INDICATION AND IMPORTANT SAFETY INFORMATION

OPDIVO®, as monotherapy or in combination with ipilimumab, is indicated for the treatment of adult patients with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma.[1]

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.

INDICATION AND IMPORTANT SAFETY INFORMATION

YERVOY® in combination with nivolumab is indicated for the treatment of unresectable or metastatic melanoma in previously untreated adults.[2]

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.

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

In previously untreated, unresectable or metastatic melanoma

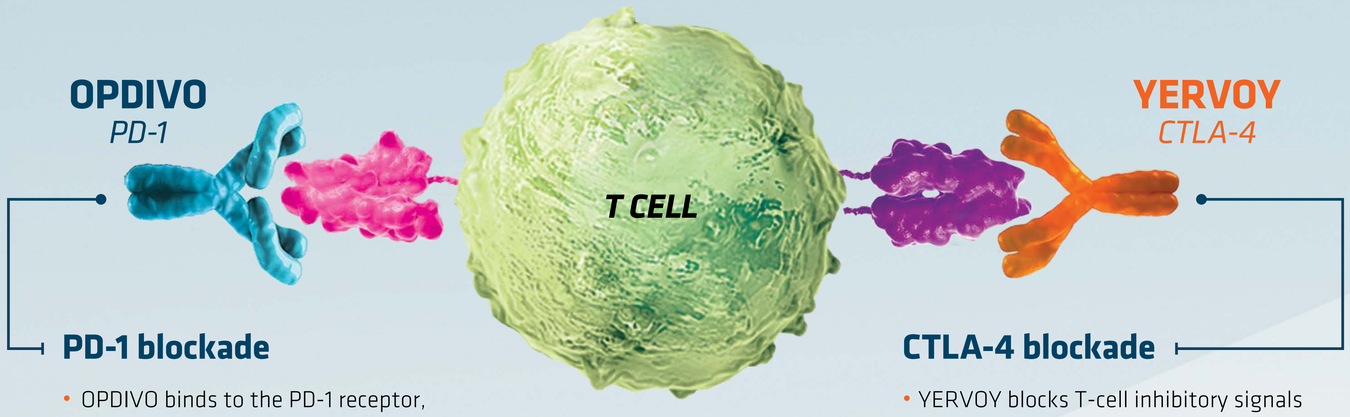
Pr OPDIVO®, as monotherapy or in combination with ipilimumab, is indicated for the treatment of adult patients with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma.[1]

Pr YERVOY® in combination with nivolumab is indicated for the treatment of unresectable or metastatic melanoma in previously untreated adults.[2]

The NCCN recommends nivolumab, in combination with ipilimumab, as a first-line therapy option in metastatic or unresectable melanoma.[3]

NCCN: National Comprehensive Cancer Network.

Paired by Science: Dual blockade of PD-1 and CTLA-4[1,2*]



PD-1 blockade

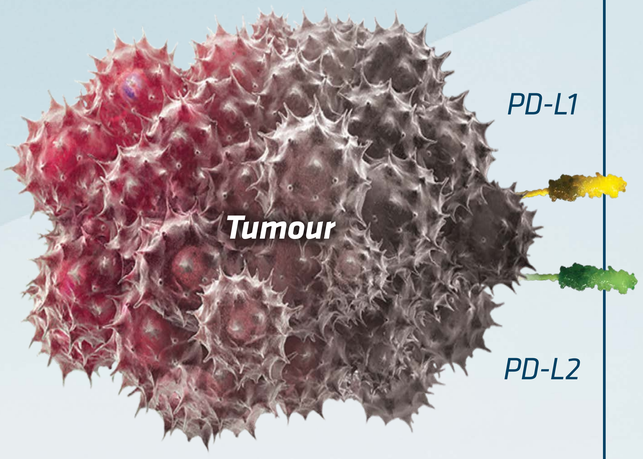
- OPDIVO binds to the PD-1 receptor, blocking its interaction with PD-L1 and PD-L2. OPDIVO releases PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response.

Adapted from OPDIVO Product Monograph[1]

CTLA-4 blockade

- YERVOY blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of tumour reactive T effector cells, which mobilize to mount a direct T-cell immune attack against tumour cells.
- CTLA-4 blockade can also reduce T regulatory cell function, which may lead to increased anti-tumour immune response. YERVOY may selectively deplete T regulatory cells at the tumour site, leading to an increased T effector/T regulatory cell ratio, which drives tumour cell death.

Adapted from YERVOY Product Monograph[2]



Dual blockade of PD-1 and CTLA-4

Combined OPDIVO and YERVOY mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone. In murine syngeneic tumour models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumour activity.

Adapted from OPDIVO Product Monograph[1]

CTLA-4: Cytotoxic T lymphocyte-associated antigen 4; PD-1: Programmed cell death protein 1; PD-L1/2: Programmed death ligand 1/2
* Clinical significance unknown.

OPDIVO (nivolumab) + Pr YERVOY (ipilimumab)

IN PREVIOUSLY UNTREATED, UNRESECTABLE OR METASTATIC MELANOMA

CheckMate 067: A phase III, randomized, double-blind study in treatment-naïve patients with advanced melanoma[1,4]

The efficacy and safety profile were evaluated in patients with previously untreated, unresectable stage III or metastatic stage IV melanoma.

