A REFERENCE GUIDE TO
REIMBURSEMENT AND CODING

YERVOY®
(ipilimumab)

INDICATIONS
YERVOY® (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma in adults and pediatric patients (12 years and older).
YERVOY® (ipilimumab) is indicated for the 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), adrenocorticotropic 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 additional Important Safety Information, including Boxed WARNING regarding immune-mediated adverse reactions, on pages 18-22 and U.S. Full Prescribing Information at the end of this document.
Bristol-Myers Squibb Is Committed to Helping Support Access

This brochure is designed to help appropriate patients get access to our medications by providing helpful reimbursement information for healthcare offices. Healthcare benefits vary significantly; therefore, it is important that oncology offices verify each patient’s insurance coverage prior to initiating therapy.

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Healthcare providers should code healthcare claims based upon the service that is rendered, the patient’s medical record, the coding requirements of each health insurer, and best coding practices. The accurate completion of reimbursement- or coverage-related documentation is the responsibility of the healthcare provider and patient. Bristol-Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.

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For reimbursement assistance, call BMS Access Support® at 1-800-861-0048, 8 AM to 8 PM ET, Monday–Friday, or visit www.BMSAccessSupport.com.
METASTATIC MELANOMA:
ICD-10-CM Codes for YERVOY® (ipilimumab)

ICD-10-CM codes are used to identify a patient’s diagnosis. On October 1, 2015, the newest version of these codes, ICD-10-CM, was implemented throughout the United States. This version replaces the previous version, ICD-9-CM.

- The ICD-10-CM diagnosis codes contain categories, subcategories, and codes. Characters for categories, subcategories, and codes may be letters or numerals.
- All categories are 3 characters
- Subcategories are either 4 or 5 characters
- Codes may be 3, 4, 5, 6, or 7 characters
- The ICD-10-CM codes for the labeled indications for YERVOY are provided below by Bristol-Myers Squibb and should be verified with the payer. Some health plan and Medicare insurers may specify which codes are covered under their policies. Please code to the level of specificity documented in the medical record. For additional coding questions, call BMS Access Support® at 1-800-861-0048 or visit www.BMSAccessSupport.com

### ICD-10-CM Codes for YERVOY®

<table>
<thead>
<tr>
<th>C43</th>
<th>Malignant melanoma of skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>C43.0</td>
<td>Malignant melanoma of lip</td>
</tr>
<tr>
<td>C43.1</td>
<td>Malignant melanoma of eyelid, including canthus*</td>
</tr>
<tr>
<td>C43.10</td>
<td>Malignant melanoma of unspecified eyelid, including canthus</td>
</tr>
<tr>
<td>C43.11</td>
<td>Malignant melanoma of right eyelid, including canthus*</td>
</tr>
<tr>
<td>C43.111</td>
<td>Malignant melanoma of right upper eyelid, including canthus</td>
</tr>
<tr>
<td>C43.112</td>
<td>Malignant melanoma of right lower eyelid, including canthus</td>
</tr>
<tr>
<td>C43.12</td>
<td>Malignant melanoma of left eyelid, including canthus*</td>
</tr>
<tr>
<td>C43.121</td>
<td>Malignant melanoma of left upper eyelid, including canthus</td>
</tr>
<tr>
<td>C43.122</td>
<td>Malignant melanoma of left lower eyelid, including canthus</td>
</tr>
</tbody>
</table>

*This is a category code and is invalid for stand-alone use. Please select one of the expanded codes listed below.

(more C43 codes on the next page)

**Note:** If infusion for antineoplastic immunotherapy is the only reason for the patient encounter, physicians and hospitals may report the code below as the primary diagnosis:

Z51.12 Encounter for antineoplastic immunotherapy

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### ICD-10-CM Codes for YERVOY® (ipilimumab) (cont’d)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C43.2</td>
<td>Malignant melanoma of ear and external auricular canal*</td>
</tr>
<tr>
<td>C43.20</td>
<td>Malignant melanoma of unspecified ear and external auricular canal</td>
</tr>
<tr>
<td>C43.21</td>
<td>Malignant melanoma of right ear and external auricular canal</td>
</tr>
<tr>
<td>C43.22</td>
<td>Malignant melanoma of left ear and external auricular canal</td>
</tr>
<tr>
<td>C43.3</td>
<td>Malignant melanoma of other and unspecified parts of face*</td>
</tr>
<tr>
<td>C43.30</td>
<td>Malignant melanoma of unspecified part of face</td>
</tr>
<tr>
<td>C43.31</td>
<td>Malignant melanoma of nose</td>
</tr>
<tr>
<td>C43.39</td>
<td>Malignant melanoma of other parts of face</td>
</tr>
<tr>
<td>C43.4</td>
<td>Malignant melanoma of scalp and neck</td>
</tr>
<tr>
<td>C43.5</td>
<td>Malignant melanoma of trunk*</td>
</tr>
<tr>
<td>C43.51</td>
<td>Malignant melanoma of anal skin</td>
</tr>
<tr>
<td>C43.52</td>
<td>Malignant melanoma of skin of breast</td>
</tr>
<tr>
<td>C43.59</td>
<td>Malignant melanoma of other part of trunk</td>
</tr>
<tr>
<td>C43.6</td>
<td>Malignant melanoma of upper limb, including shoulder*</td>
</tr>
<tr>
<td>C43.60</td>
<td>Malignant melanoma of unspecified upper limb, including shoulder</td>
</tr>
</tbody>
</table>

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**Note:** If infusion for antineoplastic immunotherapy is the only reason for the patient encounter, physicians and hospitals may report the code below as the primary diagnosis:

**Z51.12 Encounter for antineoplastic immunotherapy**

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METASTATIC MELANOMA:
ICD-10-CM Codes for YERVOY® (ipilimumab) (cont’d)

<table>
<thead>
<tr>
<th>ICD-10-CM Codes for YERVOY¹</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C43.61</td>
<td>Malignant melanoma of right upper limb, including shoulder</td>
</tr>
<tr>
<td>C43.62</td>
<td>Malignant melanoma of left upper limb, including shoulder</td>
</tr>
<tr>
<td>C43.7</td>
<td>Malignant melanoma of lower limb, including hip*</td>
</tr>
<tr>
<td>C43.70</td>
<td>Malignant melanoma of unspecified lower limb, including hip</td>
</tr>
<tr>
<td>C43.71</td>
<td>Malignant melanoma of right lower limb, including hip</td>
</tr>
<tr>
<td>C43.72</td>
<td>Malignant melanoma of left lower limb, including hip</td>
</tr>
<tr>
<td>C43.8</td>
<td>Malignant melanoma of overlapping sites of skin</td>
</tr>
<tr>
<td>C43.9</td>
<td>Malignant melanoma of skin, unspecified</td>
</tr>
</tbody>
</table>

*This is a category code and is invalid for stand-alone use. Please select one of the expanded codes listed below.

The code C43 has an Excludes 2 note under it. Per ICD-10-CM official guidelines, an Excludes 2 note under a code represents “Not included here.” An Excludes 2 note indicates that the condition excluded is not part of the condition represented by the code, but a patient may have both conditions at the same time. When an Excludes 2 note appears under a code, it is acceptable to use both the code and the excluded code together, when appropriate.¹

Under code C43, the Excludes 2 note lists the following¹:

- Malignant melanoma of skin of genital organs (C51, C52, C60, C63)
- Merkel cell carcinoma (C4A)
- Sites other than skin – code to malignant neoplasm of the site

Note: If infusion for antineoplastic immunotherapy is the only reason for the patient encounter, physicians and hospitals may report the code below as the primary diagnosis¹:

Z51.12 Encounter for antineoplastic immunotherapy

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METASTATIC MELANOMA: ICD-10-CM Codes for YERVOY® (ipilimumab) (cont’d)

For sites other than category C43, code to the malignant neoplasm of the site. Some sites where melanoma is commonly seen are shown below and on the next page.

<table>
<thead>
<tr>
<th>ICD-10-CM Codes for YERVOY¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>C21  Malignant neoplasm of anus and anal canal</td>
</tr>
<tr>
<td>C21.0 Malignant neoplasm of anus, unspecified</td>
</tr>
<tr>
<td>C21.1 Malignant neoplasm of anal canal</td>
</tr>
<tr>
<td>C51  Malignant neoplasm of vulva</td>
</tr>
<tr>
<td>C51.0 Malignant neoplasm of labium majus</td>
</tr>
<tr>
<td>C51.1 Malignant neoplasm of labium minus</td>
</tr>
<tr>
<td>C51.2 Malignant neoplasm of clitoris</td>
</tr>
<tr>
<td>C51.9 Malignant neoplasm of vulva, unspecified</td>
</tr>
<tr>
<td>C52  Malignant neoplasm of vagina</td>
</tr>
<tr>
<td>C57  Malignant neoplasm of other and unspecified female genital organs</td>
</tr>
<tr>
<td>C57.7 Malignant neoplasm of other specified female genital organs</td>
</tr>
<tr>
<td>C57.8 Malignant neoplasm of overlapping sites of female genital organs</td>
</tr>
<tr>
<td>C57.9 Malignant neoplasm of female genital organ, unspecified</td>
</tr>
</tbody>
</table>

Note: If infusion for antineoplastic immunotherapy is the only reason for the patient encounter, physicians and hospitals may report the code below as the primary diagnosis¹:

Z51.12 Encounter for antineoplastic immunotherapy

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### ICD-10-CM Codes for YERVOY® (ipilimumab) (cont’d)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C60</td>
<td>Malignant neoplasm of penis</td>
</tr>
<tr>
<td>C60.0</td>
<td>Malignant neoplasm of prepuce</td>
</tr>
<tr>
<td>C60.1</td>
<td>Malignant neoplasm of glans penis</td>
</tr>
<tr>
<td>C60.8</td>
<td>Malignant neoplasm of overlapping sites of penis</td>
</tr>
<tr>
<td>C60.9</td>
<td>Malignant neoplasm of penis, unspecified</td>
</tr>
<tr>
<td>C63</td>
<td>Malignant neoplasm of other and unspecified male genital organs</td>
</tr>
<tr>
<td>C63.0</td>
<td>Malignant neoplasm of epididymis*</td>
</tr>
<tr>
<td>C63.00</td>
<td>Malignant neoplasm of unspecified epididymis</td>
</tr>
<tr>
<td>C63.01</td>
<td>Malignant neoplasm of right epididymis</td>
</tr>
<tr>
<td>C63.02</td>
<td>Malignant neoplasm of left epididymis</td>
</tr>
<tr>
<td>C63.1</td>
<td>Malignant neoplasm of spermatic cord*</td>
</tr>
<tr>
<td>C63.10</td>
<td>Malignant neoplasm of unspecified spermatic cord</td>
</tr>
<tr>
<td>C63.11</td>
<td>Malignant neoplasm of right spermatic cord</td>
</tr>
<tr>
<td>C63.12</td>
<td>Malignant neoplasm of left spermatic cord</td>
</tr>
<tr>
<td>C63.2</td>
<td>Malignant neoplasm of scrotum</td>
</tr>
<tr>
<td>C63.7</td>
<td>Malignant neoplasm of other specified male genital organs</td>
</tr>
<tr>
<td>C63.8</td>
<td>Malignant neoplasm of overlapping sites of male genital organs</td>
</tr>
<tr>
<td>C63.9</td>
<td>Malignant neoplasm of male genital organ, unspecified</td>
</tr>
</tbody>
</table>

*This is a category code and is invalid for stand-alone use. Please select one of the expanded codes listed below.

