Now with ~2-year extended follow-up data[1]

Combining 2 proven agents* in aRCC[2,3]

OPDIVO® (nivolumab) + CABOMETYX® (cabozantinib): Superior efficacy vs sunitinib across 3 key endpoints[2†]

Secondary endpoint[2†‡]

Significant improvement in ORR vs sunitinib[2,4]

ORR: 55.7% (n=180/323 [95% CI: 50.1–61.2]) with OPDIVO + CABOMETYX vs 27.1% (n=89/328 [95% CI: 22.4–32.3]) with sunitinib (*P*<0.0001)[2]

- 8% (n=26/323) CR and 47.7% (n=154/323) PR for OPDIVO + CABOMETYX vs 4.6% (n=15/328) CR and 22.6% (n=74/328) PR for sunitinib[4]

Primary endpoint[2†‡]

The only approved I-O + TKI combination to double median PFS vs sunitinib[2,4§]

mPFS: 16.6 months (95% CI: 12.5–24.9) with OPDIVO + CABOMETYX vs 8.3 months (95% CI: 7.0–9.7) with sunitinib (HR=0.51; 95% CI: 0.41–0.64; *P*<0.0001)[2,4]

Secondary endpoint[†]

Significant OS benefit vs sunitinib with ~18-month median follow-up[4]

mOS: NR (95% CI: NR) with OPDIVO + CABOMETYX and NR (95% CI: 22.6–NR) with sunitinib (HR=0.60; 98.89% CI: 0.40–0.89; *P*=0.0010)[2,4]

Median follow-up time of 18.1 months (range: 10.6–30.6 months).[4]

Extended follow-up analysis results (median follow-up time of 23.5 months; range: 16.0–36.0 months): ORR[‡]: 54.8% (n=177/323 [95% CI: 49.2–60.3]) with OPDIVO + CABOMETYX vs 28.4% (n=93/328 [95% CI: 23.5–33.6]) with sunitinib; **CR:** 9.3% (n=30/323) with OPDIVO + CABOMETYX vs 4.3% (n=14/328) with sunitinib; **PR:** 45.5% (n=147/323) for OPDIVO + CABOMETYX vs 24.1% (n=79/328) for sunitinib; **mPFS[‡]:** 17.0 months (95% CI: 12.6–19.4) with OPDIVO + CABOMETYX vs 8.3 months (95% CI: 6.9–9.7) with sunitinib (HR=0.52; 95% CI: 0.43–0.64); **mOS:** NR (95% CI: NE) with OPDIVO + CABOMETYX and 29.5 months (95% CI: 28.4–NE) with sunitinib (HR=0.66; 95% CI: 0.50–0.87).[1]

*OPDIVO as a single agent is indicated for the treatment of patients with advanced renal cell carcinoma (aRCC) who have received prior anti-angiogenic therapy. CABOMETYX is indicated for the treatment of patients with advanced renal cell carcinoma (aRCC).[2,3]

Learn more about our newest option at opdivo-cabometyx-hcp.com

Please see the Checkmate 9ER study design in BOX A, overall response rate in BOX B, progression-free survival Kaplan-Meier curve in BOX C, and overall survival Kaplan-Meier curve in BOX D on page 2.

[†]Based on primary analysis at a median follow-up time of 18.1 months (range: 10.6–30.6 months).[4]
[‡]BICR assessed.[2]
[§]vs sunitinib in the ITT population.[2]
aRCC=advanced renal cell carcinoma; BICR=blinded independent central review; CI=confidence interval; CR=complete response; HR=hazard ratio; I-O=immuno-oncology; ITT=intent to treat; mOS=median OS; mPFS=median PFS; NE=not estimable; NR=not reached; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; TKI=tyrosine kinase inhibitor.

INDICATION

OPDIVO, in combination with cabozantinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

SELECT IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse Reactions

- Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.
- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO. Early identification and management are essential to ensure safe use of OPDIVO. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment with OPDIVO. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.
- Withhold or permanently discontinue OPDIVO depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Please see additional Important Safety Information for OPDIVO throughout this piece and US Full Prescribing Information for OPDIVO.

