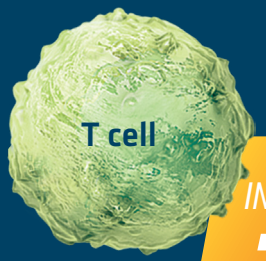
4- AND 5-YEAR *BRAF* MT DATA



*IN THE TREATMENT OF **MELANOMA**, A HIGHLY IMMUNOGENIC TUMOR[1,2]:*

TARGET THE IMMUNE SYSTEM[1*]

WITH

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

OPDIVO® is indicated for the **adjuvant** treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

OPDIVO, as a single agent, is indicated for the treatment of patients with unresectable or metastatic melanoma.

OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

OPDIVO, in combination with YERVOY®, is indicated for the treatment of patients with unresectable or **metastatic melanoma**.

SELECT IMPORTANT SAFETY INFORMATION

Summary of Warnings and Precautions

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

This graphic is for demonstration purposes only. The illustrated mechanisms may vary for each patient and may not directly correlate with clinical significance.

*Targeting of normal cells can also occur.[4,5] OPDIVO helps existing T cells discover the tumor by blocking PD-1.[6-11] YERVOY helps activate and proliferate T cells by blocking CTLA-4, and also reduces Treg function.[12]

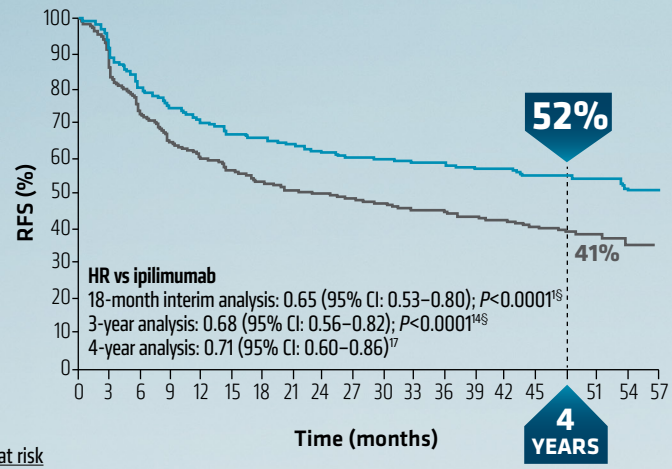
CTLA-4=cytotoxic T-lymphocyte antigen 4; MT=mutant; PD-1=programmed death receptor-1; Treg=regulatory T cell; WT=wild type.

Please see additional Important Safety Information for OPDIVO and OPDIVO in combination with YERVOY throughout and U.S. Full Prescribing Information for **OPDIVO** and **YERVOY**.

In the adjuvant treatment of patients with completely resected melanoma with lymph node involvement (Stage III) or metastatic disease (Stage IV), including *BRAF* MT and *BRAF* WT patients[1]*

OPDIVO® (nivolumab): Durable RFS benefit and the longest follow-up for any PD-1 agent in the adjuvant setting[1,13]

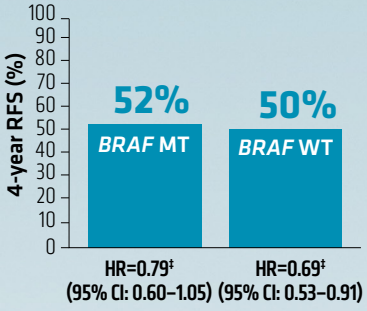
Recurrence-free survival results through 4 years[1,13]



Number at risk

OPDIVO 3 mg/kg	453	395	354	332	311	293	283	271	262	250	245	240	233	224	218	206	147	37	11	0
Ipilimumab 10 mg/kg	453	366	316	273	253	234	220	208	201	191	185	177	171	168	163	154	113	32	10	0

✓ RFS rates numerically similar across *BRAF* status[17†]



Checkmate 238 study design[1,13,16]: Checkmate 238 was a Phase 3, randomized (1:1), double-blind study of OPDIVO 3 mg/kg IV infusion over 60 minutes q2w up to 1 year§ and ipilimumab-matched placebo IV infusion q3w for 4 doses, then q12w starting at Week 24 (n=453), versus ipilimumab 10 mg/kg IV infusion over 90 minutes q3w for 4 doses, then q12w, starting at Week 24, and OPDIVO-matched placebo IV q2w (n=453), for the adjuvant treatment of patients with high-risk, completely resected Stage IIIB/C or Stage IV NED melanoma. Patients were stratified by AJCC stage and PD-L1 status. Maximum treatment duration was 1 year. The primary endpoint was RFS.

