Immune-Mediated Adverse Reactions Management Guide

INDICATIONS AND USAGE
YERVOY® (ipilimumab) is indicated for:
• Treatment of unresectable or metastatic melanoma in adults and pediatric patients (12 years and older)
• Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy

Select Important Safety Information

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS
YERVOY (ipilimumab) can result in severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.
Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests (LFTs), adrenocorticotrophic hormone (ACTH) level, and thyroid function tests, at baseline and before each dose.
Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

Please see U.S. Full Prescribing Information, including Boxed WARNING regarding immune-mediated adverse reactions.
YERVOY® (ipilimumab) Is the First FDA-Approved Immune Checkpoint Inhibitor in the Adjuvant Treatment of Fully Resected Stage III Melanoma (lymph node >1 mm)

For patients with Stage III melanoma who have undergone complete resection, YERVOY can significantly improve recurrence-free survival compared to placebo.

**Recommended Dosing for Adjuvant Treatment of Fully Resected Stage III Melanoma (lymph node >1 mm)**

- The recommended dose of YERVOY is 10 mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses followed by 10 mg/kg every 12 weeks for up to 3 years. In the event of toxicity, doses are omitted, not delayed.

**Select Important Safety Information**

**Common Adverse Reactions**

- 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%). The most common adverse reactions (≥5%) in patients who received YERVOY at 10 mg/kg were rash (50%), diarrhea (49%), fatigue (45%), pruritus (45%), headache (33%), weight loss (32%), nausea (25%), pyrexia (18%), colitis (16%), decreased appetite (14%), vomiting (13%), and insomnia (10%).

![RECURRENT-FREE SURVIVAL: Kaplan-Meier estimate](chart)

*Proportion recurrence-free=proportion of patients in the trial who remained free of recurrence (local, regional, or distant metastases, as assessed by an independent review committee) and were alive at the specified time.

The number of recurrence-free survival (RFS) events in the YERVOY arm (n=475) was 234 (49%) events (220 recurrences; 14 deaths), and in the placebo arm (n=476) was 294 (62%) events (289 recurrences; 5 deaths).

A phase 3, randomized (1:1), double-blind, placebo-controlled trial in patients with resected Stage IIIa (lymph node >1 mm), IIIb, and IIIc (with no in-transit metastases) histologically confirmed cutaneous melanoma. Patients were randomized to receive YERVOY 10 mg/kg (n=475) or placebo (n=476) as an intravenous infusion every 3 weeks for 4 doses, followed by YERVOY 10 mg/kg or placebo every 12 weeks from Week 24 to Week 156 (3 years) or until documented disease recurrence or unacceptable toxicity. The major efficacy outcome measures were RFS and overall survival (OS).
YERVOY® (ipilimumab) Is a Metastatic Melanoma Therapy
Proven in a Phase 3 Study to Deliver a Durable Long-term Survival Benefit1,3,4

- The recommended dosing of YERVOY is 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a maximum of 4 doses. In the event of toxicity, doses may be delayed, but all treatment must be administered within 16 weeks of the first dose.

Select Important Safety Information: Overall Study Safety
- In patients who received 3 mg/kg of YERVOY alone (n=131), severe to fatal immune-mediated adverse reactions were reported and included enterocolitis (7%), endocrinopathy (4%, all of whom had hypopituitarism), dermatitis (2%), hepatotoxicity (1%), neuropathy (1%), nephritis (1%), and eosinophilia (1%)
- In patients who received 3 mg/kg of YERVOY + gp100 (n=380), severe to fatal immune-mediated adverse reactions were reported and included enterocolitis (7%), hepatotoxicity (2%), dermatitis (3%), endocrinopathy (1% hypopituitarism, 1% adrenal insufficiency), neuropathy (<1%), pneumonitis (<1%), meningitis (<1%), and pericarditis (<1%)
- 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%). The most common adverse reactions (>5%) in patients who received YERVOY at 10 mg/kg were rash (50%), diarrhea (49%), fatigue (46%), pruritus (45%), headache (33%), weight loss (32%), nausea (25%), pyrexia (18%), colitis (16%), decreased appetite (14%), vomiting (13%), and insomnia (10%)
- YERVOY therapy was discontinued for adverse reactions in 10% of patients

* Due to long study enrollment period, not all patients had reached this time point at study closure. Therefore, in the YERVOY arm, 2, 1, and 0 actual patients were documented in follow-up at 48, 52, and 56 months at the time of study closure.3

