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

Release Date: Monday, April 16, 2018 12:52 pm EDT

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PRINCETON, N.J. —

The Opdivo® (nivolumab) + Yervoy® (ipilimumab) 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.1-5

Treatment with Opdivo® + Yervoy delivered higher objective response rates, including more complete responses, than sunitinib.1-3

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

PRINCETON, N.J. — BUSINESS WIRE — Bristol-Myers Squibb Company (NYSE: BMY) today announced that Opdivo (nivolumab), a T-cell immune checkpoint inhibitor medicine for intravenous use, was approved by the U.S. Food and Drug Administration (FDA) as the first Immuno-Oncology combination therapy for previously untreated 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 to a current standard of care, sunitinib. An OS benefit was observed regardless of PD-L1 expression level.1,3,5

Opdivo® + Yervoy also delivered durable responses, with a higher objective response rate (ORR) compared to sunitinib.1-3 Patients in the CheckMate -214 trial received four cycles of the Opdivo® + low-dose Yervoy combination, followed by Opdivo maintenance therapy.1-3 In the combination arm, 39% of patients received all four doses of Opdivo® + Yervoy and went on to the Opdivo monotherapy phase.1-3 Flexible dosing options are available during the Opdivo maintenance phase with 88 mg infused every four weeks or 240 mg infused every two weeks.

“An urgent 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 Robert J. Motzer, M.D., medical oncologist, Jack and Dorothy Byrne chair in clinical oncology, Memorial Sloan Kettering Cancer Center, and principal investigator of the CheckMate -214 trial. “We have demonstrated a new standard of care for patients with intermediate- and poor-risk advanced RCC, showing the potential for the combination to become a new standard of care for patients with intermediate- and poor-risk advanced RCC.1-3

Opdivo is associated with the following Warnings and Precautions: immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin lesions, adrenocortical insufficiency, auto-antibody-mediated events, and death from reactions to the immune response. Please see the Important Safety Information section below, including BOXED WARNING for Yervoy regarding immune-mediated adverse reactions.1,3

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; 95% confidence interval [CI]: 0.44 to 0.89; p<0.0001).3 The median OS was not yet reached for Opdivo® + Yervoy (95% CI: 28.2 to not estimate [NE]) and was 29.5 months for sunitinib (95% CI: 23.2 to NE).3,5

- **Objective Response Rate**: Opdivo® + Yervoy was associated with a 41.6% ORR (95% CI: 36.9 to 46.3; n=137/425) versus 24.9% for sunitinib (95% CI: 22.4 to 30.4; n=112/425).3,5

- **Complete and Partial Response Rates**: The complete response (CR) rate was 8.4% for Opdivo® + Yervoy (n=11/425) and 0.0% for sunitinib (n=4/422).3,5 The partial response (PR) rate was 32.2% for Opdivo® + Yervoy (n=137/425) and 25.4% for sunitinib (n=107/422).3,5

- **Duration of Response**: Among patients who responded, median duration of response (DOR) for Opdivo® + Yervoy was not reached (95% CI: 21.8 to NE), compared to 18.2 months for sunitinib (95% CI: 14.8 to NE).3,5

- **Progression-Free Survival (PFS)**: PFS was 24.6 months for the Opdivo® + Yervoy combination, compared to 8.4 months for sunitinib (HR 0.82; 95% CI: 0.64 to 1.05, p=0.14) which did not reach statistical significance.1,3

Among these 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.1-3 These patients historically had a poor prognosis, and although there have been a number of treatment advances over the past decade, overall options to improve overall survival are still needed.1-3 Currently, only 36% of patients with advanced RCC survive beyond one year, and only 8% live past five years.1-3

“Physicians treating advanced RCC have 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 was associated with fewer overall Grade 3 or 4 adverse reactions than sunitinib, and only 8% of patients treated with the Opdivo® + Yervoy combination required a dose reduction, which was not permitted for patients treated with the Opdivo® monotherapy. Serious adverse reactions occurred in 59% of patients receiving Opdivo® + Yervoy and in 43% of patients receiving sunitinib.1-3

“Kidney cancer is the deadliest of all urological cancers, and too many patients are faced with this grim diagnosis,” said Dana Bantle, president, KCCure. “Today’s approval of Opdivo® + Yervoy for advanced RCC, the first treatment option to increase overall survival for subgroups of patients with advanced RCC compared to sunitinib, is a significant milestone in the fight against kidney cancer. But for patients, it is more than just a new therapy option – it represents a 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 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.3 The recommended dosing for the Opdivo® + Yervoy combination is Opdivo® 3 mg/kg followed by Yervoy 1 mg/kg every four weeks for up to 36 months on the same day every three weeks for four doses. After completing four doses of the combination, Opdivo® should be administered intravenously 240 mg infused every four weeks or 88 mg infused every two weeks over 30 minutes until disease progression or unacceptable toxicity.