**Note:** If infusion for antineoplastic immunotherapy is the only reason for the patient encounter, physicians and hospitals may report the code below as the primary diagnosis:

**Z51.12 Encounter for antineoplastic immunotherapy**

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Healthcare Common Procedure Coding System (HCPCS) and Revenue Codes for YERVOY® (ipilimumab)

<table>
<thead>
<tr>
<th>Recommended HCPCS Code for YERVOY²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HCPCS Code</strong></td>
</tr>
<tr>
<td>J9228</td>
</tr>
</tbody>
</table>

Use the following claim formats when YERVOY is administered to patients on an outpatient basis and billed to health plans:

- Physician office: CMS-1500 [paper format] or ASC 837P [electronic format]
- Hospital outpatient: UB-04 [CMS-1450] [paper format] or ASC 837I [electronic format]
- **JW modifier** – Providers and suppliers are required to report the JW modifier on Part B drug claims for discarded drugs and biologicals. Also, providers and suppliers must document the amount of discarded drugs or biologicals in Medicare beneficiaries’ medical records.¹

All the coding information presented is applicable to outpatient procedures only. Please see pages 12-13 for more information.

<table>
<thead>
<tr>
<th>Revenue Codes⁴ (for Use in the Hospital Outpatient Setting)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Revenue Code</strong></td>
</tr>
<tr>
<td>0636</td>
</tr>
<tr>
<td>0335</td>
</tr>
<tr>
<td>0260</td>
</tr>
</tbody>
</table>

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Current Procedural Terminology (CPT)* Codes for YERVOY® (ipilimumab)

The CPT codes that may be appropriate when administering YERVOY appear in the table below.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>96413</td>
<td>Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug</td>
</tr>
</tbody>
</table>
| 96415    | Chemotherapy administration, IV infusion; each additional hour  
• List separately in addition to code for primary procedure  
• Use 96415 in conjunction with 96413  
• Report 96415 for infusion intervals of greater than 30 minutes beyond 1-hour increments |

Please contact the payer or BMS Access Support® for additional coding information regarding YERVOY.

*CPT codes and descriptions only are ©2019 by American Medical Association (AMA). All rights reserved. The AMA assumes no liability for data contained or not contained herein. CPT is a registered trademark of the American Medical Association.

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National Drug Codes (NDCs) Information for YERVOY® (ipilimumab)

The NDCs for YERVOY, listed below, are often necessary in addition to the appropriate J-code when filing a claim for reimbursement.

**NDC Codes for YERVOY®**

- One 200-mg (5-mg/mL), single-use vial
  - 200-mg vial = 200 billable units
  - 0003-2328-22
  - 00003-2328-22

- One 50-mg (5-mg/mL), single-use vial
  - 50-mg vial = 50 billable units
  - 0003-2327-11
  - 00003-2327-11

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5010 Electronic Transaction Coding for YERVOY® (ipilimumab)

- For electronic transactions, including 837P and 837I, the NDC is to be preceded by the qualifier N4 and followed immediately by the 11-digit NDC code for payers that require it.
- This is typically followed by the quantity qualifier, such as: UN (units), F2 (international units), GR (gram), or ML (milliliter), and the quantity administered.

<table>
<thead>
<tr>
<th>How Supplied</th>
<th>NDC</th>
<th>NDC Qualifier</th>
<th>NDC Basis of Measurement</th>
<th>Sample NDC 5010 Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-mg/10-mL (5 mg/mL) single-use vial</td>
<td>00003-2327-11</td>
<td>N4</td>
<td>ML</td>
<td>N400003232711ML10</td>
</tr>
<tr>
<td>200-mg/40-mL (5 mg/mL) single-use vial</td>
<td>00003-2328-22</td>
<td>N4</td>
<td>ML</td>
<td>N400003232822ML40</td>
</tr>
</tbody>
</table>

The example given in the far right column above demonstrates NDC quantity reporting for 1 vial of YERVOY. The actual amount of drug used can vary based on factors such as indication or patient weight. Currently, reporting NDC quantity varies from payer to payer, so the provider should consult each specific payer to determine the required format.

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Coding and Billing Units for YERVOY® (ipilimumab)

Please contact the payer or BMS Access Support® for additional information on coding and billing units.

This sample form is for informational purposes only.

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Coding and Billing Units for YERVOY® (ipilimumab) [cont’d]

Outpatient Hospital

Form Locator (FL 42): Enter a 4-digit revenue code that best describes the service provided, in accordance with hospital billing policy. For chemotherapy administration, revenue codes 0260 (IV therapy) or 0335 (radiology–therapeutic: chemotherapy-IV) could be used. CMS recommends using revenue code 0636 (drugs requiring detailed coding).8

FL 43: Enter the qualifier “N4” followed by the 11-digit NDC in positions 01-13. Additionally, report the quantity qualifier (ML) followed by the quantity administered (50 mg/10 mL or 200 mg/40 mL) beginning in position 14. For example, use “N400003232711ML10” for the 50-mg/10-mL vial or “N400003232822ML40” for the 200-mg/40-mL vial.

FL 44: Enter HCPCS code J9228, CPT code 96413, and CPT code 96415 (if needed) for time of treatment infusion. In addition, it is required that you enter J9228-JW on next line to record waste.

FL 46: Billing units are called service units and are placed here. 1 mg = 1 billing unit.

FLs 67A-67Q: Enter the site-specific ICD-10-CM diagnosis codes for the malignancy being treated.

FL 80: Some payers require detailed information about the drug in FL 80. Typically, payers require the drug name, total dosage and strength, method of administration, 11-digit NDC, and basis of measurement.

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Dosing and Administration of YERVOY® (ipilimumab)

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 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.

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.

Recommended dose modifications

Endocrine: Withhold YERVOY for symptomatic endocrinopathy. Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0-1) and who are receiving <7.5 mg prednisone or equivalent per day. Permanently discontinue YERVOY for symptomatic reactions lasting 6 weeks or longer or an inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.

Ophthalmologic: Permanently discontinue YERVOY for Grade 2-4 reactions not improving to Grade 1 within 2 weeks while receiving topical therapy or requiring systemic treatment.

All Other Organ Systems: Withhold YERVOY for Grade 2 adverse reactions. Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0-1) and who are receiving <7.5 mg prednisone or equivalent per day. Permanently discontinue YERVOY for Grade 2 reactions lasting 6 weeks or longer, an inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day, and Grade 3 or 4 adverse reactions.

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For reimbursement assistance, call BMS Access Support® at 1-800-861-0048, 8 AM to 8 PM ET, Monday–Friday, or visit www.BMSAccessSupport.com.
Determining Your Order for YERVOY® (ipilimumab)

Dosing for YERVOY is weight-based; therefore, the dosage of YERVOY will vary not only by indication, but by patient weight as well.

**Example Orders**

<table>
<thead>
<tr>
<th>Patient Weight Examples</th>
<th>YERVOY</th>
<th>Total Dosage Needed</th>
<th>Suggested Vials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metastatic Melanoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 kg (110 lbs)</td>
<td>3 mg/kg</td>
<td>150 mg</td>
<td>3 x 50 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>83 kg (183 lbs)</td>
<td>3 mg/kg</td>
<td>249 mg</td>
<td>1 x 100 mg + 1 x 50 mg</td>
</tr>
<tr>
<td><strong>Adjuvant Treatment of Fully Resected Stage III Melanoma (lymph node &gt;1 mm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 kg (110 lbs)</td>
<td>10 mg/kg</td>
<td>500 mg</td>
<td>2 x 250 mg + 2 x 50 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>83 kg (183 lbs)</td>
<td>10 mg/kg</td>
<td>830 mg</td>
<td>4 x 200 mg + 1 x 50 mg</td>
</tr>
</tbody>
</table>

**How to store YERVOY**

- YERVOY must be stored under refrigeration between 2°C and 8°C (36°F to 46°F)
- Protect vials from light
- Do not freeze or shake

Please see Important Safety Information, including Boxed WARNING regarding immune-mediated adverse reactions, on pages 18-22 and U.S. Full Prescribing Information at the end of this document.

For reimbursement assistance, call BMS Access Support® at 1-800-861-0048, 8 AM to 8 PM ET, Monday–Friday, or visit [www.BMSAccessSupport.com](http://www.BMSAccessSupport.com).
What is the Medicare reimbursement allowable for YERVOY?

**Physicians***
- The payment limit is 106% of average sales price (ASP), not including sequestration, and represents one billing unit of YERVOY, which is billed for each 1 mg.\(^{10}\)
- The amount paid to physicians for HCPCS code J9228 is published at the beginning of each calendar quarter in “Payment Allowance Limits for Medicare Part B Drugs,” which can be downloaded at [https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2019ASPFiles.html](https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2019ASPFiles.html)
- Medicare Part B will pay physicians 80% of the allowed price for J9228; the patient is responsible for 20% co-insurance, which may be covered by secondary insurance (private supplemental coverage, Medicaid, etc.)\(^{12}\)

**Hospital outpatient clinics***
Drugs paid separately under the hospital outpatient fee schedule are based on 106% of average sales price (ASP), not including sequestration, for one billing unit for the corresponding HCPCS code. This is 1 mg for J9228.\(^{10}\)
- The Payment Allowance Limits\(^{11}\) are published each quarter at [https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2019ASPFiles.html](https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2019ASPFiles.html)

**Hospital inpatient settings**
- Reimbursement in the inpatient setting is bundled into the Medicare Diagnosis Related Groups called MS-DRGs.\(^{13,14}\)
- This prospective rate changes on October 1 each year and does not allow for drugs to be paid separately\(^{15}\)

*While the statutory amount that Medicare will reimburse for a Part B Drug in a physician office will remain at ASP +6%, sequestration has resulted in a reduction to the Medicare portion of the payment to Medicare providers. Essentially, all payments from Medicare carriers to the providers (including physician offices, hospitals, etc.) will be reduced by 2%.\(^{16}\)

*See The Centers for Medicare & Medicaid Services’ (CMS) Internet Only Manual (IOM) Publication 100-04, Chapter 17-20.1.3.

Please see **Important Safety Information**, including **Boxed WARNING regarding immune-mediated adverse reactions**, on pages 18-22 and U.S. **Full Prescribing Information** at the end of this document.

For reimbursement assistance, call BMS Access Support\(^*\) at 1-800-861-0048, 8 AM to 8 PM ET, Monday–Friday, or visit [www.BMSAccessSupport.com](http://www.BMSAccessSupport.com).
Commercial Insurance Reimbursement for YERVOY® (ipilimumab)

Physicians

- Drug reimbursement, like service reimbursement, is usually based on a fee schedule.¹⁷
- The fee schedules are based on the ASP or AWP, as published by a credible source,¹⁸,¹⁹
  or an average costing methodology as determined by the payer, such as usual, customary,
  and reasonable [UC&R]²⁰

Hospital outpatient clinics

- In this setting, reimbursement is most commonly based on percentage of charges.¹⁹
- Alternatively, some hospitals use the same ASP or AWP methodologies typically used by
  physician offices.¹⁹
- Other methodologies include capitated model, cost minus submitted charges, or discount off
  submitted charges.¹⁹

Hospital inpatient settings

- Inpatient rates are prospective, meaning they are predetermined per discharge.¹³
- There are private payers that pay on a version of the DRGs.¹⁵
- There are also payers that pay on a negotiated and fixed rate per day called a "per diem."¹⁴
  There are capitated rates for inpatients as well.¹³
- New drugs may be carved out of per diems or capitated rates, if the hospital negotiates to do so.²¹

Please see Important Safety Information, including Boxed WARNING regarding immune-mediated adverse reactions, on pages 18-22 and U.S. Full Prescribing Information at the end of this document.

For reimbursement assistance, call BMS Access Support® at 1-800-861-0048, 8 AM to 8 PM ET, Monday–Friday, or visit www.BMSAccessSupport.com.
Important Safety Information for YERVOY® (ipilimumab)

**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), adrenocorticotropic 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.

**Recommended Dose Modifications**

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.

Endocrine: Withhold YERVOY for symptomatic endocrinopathy. Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0-1) and who are receiving <7.5 mg prednisone or equivalent per day. Permanently discontinue YERVOY for symptomatic reactions lasting 6 weeks or longer or an inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.

Ophthalmologic: Permanently discontinue YERVOY for Grade 2-4 reactions not improving to Grade 1 within 2 weeks while receiving topical therapy or requiring systemic treatment.

All Other Organ Systems: Withhold YERVOY for Grade 2 adverse reactions. Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0-1) and who are receiving <7.5 mg prednisone or equivalent per day. Permanently discontinue YERVOY for Grade 2 reactions lasting 6 weeks or longer, an inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day, and Grade 3 or 4 adverse reactions.

