Pr OPDIVO® (nivolumab) + Pr YERVOY® (ipilimumab)

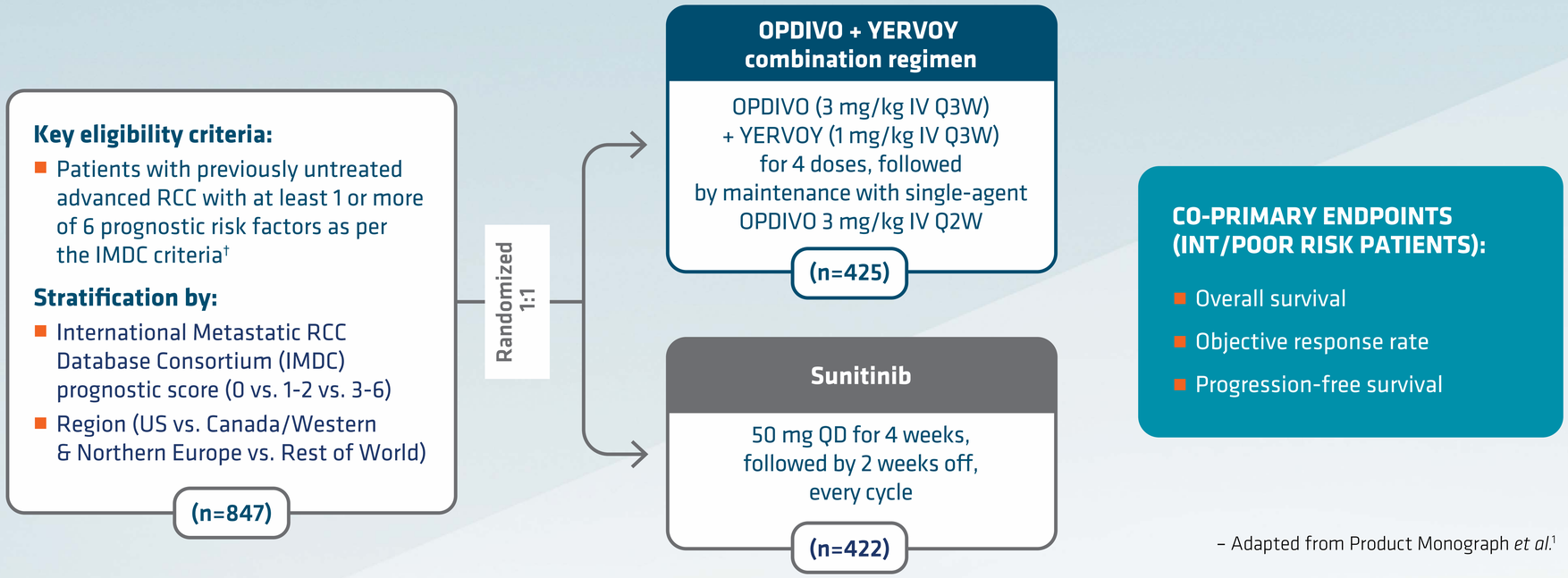
In the treatment of patients with intermediate/poor-risk advanced or metastatic RCC[1,2]

PrOPDIVO®, in combination with PrYERVOY®, is indicated for the treatment of adult patients with intermediate/poor-risk advanced or metastatic renal cell carcinoma (RCC).[1,2]

IN PREVIOUSLY UNTREATED ADVANCED RCC

CheckMate 214:
A randomized, open-label, phase 3 study of OPDIVO + YERVOY vs. sunitinib[1,4,5]

CheckMate 214 Study Design



Median follow-up at the primary analysis: 25.2 months (range: 17.5 to 33.5 months)

Median follow-up at the exploratory analysis: 49.2 months (range: 41.4 to 57.5 months)

– Adapted from Product Monograph *et al.*[1]

Treatment continued until disease progression or unacceptable toxicity. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator.

