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

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	5/2025
Dosage and Administration (2)	5/2025

----------INDICATIONS AND USAGE----------

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

Melanoma
- Treatment of unresectable or metastatic melanoma in adults and pediatric patients 12 years and older as a single agent or in combination with nivolumab. (1.1)
- Adjuvant treatment of adult 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)

Renal Cell Carcinoma (RCC)
- Treatment of adult patients with intermediate or poor risk advanced renal cell carcinoma, as first-line treatment in combination with nivolumab. (1.3)

Colorectal Cancer
- Treatment of adults and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC) in combination with nivolumab. (1.4)

Hepatocellular Carcinoma
- adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) as first-line treatment in combination with nivolumab. (1.5)
- in combination with nivolumab in adult patients with unresectable or metastatic HCC who have been previously treated with sorafenib. (1.5)

Non-Small Cell Lung Cancer (NSCLC)
- Treatment of adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with nivolumab. (1.6)
- Treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy. (1.6)

Malignant Pleural Mesothelioma
- Treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with nivolumab. (1.7)

Esophageal Cancer
- Treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma, as first line treatment in combination with nivolumab whose tumors express PD-L1 (≥1). (1.8)

----------DOSAGE AND ADMINISTRATION----------

- Administer by intravenous infusion after dilution based upon recommended infusion rate for each indication. (2)
- Unresectable or Metastatic Melanoma:
  - YERVOY 3 mg/kg every 3 weeks for a maximum of 4 doses. (2.2)
  - YERVOY 3 mg/kg immediately following nivolumab 1 mg/kg on the same day, every 3 weeks for 4 doses. After completing 4 doses of the combination, administer nivolumab as a single agent as recommended in the Full Prescribing Information for nivolumab. (2.2)
- Adjuvant Treatment of Melanoma: YERVOY 3 mg/kg every 3 weeks for 4 doses, followed by 3 mg/kg every 12 weeks for up to 4 additional doses. (2.2)
- Advanced Renal Cell Carcinoma: YERVOY 1 mg/kg immediately following nivolumab 3 mg/kg on the same day, every 3 weeks for 4 doses. After completing 4 doses of the combination, administer nivolumab as a single agent as recommended in Full Prescribing Information for nivolumab. (2.2)
- Treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in combination with nivolumab:
  - Adult and pediatric patients weighing 40 kg or greater: YERVOY 1 mg/kg immediately following nivolumab 240 mg on the same day every 3 weeks for a maximum of 4 doses. After completing the combination, administer nivolumab as a single agent as recommended in Full Prescribing Information for nivolumab. (2.2)
  - Pediatric patients weighing less than 40 kg: YERVOY 1 mg/kg immediately following nivolumab 3 mg/kg on the same day every 3 weeks for a maximum of 4 doses. After completing the combination, administer nivolumab as a single agent as recommended in Full Prescribing Information for nivolumab. (2.2)
- Hepatocellular Carcinoma: YERVOY 3 mg/kg intravenously over 30 minutes immediately following nivolumab 1 mg/kg intravenously over 30 minutes on the same day, every 3 weeks for up to 4 doses. After completing up to 4 doses of the combination, administer nivolumab as a single agent as recommended in Full Prescribing Information for nivolumab. (2.2)
- Metastatic non-small cell lung cancer:
  - YERVOY 1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks. (2.2)
  - YERVOY 1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks and 2 cycles of platinum-doublet chemotherapy. (2.2)
- Malignant pleural mesothelioma: YERVOY 1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks. (2.2)
- Esophageal squamous cell carcinoma: YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks or 360 mg every 3 weeks. (2.2)
- See full Prescribing Information for preparation and administration instructions and dosage modifications for adverse reactions.