**Immune-mediated Enterocolitis**

Immune-mediated enterocolitis, including fatal cases, can occur with YERVOY. 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

Please see accompanying U.S. Full Prescribing Information, including Boxed WARNING regarding immune-mediated adverse reactions, at the end of this document.

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Immune-mediated Enterocolitis (cont’d)

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.

Immune-mediated Hepatitis

Immune-mediated hepatitis, including fatal cases, can occur with YERVOY. 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 >5× the ULN or total bilirubin elevations >3× the ULN; Grade 3-5] occurred in 8 YERVOY-treated patients (2%), with fatal hepatic failure in 0.2% and hospitalization in 0.4%. An additional 13 patients (2.5%) experienced moderate hepatotoxicity manifested by LFT abnormalities [AST or ALT elevations >2.5× but ≤5× the ULN or total bilirubin elevation >1.5× but ≤3× 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.

Immune-mediated Dermatitis

Immune-mediated dermatitis, including fatal cases, can occur with YERVOY. 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 moderate to severe 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

Continued on next page
Important Safety Information for YERVOY® (ipilimumab) [cont’d]

Immune-mediated Dermatitis (cont’d)
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.

Immune-mediated Neuropathies
Immune-mediated neuropathies, including fatal cases, can occur with YERVOY. 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 and 1 case of severe (Grade 3) peripheral motor neuropathy were reported. Across the clinical development program of YERVOY, myasthenia gravis and additional cases of Guillain-Barré syndrome have been reported. 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 immune-mediated neuropathy occurred in 1 patient (0.2%).

Immune-mediated Endocrinopathies
Immune-mediated endocrinopathies, including life-threatening cases, can occur with YERVOY. 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 which may resemble other causes such as brain metastasis 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 treatment, 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 corticosteroids [1-2 mg/kg/day of prednisone or equivalent] and initiate appropriate hormone replacement therapy. 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%). 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 endocrinopathy (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 patients (2.3%) and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and 1 case each of hyperthyroidism and Cushings syndrome. The median time to onset of moderate to severe 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 occurred in 93 patients (20%). Of the 39 patients with Grade 3-4 immune-mediated

Continued on next page

Please see accompanying U.S. Full Prescribing Information, including Boxed WARNING regarding immune-mediated adverse reactions, at the end of this document.

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Important Safety Information for YERVOY® (ipilimumab) (cont’d)

**Immune-mediated Endocrinopathies (cont’d)**

endocrinopathies, 35 patients had hypopituitarism (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 hypopituitarism (associated with 1 or more secondary endocrinopathy, 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 hypopituitarism, 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).

**Other Immune-mediated Adverse Reactions, Including Ocular Manifestations**

Permanently discontinue YERVOY for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) 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 in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving YERVOY and may require treatment with systemic steroids to reduce the risk of permanent vision loss. Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive a CTLA-4 receptor blocking antibody either before or after allogeneic hematopoietic stem cell transplantation (HSCT). Follow patients closely for evidence of GVHD and intervene promptly. Consider the benefit versus risks of treatment with a CTLA-4 receptor blocking antibody either before or after allogeneic HSCT. In MDX010-20, 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 CA184-029, the following clinically significant immune-mediated adverse reactions were seen in <1% of YERVOY-treated patients unless specified: cytopenias, eosinophilia (2.1%), 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, polyarthritis rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, iritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, arthritis, autoimmune thyroiditis, neurosensory hypoacusis, autoimmune central neuropathy (encephalitis), myositis, polymyositis, ocular myositis, cytopenias (2.5%), and nephritis.

**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.

Please see accompanying U.S. Full Prescribing Information, including Boxed WARNING regarding immune-mediated adverse reactions, at the end of this document.

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Important Safety Information for YERVOY® (ipilimumab)  [cont’d]

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 (46%), pruritus (45%), headache (33%), weight loss (32%), nausea (25%), pyrexia (18%), colitis (16%), decreased appetite (14%), vomiting (13%), and insomnia (10%).
References


Please see Important Safety Information, including Boxed WARNING regarding immune-mediated adverse reactions, on pages 18-22 and U.S. Full Prescribing Information at the end of this document.

For reimbursement assistance, call BMS Access Support® at 1-800-861-0048, 8 AM to 8 PM ET, Monday–Friday, or visit www.BMSAccessSupport.com.
Three Simple Ways to Get Support

Contact your Access & Reimbursement Manager for general assistance and to schedule an office visit.

Call Bristol-Myers Squibb Access Support® at 1-800-861-0048 8 AM to 8 PM ET, Monday-Friday to speak with a regionally assigned specialist.

Visit www.BMSAccessSupport.com for information and resources, including the BMS Access Support program enrollment form, to help your patients with access to Bristol-Myers Squibb oncology products.

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The accurate completion of reimbursement- or coverage-related documentation is the responsibility of the healthcare provider and patient. Bristol-Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.
WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

YERVOY 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), nephritis, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions. (2.5)

Assess patients for signs and symptoms of enterocolitis, dermatitis, nephritis, and endocrinopathy and evaluate clinical chemistries including liver function tests, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at baseline and before each dose. (5.1, 5.2, 5.3, 5.4, 5.5)

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), nephritis, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions. (2.5)

Assess patients for signs and symptoms of enterocolitis, dermatitis, nephritis, and endocrinopathy and evaluate clinical chemistries including liver function tests, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at baseline and before each dose. (5.1, 5.2, 5.3, 5.4, 5.5)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use YERVOY safely and effectively. See full prescribing information for YERVOY.

YERVOY® (ipilimumab) injection, for intravenous use

Initial U.S. Approval: 2011

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RECENT MAJOR CHANGES

Warnings and Precautions, Immune-Mediated Enterocolitis/Colitis (5.1) 9/2019
Warnings and Precautions, Other Immune-Mediated Adverse Reactions (5.10) 5/2019

INDICATIONS AND USAGE

YERVOY is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody indicated for:

- Treatment of unresectable or metastatic melanoma in adults and pediatric patients (12 years and older). (1.1)
- 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. (1.2)
- Treatment of patients with intermediate or poor-risk, previously untreated advanced renal cell carcinoma, in combination with nivolumab. (1.3)
- Treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.4)

DOSAGE AND ADMINISTRATION

- Unresectable or metastatic melanoma:
  - YERVOY 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of 4 doses. (2.1)
- Adjuvant melanoma:
  - YERVOY 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 or until documented disease recurrence or unacceptable toxicity. (2.2)
- Advanced renal cell carcinoma:
  - Nivolumab 3 mg/kg administered intravenously over 30 minutes followed by YERVOY 1 mg/kg administered intravenously over 30 minutes on the same day, every 3 weeks for 4 doses, then nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks, administered intravenously over 30 minutes. (2.3)

- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer:
  - Nivolumab 3 mg/kg followed by YERVOY (ipilimumab) 1 mg/kg on the same day every 3 weeks for 4 doses, then nivolumab 240 mg every 2 weeks. (2.4)
- Permanently discontinue for severe adverse reactions. (2.5)

DOSAGE FORMS AND STRENGTHS

Injection: 50 mg/10 mL (5 mg/mL) and 200 mg/40 mL (5 mg/mL) in a single-use vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Immune-mediated adverse reactions: Permanently discontinue for severe reactions. Withhold dose for moderate immune-mediated adverse reactions until return to baseline, improvement to mild severity, or complete resolution, and patient is receiving less than 7.5 mg prednisone or equivalent per day. Administer systemic high-dose corticosteroids for severe, persistent, or recurring immune-mediated reactions. (5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 5.10)

- Immune-mediated hepatitis: Evaluate liver function tests before each dose of YERVOY. (5.2) Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation. (5.2)
- Immune-mediated endocrinopathies: Monitor clinical chemistries, ACTH level, and thyroid function tests prior to each dose. Evaluate at each visit for signs and symptoms of endocrinopathy. Institute hormone replacement therapy as needed. (5.5)
- Immune-mediated pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis. (5.6)
- Infusion reactions: Discontinue for severe and life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. (5.9)
- Embryo-Fetal toxicity: Caution is advised for the use of this drug in women who are or may become pregnant. Advise of potential risk to a fetus. (5.11, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (≥5%) with YERVOY as a single agent are fatigue, diarrhea, pruritus, rash, and colitis. Additional common adverse reactions at the 10 mg/kg dose (≥5%) include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia. (6.1)

Most common adverse reactions (≥20%) with YERVOY in combination with nivolumab are fatigue, rash, diarrhea, nausea, pyrexia, musculoskeletal pain, pruritus, abdominal pain, vomiting, cough, arthralgia, decreased appetite, dyspnea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Discontinue breastfeeding during treatment with YERVOY. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
2.4 Recommended Dosing for Colorectal Cancer

The recommended dose of YERVOY (ipilimumab) is:

- YERVOY 1 mg/kg administered as an intravenous infusion over 30 minutes, immediately following nivolumab administered on the same day, every 3 weeks for up to 4 doses or until intolerable toxicity or disease progression [see Clinical Studies (14.4)]. Review the Prescribing Information for nivolumab prior to initiation.

2.5 Recommended Dose Modifications

Recommendations for YERVOY modifications are provided in Table 1. When YERVOY is administered in combination with nivolumab, if YERVOY is withheld, nivolumab should also be withheld. Review the Prescribing Information for nivolumab for recommended dose modifications.

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.

Table 1: Recommended Treatment Modifications for Immune-Mediated Adverse Reactions of YERVOY

<table>
<thead>
<tr>
<th>Target/Organ System</th>
<th>Adverse Reaction (CTCAE v4)</th>
<th>Treatment Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>Symptomatic endocrinopathy</td>
<td>Withhold YERVOY</td>
</tr>
<tr>
<td></td>
<td></td>
<td></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>Permanently discontinue YERVOY</td>
</tr>
<tr>
<td>Ophthalmologic</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>All Other</td>
<td>Grade 2</td>
<td>Withhold YERVOY</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Grade 2 reactions lasting 6 weeks or longer</td>
<td>Permanently discontinue YERVOY</td>
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<td></td>
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<td>Permanently discontinue YERVOY</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue YERVOY</td>
</tr>
</tbody>
</table>
Twenty-nine patients (85%) with Grade 3 to 5 enterocolitis were treated with high-dose (>40 mg prednisone equivalent per day) corticosteroids, with a median dose of 80 mg/day of prednisone or equivalent; the median duration of treatment was 16 days (ranging up to 3.2 months) followed by corticosteroid taper. Of the 28 patients with moderate enterocolitis, 46% were not treated with systemic corticosteroids, 29% were treated with <40 mg prednisone or equivalent per day for a median duration of 1.2 months, and 25% were treated with high-dose corticosteroids for a median duration of 10 days prior to corticosteroid taper. Infliximab was administered to 5 (8%) of the 62 patients with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids.

Of the 34 patients with Grade 3 to 5 enterocolitis, 74% experienced complete resolution, 3% experienced improvement to Grade 2 severity, and 24% did not improve. Among the 28 patients with Grade 2 enterocolitis, 79% experienced complete resolution, 11% improved, and 11% did not improve.

Adjuvant Treatment of Melanoma

In patients receiving YERVOY 10 mg/kg in CA184-029 (NCT00363168), Grade 3 to 5 immune-mediated enterocolitis occurred in 76 patients (16%) and Grade 2 enterocolitis occurred in 68 patients (14%). Seven patients (1.5%) developed intestinal perforation and 3 patients (0.6%) died as a result of complications [see Adverse Reactions (6.1)].

The median time to onset for Grade 3 to 4 enterocolitis was 1.1 months (range: 1 day to 33.1 months) and for Grade 2 enterocolitis was 1.1 months (range: 1 day to 20.6 months).

Seventy-one patients (95%) with Grade 3 to 4 enterocolitis were treated with systemic corticosteroids. The median duration of treatment was 4.7 months (ranging up to 52.3 months).

