Checkmate 238: 5-year follow-up of OPDIVO® (nivolumab) in the adjuvant treatment of melanoma

OPDIVO is indicated for the adjuvant treatment of patients with completely resected melanoma with lymph node involvement (stage III) or metastatic (stage IV) disease, including *BRAF* MT and WT patients

MT=mutant; WT=wild-type.

OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company.

Select Important Safety Information

Summary of Warnings and Precautions

OPDIVO® (nivolumab) is associated with the following Warnings and Precautions: severe and fatal 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.

- Immune-mediated adverse reactions (IMAR), which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis and hepatotoxicity, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, and immune-mediated nephritis with renal dysfunction. Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. Withhold or permanently discontinue based on severity and type of reaction.

- Infusion-related reactions: Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions.

- Complications of allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody.

Please see Important Safety Information for OPDIVO throughout this presentation and US Full Prescribing Information for OPDIVO provided at this presentation.

Select Important Safety Information (cont’d)

- Embryo-fetal toxicity: OPDIVO® (nivolumab) can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use effective contraception.
- Increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone: 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.

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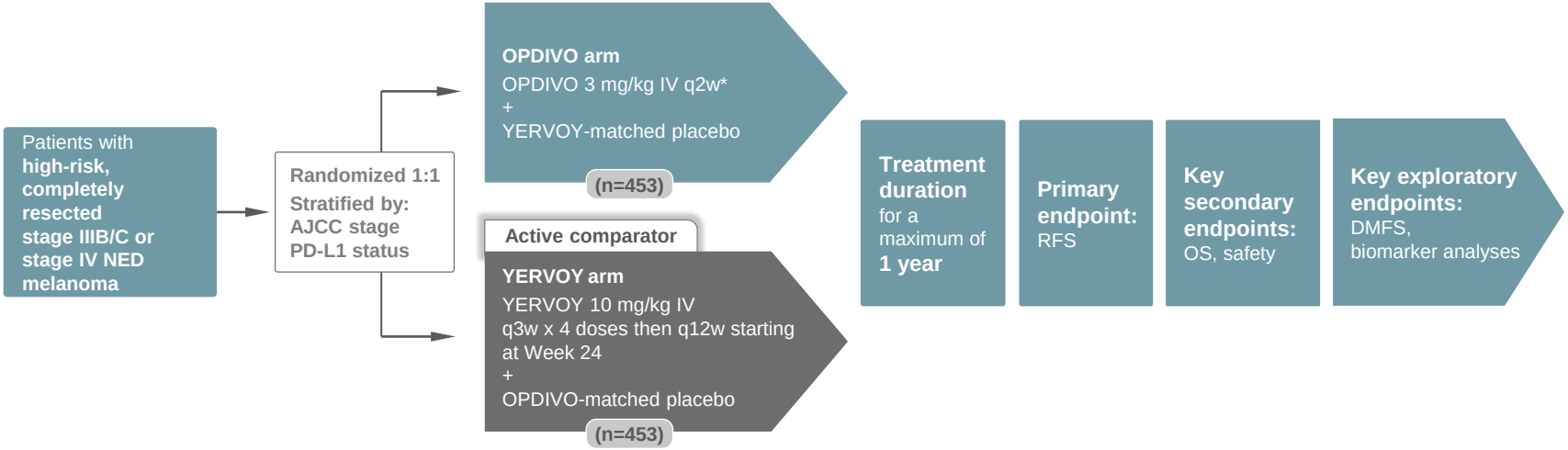
Checkmate 238: Study design

- Checkmate 238: OPDIVO® (nivolumab) monotherapy vs YERVOY ® (ipilimumab)[1-4]



- Checkmate 238 excluded patients who received prior therapy for melanoma, except for surgery for melanoma lesions, adjuvant radiation after neurosurgical resection, and prior adjuvant interferon (unless completed ≥6 months prior to randomization)[1]

*The recommended dosage of OPDIVO is either 240 mg q2w or 480 mg q4w administered as an intravenous infusion over 30 minutes until disease recurrence or unacceptable toxicity for up to 1 year.[1]
AJCC=American Joint Committee on Cancer; DMFS=distant metastasis-free survival; IV=intravenous; NED=no evidence of disease; OS=overall survival; PD-L1=programmed death ligand 1; q2w=every 2 weeks; q3w=every 3 weeks; q4w=every 4 weeks; q12w=every 12 weeks; RFS=recurrence-free survival.

1. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. 2. Weber J et al. *N Engl J Med.* 2017;377(19):1824-1835. 3. Weber J et al. *N Engl J Med.* 2017; 377(19):1824-1835 [supplementary appendix]. 4. Weber J et al. Oral presentation at SMR 2021.