Median RFS, mos (95% CI)

- 18 months (ITT): OPDIVO 3 mg/kg: NR (NR–NR); ipilimumab 10 mg/kg: NR (16.56–NR)[1]
- 4 years (ITT): OPDIVO 3 mg/kg: 52.37 (42.51–NR); ipilimumab 10 mg/kg: 24.08 (16.56–35.09)[13]

Additional details on *BRAF* subgroup data

- RFS by *BRAF* status was an exploratory pre-specified subgroup analysis at 18 months and at 4 years[13,16]
- 4-year RFS in patients receiving ipilimumab was 43.6% (n=50) for *BRAF* MT and 38.7% (n=52) for *BRAF* WT[13,17]
- 4-year *BRAF* MT: NR for OPDIVO (35.0–NR); 25.5 for ipilimumab (15.9–NR); n=194[17]
- 4-year *BRAF* WT: 46.8 for OPDIVO (36.3–NR); 16.6 for ipilimumab (11.6–35.1); n=212[17]

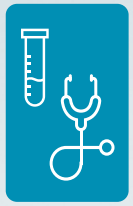
Q4W dosing offers balance between dosing frequency and the control of patient monitoring

Help control patient adherence concerns with IV administration[1,15]

Q4W dosing, just one 30-minute infusion every 4 weeks‖

Longer wait times between infusions may lead to missing important warning signs of AEs[1,16]

AE and disease recurrence monitoring¶



Physical exam and bloodwork

- OPDIVO dosing options include Q4W (480 mg IV) and Q2W (240 mg IV), both as a 30-minute infusion[1]

IV administration allows you to treat* BRAF *mutant patients as confidently as you treat your* BRAF *wild-type patients

SELECT IMPORTANT SAFETY INFORMATION

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%).

*Checkmate 238 included Stage IIIB/C and Stage IV NED patients per AJCC 7th edition.
†These data are based on RFS Kaplan-Meier estimates.[13]
§Unstratified hazard ratio.[13]
‡The recommended dose of OPDIVO is either 240 mg q2w or 480 mg q4w administered as an IV infusion over 30 minutes until disease progression or unacceptable toxicity for up to 1 year.[1]
‖The information above is not intended to imply comparative efficacy between OPDIVO dosing schedules. Selection of approved dosing frequency should be based on independent clinical judgment.
¶Per Checkmate 238 protocol, patients underwent imaging for tumor recurrence q12w for the first 2 years, then every 6 months thereafter.[1]

AJCC=American Joint Committee on Cancer; AE=adverse event; CI=confidence interval; HR=hazard ratio; ITT=intent to treat; IV=intravenous; mo=month; MT=mutant; NED=no evidence of disease; NR=not reached; PD-1=programmed death receptor-1; 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; WT=wild type.

In the adjuvant treatment of patients with completely resected melanoma with lymph node involvement (Stage III) or metastatic disease (Stage IV), including *BRAF* MT and *BRAF* WT patients[1,13]

For your next melanoma patient in the adjuvant setting, including *BRAF* mutant:

FOCUS ON 4

DURABLE 4-YEAR RFS

- **ITT 4-year RFS rate for OPDIVO® (nivolumab) was 52% vs 41% for ipilimumab[13]**
- **4-year RFS rate for *BRAF* mutant patients receiving OPDIVO was 52% vs 44% for ipilimumab[17]**

Q4W DOSING OFFERS BALANCE BETWEEN DOSING FREQUENCY AND THE CONTROL OF PATIENT MONITORING

- **IV administration allows you to treat *BRAF* mutant patients as confidently as you treat your *BRAF* wild-type patients**

4-YEAR FOLLOW-UP

- **The longest follow-up by a PD-1 agent in the adjuvant setting[13]**

Choose the #1 prescribed therapy for your next melanoma patient in the adjuvant setting[18]

SELECT IMPORTANT SAFETY INFORMATION

Infusion-Related Reactions

- OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In 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.
- In separate Phase 3 trials of YERVOY 3 mg/kg and 10 mg/kg monotherapy, infusion-related reactions occurred in 2.9% (28/982) of patients.