Of the 68 patients with moderate enterocolitis, 51 patients (75%) were treated with systemic corticosteroids with a median duration of treatment of 3.5 months (ranging up to 52.2 months). Non-corticosteroid immunosuppression, consisting almost exclusively of infliximab, was used to treat 36% of patients with Grade 3 to 4 enterocolitis and 15% of patients with a Grade 2 event.

Of the 75 patients with Grade 3 to 4 immune-mediated enterocolitis, 86% experienced complete resolution, 3% experienced improvement to Grade 1, and 11% did not improve. Among the 66 patients with Grade 2 enterocolitis, 94% experienced complete resolution, 3% experienced improvement to Grade 1, and 3% did not improve.

YERVOY 1 mg/kg administered with nivolumab 3 mg/kg

Immune-mediated colitis occurred in 10% (52/547) of patients with RCC and 7% (8/119) of patients with CRC. Median time to onset of immune-mediated colitis was 1.7 months (range: 2 days to 19.2 months) in patients with RCC and 2.4 months (range: 22 days to 5.2 months) in patients with CRC.

Immune-mediated colitis led to permanent discontinuation of YERVOY and nivolumab in 3.2% of patients with RCC or CRC (n=666) and withholding of both YERVOY and nivolumab in 3.9% [see Dosage and Administration (2.5)]. All patients with colitis required systemic corticosteroids, including 80% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 2 days (range: 1 day to 27 months). Approximately 23% of patients with immune-mediated colitis required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 88% of patients. Two patients with RCC had recurrence of colitis after re-initiation of nivolumab with YERVOY.

5.2 Immune-Mediated Hepatitis

Immune-mediated hepatitis, including fatal cases, can occur with YERVOY.

Monitor liver function tests (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 liver function test monitoring until resolution.

Permanently discontinue YERVOY in patients with severe enterocolitis and initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper 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 to 5 days or recurring after symptom improvement, if other causes are excluded.

Withhold YERVOY dosing for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for more than 1 week, initiate systemic corticosteroids at a dose of 0.5 mg/kg/day prednisone or equivalent [see Dosage and Administration (2.5)].

YERVOY as a Single Agent

Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in MDX010-20 (NCT00094653), severe, life-threatening, or fatal diarrhea of 7 or more stools above baseline, fever, leus, peritoneal signs; Grade 3 to 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 patients (1%) developed intestinal perforation, 4 patients (0.8%) died as a result of complications, and 26 patients (5%) were hospitalized for severe enterocolitis. The median time to onset of Grade 3 to 5 enterocolitis was 1.7 months (range: 11 days to 3.1 months) and for Grade 2 enterocolitis was 1.4 months (range: 2 days to 4.3 months).
Adjuvant Treatment of Melanoma

In patients receiving YERVOY 10 mg/kg in CA184-029, Grade 3 to 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 to 4 hepatitis showed evidence of toxic or autoimmune hepatitis. The median time to onset for Grade 3 to 4 hepatitis was 2.0 months (range: 1 day to 4.2 months) and for Grade 2 hepatitis was 1.4 months (range: 13 days to 6.5 months). Of the 51 patients with Grade 3 to 4 immune-mediated hepatitis, 94% experienced complete resolution, 4% experienced improvement to Grade 1, and 2% did not improve. Of the 22 patients with Grade 2 immune-mediated hepatitis, 91% experienced complete resolution and 9% did not improve.

Forty-six patients (90%) with Grade 3 to 4 hepatitis were treated with systemic corticosteroids. The median duration of treatment was 4.4 months (range up to 56.1 months). Sixteen patients (73%) with moderate hepatitis were treated with systemic corticosteroids. The median duration of treatment was 2.6 months (ranging up to 41.4 months).

Concurrent Administration with Vemurafenib

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).

**YERVOY 1 mg/kg administered with nivolumab 3 mg/kg**

Immune-mediated hepatitis occurred in 7% (38/547) of patients with RCC and 8% (10/119) with CRC. Median time to onset was 2 months (range: 14 days to 26.8 months) in patients with RCC and 2.2 months (range: 22 days to 10.5 months) in patients with CRC.

Immune-mediated hepatitis led to permanent discontinuation of YERVOY and nivolumab in 3.6% of patients with RCC or CRC (n=666) and withholding of both YERVOY and nivolumab in 3.5% [see Dosage and Administration (2.5)]. All patients with hepatitis required systemic corticosteroids, including 94% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1 month (range: 1 day to 7 months). All 19% of patients with immune-mediated hepatitis required addition of mycophenolic acid to high-dose corticosteroids. Complete resolution occurred in 83% of patients. No patients had recurrence of hepatitis after re-initiation of nivolumab with YERVOY or nivolumab alone.

### 5.3 Immune-Mediated Dermatitisskin Adverse Reactions

Immune-mediated dermatitis, including fatal cases, can occur with YERVOY.

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.

Permanently discontinue YERVOY in patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations. Administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month. Withhold YERVOY dosing in patients with moderate to severe signs and symptoms [see Dosage and Administration (2.5)].

For mild to moderate dermatitis, such as localized rash and pruritus, treat symptomatically. Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.

**YERVOY as a Single Agent**

### Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in CA184-029, Grade 3 to 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 to 4 hepatitis showed evidence of toxic or autoimmune hepatitis. The median time to onset for Grade 3 to 4 hepatitis was 2.0 months (range: 1 day to 4.2 months) and for Grade 2 hepatitis was 1.4 months (range: 13 days to 6.5 months). Of the 51 patients with Grade 3 to 4 immune-mediated hepatitis, 94% experienced complete resolution, 4% experienced improvement to Grade 1, and 2% did not improve. Of the 22 patients with Grade 2 immune-mediated hepatitis, 91% experienced complete resolution and 9% did not improve.

Sixteen patients (84%) with Grade 3 to 4 dermatitis were treated with systemic corticosteroids for a median of 21 days (ranging up to 49.2 months) resulting in complete resolution of dermatitis within a median time of 4.3 months (range up to 44.4 months). Of the 3 patients (16%) not treated with systemic or topical corticosteroids, 2 (11%) had complete resolution and 1 had improvement to Grade 1.

Of the 99 patients with Grade 2 dermatitis, 67 (68%) were treated with systemic corticosteroids for a median of 2.6 months, 16 (16%) were treated with only topical corticosteroids and 16 (16%) did not receive systemic or topical corticosteroids. Seventy-seven patients (78%) had complete resolution, 15 (15%) improved to mild (Grade 1) severity, and 7 (7%) did not improve.

**YERVOY 1 mg/kg administered with nivolumab 3 mg/kg** Immune-mediated rash occurred in 16% (90/547) of patients with RCC and 14% (17/119) of patients with CRC. Median time to onset was 1.5 months (range: 1 day to 20.9 months) in RCC and 26 days (range: 5 days to 9.8 months) in CRC.

Immune-mediated rash led to permanent discontinuation or withholding of YERVOY and nivolumab in 0.5% of patients with RCC or CRC (n=666) and withholding of YERVOY and nivolumab in 1.9% of patients with immune-mediated rash required systemic corticosteroids, including 19% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 22 days (range: 1 day to 23 months). Complete resolution occurred in 66% of patients. Immune-mediated rash recurred in approximately 3% (20/616) of patients who resumed nivolumab.

### 5.4 Immune-Mediated Neuropathies

Immune-mediated neuropathies, including fatal cases, can occur with YERVOY.

Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. 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 of severe neuropathy. Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe neuropathies. Without YERVOY dosing in patients with moderate neuropathy (not interfering with daily activities) [see Dosage and Administration (2.5)].

**YERVOY as a Single Agent**

### Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in CA184-029, Grade 3 to 5 immune-mediated neuropathy occurred in 8 patients (2%); the sole fatality was due to complications of Guillain-Barré syndrome [see Adverse Reactions (6.1)]. Moderate Grade 2 immune-mediated neuropathy occurred in 1 patient (0.2%).

The time to onset across the 9 patients with Grade 2 to 5 immune-mediated neuropathy ranged from 1 to 27.4 months. All 8 patients with Grade 3 to 5 neuropathy were treated with systemic corticosteroids (range: 3 days to 38.3 months) and also received tacrolimus. Four of the 8 patients with Grade 3 to 5 immune-mediated neuropathy experienced complete resolution, 1 improved to Grade 1, and 3 did not improve. The single patient with Grade 3 immune-mediated neuropathy experienced complete resolution without the use of corticosteroids.

**YERVOY 1 mg/kg administered with nivolumab 3 mg/kg** Among 547 RCC patients, there were 3 cases of Grade 3 paresthesia/hypohyposis.

### 5.5 Immune-Mediated Endocrinopathies

Immune-mediated endocrinopathies, including life-threatening cases, can occur with YERVOY.

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 which may resemble other causes such as brain metastasis or underlying disease. Without an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-mediated.

Monitor clinical chemistries, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at the start of treatment, 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 dosing in symptomatic patients and consider referral to an endocrinologist. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent, and initiate appropriate hormone replacement therapy [see Dosage and Administration (2.5)].

**YERVOY as a Single Agent**

### Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in CA184-029, Grade 3 to 4 immune-mediated endocrinopathies (requiring hospitalization and urgent medical intervention, or interfering with activities of daily living) Grade 3 to 4 occurred in 9 YERVOY-treated patients (1.8%). 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 endocrinopathy (requiring hormone replacement or medical intervention) Grade 3 occurred in 12 patients (23%) and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and 1 case each of hyperthyroidism and Cushing’s syndrome. The median time to onset of moderate to severe immune-mediated endocrinopathy was 2.5 months and ranged up to 4.4 months after the initiation of YERVOY. Of the 21 patients with moderate to life-threatening endocrinopathy, 17 required long-term hormone replacement therapy including, most commonly, adrenal hormones (n=10) and thyroid hormones (n=13).

Adverse Treatment of Melanoma

In patients receiving YERVOY 10 mg/kg in CAL18-029, Grade 3 to 4 immune-mediated endocrinopathies occurred in 39 patients (7%) and Grade 2 immune-mediated endocrinopathies in 93 patients (20%). Of the 39 patients with Grade 3 to 4 immune-mediated endocrinopathies, 35 patients had hypopituitarism (associated with one 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 2 immune-mediated endocrinopathy was 2.1 months (range: 9 days to 19.3 months), and 20% were reported to have resolution.

Seventy-three patients received thyroid hormones for treatment of Grade 2 to 4 immune-mediated hypothyroidism. Of these, 14 patients (19%) were able to discontinue thyroid hormone replacement therapy.

YERVOY 1 mg/kg administered with nivolumab 3 mg/kg

Hypothyroidism. Hypothyroidism occurred in 4.6% (25/547) of patients with RCC and 3.4% (4/119) of patients with CRC. Median time to onset was 2.8 months (range: 1.3 months to 7.3 months) in patients with RCC and 3.7 months (range: 2.8 to 5.5 months) in patients with CRC.

Hypothyroidism occurred in 7% (41/547) of patients with RCC and 5.9% (7/119) of patients with CRC. Median time to onset was 2.0 months to 22.3 months in RCC and 3.7 months (range: 2.5 to 13.4 months) in CRC. Adrenal insufficiency led to permanent discontinuation of YERVOY and nivolumab in 1.2% and 2.6% of patients with RCC or CRC (n=666), respectively [see Dosage and Administration (2.5)]. Approximately 72% of patients with hypothyroidism received hormone replacement therapy and 55% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 17 days (range: 1 day to 1.6 months).

Adrenal Insufficiency. Adrenal insufficiency occurred in 7% (41/547) of patients with RCC and 5.9% (7/119) patients with CRC. Median time to onset was 3.4 months (range: 2.0 months to 22.3 months) in RCC and 3.7 months (range: 2.5 to 13.4 months) in CRC. Adrenal insufficiency led to permanent discontinuation of YERVOY and nivolumab in 1.2% of patients with RCC or CRC (n=666) and withholding of YERVOY and nivolumab in 2.6% [see Dosage and Administration (2.5)]. Approximately 94% of patients with adrenal insufficiency received hormone replacement therapy and 27% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 12 days (range: 2 days to 5.6 months).