----------DOSAGE FORMS AND STRENGTHS----------

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

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Severe and Fatal Immune-Mediated Adverse Reactions: Immune-mediated adverse reactions (IMAR) can occur in any organ system or tissue, including the following: immune-mediated colitis, immune-mediated hepatitis, immune-mediated dermatologic adverse reactions, immune-mediated endocrinopathies, immune-mediated pneumonitis, and immune-mediated nephritis with renal dysfunction, and can occur at any time during treatment or after discontinuation. Monitor for symptoms and signs that may be clinical manifestations of IMAR. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone level and thyroid function including at baseline and before each dose. In general, withhold YERVOY for severe (grade 3) and permanently discontinue for life-threatening (grade 4) immune-mediated adverse reactions. See Full Prescribing Information for additional dosage modifications. (2.3, 5.1)
- Infusion-Related Reactions: Discontinue for severe and life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. (2.3, 5.2)
- Complications of allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with YERVOY. (5.3)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.4, 8.1, 8.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥20%) with YERVOY as a single agent are fatigue, diarrhea, pruritus, rash, nausea, and headache. (6.1)

Most common adverse reactions (≥20%) with YERVOY in combination with nivolumab are fatigue, diarrhea, rash, pruritus, nausea, musculoskeletal pain, pyrexia, cough, decreased appetite, vomiting, abdominal pain, dyspnea, upper respiratory tract infection, arthralgia, headache, hypothyroidism, constipation, decreased weight, and dizziness. (6.1)

Most common adverse reactions (≥20%) with YERVOY in combination with nivolumab and platinum-doublet chemotherapy are fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus. (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: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2025

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 1 of 81

FULL PRESCRIBING INFORMATION: CONTENTS *

1 INDICATIONS AND USAGE
- 1.1 Unresectable or Metastatic Melanoma
- 1.2 Adjuvant Treatment of Melanoma
- 1.3 Advanced Renal Cell Carcinoma
- 1.4 Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer
- 1.5 Hepatocellular Carcinoma
- 1.6 Metastatic Non-Small Cell Lung Cancer
- 1.7 Malignant Pleural Mesothelioma
- 1.8 Esophageal Cancer

2 DOSAGE AND ADMINISTRATION
- 2.1 Patient Selection
- 2.2 Recommended Dosage
- 2.3 Recommended Dosage Modifications for Adverse Reactions
- 2.4 Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Severe and Fatal Immune-Mediated Adverse Reactions
- 5.2 Infusion-Related Reactions
- 5.3 Complications of Allogeneic Hematopoietic Stem Cell Transplant after YERVOY
- 5.4 Embryo-Fetal Toxicity
- 5.5 Risks Associated When Administered in Combination with Nivolumab

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.6 Immunogenicity

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
- 14.1 Unresectable or Metastatic Melanoma
- 14.2 Adjuvant Treatment of Melanoma
- 14.3 Advanced Renal Cell Carcinoma
- 14.4 Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer
- 14.5 Hepatocellular Carcinoma
- 14.6 Metastatic Non-Small Cell Lung Cancer
- 14.7 Malignant Pleural Mesothelioma
- 14.8 Esophageal Cancer

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Unresectable or Metastatic Melanoma

YERVOY, as a single agent or in combination with nivolumab, is indicated for the treatment of unresectable or metastatic melanoma in adult and pediatric patients 12 years and older.

1.2 Adjuvant Treatment of Melanoma

YERVOY is indicated for the adjuvant treatment of adult patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.

1.3 Advanced Renal Cell Carcinoma

YERVOY, in combination with nivolumab, is indicated for the first-line treatment of adult patients with intermediate or poor risk advanced renal cell carcinoma (RCC).

1.4 Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer

- YERVOY, in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC).

1.5 Hepatocellular Carcinoma

- YERVOY, in combination with nivolumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC).
- YERVOY, in combination with nivolumab, is indicated for the treatment of adult patients with unresectable or metastatic HCC who have been previously treated with sorafenib.

1.6 Metastatic Non-Small Cell Lung Cancer

YERVOY, in combination with nivolumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, with no EGFR or ALK genomic tumor aberrations.

YERVOY, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations.

1.7 Malignant Pleural Mesothelioma

YERVOY, in combination with nivolumab, is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 3 of 81

1.8 Esophageal Cancer

YERVOY, in combination with nivolumab, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) whose tumors express PD-L1 (≥1) *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Information on FDA-approved tests for patient selection is available at:

https://www.fda.gov/CompanionDiagnostics

Non-Small Cell Lung Cancer

- Select patients with metastatic NSCLC for treatment with YERVOY in combination with nivolumab based on PD-L1 expression *[see Clinical Studies (14.6)]*.