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Patient baseline characteristics

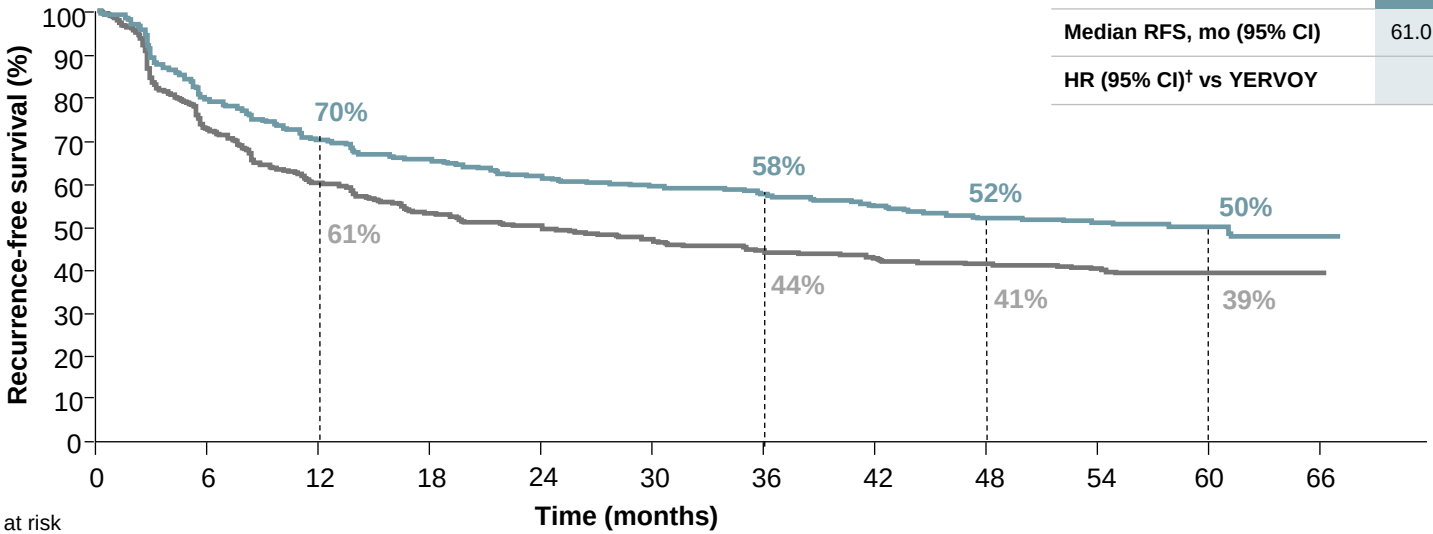
	OPDIVO® (nivolumab) (n=453)	YERVOY® (ipilimumab) (n=453)
Median age, years (range)	56 (19–83)	54 (18–86)
Male, n (%)	258 (57.0)	269 (59.4)
Stage IIIB–C, n (%)	368 (81.2)*	366 (80.8)
Macroscopic lymph node involvement (% of stage IIIB–IIIC)	217 (59.0)	214 (58.5)
Ulceration (% of stage IIIB–IIIC)	155 (42.1)	137 (37.4)
Stage IV, n (%)	82 (18.1)	87 (19.2)
M1c without brain metastases (% of stage IV)	14 (17.1)	15 (17.2)
Tumor PD-L1 expression ≥5%,† n (%)	153 (33.8)	154 (34.0)
***BRAF* mutation, n (%)**	187 (41.3)	194 (42.8)
LDH ≤ULN, n (%)	413 (91.2)	411 (90.7)
Melanoma subtype, n (%)		
Cutaneous	388 (85.7)	377 (83.2)
Mucosal	16 (3.5)	13 (2.9)
Acral	16 (3.5)	18 (4.0)

*Two additional patients had stage IIIA disease. †PD-L1 IHC 28-8 pharmDx assay.
LDH=lactate dehydrogenase; PD-L1=programmed death ligand 1; ULN=upper limit of normal.
Weber J et al. Oral presentation at SMR 2021.

Please see Important Safety Information for OPDIVO throughout this presentation and US Full Prescribing Information for OPDIVO provided at this presentation.

OPDIVO® (nivolumab): RFS analysis in the ITT population through 5 years[1-3]

	OPDIVO (n=453)	YERVOY® (ipilimumab) (n=453)
Median RFS, mo (95% CI)	61.0 (42.5–NR)*	24.1 (16.6–35.1)
HR (95% CI)† vs YERVOY	0.72 (0.60–0.86)	



Number at risk

OPDIVO	453	354	311	283	262	245	234	220	202	176	94	4
YERVOY	453	316	253	220	201	185	173	165	152	134	78	1

Interim analysis at 18 months[4,5]:
- OPDIVO vs YERVOY: HR=0.65 (95% CI: 0.53–0.80); *P*<0.0001

Final analysis at 3 years[3]:
- OPDIVO vs YERVOY: HR=0.68 (95% CI: 0.56–0.82); *P*<0.0001

Follow-up analysis at 4 years[2]:
- OPDIVO vs YERVOY: HR=0.71 (95% CI: 0.60–0.86)

*Median not stable.[1] †Stratified.[1]

CI=confidence interval; HR=hazard ratio; ITT=intent to treat; mo=month; NR=not reached; RFS=recurrence-free survival.

1. Weber J et al. Oral presentation at SMR 2021. 2. Weber J et al. Oral presentation at ESMO 2020. Abstract 1076O. 3. Weber J et al. Oral presentation at ESMO 2019. Abstract 2801. 4. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. 5. Weber J et al. *N Engl J Med*. 2017;377(19):1824-1835.