Hypothyroidism and Hyperthyroidism. Hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (119/547) of patients with RCC and 15% (18/119) of patients with CRC. Median time to onset was 2.2 months (range: 1 day to 21.4 months) in patients with RCC and 2.3 months (range: 22 days to 5.8 months) in patients with CRC. Of the 137 patients with RCC or CRC who developed hypothyroidism, approximately 81% of patients with RCC and 78% with CRC received levothyroxine.

Hypothyroidism occurred in 12% (68/547) of patients with RCC and 12% (14/119) of patients with CRC. Median time to onset was 1.4 months (range: 6 days to 14.2 months) in RCC and 1.1 months (range: 21 days to 5.4 months) in CRC. Of the 80 patients with RCC or CRC who developed hypothyroidism, approximately 15% received methimazole and 2% received carbimazole.

Type 1 Diabetes Mellitus. Diabetes occurred in 2.7% (15/547) of patients with RCC. Median time to onset was 3.2 months (range: 19 days to 16.6 months). Both YERVOY and nivolumab were withheld in 33% of patients and both were permanently discontinued in 20% of patients who developed diabetes [see Dosage and Administration (2.5)].

5.6 Immune-Mediated Pneumonitis

Immune-mediated pneumonitis, including fatal cases, can occur with nivolumab with YERVOY. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or more severe (Grade 3-4) pneumonitis, followed by corticosteroid taper. Withhold YERVOY dosing in patients with moderate to severe signs and symptoms. Permanently discontinue YERVOY for life-threatening (Grade 4) pneumonitis [see Dosage and Administration (2.5)].

YERVOY 1 mg/kg administered with nivolumab 3 mg/kg

Immune-mediated pneumonitis occurred in 4.4% (24/547) of patients with RCC and 1.7% (2/119) of patients with CRC. Median time to onset of immune-mediated pneumonitis was 2.6 months (range: 3 days to 9.2 months) in patients with RCC and 1.9 months (range: 27 days to 3 months) in patients with CRC.

Immune-mediated pneumonitis led to permanent discontinuation of YERVOY and nivolumab in 1.8% of patients with RCC or CRC (n=666) and withholding of YERVOY and nivolumab in 1.7% [see Dosage and Administration (2.5)]. All patients with pneumonitis required systemic corticosteroids, including 92% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 13 days (range: 4 days to 3.2 months). Approximately 8% required addition of infliximab to high-dose corticosteroids. Complete resolution of pneumonitis occurred in 81% of patients.

5.7 Immune-Mediated Nephritis and Renal Dysfunction

Immune-mediated nephritis can occur with nivolumab with YERVOY. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe immune-mediated nephritis. Withhold YERVOY in patients with severe nephritis. Permanently discontinue YERVOY for life-threatening (Grade 4) increased serum creatinine [see Dosage and Administration (2.5)].

YERVOY 1 mg/kg administered with nivolumab 3 mg/kg

Immune-mediated nephritis and renal dysfunction occurred in 4.6% (25/547) of patients with RCC and 1.7% (2/119) of patients with CRC. Median time to onset was 3 months (range: 1 day to 13.2 months) among these 27 patients.

Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of YERVOY and nivolumab in 1.2% of patients with RCC or CRC (n=666) and withholding of YERVOY and nivolumab in 2.5% of patients with RCC or CRC [see Dosage and Administration (2.5)]. Approximately 78% of patients with immune-mediated nephritis and renal dysfunction received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 17 days (range: 1 day to 6 months). Complete resolution occurred in 63% of patients.

5.8 Immune-Mediated Encephalitis

Immune-mediated encephalitis can occur with YERVOY. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

Withhold YERVOY in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis. Followed by corticosteroid taper. Permanently discontinue YERVOY for immune-mediated encephalitis [see Dosage and Administration (2.5)].

YERVOY 1 mg/kg administered with nivolumab 3 mg/kg

Encephalitis occurred in one patient (0.2%) with RCC approximately 4 months after initiation of YERVOY and in one patient (0.8%) with CRC 15 days after initiation of YERVOY. The patient with CRC required infliximab and high-dose corticosteroids (at least 40 mg prednisone equivalents per day).

5.9 Infusion Reactions

Severe infusion reactions can occur with nivolumab with YERVOY. Discontinue YERVOY in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions [see Dosage and Administration (2.5)].

YERVOY 1 mg/kg administered with nivolumab 3 mg/kg

Infusion-related reactions occurred in 5.1% (28/547) of patients with RCC and 4.2% (5/119) of patients with CRC.

5.10 Other Immune-Mediated Adverse Reactions

YERVOY as a Single Agent

Permanently discontinue YERVOY for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent 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 to patients who develop uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy. If uveitis and YERVOY or CRC [see Dosage and Administration (2.5)]. Uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving YERVOY and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive a CTLA-4 receptor blocking antibody either before or after allogeneic hematopoietic stem cell transplantation (HSCT). Follow patients closely for evidence of GVHD and intervene promptly. [See Adverse Reactions (6.2)] Consider the benefit versus risks of treatment with a CTLA-4 receptor blocking antibody after allogeneic HSCT.
Metastatic Melanoma

In MDX010-20, the following clinically significant immune-mediated adverse reactions were seen in less than 1% of YERVOY-treated patients: cytopenias, nephritis, pneumonia, meningoencephalitis, pericarditis, uveitis, and iritis.

Adjuvant Treatment of Melanoma

In CA184-029, the following clinically significant immune-mediated adverse reactions were seen in less than 1% of YERVOY-treated patients unless specified: cytopenias, eosinophilia (2.1%), pancreatitis (1.3%), meningitis, pneumonitis, sarcoidosis, pericarditis, uveitis, and fatal mycocarditis [see Adverse Reactions (6.1)].

Other Clinical Experience

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 less than 1% incidence unless specified: angioedema, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, epidermal necrolysis, iritis, iritis, leucopoeiesis, vasculitis, erythema multiforme, periorchitis, arthralgia, autoimmune thyroiditis, neuroendocrine hyperplasia, autoimmune central lymphopathy (encephalitis), myositis, polymyositis, ocular myositis, cytopenias (2.5%), and nephritis.

YERVOY 1 mg/kg administered with nivolumab 3 mg/kg

YERVOY can cause other clinically significant and potentially fatal immune-mediated adverse reactions. Immune-mediated adverse reactions may occur after discontinuation of YERVOY therapy. For any suspected immune-mediated adverse reactions, other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold YERVOY, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting YERVOY after completion of corticosteroid taper based on the severity of the event.

Across clinical trials of YERVOY administered with nivolumab or in trials of nivolumab administered as a single agent, the following clinically significant immune-mediated adverse reactions, some with fatal occurrence, occurred in less than 1.0% of patients: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune encephalopathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared with rates in other clinical trials or experience with therapeutics in the same class and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to YERVOY 3 mg/kg as a single agent in MDX010-20, a randomized trial in patients with unresectable or metastatic melanoma; to YERVOY 10 mg/kg as a single agent in CA184-029, a randomized trial in patients with resected Stage IIIA (>1 mm nodal involvement), IIIB, and IIC (with no in-transit metastases) cutaneous melanoma; and to YERVOY 1 mg/kg, administered in combination with nivolumab, in two trials: CHECKMATE-214 (NCT02231749), a randomized trial in previously untreated patients with advanced renal cell carcinoma, and CHECKMATE-142 (NCT02606188), an open-label, multicenter, non-randomized multiple parallel cohort trial in patients with previously treated, MSI-H or dMMR metastatic colorectal cancer.

Clinically significant adverse reactions were evaluated in a total of 982 patients treated in MDX010-20 and CA184-029 and in 21 dose-ranging trials (n=2478) administering YERVOY at doses of 0.1 to 20 mg/kg [see Warnings and Precautions (5.6)].

Unresectable or Metastatic Melanoma

The safety of YERVOY was evaluated in MDX010-20, a randomized, double-blind clinical trial in which 643 previously treated patients with unresectable or metastatic melanoma received YERVOY 3 mg/kg for 4 doses given by intravenous infusion as a single agent (n=131), YERVOY with an investigational gp100 peptide vaccine (gp100) (n=380), or gp100 peptide vaccine as a single agent (n=132) [see Clinical Studies (14.1)]. Patients in the trial received a median of 4 doses (range: 1 to 4 doses).

MDX010-20 excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation.

The trial population characteristics were: median age 57 years (range: 19 to 90), 59% male, 94% white, and baseline ECOG performance status 0 (56%).

YERVOY was discontinued for adverse reactions in 10% of patients.

Table 2 presents selected adverse reactions from MDX010-20, which occurred in at least 5% of patients in the YERVOY-containing arms and with at least 5% increased incidence over the control gp100 arm for all-grade events and at least 1% incidence over the control group for Grade 3 to 5 events.

6.2 Other Clinical Experience

Other adverse reactions were seen in less than 1% of YERVOY-treated patients unless specified: cytopenias, nephritis, and myocarditis [see Warnings and Precautions (5.6)].
Table 3: Severe to Fatal Immune-Mediated Adverse Reactions in MDX010-20 (Continued)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>YERVOY 3 mg/kg n=131</th>
<th>YERVOY 3 mg/kg qw100 n=380</th>
<th>YERVOY 10 mg/kg n=471</th>
<th>Placebo n=474</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>0</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephritis</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericarditis</td>
<td>0</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Including fatal outcome.
* Including intestinal perforation.
* Underlying etiology not established.

Adjuvant Treatment of Melanoma

The safety of YERVOY was evaluated in CA184-029, a randomized (1:1), double-blind, placebo-controlled trial in which 945 patients with resected Stage IIIA (>1 mm nodal involvement), IIIB, and IIIC (with no in-transit metastases) cutaneous melanoma received YERVOY 10 mg/kg (n=471) or placebo (n=474) administered as an intravenous infusion for 4 doses every 3 weeks followed by 2 weeks off, every cycle (n=535). In this trial, 36% of patients received YERVOY for longer than 6 months and 26% of patients received YERVOY for longer than 1 year. YERVOY-treated patients in the trial received a median of 4 doses (range: 1 to 16).

CA184-029 excluded patients with prior systemic therapy for melanoma, autoimmune disease, a condition requiring systemic immunosuppression, or a positive test for hepatitis B, hepatitis C, or HIV.

The trial population characteristics were: median age 51 years (range: 18 to 84 years), 62% male, 99% white, and baseline ECOG performance status 0 (94%).

YERVOY was discontinued for adverse reactions in 52% of patients.

Table 4 presents selected adverse reactions from CA184-029 which occurred in at least 5% of YERVOY-treated patients and with at least 5% increased incidence over the placebo group for all-grade events.

Table 4: Selected Adverse Reactions in CA184-029

<table>
<thead>
<tr>
<th>System Organ Class/Preferred Term</th>
<th>YERVOY 10 mg/kg n=471</th>
<th>Placebo n=474</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>50 2.1</td>
<td>20 0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>45 2.3</td>
<td>15 0</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>49 10</td>
<td>30 2.1</td>
</tr>
<tr>
<td>Nausea</td>
<td>25 0.2</td>
<td>18 0</td>
</tr>
<tr>
<td>Colitis</td>
<td>16 8</td>
<td>1.5 0.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 0.4</td>
<td>6 0.2</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>32 0.2</td>
<td>9 0.4</td>
</tr>
<tr>
<td>General Disorders and Administration-Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>46 2.3</td>
<td>38 1.5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18 1.1</td>
<td>4.9 0.2</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>33 0.8</td>
<td>18 0.2</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>14 0.2</td>
<td>3.4 0.2</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>10 0</td>
<td>4.4 0</td>
</tr>
</tbody>
</table>

* Incidences presented in this table are based on reports of adverse events regardless of causality.
* Includes 1 death.
nivolumab plus YERVOY-treated patients and 7.8 months (range: 1 day to 20.2+ months) in sunitinib-treated patients. In this trial, 57% of patients in the nivolumab plus YERVOY arm were exposed to treatment for greater than 6 months, and 36% of patients were exposed to treatment for greater than 1 year.