OPDIVO® (nivolumab) + CABOMETYX® (cabozantinib) tablets

BOX A

Checkmate 9ER study information[2]

Checkmate 9ER was a phase 3, randomized (1:1), open-label study of OPDIVO® (nivolumab) 240 mg IV every 2 weeks* and CABOMETYX® (cabozantinib) 40 mg orally once daily (n=323) vs sunitinib 50 mg administered orally once daily (n=328) for the first 4 weeks of a 6-week cycle (4 weeks of treatment followed by 2 weeks off) in patients with previously untreated aRCC. Patients were stratified by IMDC prognostic score, PD-L1 tumor expression†, and region, and treatment was continued until disease progression or unacceptable toxicity.* Treatment beyond RECIST-defined disease progression was permitted if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Tumor assessments were performed at baseline, after randomization at Week 12, then every 6 weeks until Week 60, and then every 12 weeks thereafter. The primary endpoint was PFS (BICR assessed). Secondary endpoints included OS and ORR (BICR assessed)

*Approved dosing: OPDIVO 240 mg IV q2w or OPDIVO 480 mg IV q4w, in combination with CABOMETYX 40 mg PO qd without food. Continue OPDIVO until disease progression, unacceptable toxicity, or up to 2 years. Continue CABOMETYX until disease progression or unacceptable toxicity.[2]

†Defined as the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry 28-8 pharmDx assay.[4]

IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; PD-L1=programmed death ligand 1; PO=orally; q2w=every 2 weeks; q4w=every 4 weeks; qd=every day; RECIST=Response Evaluation Criteria In Solid Tumors.

BOX B

Checkmate 9ER: ORR vs sunitinib[1*†]

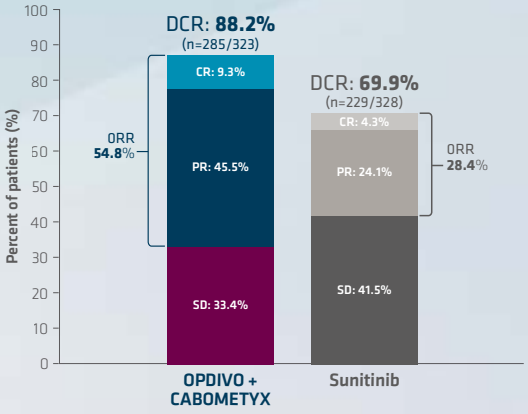
- ORR* at primary analysis (median follow-up time of 18.1 months; range: 10.6–30.6 months): 55.7% (n=180/323 [95% CI: 50.1–61.2]) with OPDIVO + CABOMETYX vs 27.1% (n=89/328 [95% CI: 22.4–32.3]) with sunitinib (*P*<0.0001); 8% (n=26/323) CR and 47.7% (n=154/323) PR for OPDIVO + CABOMETYX vs 4.6% (n=15/328) CR and 22.6% (n=74/328) PR for sunitinib[2,4]
- OPDIVO + CABOMETYX: ~90% DCR[1†]
- **The FDA does not consider SD to be a valid endpoint for the measurement of response because it may reflect the natural history of disease rather than any effect of the drug[5]**
- DCR was not pre-specified[2]

*BICR assessed.[2]

†Based on extended follow-up analysis results at a median follow-up of 23.5 months (range: 16.0–36.0 months).[1]

DCR=disease control rate; SD=stable disease.