A phase 3, double-blind, double-dummy study that randomized 676 patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin (IL-2), dacarbazine, temozolomide, fotemustine, or carboplatin. Patients were randomized in a 3:1:1 ratio to receive YERVOY 3 mg/kg in combination with an investigational peptide vaccine (gp100) (n=403), YERVOY 3 mg/kg (n=137), or gp100 (n=136). The primary endpoint was overall survival in the YERVOY + gp100 arm vs the gp100 arm.1,3

Median overall survival in the YERVOY group was 10 months (95% CI: 8.0, 13.8).1

The YERVOY overall survival curve separated at approximately 16 weeks and remained separated throughout the study period, demonstrating a higher overall survival benefit compared to the control arm.3

Please see U.S. Full Prescribing Information, including Boxed WARNING regarding immune-mediated adverse reactions.
Explore the Following Sections to Learn More About Managing Immune-Mediated Adverse Reactions:

- Immune-Mediated Enterocolitis and Gastrointestinal Adverse Reactions
- Immune-Mediated Hepatitis and Hepatic Adverse Reactions
- Immune-Mediated Dermatitis and Skin Adverse Reactions
- Immune-Mediated Neuropathies and Neuropathic Adverse Reactions
- Immune-Mediated Endocrinopathies

Recognize and Manage Immune-Mediated Adverse Reactions Associated With Therapy

Please read the Full Prescribing Information for YERVOY® (ipilimumab) for a comprehensive description of these risks and others.

- Although any organ system can be affected, the organ systems from which the most common immune-mediated adverse reactions can originate (e.g., gastrointestinal, skin) are presented.
- The following pages are grouped by organ system and provide guidance on how to appropriately manage the associated adverse reactions.

Permanent discontinuation may be required. See the following pages for information about specific immune-mediated adverse reactions.

Please see U.S. Full Prescribing Information, including Boxed WARNING regarding immune-mediated adverse reactions.
Gastrointestinal

Immune-Mediated Enterocolitis

- Immune-mediated enterocolitis, including fatal cases, can occur with YERVOY® (ipilimumab).
- Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms.
- Withhold YERVOY for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for >1 week, initiate systemic corticosteroids (0.5 mg/kg/day prednisone or equivalent).
- Permanently discontinue YERVOY in patients with severe enterocolitis and initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). Upon improvement to Grade 1, initiate corticosteroid taper and continue over at least 1 month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients.
- Consider adding anti-TNF or other immunosuppressant agents for management of immune-mediated enterocolitis unresponsive to systemic corticosteroids within 3-5 days or recurring after symptom improvement if other causes are excluded.
- In patients receiving YERVOY 3 mg/kg in MDX010-20, severe, life-threatening, or fatal (diarrhea of ≥7 stools above baseline, fever, ileus, peritoneal signs; Grade 3-5) immune-mediated enterocolitis occurred in 34 YERVOY-treated patients (7%) and moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) enterocolitis occurred in 28 YERVOY-treated patients (5%). Across all YERVOY-treated patients (n=511), 5 (1%) developed intestinal perforation, 4 (0.8%) died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis.
- Infliximab was administered to 5 (8%) of the 62 patients with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids.
- In patients receiving YERVOY 10 mg/kg in CA184-029, Grade 3-5 immune-mediated enterocolitis occurred in 76 patients (16%) and Grade 2 enterocolitis occurred in 68 patients (14%).
- Seven (1.5%) developed intestinal perforation and 3 patients (0.6%) died as a result of complications.
- 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. Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-mediated colitis if other causes are excluded.

Enterocolitis and Bowel Perforation

<table>
<thead>
<tr>
<th>Enterocolitis</th>
<th>Bowel Perforation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diarrhea</td>
<td>• Perforated signs</td>
</tr>
<tr>
<td>• Abdominal pain</td>
<td>• Ileus</td>
</tr>
<tr>
<td>• Mucus or blood in stool</td>
<td></td>
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<tr>
<td>• Fever (may or may not be present)</td>
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</tbody>
</table>

In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms.