CheckMate 067 Study Design

945 patients with previously untreated, unresectable stage III or metastatic stage IV melanoma

Other inclusion criteria:

- ECOG performance-status score 0–1
- ≥18 years of age
- Known BRAF V600 mutation status

Key exclusion criteria:

- Active brain metastases
- Ocular melanoma
- Autoimmune disease or medical conditions requiring systemic immunosuppression within 14 days of start of treatment

Randomized 1:1:1

OPDIVO + YERVOY combination regimen

OPDIVO (1 mg/kg Q3W) + YERVOY (3 mg/kg Q3W) for 4 doses, followed by maintenance with single-agent OPDIVO (3 mg/kg Q2W)

(n=314)

YERVOY monotherapy

YERVOY (3 mg/kg Q3W) 4 doses followed by placebo (Q2W)

(n=315)

OPDIVO monotherapy

OPDIVO (3 mg/kg Q2W)

(n=316)

CO-PRIMARY ENDPOINTS

- Progression-free survival
- Overall survival

SECONDARY ENDPOINTS

- Objective response rate
- Safety profile

Two formal scheduled analyses were planned.

Primary analysis of PFS:
9 months of minimum follow-up

Primary analysis of OS:
28 months of minimum follow-up

Adapted from Product Monograph and Larkin *et al.*[1,4]

Treatment continued until disease progression, unacceptable toxicity or withdrawal of consent. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator.[4]

IV: intravenously; ECOG: Eastern Cooperative Oncology Group; Q2W: once every 2 weeks; Q3W: once every 3 weeks.

IN PREVIOUSLY UNTREATED, UNRESECTABLE OR METASTATIC MELANOMA

OPDIVO + YERVOY and OPDIVO alone demonstrated a statistically significant OS benefit vs. YERVOY (primary analysis – 28 months of minimum follow-up)[1†]

45% **reduction** in risk of death

for **OPDIVO + YERVOY** vs. **YERVOY** alone (HR: 0.55 [98% CI: 0.42, 0.72; $p<0.0001$])

Number of events:
128/314 (OPDIVO + YERVOY arm)
vs. 197/315 (YERVOY arm)

37% **reduction** in risk of death

for **OPDIVO** alone vs. **YERVOY** alone (HR: 0.63 [98% CI: 0.48, 0.81; $p<0.0001$])

Number of events:
142/316 (OPDIVO arm)
vs. 197/315 (YERVOY arm)

OS | **ORR** | **PFS**

OS: overall survival; CI: confidence interval; HR: hazard ratio.

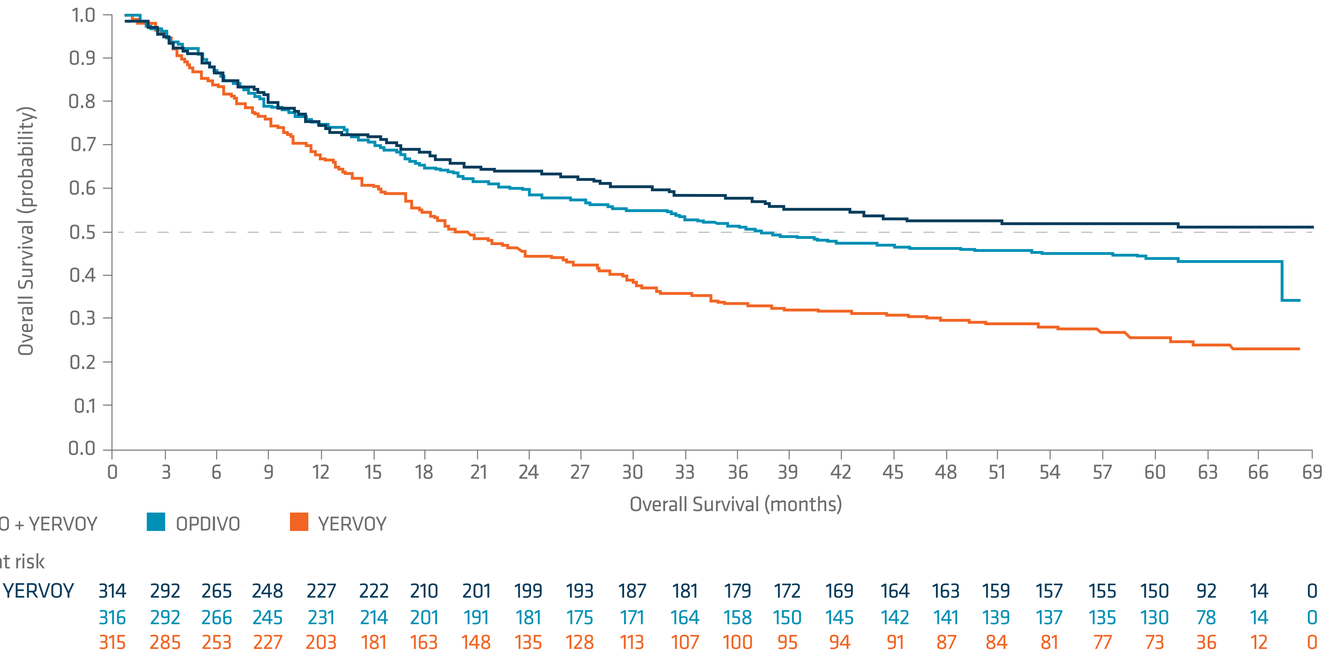
† CheckMate 067: A multicenter, double-blind, randomized trial in patients with unresectable or metastatic melanoma. Patients received OPDIVO + YERVOY (n=314), OPDIVO as a single agent (n=316), or YERVOY alone (n=315). Patients in the combination arm received OPDIVO 1 mg/kg and YERVOY 3 mg/kg every 3 weeks for the first 4 doses followed by OPDIVO 3 mg/kg as a single agent every 2 weeks. Patients in the OPDIVO single-agent arm received OPDIVO 3 mg/kg every 2 weeks. Patients in the comparator arm received YERVOY 3 mg/kg every 3 weeks for 4 doses followed by placebo every 2 weeks. Patients who had not received prior systemic anticancer therapy for unresectable or metastatic melanoma were enrolled regardless of PD-L1 expression.

