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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PRINCETON, N.J.--(BUSINESS WIRE)--Squibb Company (NYSE: BMY) today announced that Opdivo (nivolumab), a programmed death-1 (PD-1) blocker, and Yervoy (ipilimumab), a programmed death ligand 1 (PD-L1) blocker, in combination, demonstrated superior overall survival (OS), progression-free survival (PFS), complete and partial response rates, and safety versus sunitinib in the CheckMate -214 trial. The combination was approved by the U.S. Food and Drug Administration (FDA) as the first Immuno-Oncology combination for previously untreated intermediate- and poor-risk advanced renal cell carcinoma (RCC). 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.1,2,3 Yervoy also delivered durable responses, with a higher objective response rate (ORR) compared to sunitinib.1,2,3 Patients in the CheckMate -214 trial received four cycles of the Opdivo + low-dose Yervoy combination, followed by Opdivo monotherapy therapy.4,5 In the combination arm of the trial, 79% of patients received all four doses of Opdivo + Yervoy and went on to the Opdivo maintenance phase.4,5 Flexible dosing options are available during the Opdivo maintenance phase, including every 4 or 12 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 Yervoy combination helps deliver on that promise,” said Robert J. Motzer, M.D., medical oncologist and vice chair for clinical affairs at Memorial Sloan Kettering Cancer Center. “Data from the CheckMate -214 trial demonstrated superior overall survival and progression-free survival compared to sunitinib, with fewer overall Grade 3 or 4 adverse reactions than sunitinib.”

1 Opdivo is associated with the following Warnings and Precautions: immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin adverse reactions, encephalitis, and embryo-fetal 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; 96.8% confidence interval [CI]: 0.44 to 0.89; p = 0.001).1 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: 23.2 to 38.4).1,2,3

- **Objective Response Rate:** Opdivo + Yervoy was associated with a 41.6% ORR (95% CI: 36.9 to 46.5; p ≤ 0.001; n=374/922) versus 26.9% for sunitinib (95% CI: 22.4 to 31.0; p=0.0124).1,7

- **Complete and Partial Response Rates:** The complete response (CR) rate was 8.4% for Yervoy (n=31/374) and 4.2% for sunitinib (n=15/374).1,7

- **Duration of Response:** Among patients who responded, median duration of response (dura) was not yet reached (95% CI: 21.8 to NE) for Yervoy; it was not reached for sunitinib (95% CI: 14.9 to NE).1,2,3

- **Progression-Free Survival:** The median PFS was 11.6 months for the Opdivo + Yervoy combination, compared to 8.4 months for sunitinib (HR 0.58; 96.9% CI: 0.56 to 1.03; p = 0.049).1,2,3

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.6,7 These patients historically have a poor prognosis, and although there have been a number of treatment advances over the past decade, improvement in overall survival is still needed.6,7 Currently, only 30% of patients with advanced RCC survive beyond one year; and only 8% will live past five years.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 and Vice Chair for Clinical Affairs at 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 Opdivo plus Yervoy combination demonstrated a significant OS benefit regardless of PD-L1 expression level. This is a milestone for the RCC landscape for kidney cancer. But for patients, it is more than 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 population. 423 patients received Opdivo + Yervoy every three weeks for four doses, followed by Yervoy every four weeks. And 422 patients received sunitinib 50 mg once daily for four weeks, followed by two weeks off every cycle.1,7 The recommended dosing for the Opdivo + Yervoy combination is Opdivo 3 mg/kg followed by Yervoy 15 mg/kg every four weeks for 28 days. The sunitinib was dosed at 50 mg for 21 days every four weeks followed by a 7-day drug-free period.1,7,8

The primary efficacy outcome measures of the trial were OS, ORR (CR+PR), 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.1,2 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 2018.1,2,3

Select Safety Profile for the CheckMate -214 Trial

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: 23.2 to 38.4).1,2,3
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, hypothyroidism, hyperthyroidism, and adrenal insufficiency. The most frequent serious adverse reactions reported in patients treated with Yervoy® monotherapy were diarrhea, pneumonia, pneumonitis, hypophysitis, anaphylaxis, and adrenal insufficiency. Serious adverse reactions occurred in patients with and without previous prior therapy.

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. 

Common Adverse Reactions

In Checkmate 214, the most common adverse reactions reported in at least 20% of patients treated with OPDIVO 3 mg/kg with YERVOY 1 mg/kg were diarrhea (ipilimumab), ischemic colitis, increased serum creatinine, hypophysitis, constipation, and hyperglycemia. In patients receiving OPDIVO 10 mg/mL with YERVOY 5 mg/mL, the most common adverse reactions reported in at least 20% of patients were diarrhea (ipilimumab), hypophysitis, constipation, increased serum creatinine, and hyperglycemia.

Important Safety Information

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

YERVOY can result in severe and fatal immune-mediated adverse reactions. These immune-mediated adverse reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, hypophysitis, adrenal insufficiency, and colitis. Immune-mediated side effects have been reported in up to 80% of patients receiving YERVOY. The most common immune-mediated adverse reactions reported in patients treated with YERVOY monotherapy were diarrhea, pneumonia, pneumonitis, hypophysitis, anaphylaxis, and adrenal insufficiency. The most common immune-mediated adverse reactions reported in patients treated with OPDIVO 3 mg/kg with YERVOY 1 mg/kg were diarrhea, pneumonia, pneumonitis, hypophysitis, constipation, increased serum creatinine, and hyperglycemia.

