TWO 1L aRCC COMBINATIONS BASED ON OPDIVO® (nivolumab)[1]

In patients with intermediate- or poor-risk aRCC[1]

WHEN LOOKING FOR A CHANCE FOR LONG-TERM DURABLE SURVIVAL[2]

OPDIVO® (nivolumab) INJECTION FOR INTRAVENOUS USE 10 mg/mL + YERVOY® (ipilimumab) Injection for intravenous infusion

OPDIVO, in combination with YERVOY®, is indicated for the first-line treatment of patients with intermediate- or poor-risk advanced renal cell carcinoma (aRCC).[1]

Now with 4-year follow-up data[2]

Checkmate 214

In Checkmate 214 (OPDIVO + YERVOY):
Primary analysis results (median follow-up time of 25.2 months)[1,5]

- Median OS was not reached for OPDIVO + YERVOY (95% CI: 28.2–NE) vs 25.9 months for sunitinib (95% CI: 22.1–NE); HR=0.63 (99.8% CI: 0.44–0.89); *P*<0.0001[1,5]

Extended follow-up analysis results (minimum follow-up time of 48 months) for OPDIVO + YERVOY[2]

- The 48-month OS rate for OPDIVO + YERVOY was 50.0% vs 35.8% for sunitinib. Median OS was 48.1 months (95% CI: 35.6–NE) for OPDIVO + YERVOY vs 26.6 months for sunitinib (95% CI: 22.1–33.5); HR=0.65 (95% CI: 0.54–0.78)[2]

For aRCC patients who may benefit from an I-O + TKI therapy[1]

THE ONLY APPROVED I-O + TKI COMBINATION TO DOUBLE MEDIAN PFS[1,3*†‡]

As your I-O + TKI of choice

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

OPDIVO, in combination with CABOMETYX®, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (aRCC).[1]

Now with ~2-year follow-up data[4]

Checkmate 9ER

In Checkmate 9ER (OPDIVO + CABOMETYX):
Primary analysis results (median follow-up time of 18.1 months; range: 10.6–30.6 months)[1,3]

- The median PFS[‡] for OPDIVO + CABOMETYX was 16.6 months (95% CI: 12.5–24.9) vs 8.3 months (95% CI: 7.0–9.7) for sunitinib; HR=0.51 (95% CI: 0.41–0.64); *P*<0.0001[1,3]

*vs sunitinib in the ITT population.[1]
† Based on primary analysis results at a median follow-up of 18.1 months (range: 10.6–30.6 months).[3]
‡ BICR assessed.[1]
1L=first line; BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; I-O=immuno-oncology; ITT=intent to treat; NE=not evaluable; OS=overall survival; PFS=progression-free survival; TKI=tyrosine kinase inhibitor.

SELECT IMPORTANT SAFETY INFORMATION

Summary of Warnings and Precautions

- OPDIVO and YERVOY are associated with the following Warnings and Precautions: severe and fatal immune-mediated reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.

Please see additional Important Safety Information for OPDIVO and OPDIVO + YERVOY on pages 12–13 and US Full Prescribing Information for OPDIVO and YERVOY.
Please see page 2 for more information about the Checkmate 214 study design and endpoints and page 8 for more information about the Checkmate 9ER study design and endpoints.

In the 1L treatment of patients with intermediate- or poor-risk advanced renal cell carcinoma[1,6]

A chance to go 4 for 4 with OPDIVO® (nivolumab) + YERVOY® (ipilimumab)[2*†]

The only I-O combination with durable survival and durable response data at 4 years[1,2*†]

Checkmate 214 study information[1,5]

- Checkmate 214 was a phase 3, randomized (1:1), open-label study of OPDIVO 3 mg/kg IV and YERVOY 1 mg/kg IV (n=425) every 3 weeks for four doses, followed by OPDIVO 3 mg/kg IV every 2 weeks[‡] vs sunitinib (n=422) 50 mg administered orally once daily for four weeks, followed by 2 weeks off every cycle, in patients with previously untreated intermediate-/poor-risk aRCC. Patients were stratified by IMDC prognostic score and region, and treatment was continued until disease progression or unacceptable toxicity. The co-primary endpoints in IMDC intermediate-/poor-risk patients were OS, ORR,[§] and PFS[§]

Primary analysis results (median follow-up time of 25.2 months)[1,5]

- Median OS was not reached for OPDIVO + YERVOY (95% CI: 28.2–NE) vs 25.9 months for sunitinib (95% CI: 22.1–NE); HR=0.63 (99.8% CI: 0.44–0.89); *P*<0.0001[1,5]
- Confirmed ORR[§] was 41.6% (177/425 [95% CI: 36.9–46.5]; CR: 9.4% [n=40]; PR: 32.2% [n=137]) for OPDIVO + YERVOY vs 26.5% (112/422 [95% CI: 22.4–31.0]; CR: 1.2% [n=5]; PR: 25.4% [n=107]) for sunitinib (*P*<0.0001)[1]
  - Among responders, median duration of response was not yet reached (95% CI: 21.8–NE) for OPDIVO + YERVOY and 18.2 months (95% CI: 14.8–NE) for sunitinib[1]
- Median progression-free survival[§] for OPDIVO + YERVOY was 11.6 months (95% CI: 8.7–15.5) vs 8.4 months (95% CI: 7.0–10.8) for sunitinib; HR=0.82 (99.1% CI: 0.64–1.05); *P*=NS[1,5]
  - Per pre-specified analysis, progression-free survival did not meet statistical significance vs sunitinib[1,5]

Extended follow-up analysis results (minimum follow-up time of 48 months)[1,2,7]

- The 48-month OS rate for OPDIVO + YERVOY was 50.0% vs 35.8% for sunitinib. mOS was 48.1 months (95% CI: 35.6–NE) for OPDIVO + YERVOY vs 26.6 months for sunitinib (95% CI: 22.1–33.5); HR=0.65 (95% CI: 0.54–0.78)[2]
- OPDIVO + YERVOY: ORR[§]: 41.9% (n=178/425 [95% CI: 37–47]; CR: 10.4% [n=44/425]; PR: 31.5% [n=134/425]); sunitinib: ORR: 26.8% (n=113/422 [95% CI: 23–31]; CR: 1.4% [n=6/422]; PR: 25.4% [n=107/422])[2]
  - Among responders, median DOR in the follow-up analysis at a minimum of 48 months is not yet reached for OPDIVO + YERVOY (95% CI: 45.8–NE) vs 19.7 months for sunitinib (95% CI: 15.4–25.0); HR=0.45 (95% CI: 0.31–0.65)[2]
- In the 48-month follow-up analysis, all-cause adverse events occurring in >15% of patients receiving OPDIVO + YERVOY and not previously included in the primary analysis include: upper respiratory tract infection (OPDIVO + YERVOY: 21.4% Grades 1–4, 0.4% Grades 3–4; sunitinib: 14.8% Grades 1–4)[1,7]