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

IN PREVIOUSLY UNTREATED, UNRESECTABLE OR METASTATIC MELANOMA

Exploratory Analysis: Overall survival data at 5 years of minimum follow-up[1†‡]

Overall survival in Intent-to-Treat Population



Subjects at risk

OPDIVO + YERVOY	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
OPDIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
YERVOY	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

– Adapted from Product Monograph[1]

The OS results based on a longer follow-up (minimum of 5 years) were consistent with the results of the primary analysis (28 months)

OS | **ORR** | **PFS**

Median OS: Not Reached for OPDIVO + YERVOY

Median OS: 36.9 months for OPDIVO

Median OS: 19.9 months for YERVOY

OS: overall survival.

† CheckMate 067: A multicenter, double-blind, randomized trial in patients with unresectable or metastatic melanoma. Patients received OPDIVO + YERVOY (n=314), OPDIVO as a single agent (n=316), or YERVOY alone (n=315). Patients in the combination arm received OPDIVO 1 mg/kg and YERVOY 3 mg/kg every 3 weeks for the first 4 doses followed by OPDIVO 3 mg/kg as a single agent every 2 weeks. Patients in the OPDIVO single-agent arm received OPDIVO 3 mg/kg every 2 weeks. Patients in the comparator arm received YERVOY 3 mg/kg every 3 weeks for 4 doses followed by placebo every 2 weeks. Patients who had not received prior systemic anticancer therapy for unresectable or metastatic melanoma were enrolled regardless of PD-L1 expression.

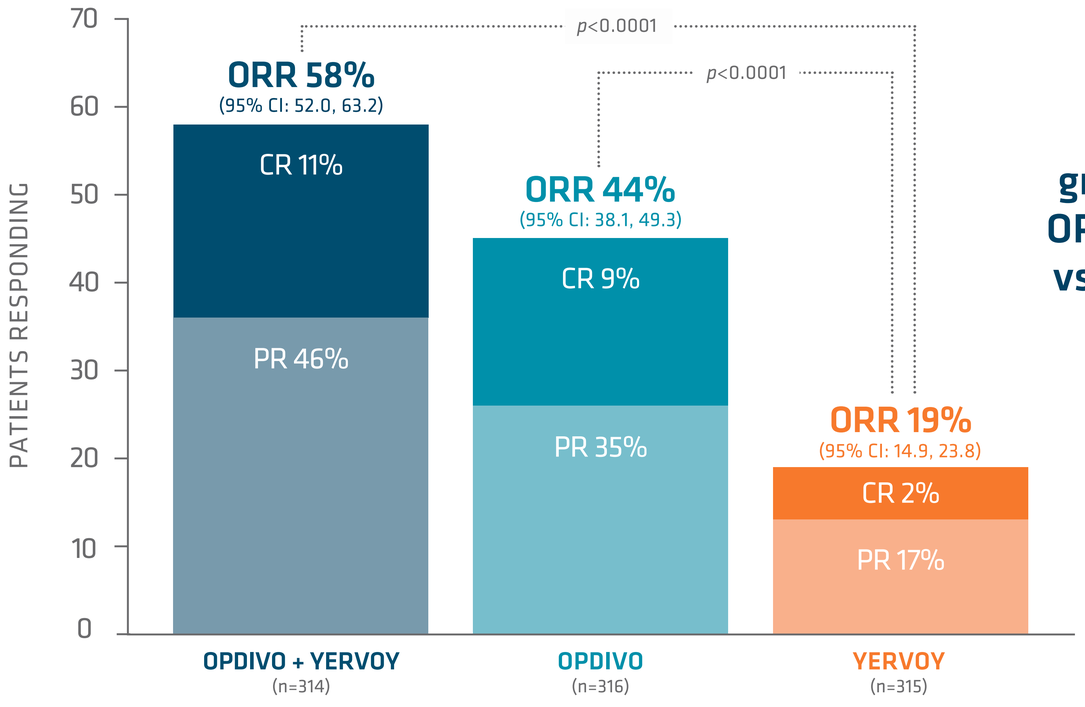
‡ Exploratory follow-up conducted for CheckMate 067. The minimum follow-up for patients at the time of this analysis was 5 years.

OPDIVO (nivolumab) + Pr YERVOY (ipilimumab)

IN PREVIOUSLY UNTREATED, UNRESECTABLE OR METASTATIC MELANOMA

OPDIVO + YERVOY and OPDIVO alone demonstrated a statistically significant improvement in objective response rate (ORR) vs. YERVOY alone (primary analysis – 9 months of minimum follow-up) (secondary endpoint)[1†]

ORR in Intent-to-Treat Population



– Adapted from Product Monograph[1]

Over 3x
greater ORR with OPDIVO + YERVOY vs. YERVOY alone ($p<0.0001$)