ORR*† at ~2-year follow-up: 54.8% (n=177/323 [95% CI: 49.2–60.3]) with OPDIVO + CABOMETYX vs 28.4% (n=93/328 [95% CI: 23.5–33.6]) with sunitinib; 9.3% (n=30/323) CR and 45.5% (n=147/323) PR for OPDIVO + CABOMETYX vs 4.3% (n=14/328) CR and 24.1% (n=79/328) PR for sunitinib[1]

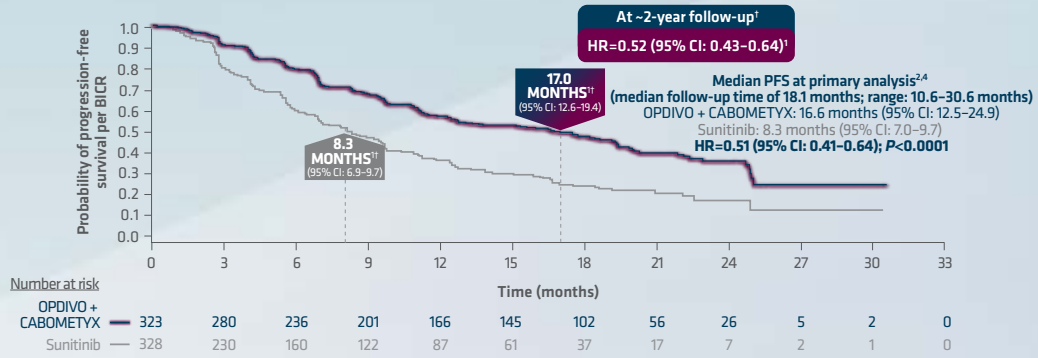


BOX C

Checkmate 9ER: Progression-free survival* in patients with aRCC[1]

*BICR assessed.[2]

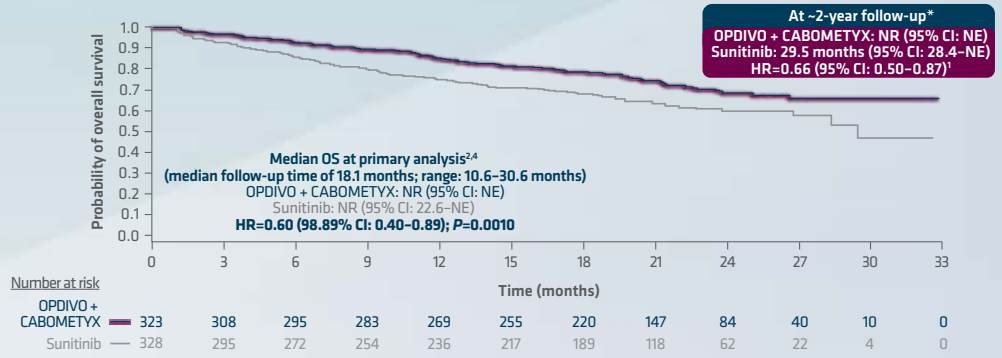
†Based on extended follow-up analysis results at a median follow-up of 23.5 months (range: 16.0–36.0 months).[1]



BOX D

Checkmate 9ER: Overall survival in patients with aRCC[1]

*Based on extended follow-up analysis results at a median follow-up of 23.5 months (range: 16.0–36.0 months).[1]



Please see Important Safety Information for OPDIVO throughout this piece and US Full Prescribing Information for OPDIVO.

INDICATIONS

OPDIVO® (nivolumab), in combination with cabozantinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

OPDIVO is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse Reactions

- Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.
- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO. Early identification and management are essential to ensure safe use of OPDIVO. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment with OPDIVO. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.
- Withhold or permanently discontinue OPDIVO depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

- OPDIVO can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients receiving OPDIVO monotherapy, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%).

Immune-Mediated Colitis

- OPDIVO can cause immune-mediated colitis. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients, including Grade 3 (1.7%) and Grade 2 (1%).

Immune-Mediated Hepatitis and Hepatotoxicity

- OPDIVO can cause immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%).
- OPDIVO in combination with cabozantinib can cause hepatic toxicity with higher frequencies of Grade 3 and 4 ALT and AST elevations compared to OPDIVO alone. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. In patients receiving OPDIVO and cabozantinib, Grades 3 and 4 increased ALT or AST were seen in 11% of patients.

