Checkmate 067: 7.5-year follow-up of OPDIVO® (nivolumab) + YERVOY® (ipilimumab) in 1L metastatic melanoma

OPDIVO, as a single agent or in combination with YERVOY, is indicated for the treatment of adult patients with unresectable or metastatic melanoma, including *BRAF* MT and WT patients

1L=first-line; MT=mutant; WT=wild-type.

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

Please see Important Safety Information for OPDIVO and YERVOY throughout this presentation and U.S. Full Prescribing Information for OPDIVO and YERVOY provided in this presentation.

7356-US-2200265 06/22

Select Important Safety Information

OPDIVO® (nivolumab) and YERVOY® (ipilimumab) are 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 nephritis with renal dysfunction, and immune-mediated dermatologic adverse reactions can occur at any time during treatment or after discontinuation. Monitor for early identification and management. Evaluate liver enzymes, creatinine, adrenocorticotropic hormone level, and thyroid function at baseline and periodically during treatment for OPDIVO, and before each dose for YERVOY. Withhold or permanently discontinue based on severity and type of reaction.

- Infusion-related reactions: Discontinue OPDIVO and YERVOY 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 OPDIVO or YERVOY.

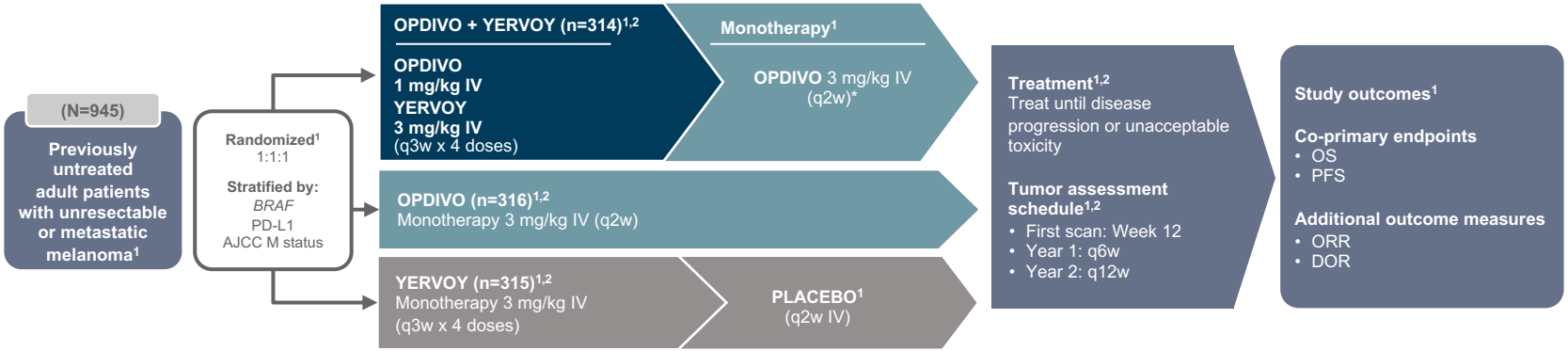
- Embryo-fetal toxicity: OPDIVO and YERVOY can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use effective contraception.

- 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.

Please see additional Important Safety Information for OPDIVO and YERVOY throughout this presentation and U.S. Full Prescribing Information for OPDIVO and YERVOY provided in this presentation.

A 3-arm phase 3 study in the 1L treatment of metastatic melanoma[1,2]

- Checkmate 067: OPDIVO® (nivolumab) + YERVOY® (ipilimumab) or OPDIVO monotherapy vs YERVOY[1]



The primary endpoints compared OPDIVO + YERVOY with YERVOY and OPDIVO monotherapy with YERVOY.[1,2]

Key exclusion criteria[1]

- Patients with active brain metastasis, ocular melanoma, autoimmune disease, a medical condition requiring systemic treatment with corticosteroids (more than 10 mg daily of a prednisone equivalent) or other immunosuppressive medication within 14 days of the start of study therapy, a positive test result for hepatitis B or C, and a history of HIV

*The recommended dose of OPDIVO is 1 mg/kg administered as an intravenous infusion over 30 minutes followed by YERVOY 3 mg/kg, administered as an intravenous infusion over 30 minutes on the same day, q3w for a maximum of 4 doses or until unacceptable toxicity, whichever occurs earlier. After completing 4 doses of the combination, administer OPDIVO as a single agent, either 240 mg q2w or 480 mg q4w, administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity. Review the Prescribing Information for YERVOY for additional information prior to initiation.[1]

1L=first-line; AJCC=American Joint Committee on Cancer; DOR=duration of response; HIV=human immunodeficiency virus; IV=intravenous; M=metastasis; ORR=overall response rate; OS=overall survival; PD-L1=programmed death-ligand 1; PFS=progression-free survival; q2w=every 2 weeks; q3w=every 3 weeks; q6w=every 6 weeks; q12w=every 12 weeks.

1. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. 2. Larkin J, et al. *N Engl J Med*. 2019;381(16):1535-1546.

Please see Important Safety Information for OPDIVO and YERVOY throughout this presentation and U.S. Full Prescribing Information for OPDIVO and YERVOY provided in this presentation.

Evaluated across a broad range of previously untreated patients[1-4]

Baseline patient characteristics[1]

	All randomized population (N=945)
Median age, years	61 (40% ≥65 years)
Gender Male	 65%
Race White	 97%
ECOG performance status 0 1	 73% 27%
AJCC Stage IV	93%
M1c stage disease	58%
LDH >ULN	36%
History of brain metastases	4%
***BRAF* mutant**	32%
PD-L1 ≥1%	58%*
PD-L1 ≥5%	26%*

*Of PD-L1–evaluable patients. PD-L1 status undetermined: n=102.[3]

AJCC=American Joint Committee on Cancer; ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; M=metastasis; MT=mutant; PD-L1=programmed death-ligand 1; ULN=upper limit of normal; WT=wild-type.

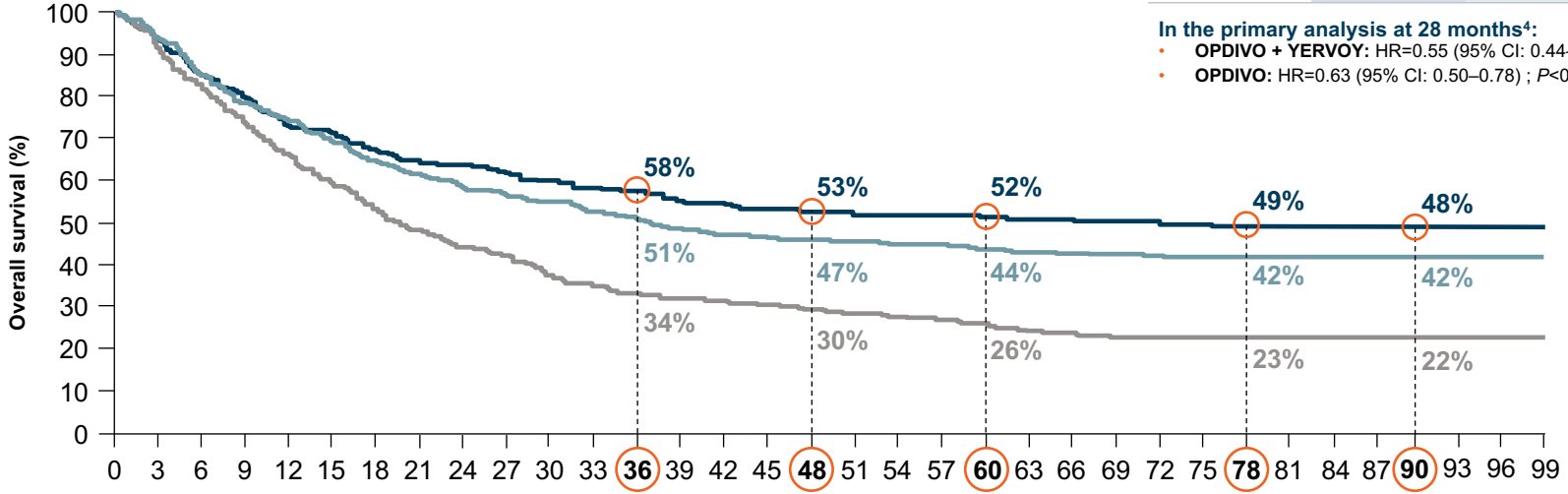
1. OPDIVO® (nivolumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. 2. Hodi FS, et al. *Lancet Oncol*. 2018;19(11):1480-1492. 3. Hodi FS, et al. *Lancet Oncol*. 2018;19(11):1480-1492[supplementary appendix]. 4. Larkin J, et al. *N Engl J Med*. 2015;373(1):23-34.