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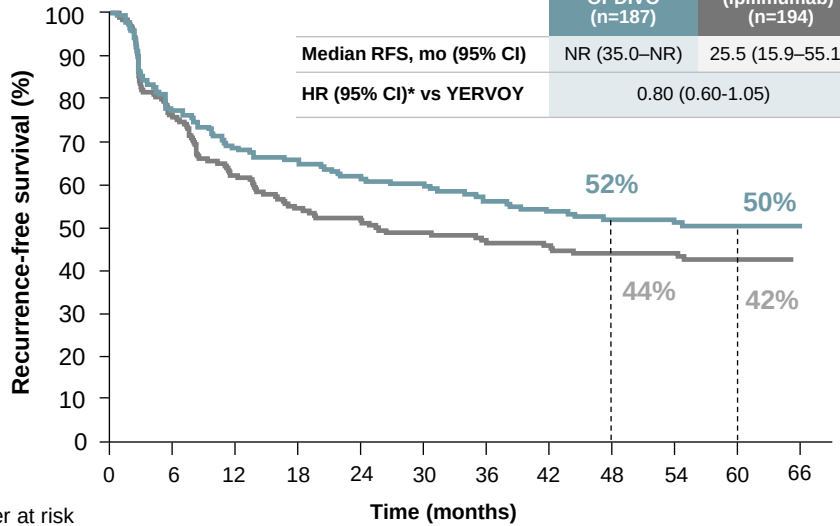
OPDIVO® (nivolumab): RFS in *BRAF* MT and WT patients[1]

BRAF MT

	OPDIVO (n=187)	YERVOY® (ipilimumab) (n=194)
Median RFS, mo (95% CI)	NR (35.0–NR)	25.5 (15.9–55.1)
HR (95% CI)* vs YERVOY	0.80 (0.60-1.05)	

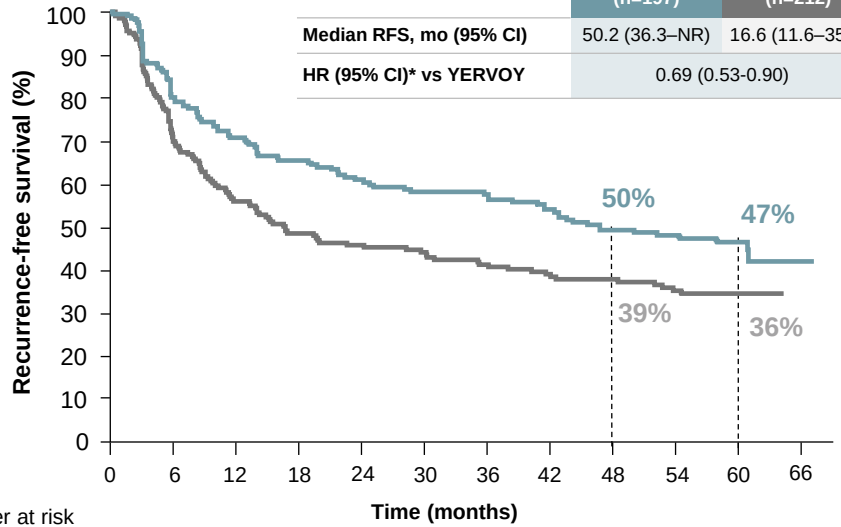


Number at risk

OPDIVO	187	142	126	119	110	103	95	90	83	72	37	2
YERVOY	194	143	113	98	91	83	78	76	70	66	40	0

BRAF WT

	OPDIVO (n=197)	YERVOY (n=212)
Median RFS, mo (95% CI)	50.2 (36.3–NR)	16.6 (11.6–35.1)
HR (95% CI)* vs YERVOY	0.69 (0.53-0.90)	



Number at risk

OPDIVO	197	155	137	121	111	104	101	94	84	73	40	1
YERVOY	212	139	110	93	85	81	76	70	64	54	31	0

RFS by *BRAF* status was an exploratory pre-specified analysis.[2]
*Unstratified.[1]
CI=confidence interval; HR=hazard ratio; mo=month; MT=mutant; NR=not reached; RFS=recurrence-free survival; WT=wild-type.
1. Weber J et al. Oral presentation at SMR 2021. 2. Weber J et al. *N Engl J Med*. 2017;377(19):1824-1835 [protocol].

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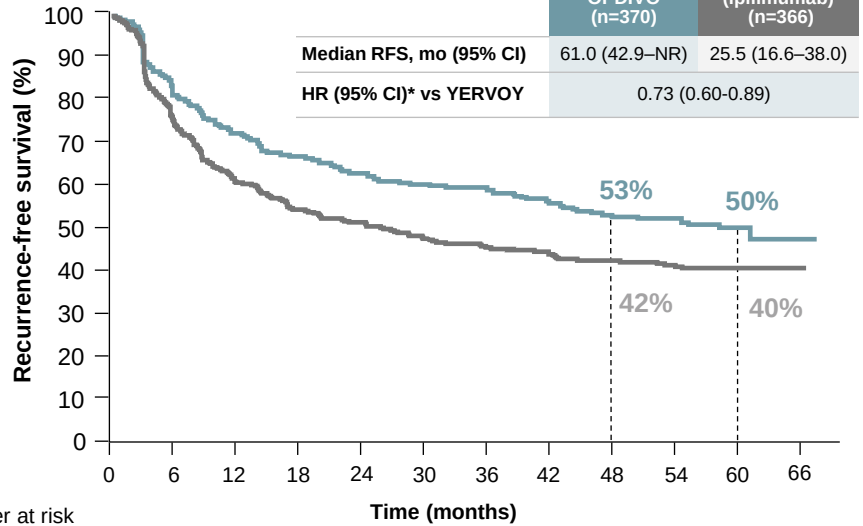
OPDIVO® (nivolumab): RFS in stages IIIB/C and IV

Stage IIIB/C

	OPDIVO (n=370)	YERVOY® (ipilimumab) (n=366)
Median RFS, mo (95% CI)	61.0 (42.9–NR)	25.5 (16.6–38.0)
HR (95% CI)* vs YERVOY	0.73 (0.60-0.89)	