Esophageal Cancer

- Select patients with unresectable or advanced or metastatic ESCC for treatment with YERVOY in combination with nivolumab based on PD-L1 expression *[see Clinical Studies (14.8)]*.
- An FDA-approved companion diagnostic for the detection of PD-L1 expression in patients with advanced or metastatic ESCC is not available.

2.2 Recommended Dosage

The recommended dosages of YERVOY as a single agent are presented in Table 1.

Administer YERVOY as a 30-minute intravenous infusion *[see Preparation and Administration (2.4)]*.

Table 1: Recommended Dosages for YERVOY as a Single Agent

Indication	Recommended YERVOY Dosage	Duration of Therapy
Unresectable or metastatic melanoma	3 mg/kg every 3 weeks	Maximum of 4 doses
Adjuvant treatment of melanoma	3 mg/kg every 3 weeks followed by 3 mg/kg every 12 weeks	Every 3 weeks up to a maximum of 4 doses Every 12 weeks for up to 4 additional doses

The recommended dosages of YERVOY in combination with other therapeutic agents are presented in Table 2. Administer YERVOY on the same day as other therapeutic agents.

Refer to the respective Prescribing Information for each therapeutic agent administered in combination with YERVOY for recommended dosage information, as appropriate.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 4 of 81

Table 2: Recommended Dosages of YERVOY in Combination with Other Therapeutic Agents*

Indication	Recommended YERVOY Dosage	Duration of Therapy
Unresectable or metastatic melanoma	3 mg/kg every 3 weeks with nivolumab 1 mg/kg	In combination with nivolumab for a maximum of 4 doses or until unacceptable toxicity, whichever occurs earlier. After completing 4 doses of combination therapy, administer nivolumab as a single agent until disease progression or unacceptable toxicity.†
Advanced renal cell carcinoma	1 mg/kg every 3 weeks with nivolumab 3 mg/kg	In combination with nivolumab for a maximum of 4 doses. After completing 4 doses of combination therapy, administer nivolumab as single agent until disease progression or unacceptable toxicity.†
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 1 mg/kg every 3 weeks with nivolumab 240 mg	In combination with nivolumab for a maximum of 4 doses.† After completing 4 doses of combination therapy, administer nivolumab as single agent until disease progression, unacceptable toxicity, or up to 2 years.†
	Pediatric patients age 12 years and older and weighing less than 40 kg: 1 mg/kg every 3 weeks with nivolumab 3 mg/kg	
Hepatocellular carcinoma	3 mg/kg every 3 weeks with nivolumab 1 mg/kg	In combination with nivolumab for a maximum of 4 doses. After completing a maximum of 4 doses of combination therapy, administer nivolumab as single agent until disease progression or unacceptable toxicity.†
Metastatic non-small cell lung cancer expressing PD-L1	1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks	In combination with nivolumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.†
Metastatic or recurrent non-small cell lung cancer	1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks and histology-based platinum-doublet chemotherapy every 3 weeks	In combination with nivolumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.†
		2 cycles of histology-based platinum-doublet chemotherapy
Malignant pleural mesothelioma	1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks	In combination with nivolumab until disease progression, unacceptable toxicity, or up to 2 years in patients

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 5 of 81

Table 2: Recommended Dosages of YERVOY in Combination with Other Therapeutic Agents*

Indication	Recommended YERVOY Dosage	Duration of Therapy
		without disease progression.†
Esophageal squamous cell carcinoma	1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks or 360 mg every 3 weeks	In combination with nivolumab until disease progression, unacceptable toxicity, or up to 2 years.

* Refer to the Prescribing Information for the agents administered in combination with YERVOY for recommended dosing information, as appropriate.

† Refer to the Prescribing Information for nivolumab for dosage information after completing use in combination with YERVOY.

2.3 Recommended Dosage Modifications for Adverse Reactions

No dose reduction for YERVOY is recommended. In general, withhold YERVOY for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue YERVOY for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, persistent moderate (Grade 2) or severe (Grade 3) reactions lasting 12 weeks or longer after last YERVOY dose (excluding endocrinopathy), or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids. Dosage modifications for YERVOY or YERVOY in combination with nivolumab for adverse reactions that require management different from these general guidelines are summarized in Table 3.