*Based on results from an extended follow-up analysis at a minimum of 48 months.[2]
†In a phase 3 trial.[2]
‡The recommended dose of OPDIVO in combination with YERVOY is OPDIVO 3 mg/kg administered as an IV infusion over 30 minutes, followed by YERVOY 1 mg/kg administered as an IV infusion over 30 minutes on the same day, every 3 weeks for 4 doses. The recommended subsequent dose of OPDIVO as a single agent is either 240 mg or 480 mg administered as an IV infusion over 30 minutes every 2 weeks or 4 weeks, respectively, until disease progression or unacceptable toxicity.[1]
§In both the primary analysis and the extended follow-up analysis, ORR and PFS were assessed by an independent radiographic review committee per RECIST v1.1.[1,2,5,8]
1L=first line; aRCC=advanced RCC; CI=confidence interval; CR=complete response; HR=hazard ratio; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; I-O=immuno-oncology; IV=intravenous; mOS=median OS; NE=not evaluable; NS=not significant; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; RECIST=Response Evaluation Criteria In Solid Tumors.

SELECT IMPORTANT SAFETY INFORMATION

Summary of Warnings and Precautions

- OPDIVO and YERVOY are associated with the following Warnings and Precautions: severe and fatal immune-mediated reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.

Please see additional Important Safety Information for OPDIVO + YERVOY on pages 12–13 and US Full Prescribing Information for OPDIVO and YERVOY.

OPDIVO® (nivolumab) INJECTION FOR INTRAVENOUS USE 10 mg/mL + YERVOY® (ipilimumab) Injection for intravenous infusion

In 1L intermediate- or poor-risk aRCC

OPDIVO® (nivolumab) + YERVOY® (ipilimumab): A chance to provide superior survival and complete response[1,5]*

Primary analysis of Checkmate 214 (median follow-up of 25.2 months)

SUPERIOR OS[1,5]

MEDIAN OS
NOT YET REACHED

For OPDIVO + YERVOY
(95% CI: 28.2–NE) vs 25.9 months for sunitinib
(95% CI: 22.1–NE); HR=0.63 (99.8% CI: 0.44–0.89); *P*<0.0001[1,5]

Patients alive at 18 months

OPDIVO + YERVOY	Sunitinib
75%	**60%**

Based upon an exploratory, not pre-specified, analysis.[9]

- The pre-specified 12-month overall survival rate was 80% (95% CI: 76–84) with OPDIVO + YERVOY vs 72% (95% CI: 67–76) with sunitinib[5,9]

SUPERIOR ORR INCLUDING HIGHER CR[1,5†]

COMPLETE RESPONSE

OPDIVO + YERVOY	Sunitinib
9.4%	**1.2%**
(n=40)	(n=5)

- Overall response rate: 41.6% (n=177, 95% CI: 36.9–46.5) for OPDIVO + YERVOY vs 26.5% (n=112, 95% CI: 22.4–31.0) for sunitinib (*P*<0.0001)[1,5]
- Partial responses: 32.2% (n=137) for OPDIVO + YERVOY vs 25.4% (n=107) for sunitinib[1,5]

Median DOR† not yet reached for OPDIVO + YERVOY (95% CI: 21.8–NE) vs 18.2 months for sunitinib (95% CI: 14.8–NE).[1,5]

Progression-free survival: OPDIVO + YERVOY demonstrated median PFS† of 11.6 months (95% CI: 8.7–15.5) vs 8.4 months (95% CI: 7.0–10.8) for sunitinib (HR=0.82, 99.1% CI: 0.64–1.05)[1,5]

- Per pre-specified analysis, PFS did not meet statistical significance[1,5]

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 or YERVOY. Early identification and management are essential to ensure safe use of OPDIVO and YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and periodically during treatment with OPDIVO and before each dose of YERVOY. 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 and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO or YERVOY 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 + YERVOY on pages 12–13 and US Full Prescribing Information for OPDIVO and YERVOY.

Co-primary endpoints: OS, ORR, and PFS.[1]
*vs sunitinib.[1]
†ORR and PFS were assessed by an independent radiographic review committee per RECIST v1.1.[1,5]

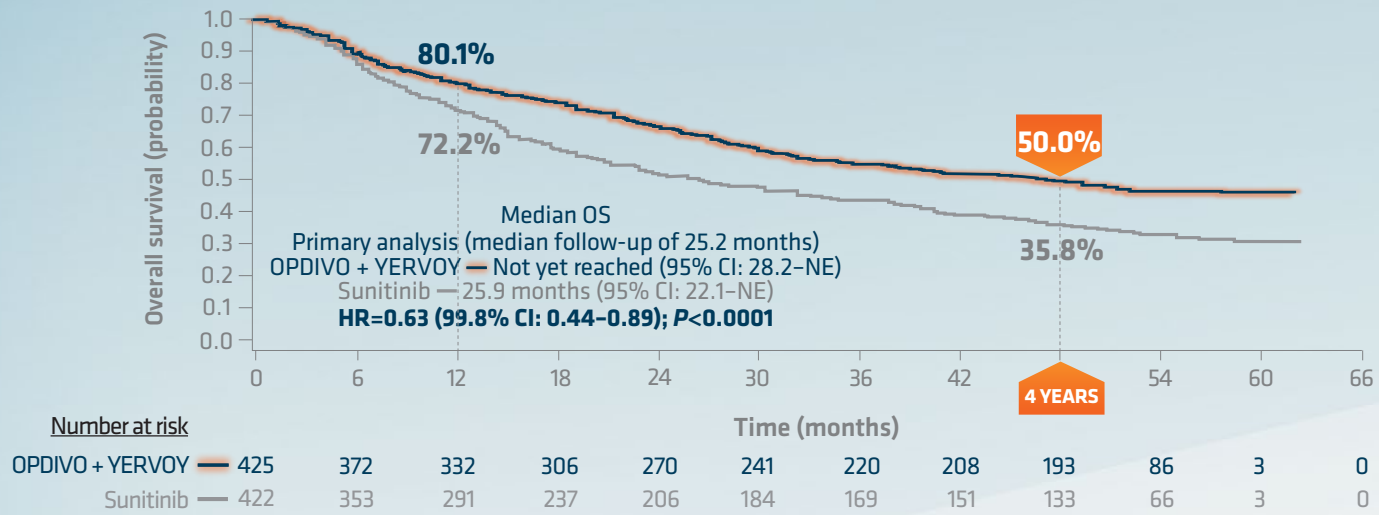
1L=first line; aRCC=advanced renal cell carcinoma; CI=confidence interval; CR=complete response; DOR=duration of response; HR=hazard ratio; NE=not evaluable; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria In Solid Tumors.