Immune-Mediated Endocrinopathies

- OPDIVO can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.
- In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994), including Grade 3 (0.4%) and Grade 2 (0.6%). In patients receiving OPDIVO and cabozantinib, adrenal insufficiency occurred in 4.7% (15/320) of patients, including Grade 3 (2.2%) and Grade 2 (1.9%).
- In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients, including Grade 3 (0.2%) and Grade 2 (0.3%).
- In patients receiving OPDIVO monotherapy, thyroiditis occurred in 0.6% (12/1994) of patients, including Grade 2 (0.2%).
- In patients receiving OPDIVO monotherapy, hyperthyroidism occurred in 2.7% (54/1994) of patients, including Grade 3 (<0.1%) and Grade 2 (1.2%).
- In patients receiving OPDIVO monotherapy, hypothyroidism occurred in 8% (163/1994) of patients, including Grade 3 (0.2%) and Grade 2 (4.8%).
- In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients, including Grade 3 (0.4%) and Grade 2 (0.3%), and 2 cases of diabetic ketoacidosis.

Immune-Mediated Nephritis with Renal Dysfunction

- OPDIVO can cause immune-mediated nephritis. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%).

Immune-Mediated Dermatologic Adverse Reactions

- OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.
- Withhold or permanently discontinue OPDIVO depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).
- In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%).

Other Immune-Mediated Adverse Reactions

- The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular:* myocarditis, pericarditis, vasculitis; *nervous system:* meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *ocular:* uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal:* pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue:* myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine:* hypoparathyroidism; *other (hematologic/immune):* hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.
- Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving OPDIVO, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss

Infusion-Related Reactions

- OPDIVO can cause severe infusion-related reactions. Discontinue OPDIVO in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) 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.

(Continued on the next page)

Please see US Full Prescribing Information for OPDIVO.

IMPORTANT SAFETY INFORMATION (cont'd)

Complications of Allogeneic Hematopoietic Stem Cell Transplantation

- Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with OPDIVO. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between OPDIVO and allogeneic HSCT.
- Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

- Based on its mechanism of action and findings from animal studies, OPDIVO 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 OPDIVO and for at least 5 months after the last dose.

Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone

- In randomized clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Lactation

- There are no data on the presence of OPDIVO in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 5 months after the last dose.

Serious Adverse Reactions

- In Checkmate 9ER, serious adverse reactions occurred in 48% of patients receiving OPDIVO and cabozantinib (n=320). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO (n=406). The most frequent serious adverse reactions reported in ≥2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia.

Common Adverse Reactions

- In Checkmate 9ER, the most common adverse reactions (≥20%) in patients receiving OPDIVO and cabozantinib (n=320) were diarrhea (64%), fatigue (51%), hepatotoxicity (44%), palmar-plantar erythrodysaesthesia syndrome (40%), stomatitis (37%), rash (36%), hypertension (36%), hypothyroidism (34%), musculoskeletal pain (33%), decreased appetite (28%), nausea (27%), dysgeusia (24%), abdominal pain (22%), cough (20%) and upper respiratory tract infection (20%). In Checkmate 025, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=406) vs everolimus (n=397) were fatigue (56% vs 57%), cough (34% vs 38%), nausea (28% vs 29%), rash (28% vs 36%), dyspnea (27% vs 31%), diarrhea (25% vs 32%), constipation (23% vs 18%), decreased appetite (23% vs 30%), back pain (21% vs 16%), and arthralgia (20% vs 14%).

References: 1. Motzer RJ, Choueiri TK, Powles T, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal cell carcinoma: outcomes by sarcomatoid histology and updated trial results with extended follow-up of CheckMate 9ER. Poster presentation at ASCO GU 2021. Abstract 308. **2.** OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. **3.** CABOMETYX [package insert]. Alameda, CA: Exelixis, Inc. **4.** Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial. Slide presentation at ESMO 2020. Presentation 6960. **5.** US Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Published December 2018. Accessed October 21, 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics.

Please see US Full Prescribing Information for OPDIVO.

Bristol Myers Squibb™

OPDIVO® (nivolumab) + CABOMETYX® (cabozantinib) tablets