When YERVOY is administered in combination with nivolumab, withhold or permanently discontinue both YERVOY and nivolumab for toxicity.

Table 3: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modifications
Immune-Mediated Adverse Reactions *[See Warnings and Precautions (5.1)]*		
Colitis	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver or Hepatitis with tumor involvement of the liver/non-HCC	AST or ALT increases to more than 3 times and up to 5 times the ULN or Total bilirubin increases to more than 1.5 times and up to 3 times the ULN	Withhold[a]
	AST or ALT more than 5 times the ULN or Total bilirubin more than 3 times the ULN	Permanently discontinue

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 6 of 81

Table 3: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modifications
Hepatitis with tumor involvement of the liver[b]/HCC[c]	Baseline AST/ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST/ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN.	Withhold[a]
	AST/ALT increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN.	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Endocrinopathies[d]	Grades 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Pneumonitis	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[a]
	Grade 4 increased blood creatinine	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Myocarditis	Grade 2, 3 or 4	Permanently discontinue
Ophthalmologic	Grade 2, 3, or 4 that does not improve to Grade 1 within 2 weeks while receiving topical therapy or that requires systemic treatment	Permanently discontinue
Other Adverse Reactions		
Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit of normal

* Based on Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03

[a] Resume in patients with complete or partial resolution (Grade 0 or 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.

[b] If AST/ALT are less than or equal to ULN at baseline, withhold or permanently discontinue YERVOY based on recommendations for hepatitis with no liver involvement.

[c] This guidance is only applicable to HCC patients who are being treated with YERVOY in combination with nivolumab.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 7 of 81

[d] Depending on clinical severity, consider withholding for Grade 2 endocrinopathy until symptom improvement with hormone replacement. Resume once acute symptoms have resolved.

2.4 Preparation and Administration

- Do not shake product.
- Visually inspect for particulate matter and discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced discoloration (solution may have pale-yellow color), or there is foreign particulate matter other than translucent-to-white, amorphous particles.

Preparation of Solution

- Allow the vial(s) to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
- Withdraw the required volume of YERVOY and transfer into an intravenous bag.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a **final concentration ranging from 1 mg/mL to 2 mg/mL**. Mix diluted solution by gentle inversion.
- After preparation, store the diluted solution either refrigerated at 2°C to 8°C (36°F to 46°F) or at room temperature of 20°C to 25°C (68°F to 77°F) for no more than 24 hours from the time of preparation to the time of infusion.
- Discard partially used or empty vials of YERVOY.

Administration

- Do not co-administer other drugs through the same intravenous line.
- Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.
- Administer diluted YERVOY solution by intravenous infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.
- When administered in combination with nivolumab, infuse nivolumab first followed by YERVOY on the same day.
- When administered with nivolumab and platinum-doublet chemotherapy, infuse nivolumab first followed by YERVOY and then platinum-doublet chemotherapy on the same day.
- Use separate infusion bags and filters for each infusion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 50 mg/10 mL (5 mg/mL) and 200 mg/40 mL (5 mg/mL) as a clear to slightly opalescent, colorless to pale-yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

YERVOY is a fully human monoclonal antibody that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, thereby removing inhibition of the immune response with the potential for

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 8 of 81

induction of immune-mediated adverse reactions. Immune-mediated adverse reactions listed herein may not be inclusive of all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting YERVOY. While immune-mediated adverse reactions usually manifest during treatment, immune-mediated adverse reactions can also manifest after discontinuation of YERVOY.

Early identification and management are essential to ensure safe use of YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and before each dose. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue YERVOY depending on severity *[see Dosage and Administration (2.3)].* In general, if YERVOY requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

<u>Immune-Mediated Colitis</u>

YERVOY can cause immune-mediated colitis, which may be fatal. 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.

YERVOY 3 mg/kg as a Single Agent

Immune-mediated colitis occurred in 12% (62/511) of patients who received YERVOY 3 mg/kg as a single agent, including Grade 3-5 (7%) and Grade 2 (5%). Colitis led to permanent discontinuation of YERVOY in 4.3% and withholding of at least one dose of YERVOY in 0.2% of patients.