OS analysis in the ITT population through 7.5 years[1-3]

	OPDIVO + YERVOY (n=314)	OPDIVO (n=316)	YERVOY (n=315)
Median OS, mos (95% CI)[2]	72.1 (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.9–24.6)
HR (95% CI) vs YERVOY[2]	0.53 (0.44–0.65)	0.63 (0.52–0.77)	–

In the primary analysis at 28 months[4]:

- **OPDIVO + YERVOY:** HR=0.55 (95% CI: 0.44–0.69); *P*<0.0001
- **OPDIVO:** HR=0.63 (95% CI: 0.50–0.78) ; *P*<0.0001



No. at risk

OPDIVO + YERVOY	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	144	143	141	138	129	58	7	0
OPDIVO	316	292	265	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	123	121	120	118	107	54	4	0
YERVOY	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	63	63	63	62	57	24	5	0

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

1. Data on file. NIVO 0151. Princeton, NJ: Bristol-Myers Squibb Company. 2. Hodi et al. Poster presentation at: ASCO 2022. 3. Wolchok JD, et al. Oral presentation at ASCO 2021. Abstract 9506. 4. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company.

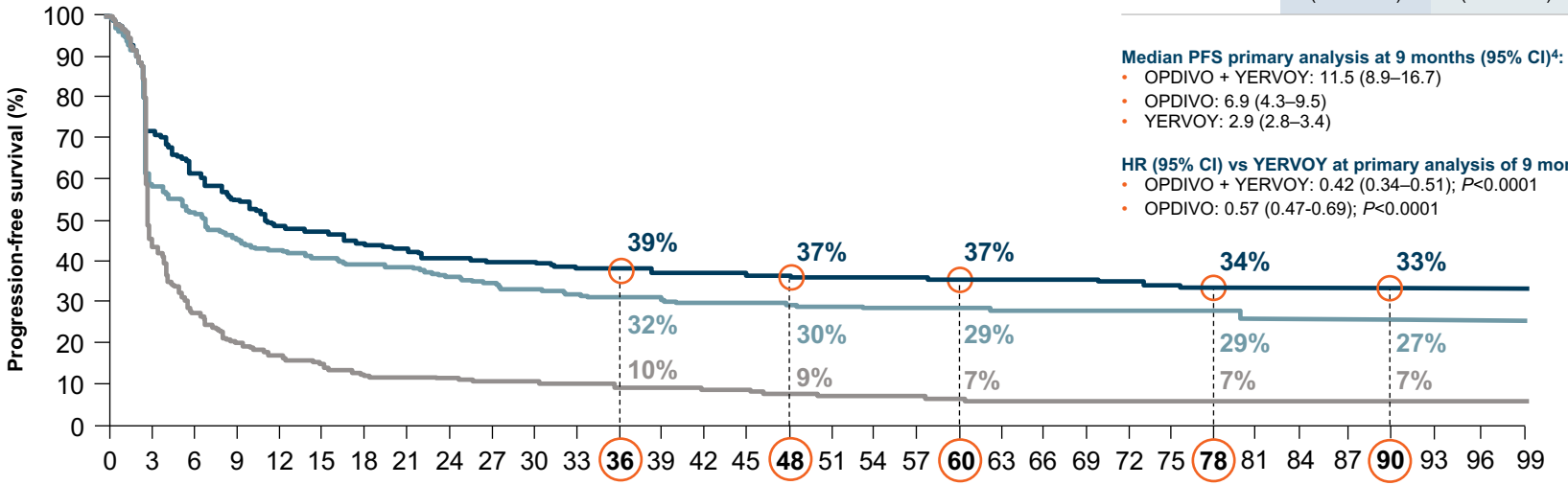
Please see Important Safety Information for OPDIVO and YERVOY throughout this presentation and U.S. Full Prescribing Information for OPDIVO and YERVOY provided in this presentation.