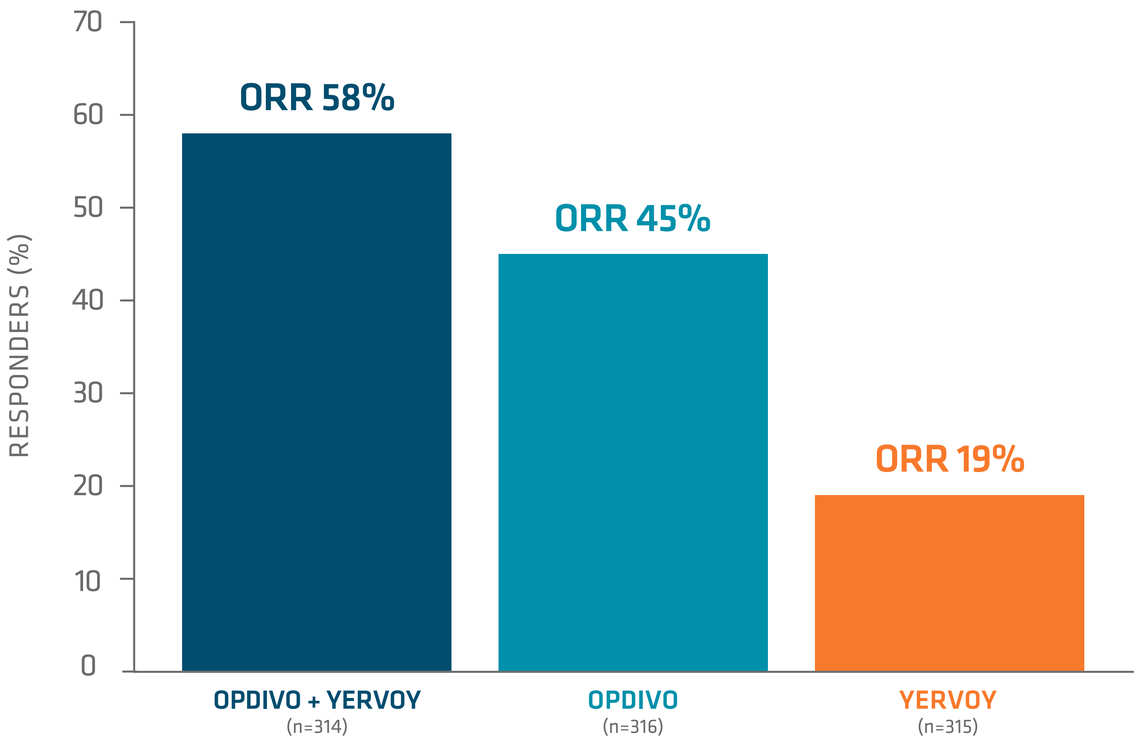
OS | ORR | PFS

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

† CheckMate 067: A multicenter, double-blind, randomized trial in patients with unresectable or metastatic melanoma. Patients received OPDIVO + YERVOY (n=314), OPDIVO as a single agent (n=316), or YERVOY alone (n=315). Patients in the combination arm received OPDIVO 1 mg/kg and YERVOY 3 mg/kg every 3 weeks for the first 4 doses followed by OPDIVO 3 mg/kg as a single agent every 2 weeks. Patients in the OPDIVO single-agent arm received OPDIVO 3 mg/kg every 2 weeks. Patients in the comparator arm received YERVOY 3 mg/kg every 3 weeks for 4 doses followed by placebo every 2 weeks. Patients who had not received prior systemic anticancer therapy for unresectable or metastatic melanoma were enrolled regardless of PD-L1 expression.

IN PREVIOUSLY UNTREATED, UNRESECTABLE OR METASTATIC MELANOMA

Exploratory Analysis: Objective rate response of the treatment arms at 5 years of minimum follow-up[4†‡]



The ORR results based on a longer follow-up (minimum of 5 years) were consistent with the result of the primary analysis (28 months)

OS | ORR | PFS

ORR: objective response rate.

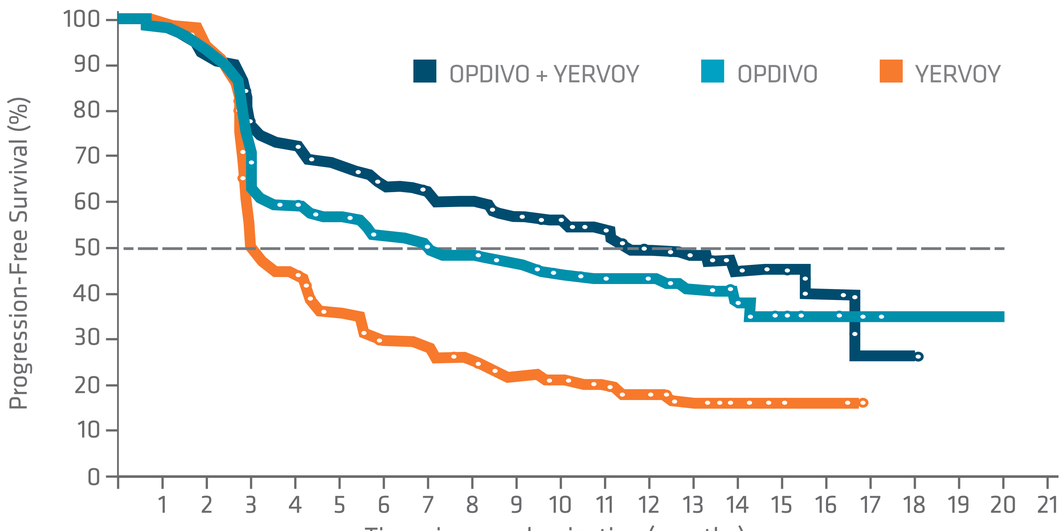
† CheckMate 067: A multicenter, double-blind, randomized trial in patients with unresectable or metastatic melanoma. Patients received OPDIVO + YERVOY (n=314), OPDIVO as a single agent (n=316), or YERVOY alone (n=315). Patients in the combination arm received OPDIVO 1 mg/kg and YERVOY 3 mg/kg every 3 weeks for the first 4 doses followed by OPDIVO 3 mg/kg as a single agent every 2 weeks. Patients in the OPDIVO single-agent arm received OPDIVO 3 mg/kg every 2 weeks. Patients in the comparator arm received YERVOY 3 mg/kg every 3 weeks for 4 doses followed by placebo every 2 weeks. Patients who had not received prior systemic anticancer therapy for unresectable or metastatic melanoma were enrolled regardless of PD-L1 expression.