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%).
- In a separate Phase 3 trial of YERVOY 3 mg/kg, the most common adverse reactions (≥5%) in patients who received YERVOY at 3 mg/kg were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%).

ITT=intent to treat; MT=mutant; PD-1=programmed death receptor-1; q4w=every 4 weeks; RFS=recurrence-free survival; WT=wild type.

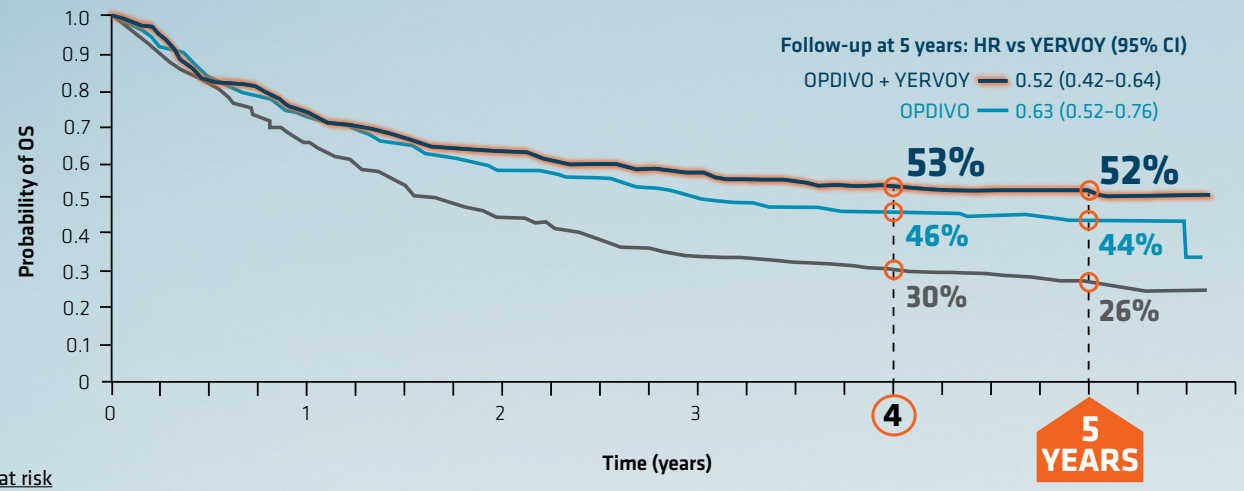
OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

Please see additional Important Safety Information for OPDIVO and OPDIVO in combination with YERVOY throughout and U.S. Full Prescribing Information for **OPDIVO** and **YERVOY**.

In the 5-year follow-up analysis of metastatic melanoma patients

OPDIVO® (nivolumab) + YERVOY® (ipilimumab): >50% of ITT patients alive at 5 years[1,19,20]

Overall survival in the ITT population through 5 years[1,19,20]



Number 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

Median OS at 5 years, yrs (95% CI, mos)[19]

- OPDIVO + YERVOY: NR (38.2–NR)
- OPDIVO: 3.1 (28.2–58.7)
- YERVOY: 1.7 (16.8–24.6)

HR vs YERVOY (95% CI)[19]

- OPDIVO + YERVOY: 0.57 (0.45–0.73)[21]
- OPDIVO: 0.64 (0.50–0.81)[21]

Checkmate 067 study design[1]: OPDIVO + YERVOY was evaluated in a double-blind, randomized study of previously untreated, unresectable, or metastatic melanoma. Patients were randomized (1:1:1) to receive OPDIVO + YERVOY (OPDIVO 1 mg/kg and YERVOY 3 mg/kg q3w for 4 doses, followed by OPDIVO monotherapy 3 mg/kg q2w*), or OPDIVO 3 mg/kg q2w, or YERVOY 3 mg/kg q3w for 4 doses plus placebo. Major efficacy outcome measures were investigator-assessed PFS and OS. Additional efficacy outcome measures were confirmed ORR and DOR.

HR for OS vs YERVOY in the primary analysis at 28 months[1]

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

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 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%). 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 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%).

*The recommended dose of OPDIVO is 1 mg/kg administered as an IV infusion over 30 minutes, followed by YERVOY 3 mg/kg administered as an IV infusion over 90 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 IV infusion over 30 minutes until disease progression or unacceptable toxicity.[1] Review the Prescribing Information for YERVOY for additional information prior to initiation.