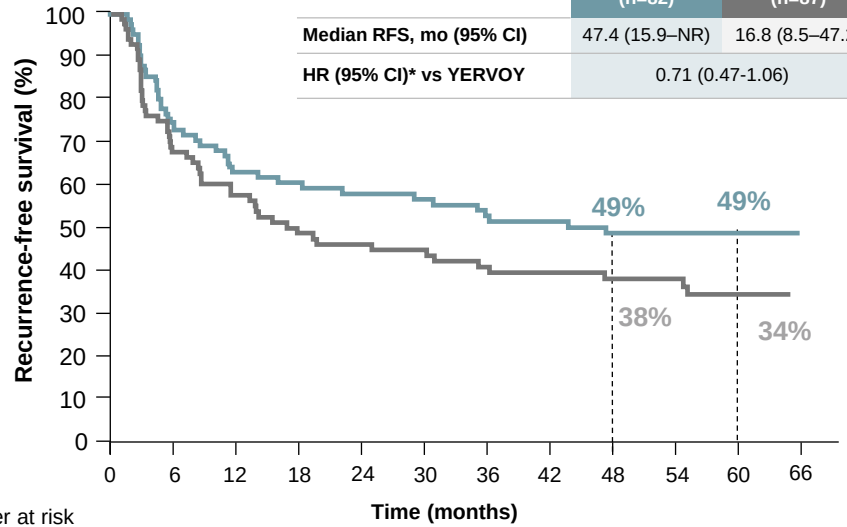


Number at risk

OPDIVO	370	294	260	235	217	201	194	181	166	143	78	4
YERVOY	366	261	208	182	165	151	143	136	126	111	68	1

Stage IV

	OPDIVO (n=82)	YERVOY (n=87)
Median RFS, mo (95% CI)	47.4 (15.9–NR)	16.8 (8.5–47.2)
HR (95% CI)* vs YERVOY	0.71 (0.47-1.06)	



Number at risk

OPDIVO	82	59	51	48	45	44	40	39	36	33	16	0
YERVOY	87	55	45	38	36	34	30	29	26	23	10	0

*Unstratified.
CI=confidence interval; HR=hazard ratio; mo=month; NR=not reached; RFS=recurrence-free survival.
Weber J et al. Oral presentation at SMR 2021.

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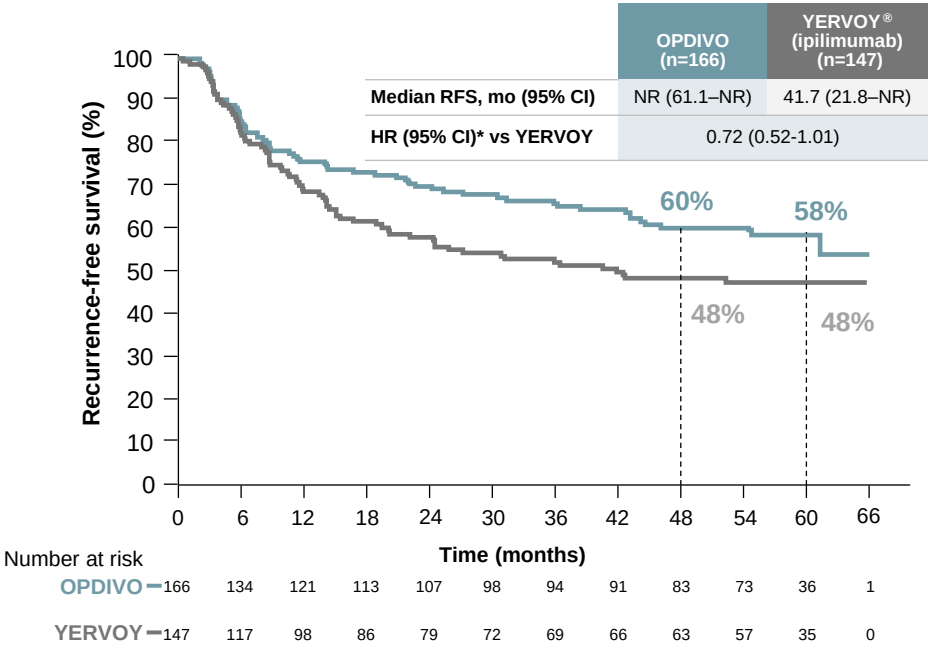
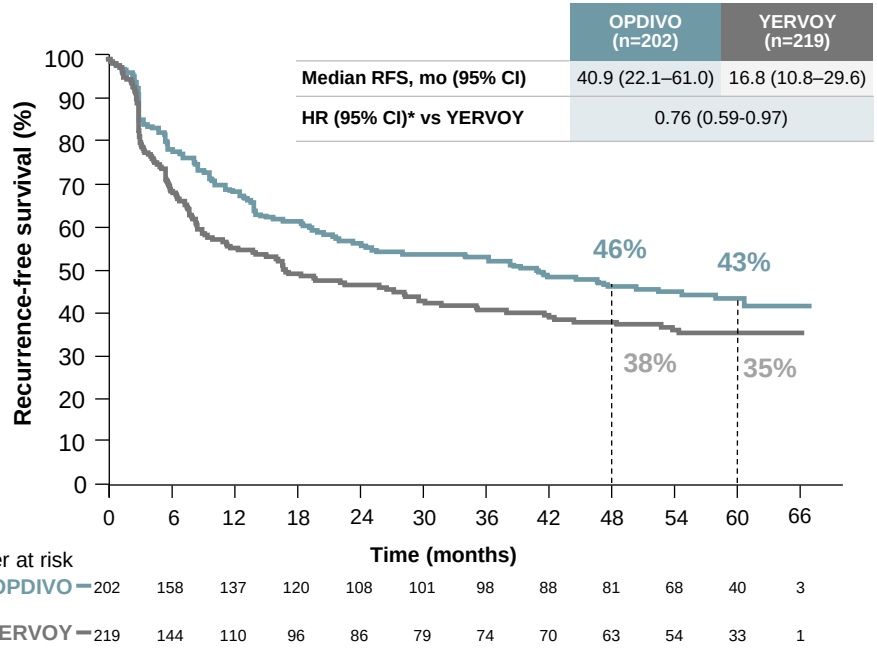
OPDIVO® (nivolumab): RFS in stages IIIB and IIIC