Immune-Mediated Pneumonitis

In Checkmate 214, the most common adverse reactions reported in at least 2% of patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, hypothyroidism, hyperthyroidism, and adrenal insufficiency. The most common serious adverse reactions reported in patients treated with YERVOY monotherapy were diarrhea, pneumonia, pneumonitis, hypophysitis, anaphylaxis, and adrenal insufficiency. Serious adverse reactions occurred in patients with and without previous prior therapy.

Immune-Mediated Colitis

Immune-mediated colitis occurring in the absence of other causes. If other causes are ruled out, consider a Vogt-Koyanagi-Harada-like syndrome (VKH). Patients with immune-mediated colitis should be closely monitored for signs and symptoms of colitis, including increased frequency of bowel movements and abdominal cramping. If other causes are ruled out, consider a Vogt-Koyanagi-Harada-like syndrome (VKH). Patients with immune-mediated colitis should be closely monitored for signs and symptoms of colitis, including increased frequency of bowel movements and abdominal cramping. If other causes are ruled out, consider a Vogt-Koyanagi-Harada-like syndrome (VKH). Patients with immune-mediated colitis should be closely monitored for signs and symptoms of colitis, including increased frequency of bowel movements and abdominal cramping. If other causes are ruled out, consider a Vogt-Koyanagi-Harada-like syndrome (VKH). Patients with immune-mediated colitis should be closely monitored for signs and symptoms of colitis, including increased frequency of bowel movements and abdominal cramping.

Immune-Mediated Hepatitis

Immune-Mediated Endocrinopathies

Immune-Mediated Nephritis and Renal Dysfunction

Immune-Mediated Skin Adverse Reactions and Dermatitis

Immune-Mediated Pneumonitis

Infusion Reactions

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, hypothyroidism, hyperthyroidism, and adrenal insufficiency. The most frequent serious adverse reactions reported in patients treated with Yervoy® monotherapy were diarrhea, pneumonia, pneumonitis, hypophysitis, anaphylaxis, and adrenal insufficiency. Serious adverse reactions occurred in patients with and without previous prior therapy.

Infusion Reactions

In Checkmate 214, the most common adverse reactions reported in at least 20% of patients treated with OPDIVO 10 mg/mL with YERVOY 5 mg/mL were diarrhea (58%), nausea (58%), pruritus (52%), rash (26%), fatigue (20%), pneumonia (20%), and hyperglycemia (18%). In patients receiving OPDIVO 10 mg/mL with YERVOY 5 mg/mL, the most common adverse reactions reported in at least 20% of patients were diarrhea (53%), nausea (39%), pruritus (39%), rash (28%), cough (28%), fatigue (20%), pneumonia (20%), and hyperglycemia (18%).

Embryo-Fetal Toxicity

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.

Checkmate 214, a randomized, controlled, double-blind phase III trial, enrolled 1,204 patients with previously treated advanced renal cell carcinoma (RCC). The primary endpoint was progression-free survival (PFS), defined as the time from randomization to the first documentation of disease progression or death from any cause. Key eligibility criteria included histologically confirmed advanced RCC, measurable disease, and a performance status of 0 to 1 on the Eastern Cooperative Oncology Group scale. Randomization was stratified by center and by prior nephrectomy status. Treatment arms included OPDIVO monotherapy (n=395) vs YERVOY monotherapy (n=395) vs OPDIVO plus YERVOY (n=514) vs placebo plus YERVOY (n=399). The median follow-up time was 3.5 years. The primary analysis was conducted after an updated analysis of a 3-year median follow-up time, which met the 85% prespecified efficacy boundary for pre-established interim efficacy analysis. The primary assessment was based on investigator-assessed PFS by blinded independent central review. Secondary endpoints included overall survival (OS), OS by tumor chromosomal status, and safety. The trial was conducted with the support of Kidney Cancer Action Group (KCAG).
This press release contains “forward-looking statements” as that term is defined in the Private Securities Litigation Reform Act of 1995. Forward-looking statements in this press release include, but are not limited to, statements regarding: the potential effect of the combination of Opdivo and Yervoy on hard-to-treat cancers; the clinical impact of nivolumab plus ipilimumab compared to nivolumab monotherapy; the potential benefit to patients of current and future I-O combinations compared to current therapies; the expected timing of additional clinical trial data; the potential for nivolumab to be used in combination with different therapies; BMS’s role in advancing the scientific understanding of I-O through its research and development activities; and the expected timing of regulatory approval(s). Actual results could differ materially from those contained in any forward-looking statement for any reason including, without limitation, the risk factors described in Bristol-Myers Squibb’s Quarterly Report on Form 10-Q, filed on August 3, 2017, and in Bristol-Myers Squibb’s other filings with the Securities and Exchange Commission. Bristol-Myers Squibb undertakes no obligation to update or revise any forward-looking statements. Investors should refer to Bristol-Myers Squibb’s periodic filings with the Securities and Exchange Commission for additional information.