Study therapy was discontinued for adverse reactions in 31% of nivolumab plus YERVOY patients and in 21% of sunitinib patients. Fifty-four percent (54%) of patients receiving nivolumab plus YERVOY and 43% of patients receiving sunitinib had a drug delay for an adverse reaction. In the sunitinib group, 53% of patients required a dose reduction; dose reductions were not permitted in the nivolumab plus YERVOY treatment group. Serious adverse reactions occurred in 59% of patients receiving nivolumab plus YERVOY and in 43% of patients receiving sunitinib. The most frequent serious adverse reactions reported in at least 2% of patients treated with nivolumab plus YERVOY were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis; in patients treated with sunitinib, they were pneumonia, pleural effusion, and dyspnea.

The most common adverse reactions (reported in at least 20% of nivolumab plus YERVOY-treated patients) were fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, vomiting, dyspnea, and decreased appetite. Table 7 summarizes adverse reactions that occurred in greater than 15% of nivolumab plus YERVOY-treated patients.

Table 7: Grade 1-4 Adverse Reactions in >15% of Patients Receiving Nivolumab plus YERVOY (CHECKMATE-214)

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Nivolumab plus YERVOY</th>
<th>Sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage (%) of Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>Grades 1-4</td>
<td>Grades 3-4</td>
</tr>
<tr>
<td>Fatigue&lt;sup&gt;a&lt;/sup&gt;</td>
<td>58</td>
<td>8</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>25</td>
<td>0.7</td>
</tr>
<tr>
<td>Edema&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16</td>
<td>0.5</td>
</tr>
<tr>
<td>Cough/productive cough</td>
<td>28</td>
<td>0.2</td>
</tr>
<tr>
<td>Dyspnea/exertional dyspnea</td>
<td>20</td>
<td>2.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38</td>
<td>4.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
<td>2.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20</td>
<td>0.9</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19</td>
<td>1.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>17</td>
<td>0.4</td>
</tr>
<tr>
<td>Rash&lt;sup&gt;b&lt;/sup&gt;</td>
<td>39</td>
<td>3.7</td>
</tr>
<tr>
<td>Pruritus/generalized pruritus</td>
<td>33</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>18</td>
<td>0.4</td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>0.9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>21</td>
<td>1.8</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain&lt;sup&gt;c&lt;/sup&gt;</td>
<td>37</td>
<td>4.0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>23</td>
<td>1.3</td>
</tr>
</tbody>
</table>

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: nivolumab plus YERVOY group (range: 490 to 538 patients) and sunitinib group (range: 485 to 523 patients).

In addition, among patients with TSH less than or equal to the ULN at baseline, a lower proportion of patients experienced a treatment-emergent elevation of TSH greater than the ULN in the nivolumab plus YERVOY group compared to the sunitinib group (31% and 81%, respectively).

Previously Treated MSI-H or dMMR Metastatic Colorectal Cancer

The safety of YERVOY was evaluated in CHECKMATE-142, an open-label, multicenter, non-randomized, multiple parallel-cohort study. In CHECKMATE-142, 119 patients with previously treated MSI-H or dMMR mCRC received YERVOY, in combination with nivolumab, in a single-arm cohort. In another single-arm cohort under CHECKMATE-142-74 patients with mCRC received nivolumab monotherapy. All patients in both cohorts had received prior fluorouracil-based chemotherapy for metastatic disease. Of those in the YERVOY plus nivolumab cohort, 69% had received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, and 29% had received an anti-EGFR antibody.

Patients in the YERVOY plus nivolumab cohort received YERVOY 1 mg/kg and nivolumab 3 mg/kg on Day 1 of each 21-day cycle for 4 doses, then nivolumab 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. Patients in the nivolumab single-agent cohort received nivolumab 3 mg/kg every 3 weeks until disease progression or unacceptable toxicity [see Clinical Studies (14.4)].

The median duration of exposure for YERVOY was 2.1 months. Serious adverse reactions occurred in 47% of YERVOY-treated patients. The most frequent serious adverse reactions reported in at least 2% of patients were colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration. The most common adverse reactions (reported in at least 20% of YERVOY-treated patients) were fatigue, diarrhea, pyrexia, musculoskeletal pain, abdominal pain, pruritus, nausea, rash, decreased appetite, and vomiting.

Table 9 summarizes adverse reactions that occurred in greater than 10% of patients receiving YERVOY. Table 10 summarizes laboratory tests that worsened from baseline in >15% of patients on nivolumab plus YERVOY (CHECKMATE-214).

Table 9: Grade 1-4 Laboratory Values Worsening from Baseline Occurring in >15% of Patients Receiving Nivolumab plus YERVOY (CHECKMATE-214)

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Nivolumab plus YERVOY</th>
<th>Sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage (%) of Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>Grades 1-4</td>
<td>Grades 3-4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>58</td>
<td>8</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>25</td>
<td>0.7</td>
</tr>
<tr>
<td>Edema</td>
<td>16</td>
<td>0.5</td>
</tr>
<tr>
<td>Cough/productive cough</td>
<td>28</td>
<td>0.2</td>
</tr>
<tr>
<td>Dyspnea/exertional dyspnea</td>
<td>20</td>
<td>2.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38</td>
<td>4.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
<td>2.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20</td>
<td>0.9</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19</td>
<td>1.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>17</td>
<td>0.4</td>
</tr>
<tr>
<td>Rash</td>
<td>39</td>
<td>3.7</td>
</tr>
<tr>
<td>Pruritus/generalized pruritus</td>
<td>33</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>18</td>
<td>0.4</td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>0.9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>21</td>
<td>1.8</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>37</td>
<td>4.0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>23</td>
<td>1.3</td>
</tr>
</tbody>
</table>

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: nivolumab plus YERVOY group (range: 490 to 538 patients) and sunitinib group (range: 485 to 523 patients).

Toxicity was graded per NCI CTCAE v4.

<sup>b</sup> Includes asthenia.

<sup>c</sup> Includes peripheral edema, peripheral swelling.

<sup>d</sup> Includes dermatitis described as acneiform, bullous, and exfoliative, drug eruption, rash described as exfoliative, erythematous, follicular, generalized, macular, maculopapular, papular, pruritic, and pustular, fixed-drug eruption.

<sup>e</sup> Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.

The most common laboratory abnormalities which have worsened compared to baseline in ≥30% of nivolumab plus YERVOY-treated patients include increased lipase, anemia, increased creatinine, increased ALT, increased AST, hyponatremia, increased amylase, and lymphopenia. Table 8 summarizes the laboratory abnormalities that occurred in greater than 15% of nivolumab plus YERVOY-treated patients.
Table 9: Adverse Reactions Occurring in ≥10% of Patients (CHECKMATE-142)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grades 3-4</th>
<th>All Grades</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>49</td>
<td>6</td>
<td>54</td>
<td>5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>36</td>
<td>0</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>7</td>
<td>0</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45</td>
<td>3.4</td>
<td>43</td>
<td>2.7</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>30</td>
<td>5</td>
<td>34</td>
<td>2.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>26</td>
<td>0.8</td>
<td>34</td>
<td>1.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20</td>
<td>1.7</td>
<td>28</td>
<td>4.1</td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>36</td>
<td>3.4</td>
<td>28</td>
<td>1.4</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14</td>
<td>0.8</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>28</td>
<td>1.7</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>25</td>
<td>4.2</td>
<td>23</td>
<td>1.4</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>11</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>9</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>20</td>
<td>1.7</td>
<td>14</td>
<td>1.4</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>19</td>
<td>0.8</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
<td>1.7</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>17</td>
<td>1.7</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>0</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>6</td>
<td>1</td>
<td>19</td>
<td>2.7</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>14</td>
<td>0.8</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>12</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>13</td>
<td>0.8</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

Toxicity was graded per NCI CTCAE v4.

* Includes asthenia.
* Includes peripheral edema and peripheral swelling.
* Includes upper abdominal pain, lower abdominal pain, and abdominal discomfort.
* Includes back pain, pain in extremity, myalgia, neck pain, and bone pain.
* Includes dermatitis, dermatitis acniform, and rash described as maculo-papular, erythematous, and generalized.
* Includes nasopharyngitis and rhinitis.

Other clinically important adverse reactions reported in less than 10% of patients receiving YERVOY in CHECKMATE-142 were encephalitis (0.8%), necrotizing myositis (0.8%), and uveitis (0.8%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of YERVOY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: graft-versus-host disease

Skin and Subcutaneous Tissue Disorders: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ipilimumab in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

Eleven (1.1%) of 1024 evaluable patients with unresectable or metastatic melanoma tested positive for treatment-emergent binding antibodies against ipilimumab (TE-ADAs) in an electrochemiluminescent (ECL) based assay. This assay had substantial limitations in detecting anti-ipilimumab antibodies in the presence of ipilimumab. Seven (4.9%) of 144 patients receiving ipilimumab and 7 (4.5%) of 156 patients receiving placebo for the adjuvant treatment of melanoma tested positive for TE-ADAs using an ECL assay with improved drug tolerance. No patients tested positive for neutralizing antibodies. No infusion-related reactions occurred in patients who tested positive for TE-ADAs.

Of 499 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-214 and CHECKMATE-142 trials, 126 (25%) were positive for anti-nivolumab antibodies and 3 (0.6%) were positive for neutralizing antibodies against nivolumab.

7 DRUG INTERACTIONS

No formal pharmacokinetic drug interaction studies have been conducted with YERVOY.
YERVOY® (ipilimumab)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on data from animal studies and its mechanism of action, YERVOY can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner [see Data]. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Human IgG1 is known to cross the placental barrier and ipilimumab is an IgG1; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus. There is insufficient human data for YERVOY exposure in pregnant women. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

A Pregnancy Safety Surveillance Study has been established to collect information about pregnancies in women who have received YERVOY. Healthcare providers are encouraged to enroll patients or have their patients enroll directly by calling 1-844-593-7869.

Data

Animal Data

In a combined study of embryo-fetal and peri-postnatal development, pregnant cynomolgus monkeys received ipilimumab every 3 weeks from the onset of organogenesis in the first trimester through parturition. No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, administration of ipilimumab at doses resulting in exposures approximately 2.6 to 7.2 times the human exposure at a dose of 3 mg/kg resulted in dose-related increases in abortion, stillbirth, premature delivery (with corresponding lower birth weight), and an increased incidence of infant mortality. In addition, developmental abnormalities were identified in the urogenital system of 2 infant monkeys exposed in utero to 30 mg/kg of ipilimumab (7.2 times the AUC in humans at the 3 mg/kg dose). One female infant monkey had unilateral renal agenesis of the left kidney and ureter, and 1 male infant monkey had an imperforate urethra with associated urinary obstruction and subcutaneous scrotal edema.

Genetically engineered mice heterozygous for CTLA-4 (CTLA-4+/-), the target for ipilimumab, appeared healthy and gave birth to healthy CTLA-4+/- heterozygous offspring. Mated CTLA-4+/- heterozygous mice also produced offspring deficient in CTLA-4 (homozygous negative, CTLA-4-/-). The CTLA-4-/- homozygous negative offspring appeared healthy at birth, exhibited signs of multigran lymphoproliferative disease by 2 weeks of age, and all died by 3 to 4 weeks of age with massive lymphoproliferation and multiorgan tissue destruction.

8.2 Lactation

Risk Summary

It is not known whether YERVOY is present in human milk. In monkeys, ipilimumab was present in milk [see Data]. There are no data to assess the effects of YERVOY on milk production. Advise women to discontinue breastfeeding during treatment with YERVOY and for 3 months following the final dose.

Data

In monkeys treated at dose levels resulting in exposures 2.6 and 7.2 times higher than those in humans at a 3 mg/kg dose, ipilimumab was present in milk at concentrations of 0.1 mcg/mL and 0.4 mcg/mL, representing a ratio of up to 0.3% of the steady-state serum concentration of the drug.

8.3 Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, YERVOY can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with YERVOY and for 3 months following the last dose of YERVOY.