OPDIVO® (nivolumab) INJECTION FOR INTRAVENOUS USE 10 mg/mL + YERVOY® (ipilimumab) Injection for intravenous infusion

In an extended follow-up analysis at 48 months in 1L intermediate- or poor-risk aRCC

OPDIVO® (nivolumab) + YERVOY® (ipilimumab): The only I-O combination with 50% of patients alive at 4 years[2]*

Checkmate 214: Overall survival in intermediate- or poor-risk patients[1,2,5,8†]



mOS at primary analysis (median follow-up time of 25.2 months)[1,5]

- OPDIVO + YERVOY: Not yet reached (95% CI: 28.2–NE)[1,5]
- Sunitinib: 25.9 months (95% CI: 22.1–NE)[1,5]
- HR=0.63 (99.8% CI: 0.44–0.89); *P*<0.0001[1,5]

mOS at extended follow-up analysis (minimum follow-up time of 48 months)[2]

- OPDIVO + YERVOY: 48.1 months (95% CI: 35.6–NE)[2]
- Sunitinib: 26.6 months (95% CI: 22.1–33.5)[2]
- HR=0.65 (95% CI: 0.54–0.78)[2]

The 48-month overall survival rate analysis was not pre-specified within the study protocol.[9]

In the primary analysis, the pre-specified 12-month overall survival rate was 80% (95% CI: 76–84) with OPDIVO + YERVOY vs 72% (95% CI: 67–76) with sunitinib. The median follow-up time was 25.2 months.[5,9]

*In a phase 3 trial.[2,5]

†Performance status is based on IMDC prognostic score (0=favorable, 1–2=intermediate, 3+=poor).[5]

1L=first line; aRCC=advanced renal cell carcinoma; CI=confidence interval; HR=hazard ratio; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; I-O=immuno-oncology; mOS=median OS; NE=not evaluable; OS=overall survival.

SELECT IMPORTANT SAFETY INFORMATION

Serious Adverse Reactions

- In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY (n=547). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis.

Common Adverse Reactions

- In Checkmate 214, the most common adverse reactions (≥20%) reported in patients treated with OPDIVO plus YERVOY (n=547) 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%).

Please see additional Important Safety Information for OPDIVO + YERVOY on pages 12–13 and US Full Prescribing Information for OPDIVO and YERVOY.

OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

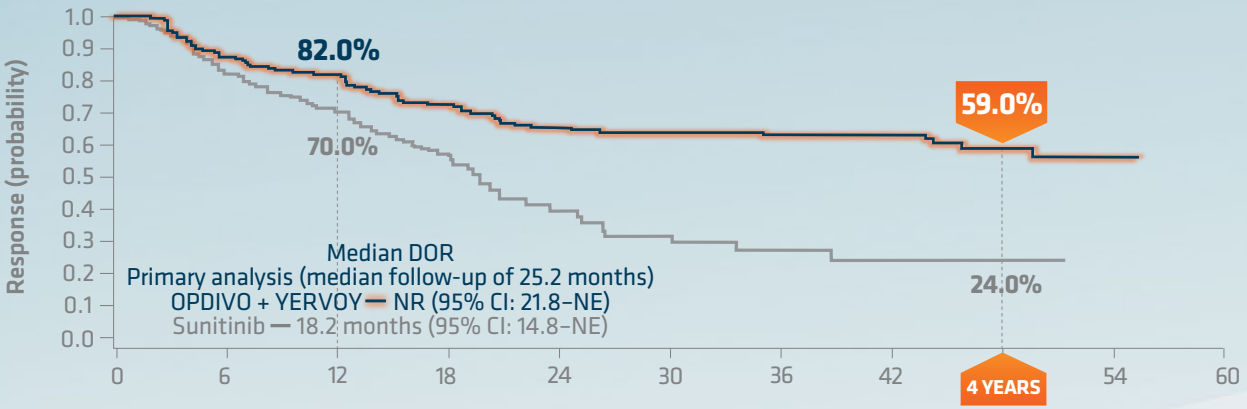
OPDIVO (nivolumab) INJECTION FOR INTRAVENOUS USE 10 mg/mL

YERVOY (ipilimumab) Injection for intravenous infusion

In an extended follow-up analysis at 48 months in 1L intermediate- or poor-risk aRCC

With OPDIVO® (nivolumab) + YERVOY® (ipilimumab), there was ~60% chance for responses to last 4 years[2,10]

Checkmate 214: Median duration of response in intermediate- or poor-risk patients[1,2,5,10]



Number at risk											
OPDIVO + YERVOY	178	145	123	104	88	78	71	57	31	2	0
Sunitinib	113	75	59	40	22	15	11	7	3	0	0

ORR* at primary analysis (median follow-up time of 25.2 months)[1,5]

- OPDIVO + YERVOY: ORR: 41.6% (n=177/425 [95% CI: 36.9–46.5]; CR: 9.4% [n=40]; PR: 32.2% [n=137])[1,5]
- Sunitinib: ORR: 26.5% (n=112/422 [95% CI: 22.4–31.0]; CR: 1.2% [n=5]; PR: 25.4% [n=107])[1,5]
- $P<0.0001$ for ORR[1]

mDOR at primary analysis (median follow-up time of 25.2 months)[1,5]