Median time to onset

<table>
<thead>
<tr>
<th>Study 2</th>
<th>Study 1 Unresectable or Metastatic Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>1.1 months (1 day-20.6 months)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>1.1 months (1 day-33.1 months)</td>
</tr>
<tr>
<td>Grade 3-5</td>
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</tr>
</tbody>
</table>

Follow-up

- Close monitoring for worsening symptoms
- Educate patient to report worsening immediately

If symptoms improve to mild (Grade 1) or resolve
- Resume YERVOY
- If steroids have been administered
  - Taper steroids over at least 1 month
  - Resume YERVOY when steroid dose is ≤0.5 mg/kg/day prednisone or equivalent per day until administration of all 4 planned doses, or 16 weeks from the first dose, whichever occurs earlier

If improved from Grade 3
- Continue steroids at the same dose until Grade 1
- Upon improvement to Grade 1 or less, initiate steroid taper over at least 1 month
- Rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients

Managing Immune-Mediated Gastrointestinal Adverse Reactions

<table>
<thead>
<tr>
<th>Symptomatic Treatment</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administer anti-diarrheal treatment</td>
<td>--</td>
</tr>
<tr>
<td>Administer anti-diarrheal treatment</td>
<td>If symptoms persist &gt;1 week, worsen, or recur</td>
</tr>
<tr>
<td>• 0.5 mg/kg/day prednisone or equivalent</td>
<td></td>
</tr>
<tr>
<td>Rule out bowel perforation</td>
<td>If symptoms persist &gt;1 week, worsen, or recur</td>
</tr>
<tr>
<td>• 1 to 2 mg/kg/day prednisone or equivalent</td>
<td></td>
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</tbody>
</table>

Gastrointestinal Tests

- Consider endoscopic evaluation

YERVOY Treatment

<table>
<thead>
<tr>
<th>Continue YERVOY</th>
<th>Without YERVOY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanently discontinue for reactions lasting 6 weeks or longer</td>
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</tr>
</tbody>
</table>

Permanently discontinue YERVOY

- If symptoms worsen
- Treat as Grade 3-4

If symptoms worsen or persist 3 to 5 days, or recur after improvement
- Consider adding anti-TNF (i.e. Infliximab) or other immunosuppressant agents for management of immune-mediated enterocolitis unresponsive to systemic corticosteroids within 3-5 days or recurring after symptom improvement.
- If other causes are excluded
Immune-Mediated Hepatitis

- Immune-mediated hepatitis, including fatal cases, can occur with YERVOY® (ipilimumab).
- Monitor LFTs (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatotoxicity before each dose of YERVOY. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of LFT monitoring until resolution. Withhold YERVOY in patients with Grade 2 hepatotoxicity. Permanently discontinue YERVOY in patients with Grade 3-4 hepatotoxicity and administer systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). When LFTs show sustained improvement or return to baseline, initiate corticosteroid tapering and continue over 1 month.
- Across the clinical development program for YERVOY, mycophenolate treatment has been administered in patients with persistent severe hepatitis despite high-dose corticosteroids.
- In patients receiving YERVOY 3 mg/kg in MDX010-20, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations >5x the ULN or total bilirubin elevation >3x the ULN; Grade 3-5) occurred in 8 YERVOY-treated patients (2%), with fatal hepatic failure in 0.2% and hospitalization for ALT abnormalities (AST or ALT elevations >2.5x but ≤5x the ULN or total bilirubin elevation >1.5x but ≤3x the ULN; Grade 2).
- In a dose-finding trial, Grade 3 increases in transaminases with or without concomitant increases in total bilirubin occurred in 6 of 10 patients who received concurrent YERVOY (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID).
- In patients receiving YERVOY 10 mg/kg in CA184-029, Grade 3-4 immune-mediated hepatitis occurred in 51 patients (11%) and moderate Grade 2 immune-mediated hepatitis occurred in 22 patients (5%).
  - Liver biopsy performed in 6 patients with Grade 3-4 hepatitis showed evidence of toxic or autoimmune hepatitis.

Hepatitis

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transaminase elevation</td>
</tr>
<tr>
<td>Total bilirubin elevation</td>
</tr>
</tbody>
</table>

In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of liver function test monitoring until resolution.