8.4 Pediatric Use

The safety and effectiveness of YERVOY have been established in pediatric patients 12 years and older for the treatment of unresectable or metastatic melanoma or for the treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of YERVOY in this age group is supported by evidence from adequate and well-controlled studies of YERVOY in adults and population pharmacokinetic data demonstrating that the exposure at doses of 3 mg/kg and 1 mg/kg in the pediatric and adult populations are comparable. In addition, the tumor biology and course of advanced melanoma and MSI-H or dMMR metastatic colorectal cancer are sufficiently similar in adults and pediatric patients 12 years and older to allow extrapolation of data from adults to pediatric patients.

The safety and effectiveness for pediatric patients 12 years and older have not been established for the adjuvant treatment of melanoma or for the treatment of renal cell carcinoma. In addition, the safety and effectiveness have not been established with YERVOY for any indication in pediatric patients less than 12 years of age.

YERVOY was evaluated in a total of 45 pediatric patients across two clinical trials. In a dose-finding trial, 33 pediatric patients with relapsed or refractory solid tumors were evaluated. The median age was 13 years (range 2 to 21 years), and 20 patients were ≥12 years old. YERVOY was administered at doses of 1, 3, 5, and 10 mg/kg intravenously over 90 minutes every 3 weeks for 4 doses and then every 12 weeks thereafter until progression or treatment discontinuation.

YERVOY was also evaluated in an open-label, single-arm trial in 12 pediatric patients ≥12 years old (range 12 to 16 years) with previously treated or untreated, unresectable Stage 3 or 4 malignant melanoma. Patients received YERVOY 3 mg/kg (4 patients) or 10 mg/kg (8 patients) intravenously over 90 minutes every 3 weeks for 4 doses. Of the 17 patients ≥12 years of age with melanoma treated with YERVOY across both studies, two patients experienced objective responses including one partial response that was sustained for 16 months. There were no responses in patients with non-melanoma solid tumors. The overall safety profile of YERVOY in children and adolescents was consistent with the safety profile in adults.

8.5 Geriatric Use

No dose adjustment is needed for patients with renal impairment [see Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

No dose adjustment is needed for patients with mild hepatic impairment (total bilirubin [TB] >1.0 to 1.5 times the upper limit of normal [ULN] or AST >ULN). YERVOY has not been studied in patients with moderate (TB >1.5 to 3.0 times ULN and any AST) or severe (TB >3 times ULN and any AST) hepatic impairment [see Clinical Pharmacology (12.3)].

10 OVERDOSAGE

There is no information on overdosage with YERVOY.

11 DESCRIPTION

Ipilimumab is a recombinant, human monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Ipilimumab is an IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture.

YERVOY is a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution for intravenous infusion, which may contain a small amount of visible fibrillar matter. This solution contains 5 mg of ipilimumab and the following inactive ingredients: diethylene triamine pentaacetic acid (DTPA) (0.04 mg), mannitol (10 mg), polysorbate 80 (vegetable origin) (0.1 mg), sodium chloride (5.85 mg), and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CTLA-4 is a negative regulator of T-cell activation. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor immune response.

12.2 Pharmacodynamics

CTLA-4 blocks the interaction of T cells with the B7 family of costimulatory molecules (B7-1 and B7-2) activating B7-1 and B7-2 in antigen-presenting cells. The interaction between CTLA-4 and B7 molecules is required for the negative regulation of T-cell responses. Ipilimumab blocks this interaction, which results in an increase in T-cell responses.
12.3 Pharmacokinetics

The pharmacokinetics (PK) of ipilimumab was studied in 785 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg every 3 weeks for 4 doses. The PK of ipilimumab is linear in the dose range of 0.3 to 10 mg/kg. Following a single administration of YERVOY every 3 weeks, the systemic accumulation was 1.5-fold or less. Steady-state concentrations of ipilimumab were reached by the third dose; the mean Cmin at steady state was 19.4 mcg/mL at 3 mg/kg and 58.1 mcg/mL at 10 mg/kg every 3 weeks. The mean value (percent coefficient of variation) based on population PK analysis for the terminal half-life (t1/2) was 15.4 days (34%) and for clearance (CL) was 16.8 mL/h (38%).

YERVOY with nivolumab: When YERVOY 1 mg/kg was administered in combination with nivolumab 3 mg/kg, the CL of ipilimumab and nivolumab were unchanged compared to when YERVOY was administered alone.

When administered in combination, the CL of ipilimumab was unchanged in the presence of anti-nivolumab antibodies and the CL of nivolumab increased by 20% in the presence of anti-nivolumab antibodies.

Specific Populations

The effects of various covariates on the PK of ipilimumab were assessed in population PK analyses. The CL of ipilimumab was recommended body weight (mg/kg) based dosing. The following factors had no clinically important effect on the CL of ipilimumab: age (range: 23 to 88 years), sex, performance status, renal impairment, mild hepatic impairment, previous cancer therapy, and baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined due to limited data available in non-Caucasian ethnic groups.

Renal Impairment: The effect of renal impairment on the CL of ipilimumab was evaluated in patients with mild (GFR 90 mL/min/1.73 m²; n=349), moderate (GFR <60 mL/min/1.73 m²; n=82), or severe (GFR <30 mL/min/1.73 m²; n=4) renal impairment compared to patients with normal renal function (GFR >90 mL/min/1.73 m²; n=350) in population PK analyses. No clinically important differences in the CL of ipilimumab were found between patients with renal impairment and patients with normal renal function [see Use in Specific Populations (8.4)].

Hepatic Impairment: The effect of hepatic impairment on the CL of ipilimumab was evaluated in patients with mild hepatic impairment (n=76) compared to patients with normal hepatic function (n=708) in the population PK analyses, and no clinically important differences in the CL of ipilimumab were found. YERVOY has not been studied in patients with moderate or severe hepatic impairment [see Use in Specific Populations (8.7)].

Pediatric Population: [see Use in Specific Populations (8.4)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of ipilimumab has not been evaluated in long-term animal studies, and the genotoxic potential of ipilimumab has not been evaluated. Fertility studies have not been performed with ipilimumab.

14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

The safety and efficacy of YERVOY were investigated in a randomized (3:1:1), double-blind, double-dummy trial (MDX010-20, NCT00094653) that included 676 randomized patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. Of these 676 patients, 403 were randomized to receive YERVOY at 3 mg/kg in combination with an investigational peptide vaccine with incomplete Freund’s adjuvant (gp100), 137 were randomized to receive YERVOY at 3 mg/kg, and 136 were randomized to receive gp100 as a single agent. The trial enrolled only patients with HLA-A2*0201 genotype; this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. The trial excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. YERVOY/placebo was administered at 3 mg/kg as an intravenous infusion every 3 weeks for 4 doses. gp100/placebo was administered at a dose of 2 mg peptide by deep subcutaneous injection every 3 weeks for 4 doses. Assessment of tumor response was performed at weeks 12 and 24, and every 3 months thereafter. Patients with evidence of objective tumor response at 12 or 24 weeks had assessment for confirmation of durability of response at 16 or 28 weeks, respectively.

The major efficacy outcome measure was overall survival (OS) in the YERVOY plus gp100 arm compared to that in the single-agent gp100 arm. Secondary efficacy outcome measures were OS in the YERVOY plus gp100 arm compared to the YERVOY arm, OS in the YERVOY arm compared to the gp100 arm, best overall response rate (BORR) at week 24 between each of the trial arms, and duration of response.

Of the randomized patients, 61%, 59%, and 54% in the YERVOY plus gp100, YERVOY, and gp100 arms, respectively, were men. Twenty-nine percent were ≥65 years of age, the median age was 57 years, 71% had M1c stage, 12% had a history of previously treated brain metastasis, 32% had ECOG performance status of 0 and 1, 23% had received aldesleukin, and 38% had elevated LDH level. Forty-one percent of patients randomized to either YERVOY-containing arm received all 4 planned doses. The median duration of follow-up was 8.9 months.

The OS results are shown in Table 11 and Figure 1.

Table 11: Overall Survival Results

<table>
<thead>
<tr>
<th>Arm</th>
<th>OS Median (months)</th>
<th>Median OS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>YERVOY</td>
<td>10</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>YERVOY+gp100</td>
<td>10</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>gp100</td>
<td>10</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Hazard Ratio (vs. YERVOY)</td>
<td>1.04</td>
<td>0.83</td>
<td>0.85</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.53, 1.30)</td>
<td>(0.55, 0.85)</td>
<td>(0.55, 0.85)</td>
</tr>
<tr>
<td>p-value</td>
<td>p=0.0026a</td>
<td>p=0.0004</td>
<td></td>
</tr>
</tbody>
</table>

a Not adjusted for multiple comparisons.

The best overall response rate (BORR) as assessed by the investigator was 5.7% (95% CI: 3.7%, 8.4%) in the YERVOY plus gp100 arm, 10.9% (95% CI: 6.3%, 17.4%) in the YERVOY arm, and 1.5% (95% CI: 0.2%, 5.2%) in the gp100 arm. The median duration of response was 11.5 months in the YERVOY plus gp100 arm and has not been reached in the YERVOY or gp100 arm.
Patients were randomized to nivolumab 3 mg/kg plus YERVOY 1 mg/kg (n=425) administered intravenously every 3 weeks for 4 doses followed by nivolumab monotherapy 3 mg/kg every two weeks or to sunitinib (n=422) administered orally 50 mg daily for 4 weeks followed by 2 weeks off, every cycle. Treatment continued until disease progression or unacceptable toxicity.

The median age was 61 years (range: 21 to 85) with 38% ≥65 years of age and 8% ≥75 years of age. The majority of patients were male (73%) and white (87%) and 26% and 74% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively.

The major efficacy outcome measures were OS, PFS (IRRC-assessed), and confirmed ORR (IRRC-assessed) in intermediate/poor-risk patients. In this population, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to nivolumab plus YERVOY as compared with sunitinib (Table 13 and Figure 3). OS benefit was observed regardless of PD-L1 expression level. The trial did not demonstrate a statistically significant improvement in PFS.

The efficacy results from CHECKMATE-214 are presented in Table 13 and Figure 3.

### 14.3 Previously Untreated Advanced Renal Cell Carcinoma

CHECKMATE-214 (NCT02231749) was a randomized (1:1), open-label study in patients with previously untreated advanced RCC. Patients were included regardless of their PD-L1 status. CHECKMATE-214 excluded patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region.

Efficacy was evaluated in intermediate/poor-risk patients with at least 1 or more of 6 prognostic risk factors as per the IMDC criteria (less than one year from time of initial renal cell carcinoma diagnosis to randomization, Karnofsky performance status <80%, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, platelet count greater than the upper limit of normal, and absolute neutrophil count greater than the upper limit of normal).
CHECKMATE-214 also randomized 249 favorable risk patients as per IMDC criteria to nivolumab plus YERVOY (n=125) or to sunitinib (n=124). These patients were not evaluated as part of the efficacy analysis population. OS in favorable risk patients receiving nivolumab plus YERVOY compared to sunitinib has a hazard ratio of 1.45 (95% CI: 0.75, 2.81). The efficacy of nivolumab plus YERVOY in previously untreated renal cell carcinoma with favorable risk disease has not been established.

14.4 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer

CHECKMATE-142 (NCT02060188) was a multicenter, non-randomized, multiple parallel-cohort, open-label study conducted in patients with locally determined dMMR or MSI-H metastatic CRC (mCRC) who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy. Key eligibility criteria were at least one prior line of treatment for metastatic disease, ECOG PS 0 or 1, and absence of the following: active brain metastases, active autoimmune disease, or medical condition requiring systemic immunosuppression.

Patients enrolled in the YERVOY and nivolumab MSI-H mCRC cohort received YERVOY 1 mg/kg and nivolumab 3 mg/kg IV every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg IV as a single agent every 2 weeks. Patients enrolled in the single-agent nivolumab MSI-H mCRC cohort received nivolumab 3 mg/kg by intravenous (IV) infusion every 2 weeks. Treatment in both cohorts continued until unacceptable toxicity or radiographic progression.

Tumor assessments were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. Efficacy outcome measures were overall response rate (ORR) as assessed by independent radiographic review committee (IRRC) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and duration of response (DOR).