Systemic corticosteroids were required in 74% (46/62) of patients with immune-mediated colitis. Five patients required coadministration of another immunosuppressant with corticosteroids. Colitis resolved in 76% of the 62 patients. One patient was withheld one or more doses of YERVOY for colitis, and no patient received additional treatment after symptom improvement.

YERVOY 1 mg/kg with 3 mg/kg Nivolumab

Immune-mediated colitis occurred in 9% (60/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (4.4%), and Grade 2 (3.7%). Colitis led to permanent discontinuation of YERVOY and nivolumab in 3.2% and withholding of YERVOY and nivolumab in 2.7% of patients.

In patients who received YERVOY 1 mg/kg with nivolumab, use of systemic corticosteroids was one of the diagnostic criteria required to identify immune-mediated colitis. Systemic

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 9 of 81

corticosteroids were therefore required in 100% (60/60) of patients with immune-mediated colitis. Approximately 23% of patients required coadministration of another immunosuppressant with corticosteroids. Colitis resolved in 95% of the 60 patients. Of the 18 patients in whom YERVOY or nivolumab was withheld for colitis, 16 received additional treatment after symptom improvement; of these, 10 had recurrence of colitis.

YERVOY 3 mg/kg with 1 mg/kg Nivolumab

Immune-mediated colitis occurred in 25% (115/456) of patients with melanoma or HCC receiving YERVOY 3 mg/kg with nivolumab 1 mg/kg every 3 weeks, including Grade 4 (0.4%), Grade 3 (14%), and Grade 2 (8%) adverse reactions. Colitis led to permanent discontinuation of YERVOY with nivolumab in 14% and withholding of treatment in 4.4% of patients.

Systemic corticosteroids were required in 100% (115/115) of patients with colitis. Approximately 23% of patients required addition of infliximab to high-dose corticosteroids. Colitis resolved in 93% of 115 patients. Of the 20 patients in whom YERVOY with nivolumab was withheld for colitis, 16 reinitiated treatment after symptom improvement, and 9 had recurrence of colitis.

Immune-Mediated Hepatitis

YERVOY 3 mg/kg as a Single Agent

Immune-mediated hepatitis occurred in 4.1% (21/511) of patients who received YERVOY 3 mg/kg as a single agent, including Grade 3-5 (1.6%) and Grade 2 (2.5%). Hepatitis led to permanent discontinuation of YERVOY in 0.4% of patients and withholding of at least one dose of YERVOY in none of the patients.

Systemic corticosteroids were required in 29% (6/21) of patients with immune-mediated hepatitis. No patients required the coadministration of another immunosuppressant with corticosteroids. Hepatitis resolved in 86% of the 21 patients.

YERVOY 3 mg/kg with Vemurafenib

The safety and effectiveness of YERVOY in combination with vemurafenib have not been established *[see Indications and Usage (1)]*. 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 or 720 mg twice daily).

YERVOY 1 mg/kg with 3 mg/kg Nivolumab

Immune-mediated hepatitis occurred in 7% (48/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 4 (1.2%), Grade 3 (4.9%), and Grade 2 (0.4%). Hepatitis led to permanent discontinuation of YERVOY and nivolumab in 3.6% and withholding of YERVOY and nivolumab in 2.6% of patients.

In patients who received YERVOY 1 mg/kg with nivolumab, use of systemic corticosteroids was one of the diagnostic criteria required to identify immune-mediated hepatitis. Systemic corticosteroids were therefore required in 100% (48/48) of patients with immune-mediated hepatitis. Approximately 19% of patients required coadministration of another immunosuppressant with corticosteroids. Hepatitis resolved in 88% of the 48 patients. Of the 17

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 10 of 81

patients in whom YERVOY or nivolumab was withheld for hepatitis, 14 received additional treatment after symptom improvement; of these, 10 had recurrence of hepatitis.