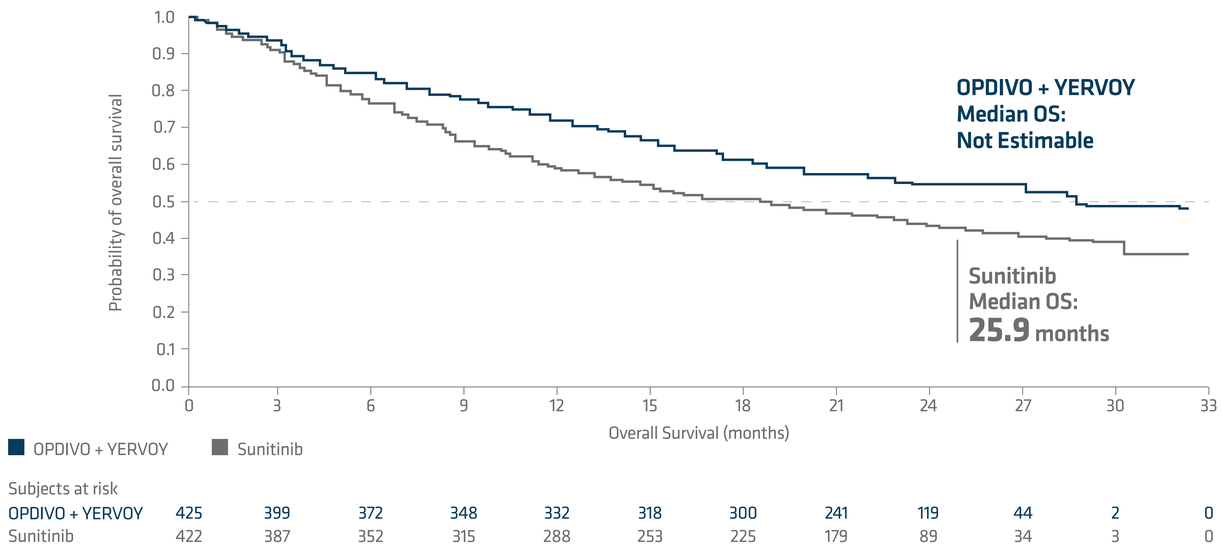
IV: intravenously; Q2W: once every 2 weeks; Q3W: once every 3 weeks; INT: intermediate.
† Less than one year from time of initial renal cell carcinoma diagnosis to randomization, Karnofsky performance status <80%, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, platelet count greater than the upper limit of normal, and absolute neutrophil count greater than the upper limit of normal.

IN INTERMEDIATE/POOR RISK PATIENTS WITH PREVIOUSLY UNTREATED, ADVANCED RCC

OPDIVO + YERVOY demonstrated superior OS vs. sunitinib (primary analysis – 17.5 months of minimum follow-up)[1†]

OS in Intermediate/Poor Risk Population

37% reduction
in instantaneous risk of death
(HR 0.63; 99.8% CI: 0.44, 0.89, p<0.0001)



Subjects at risk

OPDIVO + YERVOY	425	399	372	348	332	318	300	241	119	44	2	0
Sunitinib	422	387	352	315	288	253	225	179	89	34	3	0

– Adapted from Product Monograph[1]

The trial did not demonstrate a statistically significant improvement in PFS (co-primary endpoint): HR=0.82 (99.1% CI: 0.64, 1.05; p=0.0331); median PFS: 11.6 months (OPDIVO + YERVOY arm) vs. 8.4 (sunitinib arm).

- Number of events: 228/425 (OPDIVO + YERVOY arm) vs. 228/422 (sunitinib arm)

SURVIVAL RESULTS | ORR

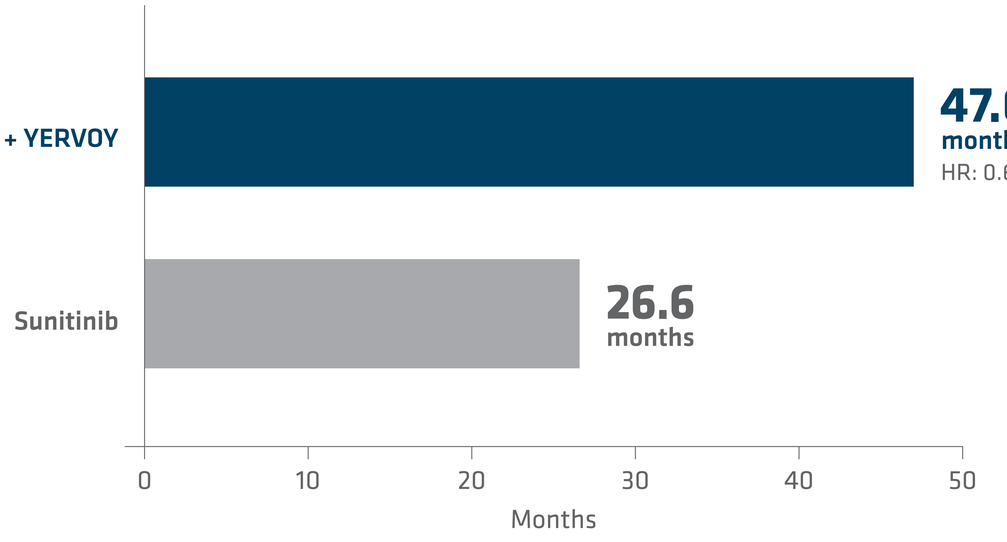
OS: overall survival; HR: hazard ratio; CI: confidence interval; PFS: progression-free survival.