Stage IIIB



Stage IIIC



*Unstratified.
CI=confidence interval; HR=hazard ratio; mo=month; NR=not reached; RFS=recurrence-free survival.
Weber J et al. Oral presentation at SMR 2021.

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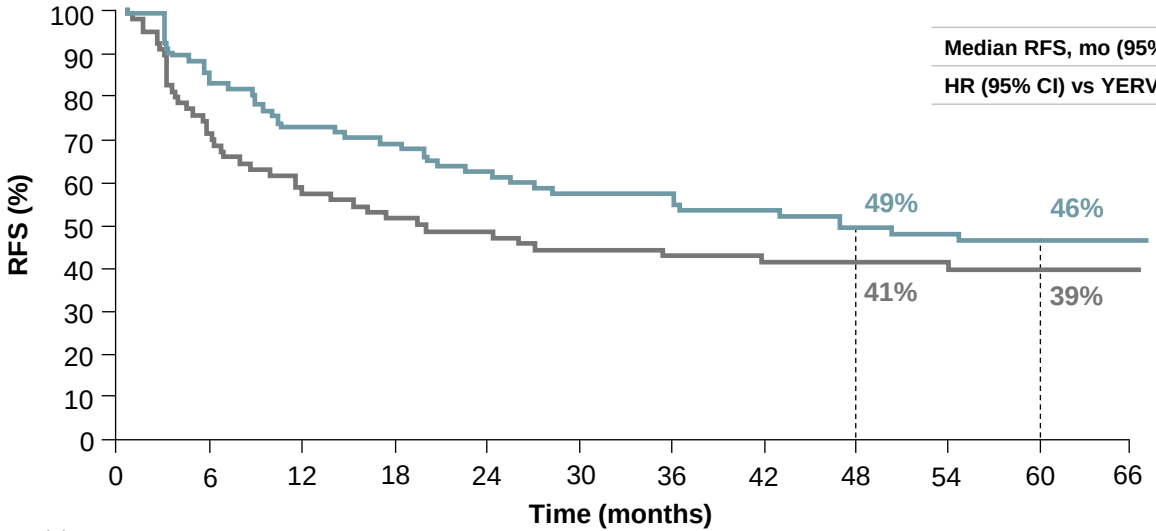
OPDIVO® (nivolumab): RFS in patients with in-transit metastases without nodal involvement

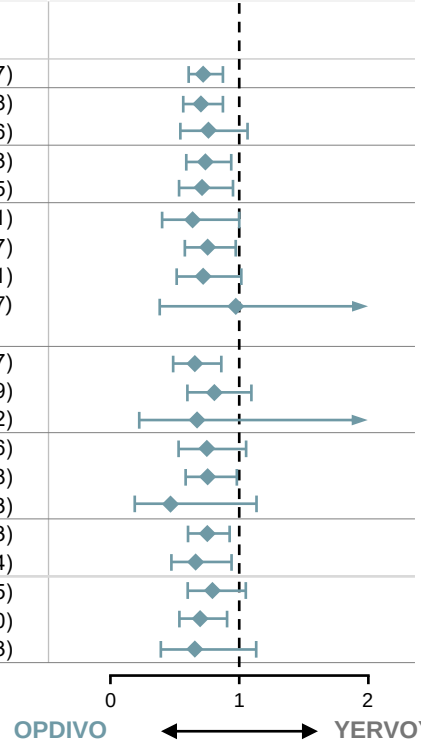
	OPDIVO (n=81)	YERVOY® (ipilimumab) (n=74)
Median RFS, mo (95% CI)	46.8 (24.2–NR)	19.1 (9.4–NR)
HR (95% CI) vs YERVOY	0.73 (0.47–1.12)	



CI=confidence interval; HR=hazard ratio; mo=month; NR=not reached; RFS=recurrence-free survival.
Data on file. BMS-REF-NIVO-0111. Princeton, NJ: Bristol-Myers Squibb Company. 2021.
Please see Important Safety Information for OPDIVO throughout this presentation and US Full Prescribing Information for OPDIVO provided at this presentation.