<table>
<thead>
<tr>
<th>Median time to onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 2</td>
</tr>
<tr>
<td>Adjuvant Treatment of Fully Resected Stage III Melanoma (lymph node &gt;1 mm)</td>
</tr>
<tr>
<td>Grade 2: 1.4 months (13 days-6.5 months)</td>
</tr>
<tr>
<td>Grade 3-4: 2.0 months (1 day-4.2 months)</td>
</tr>
</tbody>
</table>

| Study 1  |
| Unresectable or Metastatic Melanoma |
| Grade 2: Not available |
| Grade 3-4: Not available |

Managing Immune-Mediated Hepatic Adverse Reactions

**FOR SUSPECTED IMMUNE-MEDIATED ADVERSE REACTIONS, EXCLUDE OTHER CAUSES. RULE OUT INFECTIOUS OR MALIGNANT CAUSES.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (Grade 1)</td>
<td>Continue YERVOY</td>
</tr>
<tr>
<td>Moderate (Grade 2)</td>
<td>Withhold YERVOY while investigating alternate etiology. Permanently discontinue for reactions lasting 6 weeks or longer.</td>
</tr>
<tr>
<td>Severe (Grade 3) - Life-threatening (Grade 4)</td>
<td>Permanently discontinue YERVOY</td>
</tr>
</tbody>
</table>

**Steroids**

- Elevations persist for >5-7 days or worsen:
  - Consider 0.5-1.0 mg/kg/day prednisone or equivalent

**Follow-up**

- Continue monitoring LFTs prior to each dose
- Liver function tests are ≤2.5x ULN or return to baseline and total bilirubin level is ≤1.5x ULN or returns to baseline:
  - Resume to q3w monitoring
  - Resume YERVOY until administration of all 4 planned doses, or 16 weeks from the first dose, whichever occurs earlier

- When LFTs show sustained improvement or return to baseline:
  - Taper steroids over 1 month

- If AST or ALT continues to elevate to >5.0x ULN and/or total bilirubin >3.0x ULN:
  - Treat as Grade 3-4

- If labs do not decrease over 3-5 days, worsen, or rebound:
  - Add non-corticosteroid immunosuppressive medication

**Permanently discontinue for inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day**

Please see U.S. Full Prescribing Information, including Boxed WARNING regarding immune-mediated adverse reactions.
Skin

Immune-Mediated Dermatitis

- Immune-mediated dermatitis, including fatal cases, can occur with YERVOY® (ipilimumab)
- Monitor patients for signs and symptoms of dermatitis such as rash and pruritus
- Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated. Treat mild to moderate dermatitis (e.g., localized rash and pruritus) symptomatically; administer topical or systemic corticosteroids if there is no improvement within 1 week. Withhold YERVOY in patients with severe to moderate signs and symptoms. Permanently discontinue YERVOY in patients with severe, life-threatening, or fatal immune-mediated dermatitis (Grade 3-5). Administer systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month.
- In patients receiving YERVOY 3 mg/kg in MDX010-20, severe, life-threatening, or fatal immune-mediated dermatitis (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3-5) occurred in 13 YERVOY-treated patients (2.5%)
  - 1 patient (0.2%) died as a result of toxic epidermal necrolysis and 1 additional patient required hospitalization for severe dermatitis
  - There were 63 patients (12%) with moderate (Grade 2) dermatitis
- In patients receiving YERVOY 10 mg/kg in CA184-029, Grade 3-4 immune-mediated dermatitis occurred in 19 patients (4%). There were 99 patients (21%) with moderate Grade 2 dermatitis

Dermatitis

### Signs and symptoms

- Rash
- Pruritus

Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated.

### Median time to onset

<table>
<thead>
<tr>
<th>Immune-Mediated Dermatitis</th>
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<tbody>
<tr>
<td>Study 2</td>
<td>Study 1</td>
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<tr>
<td>Adjuvant Treatment of Fully Resected Stage III Melanoma (lymph node &gt;1 mm)</td>
<td>Unresectable or Metastatic Melanoma</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Grade 2</td>
</tr>
<tr>
<td>11 days (1 day-16.6 months)</td>
<td>22 days (and ranged up to 4 months from the initiation of YERVOY)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td></td>
</tr>
<tr>
<td>14 days (5-11.3 months)</td>
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</tbody>
</table>

Embryo-Fetal Toxicity

Based on its mechanism of action, 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 YERVOY and for 3 months after the last dose.

Lactation

It is not known whether YERVOY is secreted in human milk. Advise women not to breastfeed during treatment with YERVOY and for 3 months after the last dose.