YERVOY 3 mg/kg with 1 mg/kg Nivolumab

Immune-mediated hepatitis occurred in 15% (70/456) of patients with melanoma or HCC receiving YERVOY 3 mg/kg with nivolumab 1 mg/kg every 3 weeks, including Grade 4 (2.4%), Grade 3 (11%), and Grade 2 (1.8%) adverse reactions. Immune-mediated hepatitis led to permanent discontinuation of YERVOY with nivolumab in 8% and withholding of treatment in 3.5% of patients.

Systemic corticosteroids were required in 100% (70/70) of patients with hepatitis. Approximately 9% of patients with immune-mediated hepatitis required addition of mycophenolic acid to high-dose corticosteroids. Hepatitis resolved in 91% of the 70 patients. Of the 16 patients in whom YERVOY with nivolumab was withheld for hepatitis, 14 reinitiated treatment after symptom improvement, and 8 had recurrence of hepatitis.

Immune-Mediated Dermatologic Adverse Reactions

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, Stevens Johnson Syndrome, toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms). Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes. Withhold or permanently discontinue YERVOY depending on severity *[see Dosage and Administration (2.3)]*.

YERVOY 3 mg/kg as a Single Agent

Immune-mediated rash occurred in 15% (76/511) of patients who received YERVOY 3 mg/kg as a single agent, including Grade 3-5 (2.5%) and Grade 2 (12%). Rash led to permanent discontinuation of YERVOY in 0.2% and withholding of at least one dose of YERVOY in 1.4% of patients.

Systemic corticosteroids were required in 43% (33/76) of patients with immune-mediated rash. Rash resolved in 71% of the 76 patients. Of the 7 patients in whom YERVOY was withheld for rash, 3 received additional treatment after symptom improvement; of these, 1 had recurrence of rash.

YERVOY 1 mg/kg with 3 mg/kg Nivolumab

Immune-mediated rash occurred in 16% (108/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (3.5%) and Grade 2 (4.2%). Rash led to permanent discontinuation of YERVOY and nivolumab in 0.5% of patients and withholding of YERVOY and nivolumab in 2.0% of patients.

In patients who received YERVOY 1 mg/kg with nivolumab, use of systemic corticosteroids was one of the diagnostic criteria required to identify immune-mediated rash. Systemic corticosteroids were therefore required in 100% (108/108) of patients. Rash resolved in 75% of 108 patients. Of the 13 patients in whom YERVOY or nivolumab was withheld for rash, 11 received additional treatment after symptom improvement; of these, 5 had recurrence of rash.

Reference ID: 5595665

YERVOY 3 mg/kg with 1 mg/kg Nivolumab

Immune-mediated rash occurred in 28% (127/456) of patients with melanoma or HCC receiving YERVOY 3 mg/kg with nivolumab 1 mg/kg every 3 weeks, including Grade 3 (4.8%) and Grade 2 (10%) adverse reactions. Immune-mediated rash led to permanent discontinuation of YERVOY with nivolumab in 0.4% and withholding of treatment in 3.9% of patients.

Systemic corticosteroids were required in 100% (127/127) of patients with immune-mediated rash. Rash resolved in 84% of the 127 of patients. Of the 18 patients in whom YERVOY with nivolumab was withheld for rash, 15 reinitiated treatment after symptom improvement, and 8 had recurrence of rash.

Immune-Mediated Endocrinopathies

YERVOY 3 mg/kg as a Single Agent

Grade 2-5 immune-mediated endocrinopathies occurred in 4% (21/511) of patients who received YERVOY 3 mg/kg as a single agent.

Severe to life-threatening (Grade 3-4) endocrinopathies occurred in 9 patients (1.8%). All 9 of these patients had hypopituitarism with some patients having additional concomitant endocrinopathies, such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies.

Moderate (Grade 2) endocrinopathy occurred in 12 patients (2.3%), including hypothyroidism, adrenal insufficiency, hypopituitarism, hyperthyroidism and Cushing's syndrome.

Of the 21 patients with moderate to life-threatening endocrinopathy, 17 required long-term hormone replacement therapy, including adrenal hormones (n=10) and thyroid hormones (n=13).

YERVOY 1 mg/kg with 3 mg/kg Nivolumab

Hypophysitis:

YERVOY can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue YERVOY depending on severity *[see Dosage and Administration (2.3)]*.