- Not yet reached (95% CI: 21.8–NE) for OPDIVO + YERVOY vs 18.2 months (95% CI: 14.8–NE) for sunitinib[1,5]

ORR* at extended follow-up analysis (minimum follow-up time of 48 months)[2]

- OPDIVO + YERVOY: ORR: 41.9% (n=178/425 [95% CI: 37–47]; CR: 10.4% [n=44/425]; PR: 31.5% [n=134/425])[2]
- Sunitinib: ORR: 26.8% (n=113/422 [95% CI: 23–31]; CR: 1.4% [n=6/422]; PR: 25.4% [n=107/422])[2]

mDOR at extended follow-up analysis (minimum follow-up time of 48 months)[2]

- Not yet reached (95% CI: 45.8–NE) for OPDIVO + YERVOY vs 19.7 months (95% CI: 15.4–25.0) for sunitinib[2]
- HR=0.45 (95% CI: 0.31–0.65)[2]

*In both the primary analysis and the extended follow-up analysis, ORR was assessed by an independent review committee per RECIST v1.1.[1,2,5]

1L=first line; aRCC=advanced renal cell carcinoma; CI=confidence interval; CR=complete response; DOR=duration of response; HR=hazard ratio; mDOR=median DOR; NE=not evaluable; NR=not reached; ORR=overall response rate; PR=partial response; RECIST=Response Evaluation Criteria In Solid Tumors.

SELECT IMPORTANT SAFETY INFORMATION

Serious Adverse Reactions

- In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY (n=547). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis.

Common Adverse Reactions

- In Checkmate 214, the most common adverse reactions (≥20%) reported in patients treated with OPDIVO plus YERVOY (n=547) 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%).

Please see additional Important Safety Information for OPDIVO + YERVOY on pages 12–13 and US Full Prescribing Information for OPDIVO and YERVOY.

OPDIVO® (nivolumab) INJECTION FOR INTRAVENOUS USE 10 mg/mL + YERVOY® (ipilimumab) Injection for intravenous infusion

In an extended follow-up analysis at 48 months in 1L intermediate- or poor-risk aRCC

~86% of complete responses to OPDIVO® (nivolumab) + YERVOY® (ipilimumab) were ongoing at 4 years[2,11]

OPDIVO + YERVOY

44 complete responders

10.4%

Ongoing responses for 38 of 44 patients (86.4%) with OPDIVO + YERVOY at 4 years[2,11]

Sunitinib

6 complete responders

1.4%

Ongoing responses for 5 of 6 patients with sunitinib at 4 years[2,11]

86.4% of CRs were ongoing at 4 years with OPDIVO + YERVOY[11]

ORR* at primary analysis (median follow-up time of 25.2 months)[1,5]

- OPDIVO + YERVOY: ORR: 41.6% (n=177/425 [95% CI: 36.9–46.5]; CR: 9.4% [n=40]; PR: 32.2% [n=137])[1,5]
- Sunitinib: ORR: 26.5% (n=112/422 [95% CI: 22.4–31.0]; CR: 1.2% [n=5]; PR: 25.4% [n=107])[1,5]
- *P*<0.0001 for ORR[1]

ORR* at extended follow-up analysis (minimum follow-up time of 48 months)[2]

- OPDIVO + YERVOY: ORR: 41.9% (n=178/425 [95% CI: 37–47]; CR: 10.4% [n=44/425]; PR: 31.5% [n=134/425])[2]
- Sunitinib: ORR: 26.8% (n=113/422 [95% CI: 23–31]; CR: 1.4% [n=6/422]; PR: 25.4% [n=107/422])[2]

*In both the primary analysis and the extended follow-up analysis, ORR was assessed by an independent radiographic review committee per RECIST v1.1.[1,2,5]

SELECT IMPORTANT SAFETY INFORMATION

Serious Adverse Reactions

- In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY (n=547). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis.

Common Adverse Reactions

- In Checkmate 214, the most common adverse reactions (≥20%) reported in patients treated with OPDIVO plus YERVOY (n=547) 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%).

Please see additional Important Safety Information for OPDIVO + YERVOY on pages 12–13 and US Full Prescribing Information for OPDIVO and YERVOY.

1L=first line; aRCC=advanced renal cell carcinoma; CI=confidence interval; CR=complete response; ORR=overall response rate; PR=partial response; RECIST=Response Evaluation Criteria In Solid Tumors.

OPDIVO® (nivolumab) INJECTION FOR INTRAVENOUS USE 10 mg/mL + YERVOY® (ipilimumab) Injection for intravenous infusion

In 1L intermediate- or poor-risk aRCC

OPDIVO® (nivolumab) + YERVOY® (ipilimumab): The only I-O combination with a chance for durable survival and durable responses at 4 years[2]*

Extended follow-up analysis of Checkmate 214 (minimum follow-up of 48 months)

DURABLE SURVIVAL

4 YEARS[2]

Half of patients were still alive at

OPDIVO + YERVOY	Sunitinib
50.0%†	35.8%†

mOS for OPDIVO + YERVOY was 48.1 months (95% CI: 35.6–NE) vs 26.6 months (95% CI: 22.1–33.5) for sunitinib; HR=0.65 (95% CI: 0.54–0.78)[2]

DURABLE RESPONSES

4 YEARS[2]

65.2% of responders had an ongoing response at (n=116/178)

86.4% of CRs were ongoing with OPDIVO + YERVOY (n=38/44)[11]

49.6% of responders to sunitinib had an ongoing response at 4 years (n=56/113)[2]

83.3% of CRs were ongoing with sunitinib (n=5/6)[11]

mDOR not yet reached (95% CI: 45.8–NE) for OPDIVO + YERVOY vs 19.7 months (95% CI: 15.4–25.0) for sunitinib; HR=0.45 (95% CI: 0.31–0.65)[2]

mOS at primary analysis (median follow-up time of 25.2 months)[1,5]

- OPDIVO + YERVOY: Not yet reached (95% CI: 28.2–NE)[1,5]
- Sunitinib: 25.9 months (95% CI: 22.1–NE)[1,5]
- HR=0.63 (99.8% CI: 0.44–0.89); *P*<0.0001[1,5]

ORR‡ at primary analysis (median follow-up time of 25.2 months)[1,5]

