuation for Grade 3 or 4, and withhold until resolution for Grade 2. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 4.4% (24/547) of patients.

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 recurrent colitis. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated colitis occurred in 10% (52/547) 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. Withhold 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.

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 continue corticosteroids for Grade 2 or greater hypophysitis. Withhold for Grade 2 or 3 and permanently discontinue for Grade 4 or adrenal insufficiency. 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 a medical management for control of hyperthyroidism. Withhold OPDIVO 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 whom parenteral or oral corticosteroids were administered. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, 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.

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 3 mg/kg with YERVOY 1 mg/kg, immune-mediated nephritis and renal dysfunction occurred in 4.6% (25/547) 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 or TEN. Discontinue OPDIVO upon discontinuation of Grade 4 rash. For any signs or symptoms of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment; 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.

Immune-Mediated Enccephalitis

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. Encephalitis occurred in one patient receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg (0.2%) after approximately 4 months of exposure.

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: myasthenia gravis, salivary gland disorders, uveitis, and iritis. OPDIVO is not recommended for patients with active uveitis or iritis.

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. Initiate or slow the rate of infusion and withhold OPDIVO in a separate clinical trial in which patients receiving OPDIVO 3 mg/kg with YERVOY monotherapy as a 60-minute infusion, infusion-related reactions occurred in 2.2% (83/3682) 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% (284/547) of patients.

Embryo-Fetal Toxicity

Based on their mechanisms of action, action and YERVOY can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the 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 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 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=353) were fatigue (58% vs 69%), rash (39% vs 25%), diarrhea (38% vs 58%), musculoskeletal pain (37% vs 46%), 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 & Immune-Immunology: 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 designs enable us to advance I-O medicines with precision and speed. Our clinical trial center of excellence is dedicated to developing and delivering multiple I-O medicines – 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
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 and 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


Language:
English

Contact:
Bristol-Myers Squibb Company
Media Inquiries:
Laurel Sacks, 609-302-5456
laurel.sacks@bms.com
or
Tim Power, 609-252-7509
timothy.power@bms.com
or
Bill Szablewski, 609-252-5894
william.szablewski@bms.com

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