PFS analysis in the ITT population through 7.5 years[1-3]

	OPDIVO + YERVOY (n=314)	OPDIVO (n=316)	YERVOY (n=315)
Median PFS, mos (95% CI)[2]	11.5 (8.9–20.0)	6.9 (5.1–10.2)	2.9 (2.8–3.1)
HR (95% CI) vs YERVOY[2]	0.42 (0.35–0.51)	0.53 (0.44–0.64)	–

Median PFS primary analysis at 9 months (95% CI)[4]:
- OPDIVO + YERVOY: 11.5 (8.9–16.7)
- OPDIVO: 6.9 (4.3–9.5)
- YERVOY: 2.9 (2.8–3.4)

HR (95% CI) vs YERVOY at primary analysis of 9 months (95% CI)[4]:
- OPDIVO + YERVOY: 0.42 (0.34–0.51); *P*<0.0001
- OPDIVO: 0.57 (0.47-0.69); *P*<0.0001



No. at risk

OPDIVO + YERVOY	314	219	175	156	138	133	126	119	112	106	103	100	99	95	93	92	87	85	84	81	78	77	76	72	70	68	66	63	57	50	33	10	1	0
OPDIVO	316	177	151	132	120	112	106	103	97	89	84	80	78	76	73	71	69	67	66	65	62	58	57	56	54	53	50	49	44	37	21	5	0	0
YERVOY	315	135	78	58	46	42	34	32	31	29	28	26	21	19	18	18	16	15	15	15	12	11	11	10	10	9	9	9	9	9	7	3	1	0

CI=confidence interval; HR=hazard ratio; ITT=intent to treat; mo=month; PFS=progression-free survival.

1. Data on file. NIVO 0151. Princeton, NJ: Bristol-Myers Squibb Company. 2. Hodi et al. Poster presentation at: ASCO 2022. 3. Wolchok JD, et al. Oral presentation at ASCO 2021. Abstract 9506. 4. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company.

Please see Important Safety Information for OPDIVO and YERVOY throughout this presentation and U.S. Full Prescribing Information for OPDIVO and YERVOY provided in this presentation.

Select Important Safety Information

Serious Adverse Reactions

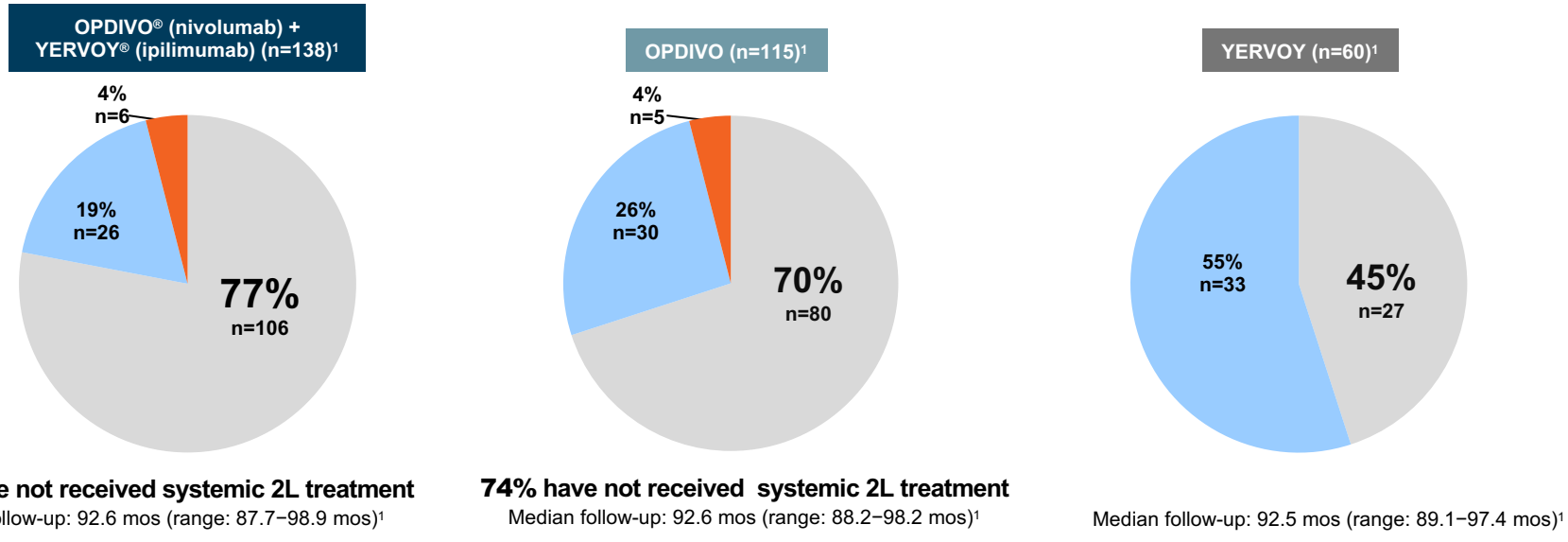
- In Checkmate 067, serious adverse reactions (74% and 44%), adverse reactions leading to permanent discontinuation (47% and 18%) or to dosing delays (58% and 36%), and Grade 3 or 4 adverse reactions (72% and 51%) all occurred more frequently in the OPDIVO® (nivolumab) plus YERVOY® (ipilimumab) arm (n=313) relative to the OPDIVO arm (n=313). The most frequent (≥10%) serious adverse reactions in the OPDIVO plus YERVOY arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.2%), colitis (10% and 1.9%), and pyrexia (10% and 1.0%).