1L=first-line; CI=confidence interval; DOR=duration of response; HR=hazard ratio; ITT=intent to treat; mo=month; NR=not reached; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; q2w=every 2 weeks; q3w=every 3 weeks; q4w=every 4 weeks; yr=year.

Please see additional Important Safety Information for OPDIVO and OPDIVO in combination with YERVOY throughout and U.S. Full Prescribing Information for **OPDIVO** and **YERVOY**.

In the 5-year follow-up analysis of metastatic melanoma patients

OPDIVO® (nivolumab) + YERVOY® (ipilimumab): 60% *BRAF* MT patients alive at 60 months[19,21]

60% ALIVE*

of 103 *BRAF* mutant patients who received OPDIVO + YERVOY first line[19,21]

HR vs YERVOY (95% CI): 0.44 (0.30–0.64)

@

60 MONTHS

YERVOY arm (n=100): 30% of ***BRAF*** MT patients were alive at 60 months[19,21*]

5-year OS in *BRAF* MT patients with OPDIVO[19,21]

- 46% of *BRAF* MT patients (n=98) were alive at 60 months; HR vs YERVOY (95% CI): 0.63 (0.44–0.90)

OS in *BRAF* WT at 5 years[19]

Median OS, years (95% CI, mos):

- OPDIVO + YERVOY: 3.3 years (27.5 mos–NR)
- OPDIVO: 2.9 years (24.1–59.2 mos)
- YERVOY: 1.5 years (14.1–22.7 mos)
- Patients were stratified by *BRAF* status at baseline[19]
- OS analysis of this pre-specified subpopulation was conducted but was not powered to detect statistical differences[22]

79% of surviving *BRAF* MT patients (n=45/57)

Of *BRAF* MT patients alive at 5 years:

~8 out of 10 only received OPDIVO + YERVOY[19,23†] and did not receive additional systemic therapy

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 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%).

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%). 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%).
- In a separate Phase 3 trial of YERVOY 3 mg/kg, the most common adverse reactions (≥5%) in patients who received YERVOY at 3 mg/kg were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%).

Please see additional Important Safety Information for OPDIVO and OPDIVO in combination with YERVOY throughout and U.S. Full Prescribing Information for **OPDIVO** and **YERVOY**.

*At the 5-year follow-up analysis. Rates are based on Kaplan-Meier estimates.[19]

† Of the 57 surviving *BRAF* MT patients in the OPDIVO + YERVOY arm included in the 5-year treatment disposition analysis, 7 were still on protocol therapy, 38 were off protocol therapy and free of 2L subsequent systemic therapy, and 12 received 2L subsequent systemic therapy.[19,29]

‡ Off protocol treatment for any reason and never received 2L systemic therapy.[19,29]

§ Percentages do not total 100 after rounding.

1L=first line; 2L=second line; CI=confidence interval; HR=hazard ratio; mo=month; MT=mutant; NR=not reached; OS=overall survival; WT=wild type.

OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) treatment recommendations for the adjuvant and metastatic settings[24]

NCCN Guidelines®
for the adjuvant treatment of cutaneous melanoma

The NCCN Guidelines for Cutaneous Melanoma recommend nivolumab (OPDIVO) as an option for adjuvant systemic therapy for certain Stage III and Stage IV melanoma in patients with no evidence of disease after complete resection.[24]*

*Category 1 recommendation for the following: patients with AJCC 7th Edition Stage IIIB/C sentinel node-positive disease, Stage III and clinically positive nodes (following wide excision and therapeutic lymph node dissection [TLND]), resectable nodal recurrence (following complete resection and TLND if not previously done), and resected Stage IV disease (no evidence of disease).[24]

Nivolumab (OPDIVO®) + ipilimumab (YERVOY®): a Category 1, preferred 1L systemic therapy option for *BRAF* mutant or wild-type metastatic or unresectable cutaneous melanoma[24]

National Comprehensive Cancer Network® (NCCN®) Category 1, Preferred Regimen[24]
Nivolumab (OPDIVO) + Ipilimumab (YERVOY) is recommended as a **Category 1, preferred first-line systemic therapy option for metastatic or unresectable disease regardless of *BRAF* mutation status[24]**

BRAF V600E/K+ patients:
An NCCN Category 1, Preferred Regimen[24]

BRAF wild-type patients:
An NCCN Category 1, Preferred Regimen[24]

Combination targeted therapy may be preferred if clinically needed for patients with *BRAF* V600 activating mutations with rapidly progressing disease and/or symptoms[24†]

Please see updated NCCN Guidelines for a complete list of all NCCN-recommended agents and other relevant information.

NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[24]
†Specific *BRAF*/MEK inhibitor combinations are recommended in these cases.[24]

MEK=mitogen-activated protein kinase kinase.

References: 1. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. **2.** Faramarzi S, Ghafouri-Fard S. Melanoma: a prototype of cancer-testis antigen-expressing malignancies. *Immunotherapy.* 2017;9(13):1103-1113. **4.** Metro G, Ricciuti B, Brambilla M, et al. The safety of nivolumab for the treatment of advanced non-small cell lung cancer. *Expert Opin Drug Saf.* 2017;16(1):101-109. **5.** Byrne EH, Fisher DE. Immune and molecular correlates in melanoma treated with immune checkpoint blockade. *Cancer.* 2017;123:2143-2153. **6.** Weber JS, Hamid O, Chasalow SD, et al. Ipilimumab increases activated T cells and enhances humoral immunity in patients with advanced melanoma. *J Immunother.* 2012;35(1):89-97. **7.** Ansell SM, Hurvitz SA, Koenig PA, et al. Phase I study of ipilimumab, an anti–CTLA-4 monoclonal antibody, in patients with relapsed and refractory B-cell non-Hodgkin lymphoma. *Clin Cancer Res.* 2009;15(20): 6446-6453. **8.** Farber DL, Yudanin NA, Restifo NP. Human memory T cells: generation, compartmentalization and homeostasis. *Nat Rev Immunol.* 2014;14(1):24-35. **9.** Felix J, Lambert J, Roelens M, et al. Ipilimumab reshapes T cell memory subsets in melanoma patients with clinical response. *Oncoimmunology.* 2016;5(7):e1136045. **10.** Pedicord VA, Montalvo W, Leiner IM, Allison JP. Single dose of anti–CTLA-4 enhances CD8+ T-cell memory formation, function, and maintenance. *Proc Natl Acad Sci U S A.* 2011;108(1):266-271. **11.** Pico de Coana Y, Wolodarski M, Poschke I, et al. Ipilimumab treatment decreases monocytic MDSCs and increases CD8 effector memory T cells in long-term survivors with advanced melanoma. *Oncotarget.* 2017;8(13):21539 21553. **12.** YERVOY [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. **13.** Ascierto PA, Del Vecchio M, Mandala M, et al. Adjuvant nivolumab versus ipilimumab in resected stage IIIB-C and stage IV melanoma: 4-year results from CheckMate 238, a multicentre, randomised, controlled phase 3 trial. *Lancet Oncol.* 2020. doi:10.1016/S1470-2045(20)30544-1. **14.** Weber J, Del Vecchio M, Mandala M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III/IV melanoma: 3-year efficacy and biomarker results from the phase 3 CheckMate 238 trial. Presented at: ESMO 2019. Abstract 2801. **15.** Seal BS, Anderson S, Shermock KM. Factors associated with adherence rates for oral and intravenous anticancer therapy in commercially insured patients with metastatic colon cancer. *J Manag Care Spec Pharm.* 2016;22(3):227-235. **16.** Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med.* 2017;377(19):1824-1835 [protocol]. **17.** Weber J, Del Vecchio M, Mandala M, et al. Adjuvant nivolumab vs ipilimumab in resected stage III/IV melanoma: 4-year recurrence-free and overall survival results from CheckMate 238. Presented at: ESMO 2020. Abstract 10760. **18.** Data on file. MEL_10 Performance_All_Time. Princeton, NJ: Bristol-Myers Squibb Company; 2020. **19.** 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. doi:10.1065/NEJMoa1910836. **20.** Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival outcomes of the CheckMate 067 phase 3 trial of nivolumab plus ipilimumab combination therapy in advanced melanoma. Presented at: ESMO 2019. Abstract 2545. **21.** 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. doi:10.1065/NEJMoa1910836 [supplemental appendix]. **22.** 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 multicentre, randomized, phase 3 trial. *Lancet Oncol.* 2018;19:1480-1492. **23.** Data on file. Nivo 488. Princeton, NJ: Bristol-Myers Squibb Company; 2019. **24.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Cutaneous Melanoma V.4.2020. ©National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed September 9, 2020. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Please see additional Important Safety Information for OPDIVO and OPDIVO in combination with YERVOY throughout and U.S. Full Prescribing Information for **OPDIVO** and **YERVOY**.