† CheckMate 214: A randomized (1:1), open-label study in patients with previously untreated advanced or metastatic RCC. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region. The primary efficacy population included intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the IMDC criteria. Patients were randomized to OPDIVO 3 mg/kg + YERVOY 1 mg/kg (n=425) administered intravenously every 3 weeks for 4 doses followed by OPDIVO monotherapy 3 mg/kg every two weeks (n=425) or to sunitinib (n=422) administered orally 50 mg daily for 4 weeks followed by 2 weeks off, every cycle. OS was assessed by an independent radiologic review committee.

IN INTERMEDIATE/POOR RISK PATIENTS WITH PREVIOUSLY UNTREATED, ADVANCED RCC

Exploratory analysis
Overall survival data at 41.4-months of minimum follow-up[1,4†‡]

Median Overall Survival in the Intermediate/Poor Risk Population



– Adapted from Product Monograph[1]

The OS results (hazard ratio) based on this longer follow-up (minimum of 41.4 months) was consistent with the results of the primary analysis (HR: 0.63 after a minimum follow-up of 17.5 months).

SURVIVAL RESULTS

ORR

OS: overall survival; HR: hazard ratio; CI: confidence interval; PFS: progression-free survival.

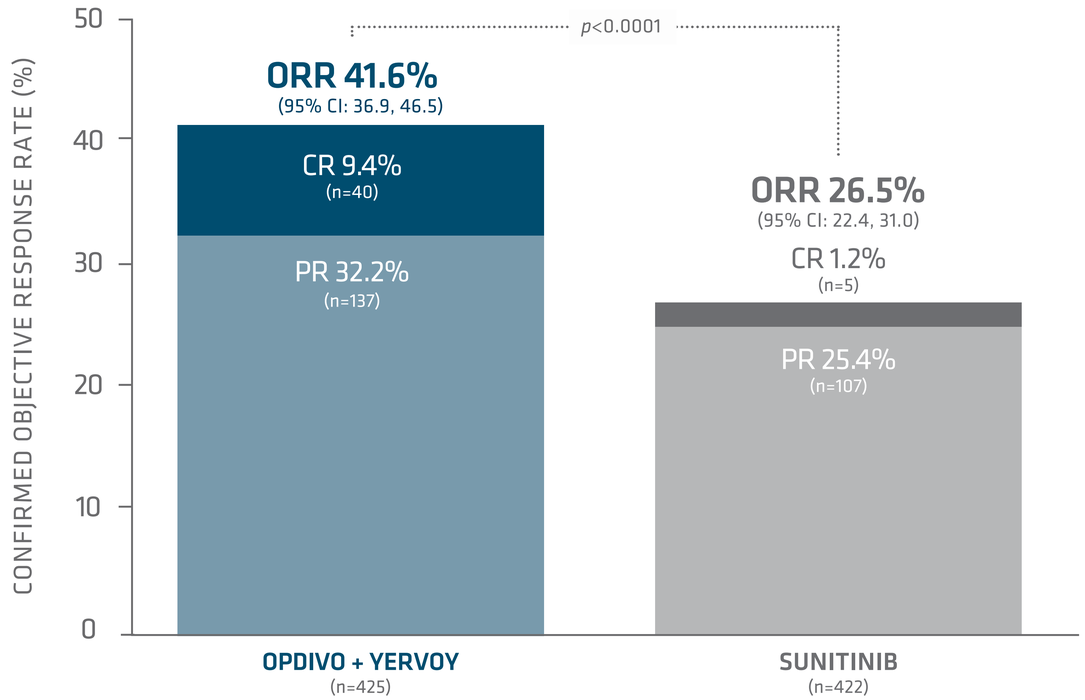
† CheckMate 214: A randomized (1:1), open-label study in patients with previously untreated advanced or metastatic RCC. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region. The primary efficacy population included intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the IMDC criteria. Patients were randomized to OPDIVO 3 mg/kg + YERVOY 1 mg/kg (n=425) administered intravenously every 3 weeks for 4 doses followed by OPDIVO monotherapy 3 mg/kg every two weeks (n=425) or to sunitinib (n=422) administered orally 50 mg daily for 4 weeks followed by 2 weeks off, every cycle. OS was assessed by an independent radiologic review committee.