A total of 119 patients were enrolled in the YERVOY plus nivolumab cohort. The median age was 58 years (range: 21 to 88), with 32% ≥65 years of age and 3% >75 years of age; 59% were male and 52% were white. Baseline ECOG PS was 0 (43%), 1 (55%), and 29% were reported to have Lynch Syndrome. Across the cohort, 69% received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; 10%, 40%, 24%, and 15% received 1, 2, 3, or ≥4 prior lines of therapy for metastatic disease, respectively, and 42% of patients had received an anti-EGFR antibody.

A total of 74 patients were enrolled in the single-agent nivolumab cohort. The median age was 58 years (range: 26 to 79) with 23% >65 years of age and 5% >75 years of age; 59% were male and 88% were white. Baseline ECOG performance status was 0 (43%), 1 (55%), or 3 (1.4%), and 36% were reported to have Lynch Syndrome. Across the 74 patients, 72% received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; 70%, 30%, 28%, 19%, and 16% received 1, 2, 3, or ≥4 prior lines of therapy for metastatic disease, respectively, and 42% of patients had received an anti-EGFR antibody.

Efficacy results are shown in Table 14.

### Table 14: Efficacy Results in CHECKMATE-142

<table>
<thead>
<tr>
<th>YERVOY plus Nivolumab</th>
<th>Nivolumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MSI-H/dMMR Cohort</strong></td>
<td><strong>MSI-H/dMMR Cohort</strong></td>
</tr>
<tr>
<td><strong>All Patients (n=119)</strong></td>
<td><strong>All Patients (n=74)</strong></td>
</tr>
<tr>
<td>IRRC Overall Response Rate: n (%)</td>
<td>IRRC Overall Response Rate: n (%)</td>
</tr>
<tr>
<td>(95% CI)²</td>
<td>(95% CI)²</td>
</tr>
<tr>
<td>58 (49%)</td>
<td>24 (32%)</td>
</tr>
<tr>
<td>(39, 58)</td>
<td>(22, 44)</td>
</tr>
<tr>
<td>Complete Response (%)</td>
<td>Complete Response (%)</td>
</tr>
<tr>
<td>5 (4.2%)</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td>(3, 7.7%)</td>
<td>(1, 1.9%)</td>
</tr>
<tr>
<td>Partial Response (%)</td>
<td>Partial Response (%)</td>
</tr>
<tr>
<td>53 (45%)</td>
<td>22 (30%)</td>
</tr>
<tr>
<td>(35, 62%)</td>
<td>(14, 42%)</td>
</tr>
</tbody>
</table>

**Duration of Response**

<table>
<thead>
<tr>
<th>Proportion with ≥6 months response duration</th>
<th>Proportion with ≥12 months response duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>83%</td>
<td>19%</td>
</tr>
<tr>
<td>89%</td>
<td>21%</td>
</tr>
<tr>
<td>63%</td>
<td>38%</td>
</tr>
<tr>
<td>67%</td>
<td>40%</td>
</tr>
</tbody>
</table>

**a** Estimated using the Clopper-Pearson method

**b** In the monotherapy cohort, 55% of the 20 patients with ongoing responses were followed for less than 12 months from the date of onset of response. In the combination cohort, 78% of the 51 patients with ongoing responses were followed for less than 12 months from the date of onset of response.

### Immunemediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and withholding or discontinuation of YERVOY, including:

- **Enterocolitis/Colitis**: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain [see Warnings and Precautions (5.1)].
- **Hepatitis**: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding [see Warnings and Precautions (5.2)].
- **Skin Adverse Reactions**: Advise patients to contact their healthcare provider immediately for rash [see Warnings and Precautions (5.3)].
- **Neuropathies**: Advise patients to contact their healthcare provider immediately for neuropathies [see Warnings and Precautions (5.4)].
- **Endocrinopathies**: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus [see Warnings and Precautions (5.5)].
- **Pneumonitis**: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction [see Warnings and Precautions (5.6)].
- **Nephritis and Renal Dysfunction**: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction [see Warnings and Precautions (5.6)].
- **Encephalitis**: Advise patients to contact their healthcare provider immediately for neurological signs or symptoms of encephalitis [see Warnings and Precautions (5.8)].

### Infusion Reactions

- Advise patients of the potential risk of infusion reaction [see Warnings and Precautions (5.9)].

### Females of Reproductive Potential

- Advise female patients that YERVOY can cause fetal harm. Advise females of reproductive potential to use effective contraception during treatment with YERVOY and for 3 months after the last dose [see Use in Specific Populations (8.3)].
- Advise female patients to contact their healthcare provider with a known or suspected pregnancy. Advise females who may have been exposed to YERVOY during pregnancy to contact Bristol-Myers Squibb at 1-800-721-5072 [see Warnings and Precautions (5.11) and Use in Specific Populations (8.1, 8.3)]. Advise patients that there is a Pregnancy Safety Surveillance Study that monitors pregnancy outcomes in women exposed to YERVOY during pregnancy, and they can be enrolled by calling 1-844-593-7869 [see Use in Specific Populations (8.1)].

### Lactation

- Advise women not to breastfeed during treatment with YERVOY and for 3 months after the last dose [see Use in Specific Populations (8.2)].
**MEDICATION GUIDE**

**YERVOY® (yur-voi)**

**injection**

**YERVOY® (ipilimumab)**

Read this Medication Guide before you start receiving YERVOY and before each infusion. There may be new information. If your healthcare provider prescribes YERVOY in combination with nivolumab, also read the Medication Guide that comes with nivolumab. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about YERVOY?

YERVOY can cause serious side effects in many parts of your body which can lead to death. These problems may happen anytime during treatment with YERVOY or after you have completed treatment. Some of these problems may happen more often when YERVOY is used in combination with nivolumab.

Call your healthcare provider right away if you develop any of these signs or symptoms or they get worse. Do not try to treat symptoms yourself.

Intestinal problems (colitis) that can cause tears or holes (perforation) in the intestines. Signs and symptoms of colitis may include:

- diarrhea (loose stools) or more bowel movements than usual
- mucus or blood in your stools
- dark, tarry, sticky stools
- stomach pain (abdominal pain) or tenderness
- you may or may not have fever

Liver problems (hepatitis) that can lead to liver failure. Signs and symptoms of hepatitis may include:

- yellowing of your skin or the whites of your eyes
- dark urine (tea colored)
- nausea or vomiting
- pain on the right side of your stomach
- bleeding or bruise more easily than normal
- decreased energy

Skin problems that can lead to severe skin reaction. Signs and symptoms of severe skin reactions may include:

- skin rash with or without itching
- sores in your mouth
- your skin blisters or peels

Nerve problems that can lead to paralysis. Symptoms of nerve problems may include:

- unusual weakness of legs, arms, or face
- numbness or tingling in hands or feet

Hormone gland problems (especially the pituitary, adrenal, and thyroid glands). Signs and symptoms that your glands are not working properly may include:

- persistent or unusual headaches
- unusual sluggishness
- feeling cold all the time
- weight gain
- changes in mood or behavior such as decreased sex drive, irritability, or forgetfulness
- dizziness or fainting

Lung problems (pneumonitis). Symptoms of pneumonitis may include:

- new or worsening cough
- chest pain
- shortness of breath

Kidney problems, including nephritis and kidney failure. Signs of kidney problems may include:

- decrease in the amount of urine
- blood in your urine
- swelling in your ankles
- loss of appetite

Inflammation of the brain (encephalitis). Signs and symptoms of encephalitis may include:

- headache
- fever
- tiredness or weakness
- confusion
- memory problems
- sleepiness
- seeing or hearing things that are not really there (hallucinations)
- seizures
- stiff neck

Eye problems. Symptoms may include:

- blurry vision, double vision, or other vision problems
- eye pain or redness

Getting medical treatment right away may keep the problem from becoming more serious.

Your healthcare provider will check you for these problems during treatment with YERVOY. Your healthcare provider may treat you with corticosteroid medicines. Your healthcare provider may need to delay or completely stop treatment with YERVOY if you have severe side effects.
What is YERVOY?
YERVOY is a prescription medicine used:

- **to treat a kind of skin cancer called melanoma.** YERVOY may be used:
  - in adults and children 12 years of age and older when melanoma has spread or cannot be removed by surgery
  - to help prevent melanoma from coming back after it and lymph nodes that contain cancer have been removed by surgery
- **in people with kidney cancer (renal cell carcinoma).** YERVOY may be used in combination with nivolumab in certain people when their cancer has spread.
- **in adults and children 12 years of age and older, with a type of colon or rectal cancer (colorectal cancer).** YERVOY in combination with nivolumab may be used when your colon or rectal cancer:
  - has spread to other parts of the body (metastatic).
  - is microsatellite stability-high (MSI-H) or mismatch repair deficient (dMMR), and
  - You have tried treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, and it did not work or is no longer working.

It is not known if YERVOY is safe and effective in children younger than 12 years of age.

Before you receive YERVOY, tell your healthcare provider about all your medical conditions, including if you:

- have immune system problems (autoimmune disease), such as ulcerative colitis, Crohn's disease, lupus, or sarcoidosis
- have had an organ transplant
- have liver problems
- are pregnant or plan to become pregnant. YERVOY can harm your unborn baby.
  - Females who are able to become pregnant should use effective birth control during treatment with YERVOY and for 3 months after the last dose of YERVOY.
  - If you become pregnant or think you are pregnant, tell your healthcare provider right away. You or your healthcare provider should contact Bristol-Myers Squibb at 1-800-721-5072 as soon as you become aware of the pregnancy.
  - Pregnancy Safety Surveillance Study: Females who become pregnant during treatment with YERVOY are encouraged to enroll in a Pregnancy Safety Surveillance Study. The purpose of this study is to collect information about the health of you and your baby. You or your healthcare provider can enroll you in the Pregnancy Safety Surveillance Study by calling 1-844-593-7869.
- are breastfeeding or plan to breastfeed. It is not known if YERVOY passes into your breast milk.
  - Do not breastfeed during treatment with YERVOY and for 3 months after the last dose of YERVOY.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive YERVOY?

- YERVOY alone is given to you into your vein through an intravenous (IV) line over 90 minutes.
- When YERVOY is used in combination with nivolumab, nivolumab is given to you into your vein through an IV line over 30 minutes. Then YERVOY is also given through an IV over 30 minutes on the same day.
- YERVOY in combination with nivolumab is usually given every 3 weeks for 4 doses. After that, nivolumab alone is usually given every 2 or 4 weeks.
- Your healthcare provider will decide how many treatments you will need.
- Your healthcare provider will do blood tests before starting and during treatment with YERVOY.
- It is important for you to keep all appointments with your healthcare provider. Call your healthcare provider if you miss an appointment. There may be special instructions for you.

What are the possible side effects of YERVOY?

YERVOY can cause serious side effects, including:

- See “What is the most important information I should know about YERVOY?”
- Severe infusion reactions. Tell your doctor or nurse right away if you get these symptoms during an infusion of YERVOY:
  - chills or shaking
  - itching or rash
  - flushing
  - difficulty breathing
  - dizziness
  - fever
  - feeling like passing out
Graft-versus-host disease, a complication that can happen after receiving a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic), may be severe, and can lead to death, if you receive YERVOY either before or after transplant. Your healthcare provider will monitor you for the following signs and symptoms: skin rash, liver inflammation, stomach-area (abdominal) pain, and diarrhea.

The most common side effects of YERVOY when used alone include:

- feeling tired
- diarrhea
- nausea
- itching
- rash
- vomiting
- headache
- weight loss
- fever
- decreased appetite
- difficulty falling or staying asleep

The most common side effects of YERVOY when used in combination with nivolumab include:

- feeling tired
- rash
- diarrhea
- vomiting
- nausea
- cough
- fever
- decreased appetite
- shortness of breath

These are not all of the possible side effects of YERVOY.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of YERVOY.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your healthcare provider or pharmacist for information about YERVOY that is written for healthcare professionals.

What are the ingredients of YERVOY?

Active ingredient: ipilimumab

Inactive ingredients: diethylene triamine pentaacetic acid (DTPA), mannitol, polysorbate 80, sodium chloride, tris hydrochloride, and Water for Injection

Manufactured by: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
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