Managing Immune-Mediated Dermatitis Adverse Reactions

**For suspected immune-mediated adverse reactions, exclude other causes.**

<table>
<thead>
<tr>
<th>Immune-Mediated Dermatitis</th>
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<tbody>
<tr>
<td>YERVOY Treatment</td>
<td>Continue YERVOY</td>
</tr>
<tr>
<td>Withhold YERVOY</td>
<td>Permanently discontinue for reactions lasting 6 weeks or longer</td>
</tr>
</tbody>
</table>

**Consultation**

- Administer
- Administer
- Dermatology

**Steroids**

- 1 to 2 mg/kg/day of prednisone or equivalent

Please see U.S. Full Prescribing Information, including Boxed WARNING regarding immune-mediated adverse reactions.
Neurologic

Immune-Mediated Neuropathies

- Immune-mediated neuropathies, including fatal cases, can occur with YERVOY® (ipilimumab)
- Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia
- Withhold YERVOY in patients with moderate neuropathy (not interfering with daily activities). Permanently discontinue YERVOY in patients with severe neuropathy (interfering with daily activities), such as Guillain-Barré-like syndromes. Institute medical intervention as appropriate for management for severe neuropathy. Consider initiation of systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe neuropathies
- In patients receiving YERVOY 3 mg/kg in MDX010-20, 1 case of fatal Guillain-Barré syndrome occurred in 8 patients (2%)
- In patients receiving YERVOY 10 mg/kg in CA184-029, Grade 3-5 immune-mediated neuropathy occurred in 8 patients (2%)
- The sole fatality was due to complications of Guillain-Barré syndrome
- Moderate Grade 2-5 immune-mediated neuropathy occurred in 1 patient (0.2%)

Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations

In Trial 1, the following clinically significant immune-mediated adverse reactions were seen in <1% of YERVOY-treated patients: cytopenias, nephritis, pneumonitis, meningitis, pericarditis, uveitis, and iritis. In Trial 2, the following clinically significant immune-mediated adverse reactions were seen in <1% of YERVOY-treated patients unless specified: cytopenias, esophagitis, gastritis (1.3%), pancreatitis (1.3%), meningitis, pneumonitis, sarcoidosis, pericarditis, uveitis, and fatal myocarditis. Across 21 dose-ranging trials administering YERVOY at doses of 0.1 to 20 mg/kg (n=2478), the following likely immune-mediated adverse reactions were also reported with ≥1% incidence unless specified: angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, iritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, arthritis, autoimmune thyroiditis, neurosensory hypacusis, autoimmune central neuropathy (encephalitis), myositis, polyarthritis, uveitis, and iritis. YERVOY impacted uveitis, iritis, and other ocular manifestations that were not observed with CTLA-4 blockade. In a phase 2b dose-ranging study (Trial 2) the most common ocular adverse event was uveitis (Grade 2-5: 4%) and all patients with severe ocular disease were observed to improve with local immunosuppressive therapy. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome for severe immune-mediated adverse reactions. Monitor patients for signs or symptoms of ocular toxicity, which may include blurred vision and reduced visual acuity. Immune-mediated ocular toxicity may be associated with retinal detachment or permanent vision loss. Administer corticosteroid eye drops for uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease unresponsive to local immunosuppressive therapy. If uveitis occurs and worsens, treat as Grade 2 or Grade 3-4, appropriately.

Managing Immune-Mediated Neuropathic Adverse Reactions

- Continue monitoring, if symptoms worsen, treat as Grade 2 or Grade 3-4, appropriately
- If symptoms resolve or improve to Grade 1:
  - Resume YERVOY until administration of all 4 planned doses, or 16 weeks from the first dose, whichever occurs earlier
  - Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia

Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations (continued)

- YERVOY impacted uveitis, iritis, and other ocular manifestations that were not observed with CTLA-4 blockade. In a phase 2b dose-ranging study (Trial 2), the most common ocular adverse event was uveitis (Grade 2-5: 4%) and all patients with severe ocular disease were observed to improve with local immunosuppressive therapy. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome for severe immune-mediated adverse reactions. Monitor patients for signs or symptoms of ocular toxicity, which may include blurred vision and reduced visual acuity. Immune-mediated ocular toxicity may be associated with retinal detachment or permanent vision loss. Administer corticosteroid eye drops for uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease unresponsive to local immunosuppressive therapy. If uveitis occurs and worsens, treat as Grade 2 or Grade 3-4, appropriately.

Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations (continued)

- YERVOY impacted uveitis, iritis, and other ocular manifestations that were not observed with CTLA-4 blockade. In a phase 2b dose-ranging study (Trial 2), the most common ocular adverse event was uveitis (Grade 2-5: 4%) and all patients with severe ocular disease were observed to improve with local immunosuppressive therapy. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome for severe immune-mediated adverse reactions. Monitor patients for signs or symptoms of ocular toxicity, which may include blurred vision and reduced visual acuity. Immune-mediated ocular toxicity may be associated with retinal detachment or permanent vision loss. Administer corticosteroid eye drops for uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease unresponsive to local immunosuppressive therapy. If uveitis occurs and worsens, treat as Grade 2 or Grade 3-4, appropriately.

- If symptoms worsen or persist:
  - Add non-corticosteroid immunosuppressive medication as per local guidelines
  - If symptoms worsen or persist:
  - Add non-corticosteroid immunosuppressive medication as per local guidelines

Please see U.S. Full Prescribing Information, including Boxed WARNING regarding immune-mediated adverse reactions.
Immune-Mediated Endocrinopathies

- Immune-mediated endocrinopathies, including life-threatening cases, can occur with YERVOY® (ipilimumab).
- Monitor patients for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms that may resemble other causes such as brain metastases or underlying disease. Unless an alternate etiology has been identified, signs or symptoms should be considered immune-mediated.
- Monitor clinical chemistries, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at the start of therapy, before each dose, and as clinically indicated based on symptoms.
- In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland.
- Withhold YERVOY in symptomatic patients and consider referral to an endocrinologist. Initiate systemic hormone replacement therapy if hypophysitis is suspected.
- In patients receiving YERVOY 3 mg/kg in MDX010-20, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3-4) occurred in 9 YERVOY-treated patients (1.8%).
- Of the 9 patients who were hospitalized for severe endocrinopathies:
  - Six of the 9 patients were hospitalized for severe hypophysitis.
  - Moderate hypophysitis (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 patients (2.3%) and consisted of hypothryoidism, adrenal insufficiency, hypopituitarism, and 1 case each of hyperthyroidism and Cushing’s syndrome.
- The median time to onset of moderate immune-mediated endocrinopathy was 2.5 months and ranged up to 4.4 months after the initiation of YERVOY.
- In patients receiving YERVOY 10 mg/kg in CA184-029, Grade 3-4 immune-mediated endocrinopathies occurred in 39 patients (8%) and Grade 2 immune-mediated endocrinopathies in 93 (20%) patients.
  - Of the 39 patients with Grade 3-4 immune-mediated endocrinopathies, 35 patients had hypophysitis (associated with 1 or more secondary endocrinopathies, e.g., adrenal insufficiency, hypogonadism, and hypothyroidism), 3 patients had hyperthyroidism, and 1 had primary hypothyroidism. The median time to onset of Grade 3-4 immune-mediated endocrinopathy was 2.2 months (range: 2 days-8 months).
  - Twenty-seven (69.2%) of the 39 patients were hospitalized for immune-mediated endocrinopathies. Of the 93 patients with Grade 2 immune-mediated endocrinopathy, 74 had primary hypophysitis (associated with 1 or more secondary endocrinopathies, e.g., adrenal insufficiency, hypogonadism, and hypothyroidism), 9 had primary hypothyroidism, 3 had hyperthyroidism, 3 had thyroiditis with hypo- or hyperthyroidism, 2 had hypogonadism, 1 had both hyperthyroidism and hypothyroidism, and 1 subject developed Graves’ ophthalmopathy. The median time to onset of Grade 2 immune-mediated endocrinopathy was 2.1 months (range: 9 days-19.3 months).

### Endocrinopathies

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Mental-status changes</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Unusual bowel habits</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
</tbody>
</table>

Patients may present with nonspecific symptoms that may resemble other causes, such as brain metastases or underlying disease. Unless an alternate etiology has been identified, signs or symptoms should be considered immune-mediated.

### Median time to onset

| Study 2 | Study 1 | Study 1
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjacent Treatment of Fully Resected Stage III Melanoma (ipilimumab + nivolumab)</td>
<td>Unresetable or Metastatic Melanoma</td>
<td>Unresetable or Metastatic Melanoma</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2.1 months (9 days-15.3 months)</td>
<td>--</td>
</tr>
<tr>
<td>Grade 2.4</td>
<td>--</td>
<td>2.5 months (and ranged up to 4.4 months after the initiation of YERVOY)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>2.2 months (7 days-8 months)</td>
<td>--</td>
</tr>
</tbody>
</table>

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### Managing Immune-Mediated Endocrinopathies