- OPDIVO + YERVOY: ORR: 41.6% (n=177/425 [95% CI: 36.9–46.5]; CR: 9.4% [n=40]; PR: 32.2% [n=137])[1,5]
- Sunitinib: ORR: 26.5% (n=112/422 [95% CI: 22.4–31.0]; CR: 1.2% [n=5]; PR: 25.4% [n=107])[1,5]
- *P*<0.0001 for ORR[1]

mDOR at primary analysis (median follow-up time of 25.2 months)[1,5]

- Not yet reached (95% CI: 21.8–NE) for OPDIVO + YERVOY vs 18.2 months (95% CI: 14.8–NE) for sunitinib[1,5]

ORR‡ at extended follow-up analysis (minimum follow-up time of 48 months)[2]

- OPDIVO + YERVOY: ORR: 41.9% (n=178/425 [95% CI: 37–47]; CR: 10.4% [n=44/425]; PR: 31.5% [n=134/425])[2]
- Sunitinib: ORR: 26.8% (n=113/422 [95% CI: 23–31]; CR: 1.4% [n=6/422]; PR: 25.4% [n=107/422])[2]

*In a phase 3 trial.[2]
†OS rates are based on Kaplan-Meier estimates.[2,8]
‡In both the primary analysis and the extended follow-up analysis, ORR was assessed by an independent radiographic review committee per RECIST v1.1.[1,2,5]

CI=confidence interval; CR=complete response; HR=hazard ratio; I-O=immuno-oncology; mDOR=median duration of response; mOS=median OS; NE=not evaluable; ORR=overall response rate; OS=overall survival; PR=partial response; RECIST=Response Evaluation Criteria In Solid Tumors.

SELECT IMPORTANT SAFETY INFORMATION

Serious Adverse Reactions

- In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY (n=547). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis.

Common Adverse Reactions

- In Checkmate 214, the most common adverse reactions (≥20%) reported in patients treated with OPDIVO plus YERVOY (n=547) 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%).

Please see additional Important Safety Information for OPDIVO + YERVOY on pages 12–13 and US Full Prescribing Information for OPDIVO and YERVOY.

OPDIVO® (nivolumab) INJECTION FOR INTRAVENOUS USE 10 mg/mL + YERVOY® (ipilimumab) Injection for intravenous infusion

Combining 2 proven agents* in aRCC[1,12]

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

SUPERIOR EFFICACY VS SUNITINIB ACROSS 3 KEY ENDPOINTS[1†]:

ORR — Secondary endpoint[1‡‡]

PFS — Primary endpoint[1‡‡]

OS — Secondary endpoint[1†]

† Based on primary analysis results at a median follow-up of 18.1 months (range: 10.6–30.6 months).[3]

NOW WITH ~2-YEAR FOLLOW-UP

OPDIVO® and CABOMETYX®: Well studied, as monotherapies or in combination, in 5 aRCC registrational trials[1,12§]

Checkmate 9ER study information[1,3]

- Checkmate 9ER was a phase 3, randomized (1:1), open-label study of OPDIVO 240 mg IV every 2 weeks[‖] and CABOMETYX 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)

Primary analysis results (median follow-up time of 18.1 months; range: 10.6–30.6 months)[1,3]

- Median PFS[‡]: 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)[1,3]
- Median OS: NR (95% CI: NR) with OPDIVO + CABOMETYX vs NR (95% CI: 22.6–NR) with sunitinib (HR=0.60; 98.89% CI: 0.40–0.89; *P*=0.0010)[1,3]
- 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)[1]
  - 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[3]

*** 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).[1,12]**

[‡] BICR assessed.[1]

[§] OPDIVO: Checkmate 025 (2L aRCC); Checkmate 214 (1L intermediate-/poor-risk aRCC, in combination with YERVOY® [ipilimumab]). CABOMETYX: METEOR (2L aRCC); CABOSUN (1L intermediate-/poor-risk aRCC). OPDIVO + CABOMETYX: Checkmate 9ER (1L aRCC).[1,12]

[‖] 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.[1]

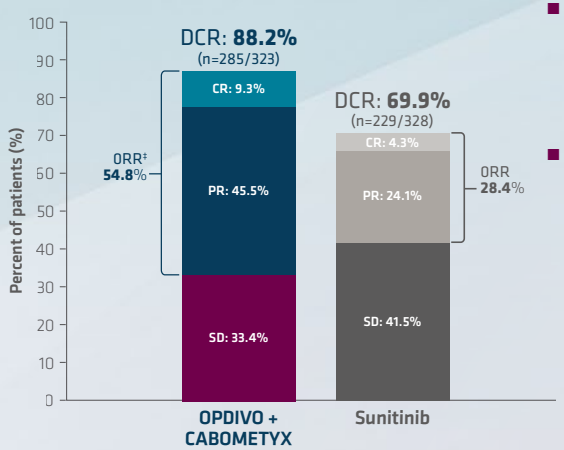
[¶] Defined as the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry 28-8 pharmDx assay.[3]

[#] Based on extended follow-up analysis results at a median follow-up of 23.5 months (range: 16.0–36.0 months).[4]

When choosing I-O + TKI therapy in aRCC

OPDIVO + CABOMETYX: ORR vs sunitinib[4‡#]

Median follow-up time of extended follow-up analysis was 23.5 months (range: 16.0–36.0 months)[4]



- Overall response rate[‡]
  - 54.8% (n=177/323) ORR for OPDIVO + CABOMETYX (95% CI: 49.2–60.3) and 28.4% (n=93/328) for sunitinib (95% CI: 23.5–33.6)
- Complete and partial response rates
  - 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

OPDIVO + CABOMETYX: ~90% DCR[4#]

- **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[13]**
- DCR was not pre-specified[1]

1L=first line; 2L=second line; aRCC=advanced renal cell carcinoma; BICR=blinded independent central review; CI=confidence interval; CR=complete response; DCR=disease control rate; HR=hazard ratio; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; I-O=immuno-oncology; IV=intravenous; NR=not reached; ORR=overall response rate; OS=overall survival; PD-L1=programmed death ligand 1; PFS=progression-free survival; PO=orally; PR=partial response; q2w=every 2 weeks; q4w=every 4 weeks; qd=every day; RECIST=Response Evaluation Criteria In Solid Tumors; SD=stable disease; TKI=tyrosine kinase inhibitor.