‡ Exploratory follow-up conducted for CheckMate 214. The minimum follow-up for patients at the time of this analysis was 41.4 months.

IN INTERMEDIATE/POOR RISK PATIENTS WITH PREVIOUSLY UNTREATED, ADVANCED RCC

OPDIVO + YERVOY demonstrated superior ORR vs. sunitinib (primary analysis – 17.5 months of minimum follow-up)[1†]

ORR in Intermediate/Poor Risk Population



– Adapted from Product Monograph[1]

In an exploratory analysis, the ORR results based on a longer follow-up (minimum of 41.4 months) were consistent with the results of the primary analysis (17.5 months).[‡]

Among responders, the mDOR for OPDIVO + YERVOY has not yet been reached: NE (95% CI: 21.8, NE) vs. 18.2 months (95% CI: 14.8, NE) with sunitinib

SURVIVAL RESULTS

ORR

ORR: objective response rate; CI: confidence interval; CR: complete response; PR: partial response; HR: hazard ratio.

† CheckMate 214: A randomized (1:1), open-label study in patients with previously untreated advanced or metastatic RCC. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region. The primary efficacy population included intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the IMDC criteria. Patients were randomized to OPDIVO 3 mg/kg + YERVOY 1 mg/kg (n=425) administered intravenously every 3 weeks for 4 doses followed by OPDIVO monotherapy 3 mg/kg every two weeks (n=425) or to sunitinib (n=422) administered orally 50 mg daily for 4 weeks followed by 2 weeks off, every cycle. OS was assessed by an independent radiologic review committee.

‡ Exploratory follow-up conducted for CheckMate 214. The minimum follow-up for patients at the time of this analysis was 41.4 months.

Generally well-tolerated safety profile[1]

Adverse reactions reported in ≥10% of patients receiving OPDIVO + YERVOY (CheckMate 214)

System Organ Class Preferred Term	OPDIVO + YERVOY (n=547)		Sunitinib (n=535)	
	Any Grade (%)	Grades 3-4 (%)	Any Grade (%)	Grades 3-4 (%)
General Disorders and Administration Site Conditions				
Fatigue	47.5	5.5	62.1	11.2
Pyrexia	14.4	0.4	6.2	0.2
Gastrointestinal Disorders				
Diarrhea	26.5	3.8	52.0	5.2
Nausea	19.9	1.5	37.8	1.1
Vomiting	10.8	0.7	20.6	1.9
Skin and Subcutaneous Tissue Disorders				
Rash	33.8	3.5	19.8	0.6
Pruritus	28.2	0.5	9.2	0
Endocrine Disorders				
Hypothyroidism	15.7	0.4	25.0	0.2
Hyperthyroidism	11.2	0.7	2.2	0
Metabolism and Nutrition Disorders				
Decreased appetite	13.7	1.3	24.9	0.9
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain	14.8	1.5	14.0	0.4
Arthralgia	13.9	0.9	7.3	0

– Adapted from Product Monograph[1]

- Grade 3–4 adverse reactions (ARs) were reported in 46% of OPDIVO + YERVOY patients and in 63% of sunitinib patients.
- Serious adverse events occurred in 30% of patients receiving OPDIVO + YERVOY and in 15% of patients receiving sunitinib. The most frequent serious adverse reactions reported in at least 1% of patients were diarrhea, pneumonitis, hypophysitis, adrenal insufficiency, colitis, hyponatremia, increased ALT, pyrexia and nausea.
- Based on an extended follow-up with a minimum of 41.4 months, there were no new safety signals observed and the safety profile of OPDIVO + YERVOY remained consistent with the pre-specified interim analysis.
  - At this follow-up, there were 8 treatment-related deaths associated with OPDIVO + YERVOY vs. 4 in patients treated with sunitinib