Common Adverse Reactions

- In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO plus YERVOY arm (n=313) were fatigue (62%), diarrhea (54%), rash (53%), nausea (44%), pyrexia (40%), pruritus (39%), musculoskeletal pain (32%), vomiting (31%), decreased appetite (29%), cough (27%), headache (26%), dyspnea (24%), upper respiratory tract infection (23%), arthralgia (21%), and increased transaminases (25%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO arm (n=313) were fatigue (59%), rash (40%), musculoskeletal pain (42%), diarrhea (36%), nausea (30%), cough (28%), pruritus (27%), upper respiratory tract infection (22%), decreased appetite (22%), headache (22%), constipation (21%), arthralgia (21%), and vomiting (20%).

Please see additional Important Safety Information for OPDIVO and YERVOY throughout this presentation and U.S. Full Prescribing Information for OPDIVO and YERVOY provided in this presentation.

Patients alive and treatment free at 7.5 years in the ITT population[1]



81% have not received systemic 2L treatment
Median follow-up: 92.6 mos (range: 87.7−98.9 mos)[1]

74% have not received systemic 2L treatment
Median follow-up: 92.6 mos (range: 88.2−98.2 mos)[1]

Median follow-up: 92.5 mos (range: 89.1−97.4 mos)[1]

- Of patients who were alive and treatment free at 7.5 years, 58.5% on OPDIVO + YERVOY, 32.5% on OPDIVO, and 44.4% on YERVOY discontinued due to study drug toxicity; 4.7% on OPDIVO + YERVOY, 5.0% on OPDIVO, and 7.4% on YERVOY discontinued due to disease progression. Patients also discontinued for other reasons[2]

2L=second-line; ITT=intent to treat; mo=month.

1. Hodi et al. Long-term survival in advanced melanoma for patients treated with nivolumab plus ipilimumab in CheckMate 067. Poster presentation at: ASCO 2022. 2. Data on file. NIVO 0151. Princeton, NJ: Bristol-Myers Squibb Company.

Please see Important Safety Information for OPDIVO and YERVOY throughout this presentation and U.S. Full Prescribing Information for OPDIVO and YERVOY provided in this presentation.

Patients alive and treatment free at 7.5 years in the ITT population[1]

Additional details on patients who were alive and treatment free* at the 7.5-year database lock in Checkmate 067[1]

	OPDIVO® (nivolumab) + YERVOY® (ipilimumab) (n=106)	OPDIVO (n=80)	YERVOY (n=27)
Reason for discontinuation (%)			
Disease progression	4.7	5.0	7.4
Drug-related toxicity	58.5	32.5	44.4
Other reasons	36.8	62.5	48.2
Treatment-free interval (mos)†			
Median	81.4	59.6	71.0
Duration of treatment (mos)			
Median	10.6	33.8	23.2
Patients who received 4 doses of OPDIVO + YERVOY (%)	69.8	–	–

- The median duration of study therapy was 10.6 mos (range: 0–93.4 mos) for OPDIVO + YERVOY, 33.8 mos (range: 0.5–92.9 mos) for OPDIVO, and 23.2 mos (range: 0.9–49.9 mos) for YERVOY[1]

*Alive and off study treatment for any reason and never received subsequent systemic therapy.[2] †All treated patients alive and in follow-up at 7.5 years (OPDIVO + YERVOY: n=138, OPDIVO: n=115, YERVOY: n=60).[1]