Hypophysitis occurred in 4.4% (29/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 4 (0.3%), Grade 3 (2.4%), and Grade 2 (0.9%). Hypophysitis led to permanent discontinuation of YERVOY and nivolumab in 1.2% and withholding of YERVOY with nivolumab in 2.1% of patients. Approximately 72% of patients with hypophysitis received hormone replacement therapy. Systemic corticosteroids were required in 72% (21/29) of patients with immune-mediated hypophysitis. Hypophysitis resolved in 59% of the 29 patients. Of the 14 patients in whom YERVOY or nivolumab was withheld for hypophysitis, 11 received additional treatment after symptom improvement; of these, 2 had recurrence of hypophysitis.

Adrenal Insufficiency:

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 12 of 81

Adrenal insufficiency occurred in 7% (48/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 4 (0.3%), Grade 3 (2.5%), and Grade 2 (4.1%). Adrenal insufficiency led to permanent discontinuation of YERVOY with nivolumab in 1.2% and withholding of YERVOY with nivolumab in 2.1% of patients. Approximately 94% of patients with adrenal insufficiency received hormone replacement therapy. Systemic corticosteroids were required in 94% (45/48) of patients with adrenal insufficiency. Adrenal insufficiency resolved in 29% of the 48 patients. Of the 14 patients in whom YERVOY or nivolumab was withheld for adrenal insufficiency, 11 received additional treatment after symptom improvement; of these, 2 had recurrence of adrenal insufficiency.

Hyperthyroidism:

Hyperthyroidism occurred in 12% (80/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (0.6%) and Grade 2 (4.5%). No patients discontinued YERVOY for hyperthyroidism. Hyperthyroidism led to withholding of YERVOY with nivolumab in 2.3% of patients. Approximately 19% received a thyroid synthesis inhibitor. Systemic corticosteroids were required in 20% (16/80) of patients with hyperthyroidism. Hyperthyroidism resolved in 85% of the 80 patients. Of the 15 patients in whom YERVOY or nivolumab was withheld for hyperthyroidism, 11 received additional treatment after symptom improvement; of these, 3 had recurrence of hyperthyroidism.

Hypothyroidism:

Hypothyroidism occurred in 18% (122/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (0.6%) and Grade 2 (11%). Hypothyroidism led to permanent discontinuation of YERVOY with nivolumab in 0.2% and withholding of YERVOY with nivolumab in 1.4% of patients. Approximately 82% received thyroid hormone replacement. Systemic corticosteroids were required in 7% (9/122) of patients with hypothyroidism. Hypothyroidism resolved in 27% of the 122 patients. Of the 9 patients in whom YERVOY or nivolumab was withheld for hypothyroidism, 5 received additional treatment after symptom improvement; of these, one patient had recurrence of hypothyroidism.

Thyroiditis:

Thyroiditis occurred in 2.7% (22/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (4.5%) and Grade 2 (2.2%). Thyroiditis led to permanent discontinuation of YERVOY with nivolumab in 0.2% and withholding of YERVOY with nivolumab in 0.8% of patients. Systemic corticosteroids were required in 18% (4/22) of patients with thyroiditis. Thyroiditis resolved in 64% of the 22 patients. Of the 5 patients in whom YERVOY or nivolumab was withheld for thyroiditis, 5 received additional treatment after symptom improvement; of these, no patients had recurrence of thyroiditis.

Type 1 Diabetes Mellitus:

Diabetes occurred in 2.7% (15/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 4 (0.6%), Grade 3 (0.3%), and Grade 2

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 13 of 81

(0.9%). Diabetes led to the permanent discontinuation of YERVOY with nivolumab in 0.5% and withholding of YERVOY with nivolumab in 0.5% of patients. Systemic corticosteroids were required in 7% (1/15) of patients with diabetes. Diabetes resolved in 27% of the 15 patients. Of the 3 patients in whom YERVOY or nivolumab was withheld for diabetes, 2 received additional treatment after symptom improvement; of these, none had recurrence of diabetes.

