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

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Terms:
Immunotherapy, ipilimumab, kidney, nivolumab, NSCLC, nivolumab, Yervoy, renal, RCC, renal cell carcinoma, CheckMate, BMS, Bristol-Myers Cancer, cancer, cancer patient, tumor, treatment, immune system, immune-mediated, immune checkpoint, PD-1, PD-L1, immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin adverse reactions, encephalitis, 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.

Dateline City: PRINCETON, NJ.

The Opdivo® plus 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® and Yervoy® was associated with fewer overall 3 or 4 adverse reactions than sunitinib.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 The median OS was not yet reached for Opdivo® + Yervoy® (95% CI: 28.2 to not estimable [NE]) and was 29.5 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 46.3; 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=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 (durable response) 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 (PFS)**: The 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 Renal Cell Carcinoma Database Consortium criteria.1,2 These patients historically have had poor progress, and although there have been a number of treatment advances over the past decade, additional options to improve overall survival are still needed.1,2 Currently, only 36% of patients with advanced RCC survive beyond one year, and only 8% will live past five years.1,2

"Physicians treating advanced RCC have had few options to help achieve the goal of improved survival," said Robert J. Metzger, 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® and 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. Fifty-four percent (54%) of patients receiving Opdivo® + Yervoy® and 43% of patients receiving sunitinib had a dose delay for an adverse event. 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 Dana 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 population, 420 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 Yervoy® 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.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 2018.1,2,10

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, hyphophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and rash.1,2 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%), dyspepsia (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.13 Clear-cell RCC is the most prevalent type of RCC and constitutes 70% to 80% of all patients.1,2 Renal cell carcinoma is approximately twice as common in men as in women.1,2 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/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 and improve their quality of life. We are dedicated to advancing therapeutics across multiple therapeutic areas, including oncology, immunology, cardiovascular disease, and infectious disease. Our deep expertise and innovative clinical trial design allow us to explore new and innovative treatment approaches that can potentially provide important outcomes for these patients.

Our differentiated clinical development program is studying the effects of OPDIVO, nivolumab, atezolizumab, and other checkpoint inhibitors in combination with other agents, including chemotherapy, targeted therapy, and biological agents. This approach allows us to explore the potential of these agents in a variety of disease settings and to identify patients who may benefit from these therapies.

The majority of our efforts are focused on the discovery and development of immunotherapy and targeted therapies. We are committed to advancing therapeutics across multiple tumor types and potentially benefiting patients with cancer in need of new treatment options.

We understand the importance of providing patients with access to innovative therapies. Our comprehensive reimbursement support can be obtained by calling BMS Access Support at 1-866-831-0484 or by visiting www.bmsaccesssupport.com.

Bristol-Myers Squibb and Onco-Hematology: Advancing Oncology Research

Bristol-Myers Squibb is a global biopharmaceutical company that focuses on developing innovative medicines that help patients and improve their quality of life. Our differentiated clinical development program is studying the effects of OPDIVO, nivolumab, atezolizumab, and other checkpoint inhibitors in combination with other agents, including chemotherapy, targeted therapy, and biological agents. This approach allows us to explore the potential of these agents in a variety of disease settings and to identify patients who may benefit from these therapies.

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About Bristol-Myers Squibb's Patients' Access Support

Bristol-Myers Squibb is committed to providing access to innovative therapies. Our patients are the cornerstone of our efforts, and we are dedicated to advancing therapeutics across multiple tumor types and potentially benefiting patients with cancer in need of new treatment options.

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About Bristol-Myers Squibb and Onco-Hematology 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.

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Bristol-Myers Squibb Forward-Looking Statement

This 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

9. Surveillance, Epidemiology, and End Results Program. Kidney and Renal Pelvis Cancer SEER Survival Rates by Time Since Diagnosis, 2003-2013 By Stage at Diagnosis. National Cancer Institute. https://seer.cancer.gov/explorer/application.php?site=72&data_type=4&graph_type=6&compareBy=stage&chk_sex_1=1&chk_sex_3=3&chk_sex_2=2&chk_race_1=1&chk_age_range_1=1&chk_stage_101=1&chk_stage_106=1&advopt_precision=1&showDataFor=sex_1_and_race_1_and_age_range_1

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