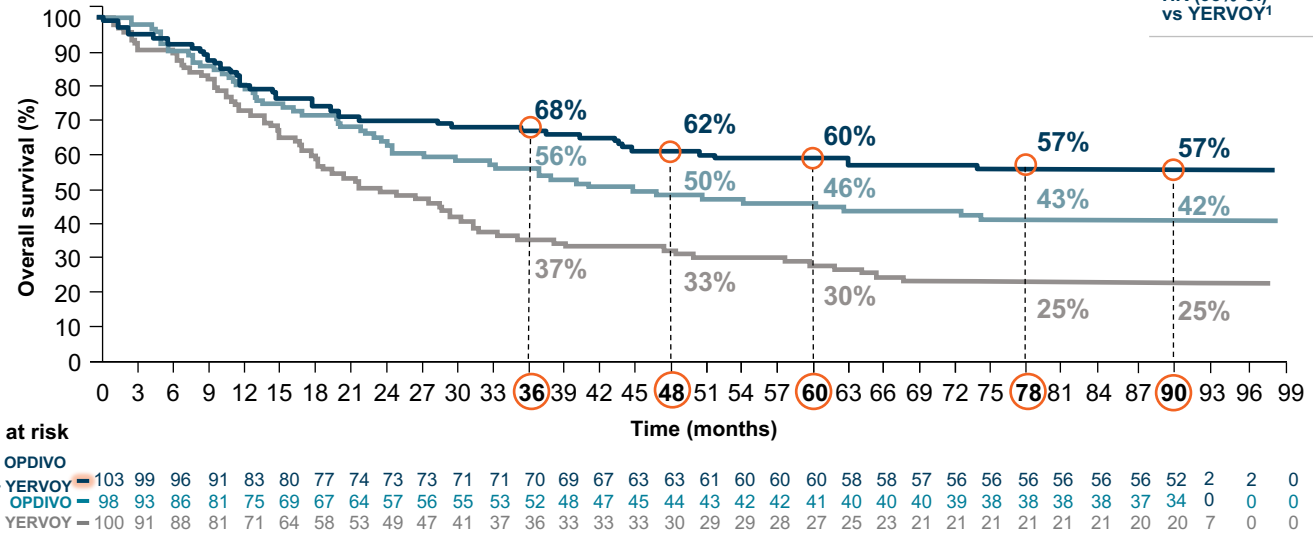
ITT=intent to treat; mo=month.

1. Data on file. NIVO 0151. Princeton, NJ: Bristol-Myers Squibb Company. 2. Hodi et al. Long-term survival in advanced melanoma for patients treated with nivolumab plus ipilimumab in CheckMate 067. Poster presentation at: ASCO 2022.

OS in patients with *BRAF* MT tumors through 7.5 years[1-3]

	OPDIVO + YERVOY (n=28)	OPDIVO (n=23)	YERVOY (n=28)
Median OS, mos (95% CI)[1]	NR (50.7–NR)	45.5 (26.4–93.6)	24.6 (17.9–31.0)
HR (95% CI) vs YERVOY[1]	0.43 (0.29–0.63)	0.65 (0.46–0.93)	–

BRAF MT subgroup: OS at 7.5 years[1-3]



No. at risk

OPDIVO + YERVOY	103	99	96	91	83	80	77	74	73	73	71	71	70	69	67	63	63	61	60	60	60	58	58	57	56	56	56	56	56	56	52	2	2	0
OPDIVO	98	93	86	81	75	69	67	64	57	56	55	53	52	48	47	45	44	43	42	42	41	40	40	40	39	38	38	38	38	37	34	0	0	0
YERVOY	100	91	88	81	71	64	58	53	49	47	41	37	36	33	33	33	30	29	29	28	27	25	23	21	21	21	21	21	21	20	20	7	0	0

Median OS in *BRAF* WT patients at 7.5 years, mos (95% CI)[1]:

- OPDIVO + YERVOY: 39.1 (27.5–87.0)
- OPDIVO: 34.4 (24.1–59.2)
- YERVOY: 18.5 (14.1–22.7)

HR vs YERVOY in *BRAF* WT patients at 7.5 years (95% CI)[1]:

- OPDIVO + YERVOY: 0.59 (0.47–0.75)
- OPDIVO: 0.62 (0.49–0.78)

Patients were stratified by *BRAF* status at baseline.[4]

OS analysis of this pre-specified subpopulation was not powered to detect statistical differences.[5]

1L=first-line; CI=confidence interval; HR=hazard ratio; mo=month; MT=mutant; NR=not reached; OS=overall survival; WT=wild-type.

1. Data on file. NIVO 0151. Princeton, NJ: Bristol-Myers Squibb Company. 2. Hodi et al. Poster presentation at: ASCO 2022. 3. Wolchok JD, et al. Oral presentation at ASCO 2021. Abstract 9506. 4. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2019;381 (16): 1535-1546. 5. Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (Checkmate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncol*. 2018; 19(11):1480-1492.