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

OPDIVO (nivolumab) + YERVOY (ipilimumab)

INDICATIONS

OPDIVO® (nivolumab), as a single agent, is indicated for the treatment of patients with unresectable or metastatic melanoma.

OPDIVO, in combination with YERVOY® (ipilimumab), is indicated for the treatment of patients with unresectable or metastatic melanoma.

OPDIVO is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse Reactions

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

Immune-Mediated Pneumonitis

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

Immune-Mediated Colitis

- OPDIVO and YERVOY can cause immune-mediated colitis, which may be fatal. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients, including Grade 3 (1.7%) and Grade 2 (1%). In patients receiving OPDIVO 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%).
- In a separate Phase 3 trial of YERVOY 3 mg/kg monotherapy, immune-mediated colitis occurred in 12% (62/511) of patients, including Grade 3-5 (7%) and Grade 2 (5%).

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%).
- In a separate Phase 3 trial of YERVOY 3 mg/kg monotherapy, immune-mediated hepatitis occurred in 4.1% (21/511) of patients, including Grade 3-5 (1.6%) and Grade 2 (2.5%).

Immune-Mediated Endocrinopathies

- OPDIVO and YERVOY can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.
- In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994), including Grade 3 (0.4%) and Grade 2 (0.6%). In patients receiving OPDIVO 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.
- In a separate Phase 3 trial of YERVOY 3 mg/kg monotherapy, Grade 2-5 immune-mediated endocrinopathies occurred in 4% (21/511) of patients. Severe to life-threatening (Grade 3-4) endocrinopathies occurred in 9 (1.8%) patients. All 9 patients had hypopituitarism, and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies. Moderate (Grade 2) endocrinopathy occurred in 12 patients (2.3%), including hypothyroidism, adrenal insufficiency, hypopituitarism, hyperthyroidism and Cushing's syndrome.

Immune-Mediated Nephritis with Renal Dysfunction

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

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%).
- In a separate Phase 3 trial of YERVOY 3 mg/kg monotherapy, immune-mediated rash occurred in 15% (76/511) of patients, including Grade 3-5 (2.5%) and Grade 2 (12%).

Please see additional Important Safety Information for OPDIVO and OPDIVO in combination with YERVOY throughout and U.S. Full Prescribing Information for **OPDIVO** and **YERVOY**.

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IMPORTANT SAFETY INFORMATION (cont'd)

Other Immune-Mediated Adverse Reactions

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

Infusion-Related Reactions

- OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In 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.
- In separate Phase 3 trials of YERVOY 3 mg/kg and 10 mg/kg monotherapy, infusion-related reactions occurred in 2.9% (28/982) 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 OPDIVO in combination with YERVOY throughout and U.S. Full Prescribing Information for **OPDIVO** and **YERVOY**.

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

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

Lactation

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

Serious Adverse Reactions

- In Checkmate 037, serious adverse reactions occurred in 41% of patients receiving OPDIVO (n=268). Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse drug reactions reported in 2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. In Checkmate 066, serious adverse reactions occurred in 36% of patients receiving OPDIVO (n=206). Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%). 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%). 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 037, the most common adverse reaction (≥20%) reported with OPDIVO (n=268) was rash (21%). In Checkmate 066, the most common adverse reactions (≥20%) reported with OPDIVO (n=206) vs dacarbazine (n=205) were fatigue (49% vs 39%), musculoskeletal pain (32% vs 25%), rash (28% vs 12%), and pruritus (23% vs 12%). 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%). 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%).
- In a separate Phase 3 trial of YERVOY 3 mg/kg, the most common adverse reactions (≥5%) in patients who received YERVOY at 3 mg/kg were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%).

Clinical Trials and Patient Populations

Checkmate 037 – previously treated metastatic melanoma; **Checkmate 066** – previously untreated metastatic melanoma; **Checkmate 067** – previously untreated metastatic melanoma, as a single agent or in combination with YERVOY; **Checkmate 238** – adjuvant treatment of melanoma

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

OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

Bristol Myers Squibb™

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