ADVERSE REACTIONS | LAB VALUES | imARs

Generally well-tolerated safety profile[1]

Laboratory abnormalities worsening from baseline occurring in >15% of patients on OPDIVO + YERVOY (CheckMate 214)†

Laboratory Abnormality	OPDIVO + YERVOY (n=547)		Sunitinib (n=535)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	43	3.0	64	8.8
Lymphopenia	36	5.1	63	14.3
Chemistry				
Increase lipase	48	20.1	51	20.2
Increased creatinine	43	2.1	46	1.5
Increased ALT	41	6.5	44	2.7
Increased AST	40	4.8	60	2.1
Increased amylase	39	12.2	33	7.2
Hyponatremia	39	9.9	36	7.3
Increased alkaline phosphatase	29	2.0	32	1.0
Hyperkalemia	29	2.4	28	2.9
Hypocalcemia	22	0.4	36	0.6
Hypomagnesemia	19	0.4	28	1.8

– Adapted from Product Monograph[1]

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO + YERVOY group (range: 490 to 538 patients) and sunitinib group (range: 485 to 523 patients).

ADVERSE REACTIONS | LAB VALUES | imARs

Immune-related adverse reactions (imARs)[1]

Incidence and Resolution of imArs associated with OPDIVO (3 mg/kg) in combination with YERVOY (1 mg/kg) in RCC (n=547)

Immune-mediated adverse reaction	Incidence (all grades), %	Time to onset, median (min, max), months	Resolution (all grades), %	Time to resolution, median (min, max), weeks
Endocrinopathies	32.5%	1.9 (0.0-22.3)	43%	(0.4-130.3+)
Gastrointestinal	28.2%	1.2 (0.0-24.7)	92%	2.4 (0.1-103.0+)
Hepatic	18.5%	2.0 (0.4-26.8)	85%	6.1 (0.1+-82.9+)
Pulmonary	6.2%	2.6 (0.25-20.6)	91%	6.1 (0.7-85.9+)
Renal	48.8%	0.9 (0.0-17.9)	72%	11.6 (0.1-126.7+)
Skin	8.8%	2.1 (0.0-16.1)	77%	13.2 (0.1+-106.0+)

– Adapted from Product Monograph[1]

OPDIVO in combination with YERVOY can cause severe and fatal immune-mediated adverse reactions, including pneumonitis, interstitial lung disease, encephalitis, myocarditis, SJS, TEN and autoimmune hemolytic anemia.

Immune-mediated adverse reactions may involve any organ system. While most of these reactions occurred during treatment, onset months after the last dose has been reported.

SJS: Stevens-Johnson Syndrome; TEN: toxic epidermal necrolysis.

High dose corticosteroid use[1]

Percentage of patients on OPDIVO + YERVOY who received HDCS to treat their immune-mediated adverse reaction

Immune-mediated adverse reaction	Patients who received HDCS N=547, %, (n)	Duration of HDCS, median (min, max), weeks	Patients who permanently discontinued Tx, %, (n)
Endocrinopathies	8% (n=45)	2.1 (0.1-24.3)	2.9% (n=16)
Gastrointestinal	7% (n=40)	3.1 (0.1-99.6)	4.0% (n=22)
Hepatic	6% (n=35)	4.0 (0.1-9.7)	4.4% (n=24)
Pulmonary	4% (n=20)	2.4 (0.6-14.0)	2.2% (n=12)
Skin	3% (n=19)	2.3 (0.1-100.3)	1.5% (n=8)
Renal	2% (n=13)	2.1 (0.6-25.7)	1.3% (n=7)

– Adapted from Product Monograph[1]

- For the specific imARs listed, approximately **31.4%** of patients treated with OPDIVO + YERVOY required high dose corticosteroid.
- Resolving immune-mediated endocrinopathies may have also required hormone replacement therapy.

Recommended dosing for OPDIVO + YERVOY combination therapy[1]

Administer OPDIVO followed by YERVOY on the same day.

OPDIVO
Infused IV over 30 minutes
+
YERVOY
Infused IV over 30 minutes

OPDIVO + YERVOY COMBINATION PHASE

Week 0	Week 3	Week 6	Week 9
3 mg/kg	3 mg/kg	3 mg/kg	3 mg/kg
1 mg/kg	1 mg/kg	1 mg/kg	1 mg/kg

OPDIVO MONOTHERAPY PHASE

OPDIVO
Q4W (480 mg)*
OR
Q2W (240 mg)†
OR
Q2W (3 mg/kg)†

Continue treatment as long as clinical benefit is observed or until treatment is no longer tolerable

Flexibility of Q2W or Q4W dosing options in the monotherapy phase.