‡ Exploratory follow-up conducted for CheckMate 067. The minimum follow-up for patients at the time of this analysis was 5 years.

IN PREVIOUSLY UNTREATED, UNRESECTABLE OR METASTATIC MELANOMA

OPDIVO + YERVOY and OPDIVO alone demonstrated a statistically significant improvement in progression-free survival (PFS) vs. YERVOY alone (primary analysis – 9 months of minimum follow-up)[1†]

PFS in Intent-to-Treat Population



Subjects at risk								
OPDIVO + YERVOY	314	219	173	151	65	11	1	0
OPDIVO	316	177	147	124	50	9	1	0
YERVOY	315	137	77	54	24	4	0	0

– Adapted from Product Monograph[1]

58% reduced instantaneous risk of disease progression or death
with OPDIVO + YERVOY vs. YERVOY alone,
(HR: 0.42 [99.5% CI: 0.31, 0.57; p<0.0001])

43% reduced instantaneous risk of disease progression or death
with OPDIVO alone vs. YERVOY alone,
(HR: 0.57 [99.5% CI: 0.43, 0.76; p<0.0001])

OS | ORR | PFS

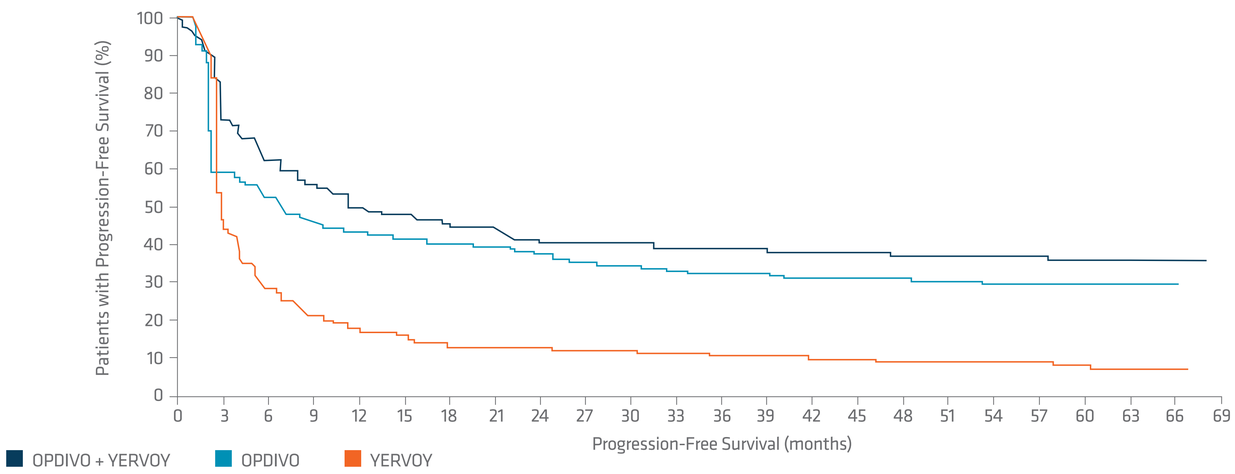
CI: confidence interval; PFS: progression-free survival; HR: hazard ratio.

† CheckMate 067: A multicenter, double-blind, randomized trial in patients with unresectable or metastatic melanoma. Patients received OPDIVO + YERVOY (n=314), OPDIVO as a single agent (n=316), or YERVOY alone (n=315). Patients in the combination arm received OPDIVO 1 mg/kg and YERVOY 3 mg/kg every 3 weeks for the first 4 doses followed by OPDIVO 3 mg/kg as a single agent every 2 weeks. Patients in the OPDIVO single-agent arm received OPDIVO 3 mg/kg every 2 weeks. Patients in the comparator arm received YERVOY 3 mg/kg every 3 weeks for 4 doses followed by placebo every 2 weeks. Patients who had not received prior systemic anticancer therapy for unresectable or metastatic melanoma were enrolled regardless of PD-L1 expression.

IN PREVIOUSLY UNTREATED, UNRESECTABLE OR METASTATIC MELANOMA

Exploratory Analysis: Progression-free survival data at 5 years of minimum follow-up[1†‡]

Progression-Free Survival in the Intent-to-Treat Population



Subjects at risk

OPDIVO + YERVOY	314	218	174	155	136	131	124	117	110	104	101	97	95	91	90	88	82	79	76	69	45	19	2	0
OPDIVO	316	177	151	132	120	112	106	103	97	88	84	80	78	76	73	71	68	66	65	60	40	13	1	0
YERVOY	315	136	78	58	46	42	34	32	31	29	28	26	21	19	18	17	15	15	15	11	8	1	0	

– Adapted from Product Monograph[1]

The PFS results based on a longer-term follow-up (minimum of 5 years) were consistent with the results of the primary analysis (28 months)

