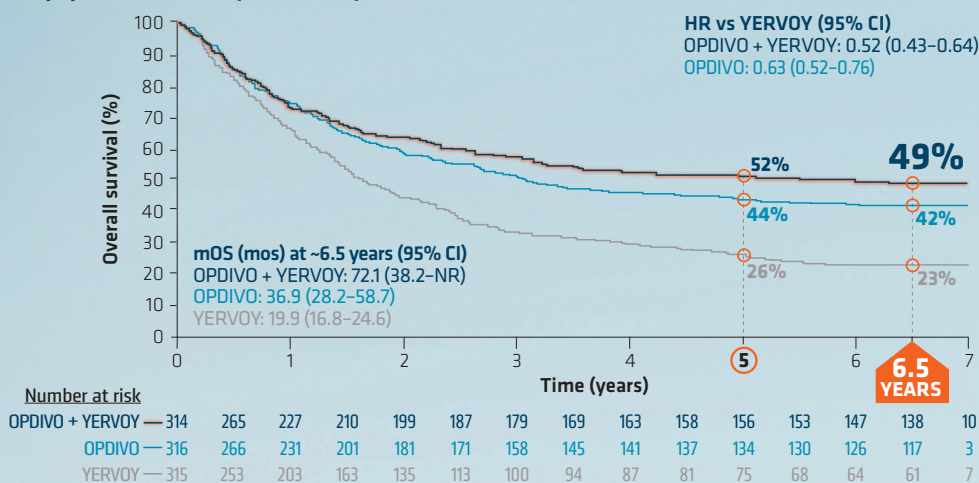


# At the ~6.5-year follow-up: OPDIVO® (nivolumab) + YERVOY® (ipilimumab) delivered a chance for long-term survival in patients with advanced melanoma<sup>1-4</sup>

ITT population: OS analysis at ~6.5 years<sup>1,2</sup>

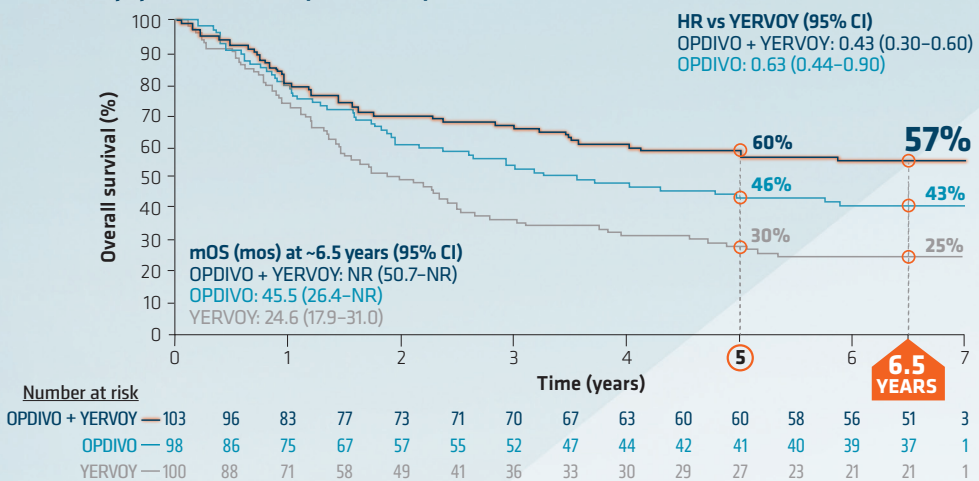


■ HR vs YERVOY (95% CI) in the primary analysis at 28 months<sup>3</sup>: OPDIVO + YERVOY: 0.55 (0.44-0.69);  $P < 0.0001$ ; OPDIVO: 0.63 (0.50-0.78);  $P < 0.0001$

**~8 out of 10 surviving ITT patients in the OPDIVO + YERVOY arm were off treatment and had not received any subsequent systemic therapy at 6.5 years<sup>1</sup>**

- In the OPDIVO + YERVOY arm of the ITT population: 77% of surviving patients were treatment free and never received subsequent systemic therapy (n=112/145), 5% were still on study therapy (n=7/145), and 18% received subsequent systemic therapy (n=26/145)<sup>1</sup>
- In the OPDIVO arm of the ITT population: 69% of surviving patients were treatment free and never received subsequent systemic therapy (n=84/122), 7% were still on study therapy (n=8/122), and 25% received subsequent systemic therapy (n=30/122)<sup>1</sup>
- In the YERVOY arm of the ITT population: 43% of surviving patients were treatment free and never received subsequent systemic therapy (n=27/63) and 57% received subsequent systemic therapy (n=36/63)<sup>1</sup>

BRAF MT\* population: OS analysis at ~6.5 years<sup>1</sup>



\*Patients were stratified by BRAF status at baseline. OS analysis of this pre-specified subpopulation was not powered to detect statistical differences.<sup>2,4</sup>

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

## INDICATION

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

## 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%).

(continued on the next page)

Please see additional Important Safety Information for OPDIVO and YERVOY on next page and US Full Prescribing Information for OPDIVO and YERVOY.





## 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.
- 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%).

#### 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 OPDIVO in combination with YERVOY 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.

#### 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 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 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 YERVOY on previous page and US Full Prescribing Information for OPDIVO and YERVOY.

**References:** 1. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Checkmate 067: 6.5-year outcomes in patients with advanced melanoma. Oral presentation at ASCO 2021. Abstract 9506. 2. 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. 3. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. 4. 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.