SELECT IMPORTANT SAFETY INFORMATION

Summary of Warnings and Precautions

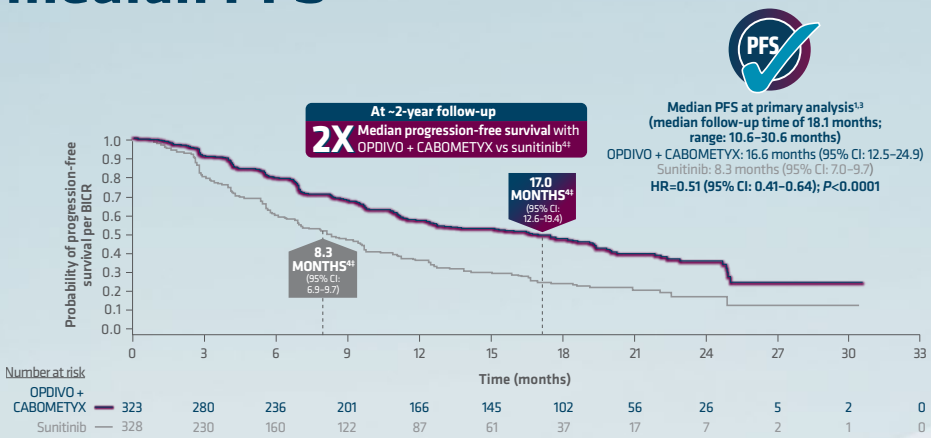
- OPDIVO is associated with the following Warnings and Precautions: severe and fatal immune-mediated reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.

Please see additional Important Safety Information for OPDIVO on pages 12–13 and US Full Prescribing Information for OPDIVO.

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

When choosing I-O + TKI therapy in aRCC

OPDIVO® (nivolumab) + CABOMETYX® (cabozantinib): The only approved I-O + TKI combination to double median PFS[1,3,4*†‡§]



Median PFS§ at primary analysis (median follow-up time of 18.1 months; range 10.6–30.6 months)[1,3]

- OPDIVO + CABOMETYX: 16.6 months (95% CI: 12.5–24.9)
- Sunitinib: 8.3 months (95% CI: 7.0–9.7)
- HR=0.51 (95% CI: 0.41–0.64); *P*<0.0001

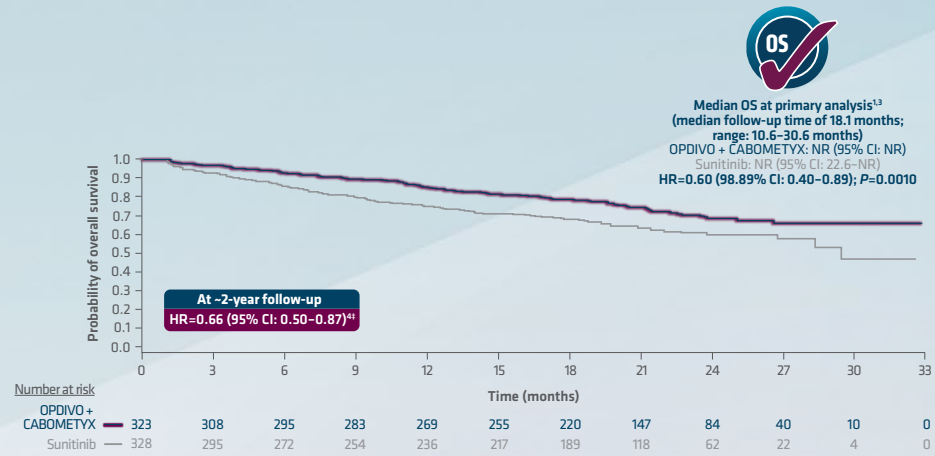
Median PFS§ at extended follow-up analysis (median follow-up time of 23.5 months; range: 16.0–36.0 months)[4]

- OPDIVO + CABOMETYX: 17.0 months (95% CI: 12.6–19.4)
- Sunitinib: 8.3 months (95% CI: 6.9–9.7)
- HR=0.52 (95% CI: 0.43–0.64)

When choosing I-O + TKI therapy in aRCC

OPDIVO + CABOMETYX: OS at ~2-year median follow-up[1,3,4‡]

34% reduction in the risk of death was observed at nearly 2 years[4]



Median OS at primary analysis (median follow-up time of 18.1 months; range: 10.6–30.6 months)[1,3]

- OPDIVO + CABOMETYX: NR (95% CI: NR)
- Sunitinib: NR (95% CI: 22.6–NR)
- HR=0.60 (98.89% CI: 0.40–0.89); *P*=0.0010

Median OS at extended follow-up analysis (median follow-up time of 23.5 months; range: 16.0–36.0 months)[4]

- OPDIVO + CABOMETYX: NR (95% CI: NE)
- Sunitinib: 29.5 months (95% CI: 28.4–NE)
- HR=0.66 (95% CI: 0.50–0.87)

SELECT IMPORTANT SAFETY INFORMATION

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.

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%).

*vs sunitinib in the ITT population.[1]

†Based on primary analysis results at a median follow-up of 18.1 months (range: 10.6–30.6 months).[3]

‡Based on extended follow-up analysis results at a median follow-up of 23.5 months (range: 16.0–36.0 months).[4]

§BICR assessed.[1]

aRCC=advanced renal cell carcinoma; BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; I-O=immuno-oncology; ITT=intent to treat; NE=not estimable; NR=not reached; OS=overall survival; PFS=progression-free survival; TKI=tyrosine kinase inhibitor.

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

Please see additional Important Safety Information for OPDIVO on pages 12–13 and US Full Prescribing Information for OPDIVO.