OS | ORR | PFS

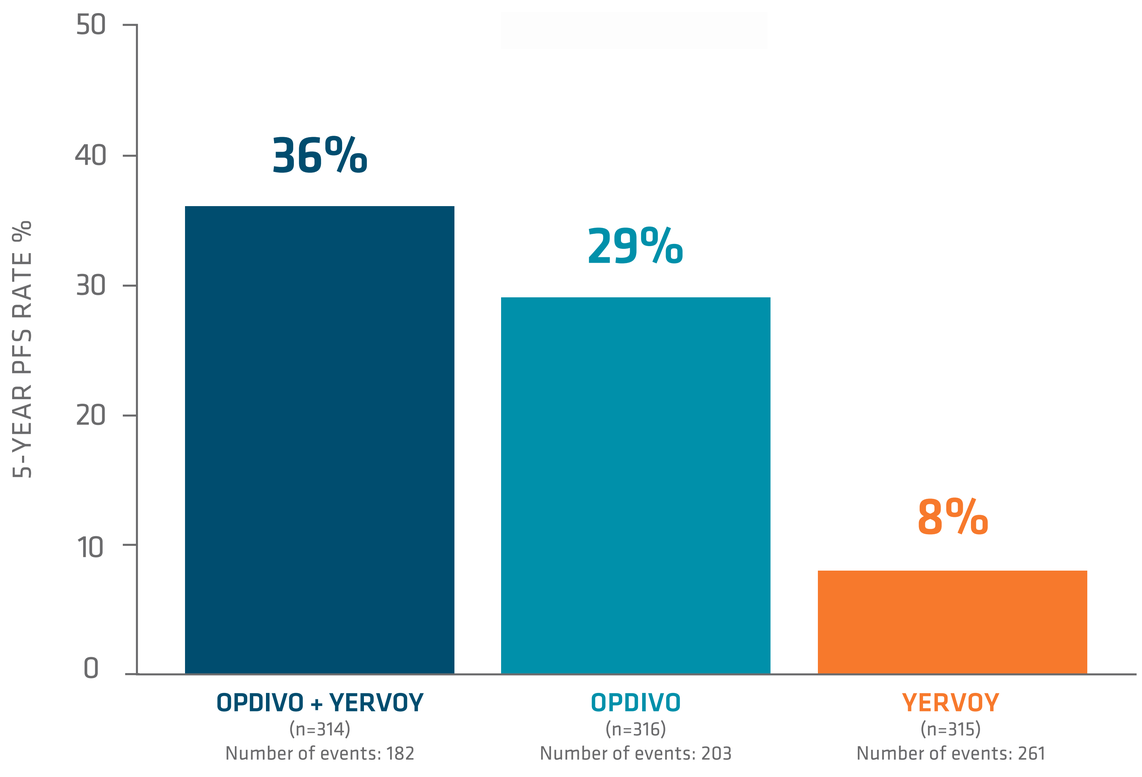
PFS: progression-free survival.

† CheckMate 067: A multicenter, double-blind, randomized trial in patients with unresectable or metastatic melanoma. Patients received OPDIVO + YERVOY (n=314), OPDIVO as a single agent (n=316), or YERVOY alone (n=315). Patients in the combination arm received OPDIVO 1 mg/kg and YERVOY 3 mg/kg every 3 weeks for the first 4 doses followed by OPDIVO 3 mg/kg as a single agent every 2 weeks. Patients in the OPDIVO single-agent arm received OPDIVO 3 mg/kg every 2 weeks. Patients in the comparator arm received YERVOY 3 mg/kg every 3 weeks for 4 doses followed by placebo every 2 weeks. Patients who had not received prior systemic anticancer therapy for unresectable or metastatic melanoma were enrolled regardless of PD-L1 expression.

‡ Exploratory follow-up conducted for CheckMate 067. The minimum follow-up for patients at the time of this analysis was 5 years.

IN PREVIOUSLY UNTREATED, UNRESECTABLE OR METASTATIC MELANOMA

Exploratory Analysis: PFS of the treatment arms at 5 years of minimum follow-up[4-6†‡]



The PFS results based on a longer-term follow-up (minimum of 5 years) were consistent with the results of the primary analysis (28 months)

OS | ORR | PFS

PFS: progression-free survival.

† CheckMate 067: A multicenter, double-blind, randomized trial in patients with unresectable or metastatic melanoma. Patients received OPDIVO + YERVOY (n=314), OPDIVO as a single agent (n=316), or YERVOY alone (n=315). Patients in the combination arm received OPDIVO 1 mg/kg and YERVOY 3 mg/kg every 3 weeks for the first 4 doses followed by OPDIVO 3 mg/kg as a single agent every 2 weeks. Patients in the OPDIVO single-agent arm received OPDIVO 3 mg/kg every 2 weeks. Patients in the comparator arm received YERVOY 3 mg/kg every 3 weeks for 4 doses followed by placebo every 2 weeks. Patients who had not received prior systemic anticancer therapy for unresectable or metastatic melanoma were enrolled regardless of PD-L1 expression.

‡ Exploratory follow-up conducted for CheckMate 067. The minimum follow-up for patients at the time of this analysis was 5 years.

OPDIVO (nivolumab) + Pr YERVOY (ipilimumab)

Generally well-tolerated safety profile[1]

Adverse reactions reported in ≥10% of patients in either study group (CheckMate 067)†

System Organ Class Preferred Term	OPDIVO + YERVOY (n=313)		OPDIVO (n=313)		YERVOY (n=311)	
	Any Grade (%)	Grades 3-4 (%)	Any Grade (%)	Grades 3-4 (%)	Any Grade (%)	Grades 3-4 (%)
General Disorders and Administration Site Conditions						
Fatigue	45.7	4.2	40.9	1.3	33.4	1.6
Pyrexia	19.2	0.6	7.0	0	6.8	0.3
Gastrointestinal Disorders						
Diarrhea	45.4	9.6	21.4	2.9	33.8	5.8
Nausea	28.1	2.2	13.1	0	16.4	0.6
Vomiting	16.0	2.6	7.0	0.3	7.7	0.3
Abdominal pain	12.8	0.3	8.3	0	11.3	1.0
Colitis	13.1	8.6	2.9	1.3	11.6	8.4
Skin and Subcutaneous Tissue Disorders						
Rash‡	46.6	5.4	30.4	1.6	36.7	2.6
Pruritus	35.8	1.9	21.4	0.3	36.3	0.3
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	13.4	0.3	9.3	0.3	6.8	0
Musculoskeletal pain§	8.6	0.3	10.9	0.3	8.4	0
Metabolism and Nutrition Disorders						
Decreased appetite	19.2	1.3	11.5	0	13.2	0.3

– Adapted from Product Monograph[1]

† Incidences presented in this table are based on reports of drug-related adverse events.