* 6 weeks after the last dose of the combination of OPDIVO + YERVOY.
† 3 weeks after the last dose of the combination of OPDIVO + YERVOY.

- Treatment may be continued for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.
- Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed.
- Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.
- Please see the OPDIVO Product Monograph for complete treatment modification and administration instructions. When OPDIVO is used in combination with YERVOY, please refer to the YERVOY Product Monograph prior to initiation of treatment.

OPDIVO (nivolumab) + Pr YERVOY (ipilimumab)

In the treatment of patients with intermediate/poor-risk advanced or metastatic RCC[1,2]

At the primary analysis, 17.5 months of minimum follow-up[1†]

OPDIVO + YERVOY demonstrated superior OS benefit vs. sunitinib[1,4]

37% reduction in risk of death during the overall study period (HR 0.63; 99.8% CI: 0.44, 0.89, $p<0.0001$)

Number of events: 140/425 (OPDIVO + YERVOY arm) vs. 188/422 (sunitinib arm)

The trial did not demonstrate a statistically significant improvement in PFS[1]

HR=0.82 (99.1% CI: 0.64, 1.05; $p=0.0331$); median PFS: 11.6 months (OPDIVO + YERVOY arm) vs. 8.4 (sunitinib arm).

Number of events: 228/425 (OPDIVO + YERVOY arm) vs. 228/422 (sunitinib arm)

Median duration of response was evaluated in OPDIVO + YERVOY vs. sunitinib[1]

Among responders, the mDOR for OPDIVO + YERVOY has not yet been reached: NE (95% CI: 21.8, NE) vs. 18.2 months (95% CI: 14.8, NE) with sunitinib

Exploratory analysis – overall survival data at 41.4-months of minimum follow-up[1†‡]

Median OS: 47.0 months for OPDIVO + YERVOY vs. 26.6 months for sunitinib (HR: 0.66)

- The OS results (hazard ratio) based on this longer follow-up (minimum of 41.4 months) was consistent with the results of the primary analysis (HR: 0.63 after a minimum follow-up of 17.5 months).

EFFICACY DATA | SAFETY PROFILE

OS: overall survival; PFS: progression-free survival; mDOR: median duration of response; HR: Hazard ratio; CI: confidence interval; NE: not estimable.

† CheckMate 214: A randomized (1:1), open-label study in patients with previously untreated advanced or metastatic RCC. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region. The primary efficacy population included intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the IMDC criteria. Patients were randomized to OPDIVO 3 mg/kg plus ipilimumab 1 mg/kg (n=425) administered intravenously every 3 weeks for 4 doses followed by OPDIVO monotherapy 3 mg/kg every two weeks (n=425) or to sunitinib (n=422) administered orally 50 mg daily for 4 weeks followed by 2 weeks off, every cycle. OS was assessed by an independent radiologic review committee.

‡ Exploratory follow-up conducted for CheckMate 214. The minimum follow-up for patients at the time of this analysis was 41.4 months.

OPDIVO (nivolumab) + Pr YERVOY (ipilimumab)

In the treatment of patients with intermediate/poor-risk advanced or metastatic RCC[1,2]

Generally well-tolerated safety profile[1]

- Grade 3–4 adverse reactions (ARs) were reported in 46% of OPDIVO + YERVOY patients and in 63% of sunitinib patients.
- For the specific imARs listed, approximately **31.4%** of patients treated with OPDIVO + YERVOY required high dose corticosteroid.
- At the prespecified interim analysis (minimum follow-up of 17.5 months), the most frequent serious adverse reactions (any grade) reported in at least 1% of patients were diarrhea (26.5%), pneumonitis (6.2%), hypophysitis (4.0%), adrenal insufficiency (5.3%), colitis (3.7%), hyponatremia (4.4%), increased ALT (grade 3-4: 6.5%), pyrexia (14.4%) and nausea (19.9%).¶
- Based on an extended follow-up with a minimum of 41.4 months, there were no new safety signals observed and the safety profile of OPDIVO + YERVOY remained consistent with the pre-specified interim analysis.

OPDIVO + YERVOY can cause severe and fatal imARs, that may involve any organ system. While most of these reactions occurred during treatment, onset months after the last dose has been reported.