Selected safety profile

Select safety results in Checkmate 067

Adverse reactions occurring in ≥10% in OPDIVO® (nivolumab) + YERVOY® (ipilimumab) or OPDIVO arm*

	OPDIVO + YERVOY (n=313)		OPDIVO (n=313)		YERVOY (n=311)	
Adverse reactions	**All grades (%)**	**Grades 3–4 (%)**	**All grades (%)**	**Grades 3–4 (%)**	**All grades (%)**	**Grades 3–4 (%)**
General disorders						
Fatigue†	62	7	59	1.6	51	4.2
Pyrexia	40	1.6	16	0	18	0.6
Gastrointestinal disorders						
Diarrhea	54	11	36	5	47	7
Nausea	44	3.8	30	0.6	31	1.9
Vomiting	31	3.8	20	1.0	17	1.6
Skin and subcutaneous tissue disorders						
Rash‡	53	6	40	1.9	42	3.5
Vitiligo	9	0	10	0.3	5	0
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain§	32	2.6	42	3.8	36	1.9
Arthralgia	21	0.3	21	1.0	16	0.3
Metabolism and nutrition disorders						
Decreased appetite	29	1.9	22	0	24	1.3
Respiratory, thoracic, and mediastinal disorders						
Cough/productive cough	27	0.3	28	0.6	22	0
Dyspnea/exertional dyspnea	24	2.9	18	1.3	17	0.6
Infections						
Upper respiratory tract infection‖	23	0	22	0.3	17	0
Endocrine disorders						
Hypothyroidism	19	0.6	11	0	5	0
Hyperthyroidism	11	1.3	6	0	1	0
Investigations						
Decreased weight	12	0	7	0	7	0.3
Vascular disorders						
Hypertension¶	7	2.2	11	5	9	2.3

No overall differences in safety or efficacy were reported between older and younger patients

Toxicity was graded per NCI CTCAE v4.

*ARs occurring at a higher incidence than in the YERVOY arm (between-arm difference of ≥5% [all grades] or ≥2% [Grades 3–4]). †Includes asthenia and fatigue. ‡Includes pustular rash, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, exfoliative dermatitis, psoriasiform dermatitis, drug eruption, exfoliative rash, erythematous rash, generalized rash, macular rash, maculopapular rash, morbilliform rash, papular rash, papulosquamous rash, and pruritic rash. §Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain. ‖Includes upper respiratory tract infection, nasopharyngitis, pharyngitis, and rhinitis. ¶Includes hypertension and blood pressure increased.

AR=adverse reaction.

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

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Incidence and resolution of immune-related adverse reactions in the OPDIVO® (nivolumab) + YERVOY® (ipilimumab) arm[1-3]*

Incidence and resolution of IRAEs seen with OPDIVO + YERVOY

	Any-grade IRAEs		Grade 3–5 IRAEs	
	Incidence, (n)	Resolution	Incidence, (n)	Resolution
Pneumonitis	(20) 6%	100%	(4) 1%	100%
Diarrhea/colitis	(79) 25%	95%	(49) 16%	98%
Hepatitis	(45) 14%	91%	(38) 12%	92%
Nephritis and renal dysfunction	(8) 3%	88%	(7) 2%	86%
Rash	(72) 23%	89%	(12) 4%	100%
Hypersensitivity	(2) 1%	50%	(0) 0%	NA
Endocrinopathies				
Hypophysitis	(26) 8%	50%	(9) 3%	78%
Adrenal insufficiency	(13) 4%	15%	(5) 2%	20%
Hypothyroidism/thyroiditis	(6) 2%	100%	(1) 0.3%	100%
Hyperthyroidism	(7) 2%	86%	(1) 0.3%	100%
Diabetes mellitus	(0) 0%	NA	(0) 0%	NA

IRAE analyses were limited to subjects who received immune-modulating medication for treatment of the event, with the exception of endocrine events.[2]

*Resolution was defined as improvement to Grade 0 or baseline grade per investigator assessment for all clustered events in a given category that occurred in a patient.[3]

IRAE=immune-related adverse event; NA=not available.

1. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. 2. Data on file. NIVO 450. Princeton, NJ: Bristol-Myers Squibb Company; 2019.
3. Hodi FS, et al. *Lancet Oncol*. 2018;19(11):1480-1492 [supplementary appendix].

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

Immune-Mediated Pneumonitis

- OPDIVO and YERVOY can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients receiving OPDIVO monotherapy, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated pneumonitis occurred in 7% (31/456) of patients, including Grade 4 (0.2%), Grade 3 (2.0%), and Grade 2 (4.4%).