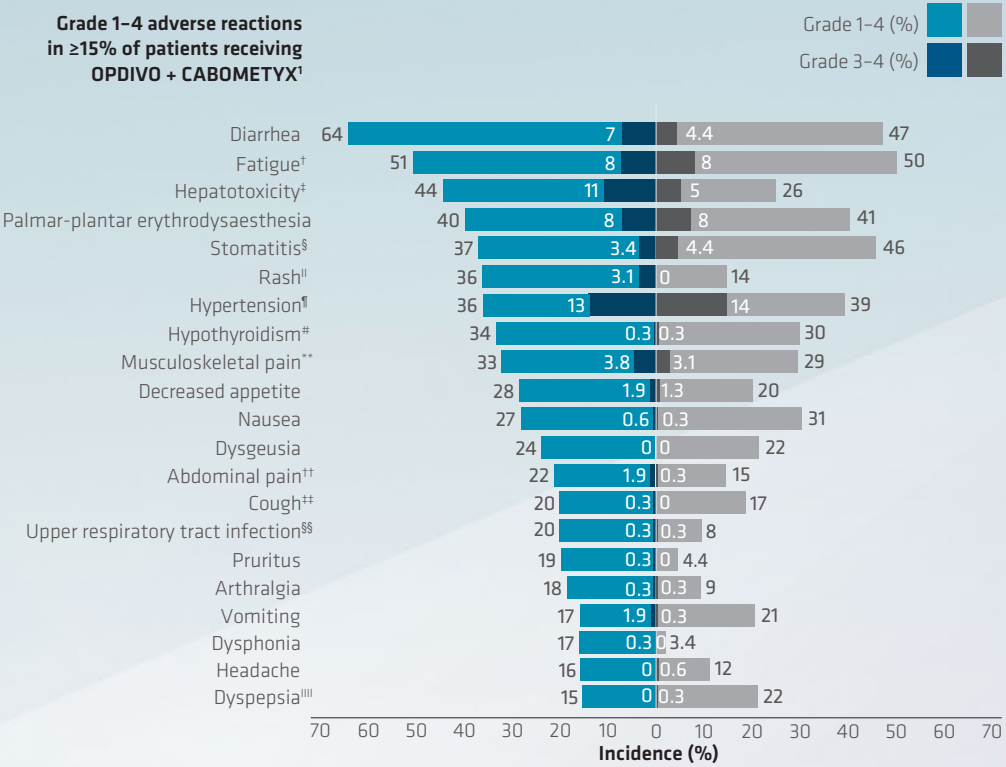
When choosing I-O + TKI therapy in aRCC

What are your safety expectations for I-O + TKI therapy?

Grade 3–5 adverse reactions were similar with OPDIVO® (nivolumab) + CABOMETYX® (cabozantinib) vs sunitinib (75% vs 71%)[3]

Reactions, %*	OPDIVO + CABOMETYX (n=320)[1]		Sunitinib (n=320)[1]	
	Grades 1–5	Grades 3–5	Grades 1–5	Grades 3–5
All-cause adverse reactions[3]	100	75	99	71

Grade 1–4 adverse reactions in ≥15% of patients receiving OPDIVO + CABOMETYX[1]



Discontinuation rate due to the same adverse reaction occurring at the same time:

OPDIVO **AND** CABOMETYX

5.6%[1,14]

- Adverse reactions leading to discontinuation of either OPDIVO or CABOMETYX occurred in 19.7% of patients: 6.6% OPDIVO only, 7.5% CABOMETYX only, and 5.6% OPDIVO + CABOMETYX due to the same adverse reaction at the same time[1,14]
- Adverse reactions leading to dose interruption or reduction of either OPDIVO or CABOMETYX occurred in 83% of patients: 3% OPDIVO only, 46% CABOMETYX only, 21% both drugs due to the same adverse reaction at the same time, and 6% both drugs sequentially[1]

Toxicity was graded per NCI CTCAE v4.[1]

* Includes reactions that occurred on therapy or within 30 days after the end of the treatment period of all treated patients.[3]

† Includes asthenia.[1]

‡ Includes hepatotoxicity, ALT increased, AST increased, blood alkaline phosphatase increased, gamma-glutamyl transferase increased, autoimmune hepatitis, blood bilirubin increased, drug induced liver injury, hepatic enzyme increased, hepatitis, hyperbilirubinemia, liver function test increased, liver function test abnormal, transaminases increased, hepatic failure.[1]

§ Includes mucosal inflammation, aphthous ulcer, mouth ulceration.[1]

‖ Includes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic.[1]

¶ Includes blood pressure increased, blood pressure systolic increased.[1]

Includes primary hypothyroidism.[1]

** Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.[1]

†† Includes abdominal discomfort, abdominal pain lower, abdominal pain upper.[1]

‡‡ Includes productive cough.[1]

§§ Includes nasopharyngitis, pharyngitis, rhinitis.[1]

‖‖ Includes gastroesophageal reflux disease.[1]

SELECT IMPORTANT SAFETY INFORMATION

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.

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%).

ALT=alanine aminotransferase; aRCC=advanced renal cell carcinoma; AST=aspartate aminotransferase; I-O=immuno-oncology; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; TKI=tyrosine kinase inhibitor.

Please see additional Important Safety Information for OPDIVO on pages 12–13 and US Full Prescribing Information for OPDIVO.

OPDIVO (nivolumab) + CABOMETYX® (cabozantinib) tablets

When choosing I-O + TKI therapy in aRCC

OPDIVO® (nivolumab) + CABOMETYX® (cabozantinib): Superior efficacy across 3 endpoints vs sunitinib from the combination of 2 proven agents[1,12*†]

OPDIVO + CABOMETYX is indicated for the first-line treatment of advanced renal cell carcinoma, across all IMDC risk categories[1]

PRIMARY ANALYSIS

Superior efficacy across 3 key endpoints[1†]

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)[1]

- 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[3]

Double median PFS vs sunitinib (primary endpoint)[1,3‡]

- Median PFS[‡]: 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)

Significant OS benefit vs sunitinib with ~18-month median follow-up[1,3]

- Median OS: 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)

Safety data you may not have expected

- Rate of Grade 3–5 adverse reactions was 75% with OPDIVO + CABOMETYX and 71% with sunitinib[3]
- Rate of discontinuation due to adverse reactions was 19.7% (6.6% OPDIVO alone; 7.5% CABOMETYX alone; 5.6% both drugs due to same adverse reaction occurring at the same time)[1,14]

Combine 2 established clinical legacies[1,12*]

- Well-studied individual agents with 5 aRCC registrational trials[§] (either monotherapy or in combination)[1,12]

***OPDIVO as a single agent is indicated for the treatment of patients with aRCC who have received prior anti-angiogenic therapy. CABOMETYX is indicated for the treatment of patients with aRCC.[1,12]**

[†]Based on primary analysis results at a median follow-up of 18.1 months(range: 10.6–30.6 months).[3]

[‡]BICR assessed.[1]

[§]OPDIVO: Checkmate 025 (2L aRCC); Checkmate 214 (1L intermediate-/poor-risk aRCC, in combination with YERVOY® [ipilimumab]). CABOMETYX: METEOR (2L aRCC); CABOSUN (1L intermediate-/poor-risk aRCC). OPDIVO + CABOMETYX: Checkmate 9ER (1L aRCC).[1,12]

1L=first line; 2L=second line; aRCC=advanced renal cell carcinoma; BICR=blinded independent central review; CI=confidence interval; CR=complete response; HR=hazard ratio; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; I-O=immuno-oncology; NR=not reached; ORR=overall response rate; OS=overall survival; PR=partial response; PFS=progression-free survival; TKI=tyrosine kinase inhibitor.