OPDIVO® (nivolumab): RFS HR in pre-specified subgroup analysis

Subgroup		OPDIVO 3 mg/kg No. of events (No. of subjects)	YERVOY® (ipilimumab) 10 mg/kg No. of events (No. of subjects)	Unstratified HR* (95% CI)
Overall	Overall	218 (453)	257 (453)	0.73 (0.61–0.87)
Age	<65 years	147 (333)	184 (339)	0.70 (0.57–0.88)
	≥65 years	71 (120)	73 (114)	0.76 (0.55–1.06)
Sex	Male	131 (258)	157 (269)	0.74 (0.59–0.93)
	Female	87 (195)	100 (184)	0.71 (0.54–0.95)
Stage	IIIB	65 (166)	74 (147)	0.72 (0.52–1.01)
	IIIC	111 (202)	131 (219)	0.76 (0.59–0.97)
	IV M1a–M1b	32 (62)	43 (66)	0.64 (0.40–1.01)
	IV M1c	9 (20)	9 (21)	0.98 (0.39–2.47)
	Not reported	1 (1)	0 (0)	–
Stage III: ulceration	Absent	81 (201)	115 (213)	0.65 (0.49–0.87)
	Present	89 (155)	83 (137)	0.81 (0.60–1.09)
	Not reported	6 (14)	7 (16)	0.67 (0.22–2.02)
Stage III: lymph node involvement	Microscopic	58 (128)	72 (134)	0.75 (0.53–1.06)
	Macroscopic	109 (217)	122 (214)	0.75 (0.58–0.98)
	Not reported	9 (25)	11 (18)	0.47 (0.19–1.13)
PD-L1 status†	<5% or indeterminate	161 (300)	183 (299)	0.75 (0.61–0.93)
	≥5%	57 (153)	74 (154)	0.66 (0.47–0.94)
***BRAF* mutation status‡**	Mutant	90 (187)	106 (194)	0.80 (0.60–1.05)
	Wild-type	100 (197)	125 (212)	0.69 (0.53–0.90)
	Not reported	28 (69)	26 (47)	0.66 (0.39–1.13)

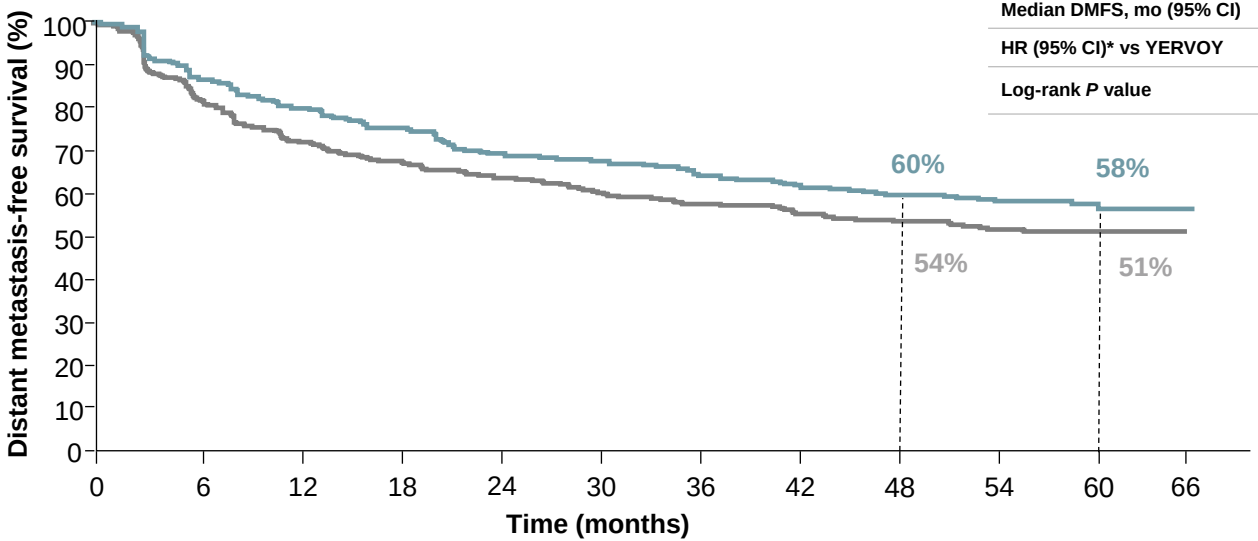


*Stratified HR=0.72 (95% CI: 0.60–0.86). †PD-L1 IHC 28-8 pharmDx assay. ‡V600E/K.
CI=confidence interval; HR=hazard ratio; no=number; PD-L1=programmed cell death ligand 1; RFS=recurrence-free survival.
Weber J et al. Oral presentation at SMR 2021. [

Please see Important Safety Information for OPDIVO throughout this presentation and US Full Prescribing Information for OPDIVO provided at this presentation.

OPDIVO® (nivolumab): DMFS in stage IIIB/C resected melanoma

	OPDIVO (n=370)	YERVOY® (ipilimumab) (n=366)
Median DMFS, mo (95% CI)	NR	NR (42.4–NR)
HR (95% CI)* vs YERVOY	0.79 (0.63–0.99)	
Log-rank *P* value	0.0397	