Important Safety Information (cont'd)

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

Immune-Mediated Colitis

- OPDIVO® (nivolumab) and YERVOY® (ipilimumab) can cause immune-mediated colitis, which may be fatal. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients, including Grade 3 (1.7%) and Grade 2 (1%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated colitis occurred in 25% (115/456) of patients, including Grade 4 (0.4%), Grade 3 (14%) and Grade 2 (8%).

Immune-Mediated Hepatitis and Hepatotoxicity

- OPDIVO and YERVOY can cause immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated hepatitis occurred in 15% (70/456) of patients, including Grade 4 (2.4%), Grade 3 (11%), and Grade 2 (1.8%).

Important Safety Information (cont'd)

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

Immune-Mediated Endocrinopathies

- OPDIVO® (nivolumab) and YERVOY® (ipilimumab) can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.
- In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994), including Grade 3 (0.4%) and Grade 2 (0.6%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, adrenal insufficiency occurred in 8% (35/456), including Grade 4 (0.2%), Grade 3 (2.4%), and Grade 2 (4.2%).
- 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 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hypophysitis occurred in 9% (42/456), including Grade 3 (2.4%) and Grade 2 (6%).
- 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 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hyperthyroidism occurred in 9% (42/456) of patients, including Grade 3 (0.9%) and Grade 2 (4.2%).
- 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 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hypothyroidism occurred in 20% (91/456) of patients, including Grade 3 (0.4%) and Grade 2 (11%).
- 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.

Important Safety Information (cont'd)

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

Immune-Mediated Nephritis with Renal Dysfunction

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

Immune-Mediated Dermatologic Adverse Reactions

- OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.
- YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes.
- Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).
- In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated rash occurred in 28% (127/456) of patients, including Grade 3 (4.8%) and Grade 2 (10%).

Important Safety Information (cont'd)

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

Other Immune-Mediated Adverse Reactions

- The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO® (nivolumab) monotherapy or OPDIVO in combination with YERVOY® (ipilimumab) or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular:* myocarditis, pericarditis, vasculitis; *nervous system*: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *ocular:* uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal:* pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue:* myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine:* hypoparathyroidism; *other (hematologic/immune):* hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.
- In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: *nervous system:* autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; *cardiovascular:* angiopathy, temporal arteritis; *ocular:* blepharitis, episcleritis, orbital myositis, scleritis; *gastrointestinal:* pancreatitis (1.3%); *other (hematologic/immune):* conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis.
- Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving OPDIVO and YERVOY, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Important Safety Information (cont'd)

Infusion-Related Reactions

- OPDIVO® (nivolumab) and YERVOY® (ipilimumab) can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 2.5% (10/407) of patients.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation

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

Embryo-Fetal Toxicity

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

Please see additional Important Safety Information for OPDIVO and YERVOY throughout this presentation and U.S. Full Prescribing Information for OPDIVO and YERVOY provided in this presentation.

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 or YERVOY® (ipilimumab) 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 067, serious adverse reactions (74% and 44%), adverse reactions leading to permanent discontinuation (47% and 18%) or to dosing delays (58% and 36%), and Grade 3 or 4 adverse reactions (72% and 51%) all occurred more frequently in the OPDIVO plus YERVOY arm (n=313) relative to the OPDIVO arm (n=313). The most frequent (≥10%) serious adverse reactions in the OPDIVO plus YERVOY arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.2%), colitis (10% and 1.9%), and pyrexia (10% and 1.0%).

Important Safety Information (cont'd)

Common Adverse Reactions

- In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO® (nivolumab) plus YERVOY® (ipilimumab) arm (n=313) were fatigue (62%), diarrhea (54%), rash (53%), nausea (44%), pyrexia (40%), pruritus (39%), musculoskeletal pain (32%), vomiting (31%), decreased appetite (29%), cough (27%), headache (26%), dyspnea (24%), upper respiratory tract infection (23%), arthralgia (21%), and increased transaminases (25%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO arm (n=313) were fatigue (59%), rash (40%), musculoskeletal pain (42%), diarrhea (36%), nausea (30%), cough (28%), pruritus (27%), upper respiratory tract infection (22%), decreased appetite (22%), headache (22%), constipation (21%), arthralgia (21%), and vomiting (20%).

Please see U.S. Full Prescribing Information for OPDIVO and YERVOY provided at this presentation.