SELECT IMPORTANT SAFETY INFORMATION

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.

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%).

Please see additional Important Safety Information for OPDIVO on pages 12–13 and US Full Prescribing Information for OPDIVO.

OPDIVO (nivolumab) + CABOMETYX (cabozantinib) tablets

INDICATIONS

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the first-line treatment of patients with intermediate or poor risk advanced renal cell carcinoma (RCC).

OPDIVO, 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 or YERVOY. Early identification and management are essential to ensure safe use of OPDIVO and YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and periodically during treatment with OPDIVO and before each dose of YERVOY. 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 and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO or YERVOY 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 and YERVOY 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%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated pneumonitis occurred in 3.9% (26/666) of patients, including Grade 3 (1.4%) and Grade 2 (2.6%).

Immune-Mediated Colitis

- OPDIVO and YERVOY can cause immune-mediated colitis, which may be fatal. 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%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated colitis occurred in 9% (60/666) of patients, including Grade 3 (4.4%) and Grade 2 (3.7%).

Immune-Mediated Hepatitis and Hepatotoxicity

- OPDIVO and YERVOY 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%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated hepatitis occurred in 7% (48/666) of patients, including Grade 4 (1.2%), Grade 3 (4.9%), 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 and YERVOY 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 and YERVOY 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 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, adrenal insufficiency occurred in 7% (48/666) of patients, including Grade 4 (0.3%), Grade 3 (2.5%), and Grade 2 (4.1%). 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 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hypophysitis occurred in 4.4% (29/666) of patients, including Grade 4 (0.3%), Grade 3 (2.4%), and Grade 2 (0.9%).
- In patients receiving OPDIVO monotherapy, thyroiditis occurred in 0.6% (12/1994) of patients, including Grade 2 (0.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, thyroiditis occurred in 2.7% (22/666) of patients, including Grade 3 (4.5%) and Grade 2 (2.2%).
- 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 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hyperthyroidism occurred in 12% (80/666) of patients, including Grade 3 (0.6%) and Grade 2 (4.5%).
- 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 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hypothyroidism occurred in 18% (122/666) of patients, including Grade 3 (0.6%) and Grade 2 (11%).

Immune-Mediated Nephritis with Renal Dysfunction

- OPDIVO and YERVOY 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%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated nephritis with renal dysfunction occurred in 4.1% (27/666) of patients, including Grade 4 (0.6%), Grade 3 (1.1%), and Grade 2 (2.2%).

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.
- YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes.
- Withhold or permanently discontinue OPDIVO and YERVOY 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%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated rash occurred in 16% (108/666) of patients, including Grade 3 (3.5%) and Grade 2 (4.2%).

(Continued on the next page)

OPDIVO® (nivolumab) INJECTION FOR INTRAVENOUS USE 10 mg/mL + YERVOY® (ipilimumab) Injection for intravenous infusion

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

Please see US Full Prescribing Information for OPDIVO and YERVOY.

IMPORTANT SAFETY INFORMATION (cont'd)

Severe and Fatal Immune-Mediated Adverse Reactions (cont'd)

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® (nivolumab) monotherapy or OPDIVO in combination with YERVOY® (ipilimumab) 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.
- In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: *nervous system:* autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; *cardiovascular:* angiopathy, temporal arteritis; *ocular:* blepharitis, episcleritis, orbital myositis, scleritis; gastrointestinal: pancreatitis (1.3%); *other (hematologic/immune):* conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis.
- 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 and YERVOY, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Infusion-Related Reactions

- OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY 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. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 5.1% (28/547) of patients.

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 or YERVOY. 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 or YERVOY and allogeneic HSCT.
- Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO and YERVOY prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

- Based on its mechanism of action and findings from animal studies, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and YERVOY 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 or YERVOY 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 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY (n=547). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis. 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 214, the most common adverse reactions (≥20%) reported in patients treated with OPDIVO plus YERVOY (n=547) 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%). 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%).

Please see US Full Prescribing Information for OPDIVO and YERVOY.

References: 1. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. **2.** Albiges L, Tannir NM, Burotto M, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma in CheckMate 214: 4-year follow-up and subgroup analysis of patients without nephrectomy. Poster presentation at ESMO 2020. Abstract 711P. **3.** 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. **4.** 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. **5.** Motzer RJ, Tannir NM, McDermott DF, et al; for CheckMate 214 Investigators. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med.* 2018;378(14):1277-1290. **6.** YERVOY [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. **7.** Data on file. NIVO 593. Princeton, NJ: Bristol-Myers Squibb Company; 2020. **8.** Data on file. NIVO 54859. Princeton, NJ: Bristol-Myers Squibb Company; 2020. **9.** Motzer RJ, Tannir NM, McDermott DF, et al; for CheckMate 214 Investigators. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med.* 2018;378(14):1277-1290 [protocol]. **10.** Data on file. NIVO 586. Princeton, NJ: Bristol-Myers Squibb Company; 2020. **11.** Data on file. NIVO 587. Princeton, NJ: Bristol-Myers Squibb Company; 2020. **12.** CABOMETYX [package insert]. Alameda, CA: Exelixis, Inc. **13.** US Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Published December 2018. Accessed December 22, 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics. **14.** Data on file. NIVO 55447. Princeton, NJ: Bristol-Myers Squibb Company; 2020.

OPDIVO® (nivolumab) INJECTION FOR INTRAVENOUS USE 10 mg/mL + YERVOY® (ipilimumab) Injection for intravenous infusion

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

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