The primary efficacy outcomes measured at 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.1,3 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 2018.1-3
In Checkmate 214, the most common adverse reactions reported in at least 20% of patients treated with OPDIVO plus YERVOY (nivolumab) vs sunitinib were fatigue (58% vs 43%), rash (39% vs 20%), diarrhoea (38% vs 28%), musculoskeletal pain (39% vs 21%), nausea (39% vs 30%), cough (28% vs 14%), pyrexia (27% vs 5%), arthralgia (23% vs 23%), decreased appetite (21% vs 30%), and decreased weight (21% 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 (nivolumab) vs sunitinib were fatigue (58% vs 43%), rash (39% vs 20%), diarrhoea (38% vs 28%), musculoskeletal pain (39% vs 21%), nausea (39% vs 30%), cough (28% vs 14%), pyrexia (27% vs 5%), arthralgia (23% vs 23%), decreased appetite (21% vs 30%) and decreased weight (21% vs 12%).

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

INDICATION

OPDIVO (nivolumab), in combination with YERVOY (nivolumab), 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 dermatitis, colitis, hepatitis, endocrinopathies, and pancreatitis.4, 27, 28, 29, 30, 31, 32, 33

In clinical trials, 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, enteritis, and endocrinopathies and evaluate clinical chemistry and laboratory function tests (e.g., full blood count, creatinine, electrolyte levels, liver enzymes) prior to treatment and 1-2 weeks after treatment. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated reactions occurred in 4.4% (24/547) of patients.

Immune-Mediated Pneumonitis

Immune-Mediated Colitis

Immune-Mediated Hepatitis

Immune-Mediated Endocrinopathies

Immune-Mediated Nephritis and Renal Dysfunction

Immune-Mediated Skin Adverse Reactions and Dermatitis

Immune-Mediated Eosinophilia

Other Immune-Mediated Adverse Reactions

Infusion Reactions

Embryo-Fetal Toxicity

Lactation

Serious Adverse Reactions

Nursing

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.

In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY and in 53% of patients receiving sunitinib. The most frequent serious adverse reactions reported in Checkmate 214 for OPDIVO plus YERVOY were fatigue (28% vs 18%), diarrhoea (28% vs 15%), dyspnoea (28% vs 21%), nausea (28% vs 23%), vomiting (27% vs 20%), pyrexia (26% vs 19%), arthralgia (23% vs 18%), and decreased appetite (21% vs 29%).

In Checkmate 214, 214 serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY and in 53% of patients receiving sunitinib. The most frequent serious adverse reactions reported in Checkmate 214 for OPDIVO plus YERVOY were fatigue (28% vs 18%), diarrhoea (28% vs 15%), dyspnoea (28% vs 21%), nausea (28% vs 23%), vomiting (27% vs 20%), pyrexia (26% vs 19%), arthralgia (23% 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 researching 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 tumor types with 24 clinical-stage molecularly targeted different immune system pathways. Our deep expertise and innovative clinical trial designs position us at the forefront of I-O.

Our forward-looking statements are based on current expectations of Bristol-Myers Squibb Company regarding the research, development and commercialization of our 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 those expected. For more information about Bristol-Myers Squibb Company, visit us online at BMS.com or follow us on LinkedIn, Twitter, YouTube and Facebook.

References
11. Nivolumab (ipilimumab) + nivolumab (ipilimumab) for treatment-naive advanced or metastatic renal cell carcinoma (NCC): results from CheckMate 214, including overall survival by subgroup. Presentation: Society for Immunotherapy of Cancer Annual Meeting; November, 2017; National Harbor; Maryland.

Language: English

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NYSE

BMS approves Ipilimumab combination therapy as first-line treatment for certain patients with advanced #KidneyCancer