‡ Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash papulosquamous, rash vesicular, rash generalised, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform and drug eruption.

§ Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.

ADVERSE REACTIONS | LAB VALUES | imARs

Generally well-tolerated safety profile[1]

Adverse reactions reported in ≥10% of patients in either study group (CheckMate 067)†

System Organ Class Preferred Term	OPDIVO + YERVOY (n=313)		OPDIVO (n=313)		YERVOY (n=311)	
	Any Grade (%)	Grades 3-4 (%)	Any Grade (%)	Grades 3-4 (%)	Any Grade (%)	Grades 3-4 (%)
Endocrine Disorders						
Hypothyroidism	16.3	0.3	10.2	0	4.5	0
Hyperthyroidism	10.9	1.0	4.8	0	1.0	0
Respiratory, Thoracic, and Mediastinal Disorders						
Dyspnea	11.8	1.0	7.0	0.3	4.5	0
Nervous System Disorders						
Headache	10.9	0.6	7.7	0	8.0	0.3

– Adapted from Product Monograph[1]

The overall frequency of drug-related SAEs and AEs leading to discontinuation were higher in the OPDIVO + YERVOY than the monotherapy groups.

- Overall frequency of drug-related SAEs was 48.6%, 9.9% and 22.5% in the OPDIVO + YERVOY, OPDIVO monotherapy and YERVOY group, respectively.
- Discontinuation due to AEs was 47.0%, 18.2% and 25.1% in the OPDIVO + YERVOY, OPDIVO monotherapy and YERVOY group, respectively.

Based on a follow-up of 60 months, there were no new safety signals observed and therefore no meaningful changes occurred in the safety profile of OPDIVO and OPDIVO + YERVOY.

SAEs: serious adverse events; AE: adverse events.
† Incidences presented in this table are based on reports of drug-related adverse events.

ADVERSE REACTIONS | LAB VALUES | imARs

Generally well-tolerated safety profile[1]

Selected laboratory abnormalities worsening from baseline occurring in >10% of patients on OPDIVO + YERVOY or OPDIVO and at a higher incidence than in YERVOY arm (between arm difference of ≥5% [all Grades] or ≥2% [Grades 3-4]) (CheckMate 067)†

Laboratory Abnormality	OPDIVO + YERVOY (n=313)		OPDIVO (n=313)		YERVOY (n=311)	
	Any Grade (%)	Grades 3-4 (%)	Any Grade (%)	Grades 3-4 (%)	Any Grade (%)	Grades 3-4 (%)
Decreased hemoglobin‡	52	2.7	41	2.6	41	5.6
Decreased platelet count	12	1.4	10	0.3	5	0.3
Decreased leukocytes	14	0.3	19	0.3	6	0.3
Decreased lymphocytes (Absolute)	39	5.1	41	4.9	29	4.0
Decreased absolute neutrophil count	14	0.7	16	0.3	6	0.3
Increased alkaline phosphatase	41	5.9	27	2.0	23	2.0
Increased ALT	55	15.8	25	3.0	29	2.7
Increased AST	52	13.4	29	3.7	29	1.7
Bilirubin, total	15	1.7	11	1.0	6	0
Increased creatinine	26	2.7	18	0.7	16	1.3
Increased amylase	27	9.5	19	2.7	15	1.6
Increased lipase	43	21.7	32	12	24	6.6
Hyperglycemia	52	5.3	47	7.4	28	0
Hyponatremia	45	9.9	22	3.3	26	6.7
Hypocalcemia	32	1.1	16	0.7	21	0.7
Hypokalemia	18	4.4	9	1.3	10	1.3

– 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 (range: 75 to 297); single-agent OPDIVO (range: 81 to 307); YERVOY (range: 61 to 304).

‡ Grade 4 for hemoglobin is not applicable per anemia criteria in CTCAE v4.0.

ADVERSE REACTIONS | LAB VALUES | imARs

Immune-related adverse reactions (imARs)[1]

Incidence and resolution of imARs associated with OPDIVO (1 mg/kg) in combination with YERVOY (3 mg/kg) in melanoma (N=448)

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	31.4%	1.5 (0.0-10.1)	45.4%	(0.4-155.4+)
Gastrointestinal	46.7%	1.2 (0.0-22.6)	89%	3.0 (0.1-159.4)
Hepatic	29.5%	1.4 (0.0-30.1)	94%	5.1 (0.1-106.9)
Pulmonary	7.8%	2.3 (0.7-6.7)	94.3%	6.1 (0.3-35.1)
Renal	5.1%	2.6 (0.5-14.7)	91.3%	2.14 (0.1-125.1+)
Skin	65.0%	0.5 (0.0-19.4)	66%	11.4 (0.1-150.1+)

– 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.

