At the ~6.5-year follow-up: **OPDIVO® (nivolumab) + YERVOY® (ipilimumab)** delivered a chance for long-term survival in patients with advanced melanoma\(^1\)\(^-4\)

**ITT population: OS analysis at ~6.5 years**\(^1\)\(^,2\)

<table>
<thead>
<tr>
<th>mOS (mos) at ~6.5 years (95% CI)</th>
<th>OPDIVO + YERVOY: 72.1 (38.2–NR)</th>
<th>OPDIVO: 36.9 (28.2–58.7)</th>
<th>YERVOY: 19.3 (16.8–24.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (%)</td>
<td>52%</td>
<td>49%</td>
<td>36%</td>
</tr>
<tr>
<td>Number at risk</td>
<td>OPDIVO + YERVOY: 314</td>
<td>OPDIVO: 316</td>
<td>YERVOY: 315</td>
</tr>
<tr>
<td>Time (years)</td>
<td>1 2 3</td>
<td>4 5 6</td>
<td>7</td>
</tr>
</tbody>
</table>

**BRAF MT\(^*\) population: OS analysis at ~6.5 years**\(^1\)

<table>
<thead>
<tr>
<th>mOS (mos) at ~6.5 years (95% CI)</th>
<th>OPDIVO + YERVOY: NR (50.7–NR)</th>
<th>OPDIVO: 45.5 (26.4–NR)</th>
<th>YERVOY: 24.6 (17.3–31.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (%)</td>
<td>60%</td>
<td>57%</td>
<td>43%</td>
</tr>
<tr>
<td>Number at risk</td>
<td>OPDIVO + YERVOY: 103</td>
<td>OPDIVO: 88</td>
<td>YERVOY: 100</td>
</tr>
<tr>
<td>Time (years)</td>
<td>1 2 3</td>
<td>4 5 6</td>
<td>7</td>
</tr>
</tbody>
</table>

**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 31% (61/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.7%), 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% (55/1994) 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)
Other Immune-Mediated Adverse Reactions

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 were observed, some with fatal outcome, in <1% of patients unless otherwise specified: nervous system: autoimmune encephalitis (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; cardiovascular: angioedema; temporal arteritis; ocular: blepharitis, epidermolysis, orbital myositis, sciotic; gastrointestinal: pancreatitis (1.3%); other (hematologic/immune): conjunctivitis, cytopenias (2.5%), eosinophilia (2%), erythema multiforme, hypersensitivity vasculitis, neurosensorial hearing loss, psychosis.

Some ocular IMR cases may 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-Koyanaghi–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. OPDIVO can cause anaphylactic reactions. Discontinue OPDIVO and YERVOY in patients who develop anaphylaxis. 

In patients receiving OPDIVO monotherapy, infusion-related reactions occurred in 2.4% (95/3951) of patients, including Grade 3 (0.2%), and Grade 2 (2.4%). In patients receiving OPDIVO 3 mg/kg with YERVOY, infusion-related reactions occurred in 3.1% (119/3837) of patients, including Grade 3 (1.2%) and Grade 2 (0.9%). In patients receiving OPDIVO 3 mg/kg with YERVOY 10 mg/kg, infusion-related reactions occurred in 4.1% (156/3837) of patients, including Grade 3 (0.5%) and Grade 2 (0.6%). In patients receiving OPDIVO 3 mg/kg with YERVOY 10 mg/kg, infusion-related reactions occurred in 4.6% (176/3837) of patients, including Grade 3 (0.5%) and Grade 2 (0.6%).

**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, severe 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 55%) 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 (38%), vomiting (31%), decreased appetite (29%), and comorbidities, myasthenia gravis (including exudation), Guillain–Barre syndrome, nerve paresthesia, autoimmunity neuropathy, ocular: uveitis, arthritis, and other ocular inflammatory toxicities can occur: gastrointestinal: pancreatitis to include increases in serum amylase and lipase levels, gastrolesion, duodenitis, musculoskeletal and connective tissue: myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; endocrine: hyperglycemia, hyponatremia (hereditary angioedema): immune: hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kiikuchi lymphadenitis), sarcoidosis, immune thymocytomopathy purpura, solid organ transplant rejection.

**References**