EFFICACY DATA

SAFETY PROFILE

imARs: immune-related adverse reactions.

† CheckMate 214: A randomized (1:1), open-label study in patients with previously untreated advanced or metastatic RCC. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region. The primary efficacy population included intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the IMDC criteria. Patients were randomized to OPDIVO 3 mg/kg plus ipilimumab 1 mg/kg (n=425) administered intravenously every 3 weeks for 4 doses followed by OPDIVO monotherapy 3 mg/kg every two weeks (n=425) or to sunitinib (n=422) administered orally 50 mg daily for 4 weeks followed by 2 weeks off, every cycle. OS was assessed by an independent radiologic review committee.

‡ Exploratory follow-up conducted for CheckMate 214. The median follow-up for patients at the time of this analysis was 49.2 months.

¶ Values for adverse reactions obtained from Table 16: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-214. Value for increased ALT obtained from Table 32: Laboratory Abnormalities Worsening from Baseline in Occurring in >15% of patients on OPDIVO + YERVOY.

Guideline recommendations[3,6]

KCRNC recommendations

The KCRNC recommends nivolumab, in combination with ipilimumab, as a first-line therapy option in intermediate/poor-risk advanced clear-cell RCC.[3]

NCCN recommendations

The NCCN recommends nivolumab, in combination with ipilimumab, as a first-line systemic therapy option in intermediate/poor-risk stage IV RCC with clear-cell histology.[6]

For complete recommendations, please refer to the:

Management of advanced kidney cancer:

KCRNC consensus update 2021 for complete recommendations

NCCN Guidelines for Kidney Cancer – V.1.2022

KCRNC: Kidney Cancer Research Network of Canada; NCCN: National Comprehensive Cancer Network.

OPDIVO Safety Information[1]

Clinical use:

Efficacy and safety not established in pediatric patients.

Most serious warnings and precautions:

Severe/fatal immune-mediated adverse reactions (imARs): OPDIVO as monotherapy or in combination with YERVOY (ipilimumab) can cause severe and fatal immune-mediated adverse reactions, including pneumonitis, interstitial lung disease, encephalitis, myocarditis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and autoimmune hemolytic anemia. Immune-mediated adverse reactions may involve any organ system. Onset may occur during treatment or months after the last dose. Early diagnosis and appropriate management are essential to minimize potential life-threatening complications. Monitor patients for signs and symptoms of imARs and appropriately manage with treatment modifications. Permanently discontinue for any severe imARs that recur and for any life-threatening imARs.

Administration: Administer OPDIVO under the supervision of physicians experienced in the treatment of cancer.

Allogeneic hematopoietic stem cell transplantation (HSCT): Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO. Preliminary results from the follow-up of patients undergoing allogeneic HSCT after previous exposure to nivolumab showed a higher than expected number of cases of acute graft-versus-host disease (GVHD) and transplant-related mortality. Complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT. Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grades 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic venoocclusive disease (VOD), and other immune-mediated adverse reactions, and intervene promptly.

Multiple myeloma: Increased mortality in patients with multiple myeloma [not an approved indication] when OPDIVO is added to a thalidomide analogue and dexamethasone. Treatment of patients with multiple myeloma with a PD-1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Other relevant warnings and precautions:

- imARs have occurred at higher frequencies when OPDIVO was administered in combination with YERVOY vs. OPDIVO alone.
- Severe cases of these imARs have been observed, including fatal cases. Monitor patients for signs and symptoms of:
  - Cardiac adverse events and pulmonary embolism with combination therapy
  - Endocrinopathies, including hypothyroidism, hyperthyroidism, hypoparathyroidism, adrenal insufficiency, hypophysitis, diabetes mellitus, and diabetic ketoacidosis
  - Diarrhea, additional symptoms of colitis, and cytomegalovirus (CMV) infection/reactivation
  - Hepatotoxicity, including hepatitis
  - Pneumonitis or interstitial lung disease
  - Nephrotoxicity, including nephritis and renal failure
  - Rash, Stevens-Johnson syndrome, toxic epidermal necrolysis
  - Encephalitis
  - Aplastic anemia
  - Autoimmune hemolytic anemia
  - Myotoxicity (myositis, myocarditis, and rhabdomyolysis)
  - Other imARs, including solid organ transplant rejection and rapid-onset and severe graft-versus-host disease (GVHD)
- Infusion reaction
- Patients on controlled sodium diet
- Haemophagocytic lymphohistiocytosis (HLH)
- Pregnancy and nursing women
- Has not been studied in patients with moderate or severe hepatic or severe renal impairment

For more information:

Please consult the OPDIVO Product Monograph at https://www.bms.com/assets/bms/ca/documents/productmonograph/OPDIVO_EN_PM.pdf for important information relating to adverse reactions, drug interactions, and dosing, which have not been discussed in this piece.