Number at risk

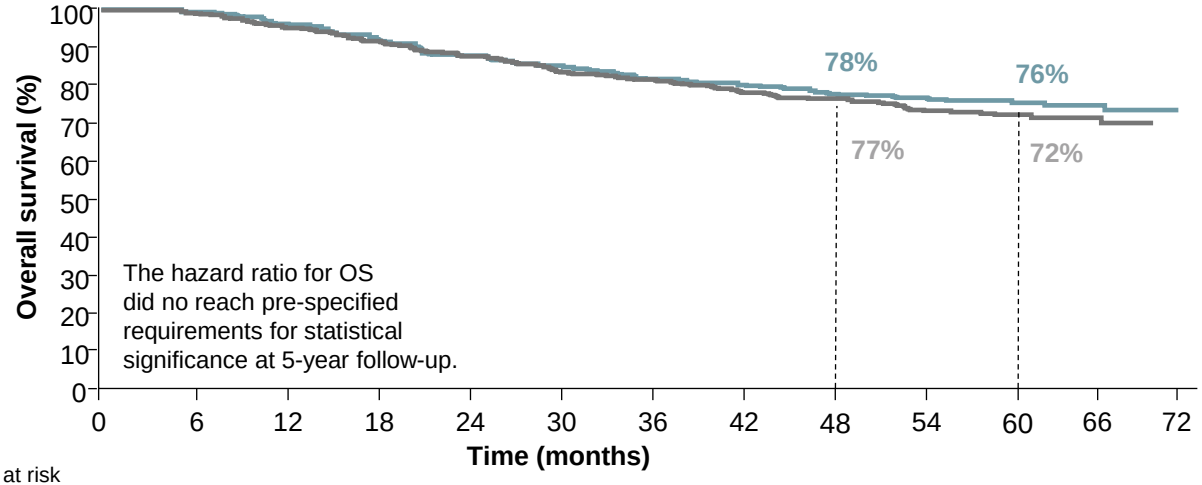
OPDIVO	370	312	284	256	232	220	210	197	182	156	87	4
YERVOY	366	287	244	222	206	188	173	163	150	130	76	2

*Stratified.
CI=confidence interval; DMFS=distant metastasis-free survival; HR=hazard ratio; mo=month; NR=not reached.
Weber J et al. Oral presentation at SMR 2021.

Please see Important Safety Information for OPDIVO throughout this presentation and US Full Prescribing Information for OPDIVO provided at this presentation.

OPDIVO® (nivolumab): OS in the ITT population[1]

	OPDIVO (n=453)	YERVOY® (ipilimumab) (n=453)
Median OS, mo (95% CI)	NR	NR
HR (95% CI)* vs YERVOY	0.86 (0.66–1.12)	



- At the 60-month analysis, there were 228 total events (108 for OPDIVO and 120 for YERVOY) vs the 302 events anticipated[1]
- Current total events yield ~75% power to detect a significant difference between OPDIVO and YERVOY[1,2]

*Stratified.[1]

CI=confidence interval; HR=hazard ratio; ITT=intent to treat; mo=month; NR=not reached; OS=overall survival.

1. Weber J et al. Oral presentation at SMR 2021. 2. Ascierto PA et al. *Lancet Oncol*. 2020;21:1465-1477.

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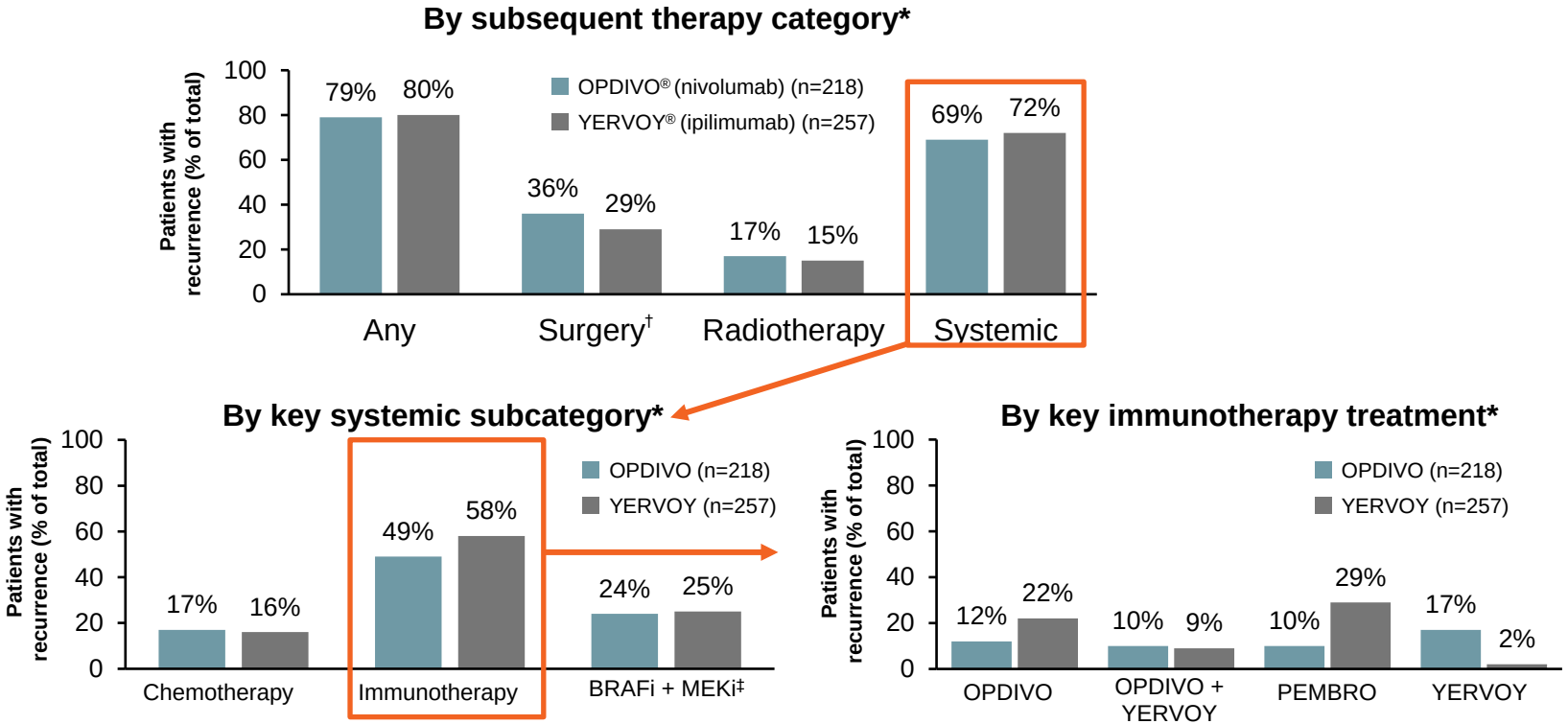
Subsequent therapy in patients with recurrence