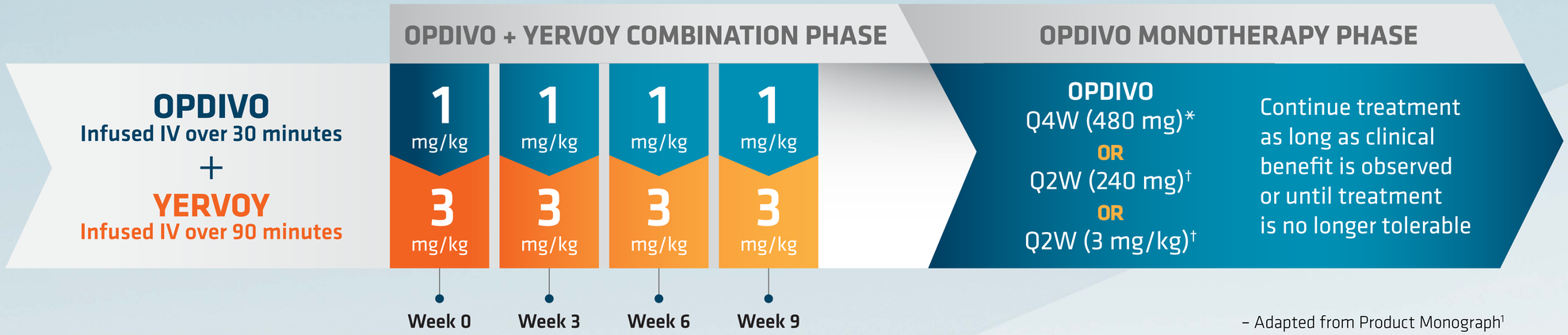
Immune-mediated adverse reactions may involve any organ system. While most of these reactions occurred during treatment, onset months after the last dose has been reported.

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

ADVERSE REACTIONS | LAB VALUES | imARs

Recommended dosing for OPDIVO + YERVOY combination therapy[1]

Administer OPDIVO followed by YERVOY on the same day.



Flexibility of Q2W or Q4W dosing options in the monotherapy phase

– Adapted from Product Monograph[1]

* 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.

In previously untreated, unresectable or metastatic melanoma[1,2]

At the primary analysis, OPDIVO + YERVOY[1†ʃ]

Demonstrated a statistically significant OS benefit vs. YERVOY[1]

- **45% reduced risk of death** (HR: 0.55 [98% CI: 0.42, 0.72; $p<0.0001$])
  Number of events: 128/314 (OPDIVO + YERVOY arm) vs. 197/315 (YERVOY arm)

Improved ORR vs. YERVOY[1]

- **3x greater ORR** for OPDIVO + YERVOY shown vs. YERVOY ($p<0.0001$)
  - ORR of 58% for OPDIVO + YERVOY patients (complete response [11%], partial response [46%])
  - ORR of 44% for OPDIVO patients (complete response [9%], partial response [35%])
  - ORR of 19% (95% CI: 15, 24) for YERVOY patients (complete response [2%], partial response [17%])

Demonstrated a statistically significant improvement in PFS vs. YERVOY alone[1]

- **58% reduced risk of disease progression or death** with OPDIVO + YERVOY vs. YERVOY alone (HR: 0.42 [99.5% CI: 0.31, 0.57; $p<0.0001$])
  Number of events: 151/314 (OPDIVO + YERVOY arm) vs. 234/315 (YERVOY arm)

The OS, ORR, PFS results based on a longer follow-up (minimum of 5 years) were consistent with the results of the primary analysis (28 months).

EFFICACY DATA | SAFETY PROFILE

OS: overall survival; PFS: progression-free survival; ORR: objective response rate; CI: confidence interval; CR: complete response; PR: partial response; HR: Hazard ratio.

† CheckMate 067: A multicenter, double-blind, randomized trial in patients with unresectable or metastatic melanoma. Patients received OPDIVO + YERVOY (n=314), OPDIVO as a single agent (n=316), or YERVOY alone (n=315). Patients in the combination arm received OPDIVO 1 mg/kg and YERVOY 3 mg/kg every 3 weeks for the first 4 doses followed by OPDIVO 3 mg/kg as a single agent every 2 weeks. Patients in the OPDIVO single-agent arm received OPDIVO 3 mg/kg every 2 weeks. Patients in the comparator arm received YERVOY 3 mg/kg every 3 weeks for 4 doses followed by placebo every 2 weeks. Patients who had not received prior systemic anticancer therapy for unresectable or metastatic melanoma were enrolled regardless of PD-L1 expression.

ʃ Overall survival data was based on a minimum follow-up of 28 months whereas the progression-free survival and objective response rate data was based on a minimum follow-up of 9 months.

OPDIVO (nivolumab) + YERVOY (ipilimumab)

In previously untreated, unresectable or metastatic melanoma[1,2]

OPDIVO + YERVOY had a generally well-tolerated safety profile

- The most common adverse reactions in either the OPDIVO + YERVOY or the OPDIVO monotherapy arm (≥20% of patients) were fatigue (45.7%), rash (46.6%), diarrhea (45.4%), nausea (28.1%) and pruritis (35.8%).
- Based on a follow-up of 60 months, there were no new safety signals observed and therefore no meaningful changes occurred in the safety profile of OPDIVO and OPDIVO + YERVOY.

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

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.

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4. Larkin J *et al*. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med* 2019; 381:1535-1546.

5. Larkin J *et al.* Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma – Supplementary Appendix. *N Engl J Med* 2019; 381:1535-1546.

6. Data on file – 5-year PFS (# of events). Bristol-Myers Squibb Canada Co.

Bristol Myers Squibb

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OPDIVO (nivolumab) + Pr YERVOY (ipilimumab)