The Product Monograph is also available by calling us at: 1-866-463-6267.

YERVOY Safety Information[2]

Clinical use:

Efficacy and safety not established in pediatric patients.

Contraindication:

In patients with active, life-threatening autoimmune disease, or with organ transplantation graft where further immune activation is potentially imminently life threatening.

Most serious warnings and precautions:

Severe/fatal immune-mediated adverse reactions (imARs): YERVOY as monotherapy or in combination with OPDIVO (nivolumab) can cause severe/fatal imARs, including enterocolitis, intestinal perforation, hepatitis, dermatitis (incl. toxic epidermal necrolysis), Stevens-Johnson syndrome, neuropathy, endocrinopathy, pneumonitis, interstitial lung disease, myocarditis, encephalitis, myasthenia gravis, autoimmune hemolytic anemia, and other organ system toxicities. Most occurred during the induction period; onset months after the last dose has been reported. Early diagnosis and appropriate management are essential to minimize life-threatening complications. Monitor patients for signs and symptoms suggestive of imARs. Permanently discontinue treatment for any severe imAR reaction that recurs and for any life-threatening imAR.

Consult the OPDIVO (nivolumab) Product Monograph prior to initiation of YERVOY in combination with OPDIVO.

Administration: Administer YERVOY under the supervision of physicians experienced in the treatment of cancer.

Other relevant warnings and precautions:

- imARs have occurred at higher frequencies when YERVOY was administered in combination with OPDIVO vs. YERVOY alone
- Patients who have had a severe or life-threatening skin adverse reaction on a prior cancer immune stimulatory therapy
- Severe cases of these imARs have been observed, including fatal cases. Monitor for signs/symptoms of:
  - Gastrointestinal adverse reactions
  - Hepatic adverse reactions
  - Pulmonary adverse reactions
  - Skin adverse reactions
  - Encephalitis
  - Neuropathies
  - Endocrinopathies
- Other imARs including ocular events
- Haemophagocytic lymphohistiocytosis (HLH)
- Vogt-Koyanagi-Harada syndrome
- Serous retinal detachment
- Graft-versus-host disease (GVHD)
- Solid organ transplant rejection in the post-marketing setting
- Infusion reaction
- Patients on immunosuppressive therapy for life-threatening disease or condition
- Autoimmune hemolytic anemia
- Myotoxicity (myositis, myocarditis, and rhabdomyolysis)
- Patients on controlled sodium diet
- Concurrent administration with vemurafenib
- Patient counseling information: imARs and fatigue
- Not studied in patients with hepatic impairment
- Not studied in patients with renal impairment
- Pregnancy and nursing women
- Close monitoring required: liver function tests, thyroid function test, electrolytes, any signs of imARs.

For more information:

Please consult the YERVOY Product Monograph at https://www.bms.com/assets/bms/ca/documents/productmonograph/YERVOY_EN_PM.pdf for important information relating to adverse reactions, management of imARs, drug interactions, and dosing information, which have not been discussed in this piece.

The Product Monograph is also available by calling us at: 1-866-463-6267.

REFERENCES

References:

1. OPDIVO Product Monograph. Bristol-Myers Squibb Canada Co.

2. YERVOY Product Monograph. Bristol-Myers Squibb Canada Co.

3. Canil C *et al*. Management of advanced kidney cancer: Kidney Cancer Research Network of Canada (KCRNC) consensus update 2021. Available at: https://doi.org/10.5489/cuaj.7245.

4. Motzer RJ, *et al*. Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial. *J Immunother Cancer* 2020;8(2):1-12.

5. Motzer RJ, *et al*. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 2018;378:1277-90.

6. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Kidney Cancer. Version 1. 2022. July 1, 2021. Accessed on August 23, 2021: https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf.

Bristol Myers Squibb

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REVIEWED BY PAAB

OPDIVO (nivolumab) + Pr YERVOY (ipilimumab)