<table>
<thead>
<tr>
<th>Asymptomatic TSH Elevation</th>
<th>Symptomatic Endocrinopathy</th>
<th>Suspicion of Adrenal Crisis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>YERVOY Treatment</strong></td>
<td><strong>Continue YERVOY</strong></td>
<td><strong>Consider endocrinology</strong></td>
</tr>
<tr>
<td><strong>Without YERVOY</strong></td>
<td><strong>Permanently discontinue for reactions lasting 6 weeks or longer</strong></td>
<td><strong>Endocrinology</strong></td>
</tr>
</tbody>
</table>

**Monitoring**

- If TSH <0.5x LLN, or TSH >2x ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycle as clinically indicated
- Evaluate endocrine function
- Consider pituitary scan for hypophysitis
- Repeat labs in 1 to 3 weeks/NB in 1 month if symptoms persist but normal lab/pituitary scan

**Consultation**

- Consider endocrinology
- Consider endocrinology

**Steroids**

- 1-2 mg/kg/day prednisone or equivalent, if symptomatic with abnormal lab/pituitary scan
- Stress-dose of IV steroids with mineralocorticoid activity

**Hormone Replacement**

- Initiate if symptomatic with abnormal lab/pituitary scan
- Long-term hormone replacement therapy may be necessary

**IV Fluids**

- Administer

### Follow-up

- Continue standard monitoring

**If improved (with or without hormone therapy)**

- **Resume YERVOY** when steroid dose is ≤7.5 mg prednisone or equivalent until administration of all 4 planned doses, or 16 weeks from the first dose, whichever occurs earlier
- Taper steroids over at least 1 month
- Continue standard monitoring
- Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component

**When adrenal crisis ruled out**

- **Treat as Symptomatic Endocrinopathy**

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*Please see U.S. Full Prescribing Information, including Boxed WARNING regarding immune-mediated adverse reactions.*
Please see U.S. Full Prescribing Information, including Boxed WARNING regarding immune-mediated adverse reactions.
## Treatment Modifications in Response to Immune-Mediated Adverse Reactions

<table>
<thead>
<tr>
<th>TARGET/ORGANSYSTEM</th>
<th>ADVERSE REACTION (CTCAE V3)</th>
<th>TREATMENT MODIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine</strong></td>
<td>Symptomatic endocrinopathy</td>
<td>Withhold YERVOY</td>
</tr>
<tr>
<td></td>
<td>Permanently discontinue YERVOY</td>
<td>Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0 to 1) and who are receiving less than 7.5 mg prednisone or equivalent per day</td>
</tr>
<tr>
<td></td>
<td>• Symptomatic reactions lasting 6 weeks or longer</td>
<td>Permanently discontinue YERVOY</td>
</tr>
<tr>
<td></td>
<td>• Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day</td>
<td></td>
</tr>
<tr>
<td><strong>Ophthalmologic</strong></td>
<td>Grade 2 through 4 reactions</td>
<td>Permanently discontinue YERVOY</td>
</tr>
<tr>
<td></td>
<td>• not improving to Grade 1 within 2 weeks while receiving topical therapy or requiring systemic treatment</td>
<td></td>
</tr>
<tr>
<td><strong>All Other</strong></td>
<td>Grade 2</td>
<td>Withhold YERVOY</td>
</tr>
<tr>
<td></td>
<td>Grade 2 reactions lasting 6 weeks or longer</td>
<td>Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0 to 1) and who are receiving less than 7.5 mg prednisone or equivalent per day</td>
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<tr>
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</tr>
<tr>
<td></td>
<td>• Grade 3 or 4</td>
<td></td>
</tr>
</tbody>
</table>

CTCAE - Common Terminology Criteria for Adverse Events.

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

### Recommended Dosing

**Unresectable or metastatic melanoma:** The recommended dose of YERVOY is 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of 4 doses. In the event of toxicity, doses may be delayed, but all treatment must be administered within 16 weeks of the first dose.

**Adjuvant treatment of fully resected Stage III melanoma (lymph node >1 mm):** The recommended dose of YERVOY is 10 mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses followed by 10 mg/kg every 12 weeks for up to 3 years. In the event of toxicity, doses are omitted, not delayed.

### References

Please see U.S. Full Prescribing Information, including **Boxed WARNING** regarding immune-mediated adverse reactions.

Please visit www.YERVOY.com or call 1-855-YERVOY1 (1-855-937-8691)

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