*Some patients received >1 post-protocol therapy type/agent. †Included diagnostic checks and biopsy. ‡Dabrafenib and trametinib and/or cobimetinib and vemurafenib.
BRAFi=BRAF inhibitor; MEKi=mitogen-activated protein kinase inhibitor

Weber J et al. Oral presentation at SMR 2021.

Select safety results in Checkmate 238

Adverse reactions occurring in ≥10% of patients treated with OPDIVO® (nivolumab)[1,2]

		OPDIVO 3 mg/kg (n=452)		YERVOY® (ipilimumab) 10 mg/kg (n=453)	
		Any grade	Grades 3–4	Any grade	Grades 3–4
Discontinuation due to adverse events, %		9	-	42	-
Grade 3–4 adverse events, %		-	25.4	-	55.2
General disorders, %	Fatigue*	57	0.9	55	2.4
Gastrointestinal disorders, %	Diarrhea	37	2.4	55	11
	Nausea	23	0.2	28	0
	Abdominal pain†	21	0.2	23	0.9
	Constipation	10	0	9	0
Skin and subcutaneous tissue disorders, %	Rash‡	35	1.1	47	5.3
	Pruritus	28	0	37	1.1
Musculoskeletal and connective tissue disorders, %	Musculoskeletal pain§	32	0.4	27	0.4
	Arthralgia	19	0.4	13	0.4
Nervous system disorders, %	Headache	23	0.4	31	2.0
	Dizziness‖	11	0	8	0
Infections, %	Upper respiratory tract infection¶	22	0	15	0.2
Respiratory, thoracic, and mediastinal disorders, %	Cough/productive cough	19	0	19	0
	Dyspnea/exertional dyspnea	10	0.4	10	0.2
Endocrine disorders, %	Hypothyroidism#	12	0.2	7.5	0.4

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[1]
*Includes asthenia.[1] †Includes abdominal discomfort, lower abdominal pain, upper abdominal pain, and abdominal tenderness.[1] ‡Includes dermatitis also described as acneiform, allergic, bullous, or exfoliative and rash described as generalized, erythematous, macular, papular, maculopapular, pruritic, pustular, vesicular, or butterfly, and drug eruption.[1] §Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, spinal pain, and pain in extremity.[1] ‖Includes postural dizziness and vertigo.[1] ¶Includes upper respiratory tract infection, including viral respiratory tract infection, lower respiratory tract infection, rhinitis, pharyngitis, and nasopharyngitis.[1] #Includes secondary hypothyroidism and autoimmune hypothyroidism.[1]

1. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. 2. Weber J et al. *N Engl J Med*. 2017;377(19):1824-1835.

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

Immune-Mediated Pneumonitis

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

Please see additional Important Safety Information for OPDIVO throughout this presentation and US Full Prescribing Information for OPDIVO provided at this presentation.

Important Safety Information (cont'd)

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

Immune-Mediated Colitis

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

Immune-Mediated Hepatitis and Hepatotoxicity

- OPDIVO can cause immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%).

Important Safety Information (cont'd)

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

Immune-Mediated Endocrinopathies

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

Immune-Mediated Nephritis and Renal Dysfunction

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

Please see additional Important Safety Information for OPDIVO throughout this presentation and US Full Prescribing Information for OPDIVO provided at this presentation.

Important Safety Information (cont'd)

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

Immune-Mediated Dermatologic Adverse Reactions

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

Other Immune-Mediated Adverse Reactions

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

Important Safety Information (cont'd)

Infusion-Related Reactions

- OPDIVO® (nivolumab) can cause severe infusion-related reactions. Discontinue OPDIVO in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation

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

Embryo-Fetal Toxicity

- Based on its mechanism of action and findings from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months after the last dose.

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Important Safety Information (cont'd)

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

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

Lactation

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

Serious Adverse Reactions

- In Checkmate 238, serious adverse reactions occurred in 18% of patients receiving OPDIVO (n=452). Grade 3 or 4 adverse reactions occurred in 25% of OPDIVO-treated patients (n=452). The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of OPDIVO-treated patients were diarrhea and increased lipase and amylase.

Common Adverse Reactions

- In Checkmate 238, the most common adverse reactions (≥20%) reported in OPDIVO-treated patients (n=452) vs ipilimumab-treated patients (n=453) were fatigue (57% vs 55%), diarrhea (37% vs 55%), rash (35% vs 47%), musculoskeletal pain (32% vs 27%), pruritus (28% vs 37%), headache (23% vs 31%), nausea (23% vs 28%), upper respiratory infection (22% vs 15%), and abdominal pain (21% vs 23%). The most common immune-mediated adverse reactions were rash (16%), diarrhea/colitis (6%), and hepatitis (3%).

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