YERVOY 3 mg/kg with 1 mg/kg Nivolumab

Hypophysitis:

Hypophysitis occurred in 9% (42/456) of patients with melanoma or HCC receiving YERVOY 3 mg/kg with nivolumab 1 mg/kg every 3 weeks, including Grade 3 (2.4%) and Grade 2 (6%) adverse reactions. Hypophysitis led to permanent discontinuation of YERVOY with nivolumab in 0.9% and withholding of treatment in 4.2% of patients.

Approximately 86% of patients with hypophysitis received hormone replacement therapy. Systemic corticosteroids were required in 88% (37/42) of patients with hypophysitis. Hypophysitis resolved in 38% of the 42 patients. Of the 19 patients in whom YERVOY with nivolumab was withheld for hypophysitis, 9 reinitiated treatment after symptom improvement, and 1 had recurrence of hypophysitis.

Adrenal Insufficiency:

Adrenal insufficiency occurred in 8% (35/456) of patients with melanoma or HCC receiving YERVOY 3 mg/kg with nivolumab 1 mg/kg every 3 weeks, including Grade 4 (0.2%), Grade 3 (2.4%), and Grade 2 (4.2%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of YERVOY with nivolumab in 0.4% of patients and withholding of treatment in 2.0% of patients.

Approximately 71% (25/35) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 37% of the 35 patients. Of the 9 patients in whom YERVOY with nivolumab was withheld for adrenal insufficiency, 7 reinitiated treatment after symptom improvement, and all required hormone replacement therapy for their ongoing adrenal insufficiency.

Hypothyroidism:

Hypothyroidism occurred in 20% (91/456) of patients with melanoma or HCC receiving YERVOY 3 mg/kg with nivolumab 1 mg/kg every 3 weeks, including Grade 3 (0.4%) and Grade 2 (11%) adverse reactions. Hypothyroidism led to permanent discontinuation of YERVOY with nivolumab in 0.9% of patients and withholding of treatment in 0.9% of patients.

Approximately 89% of patients with hypothyroidism received levothyroxine. Systemic corticosteroids were required in 2.2% (2/91) of patients with hypothyroidism. Hypothyroidism resolved in 41% of the 91 patients. Of the 4 patients in whom YERVOY with nivolumab was withheld for hypothyroidism, 2 reinitiated treatment after symptom improvement, and none had recurrence of hypothyroidism.

Hyperthyroidism:

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 14 of 81

Hyperthyroidism occurred in 9% (42/456) of patients with melanoma or HCC receiving YERVOY 3 mg/kg with nivolumab 1 mg/kg every 3 weeks, including Grade 3 (0.9%) and Grade 2 (4.2%) adverse reactions. Hyperthyroidism led to permanent discontinuation of YERVOY with nivolumab in no patients and withholding of treatment in 2.4% of patients.

Approximately 26% of patients with hyperthyroidism received methimazole and 21% received carbimazole. Systemic corticosteroids were required in 17% (7/42) of patients. Hyperthyroidism resolved in 91% of the 42 patients. Of the 11 patients in whom YERVOY with nivolumab was withheld for hyperthyroidism, 8 reinitiated treatment after symptom improvement, and 1 had recurrence of hyperthyroidism.

Immune-Mediated Pneumonitis

YERVOY 1 mg/kg with 3 mg/kg Nivolumab

Immune-mediated pneumonitis occurred in 3.9% (26/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (1.4%) and Grade 2 (2.6%). Pneumonitis led to permanent discontinuation of YERVOY and nivolumab in 1.8% and withholding of YERVOY and nivolumab in 1.5% of patients.

In patients who received YERVOY 1 mg/kg with nivolumab, use of systemic corticosteroids was one of the diagnostic criteria required to identify immune-mediated pneumonitis. Systemic corticosteroids were therefore required in 100% (26/26) of patients with immune-mediated pneumonitis. Approximately 8% required coadministration of another immunosuppressant with corticosteroids. Pneumonitis resolved in 92% of the 26 patients. Of the 10 patients in whom YERVOY or nivolumab was withheld for pneumonitis, 10 received additional treatment after symptom improvement; of these, 4 had recurrence of pneumonitis.

In NSCLC, immune-mediated pneumonitis occurred in 9% (50/576) of patients receiving YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4.0%) immune-mediated pneumonitis. Four patients (0.7%) died due to pneumonitis. The median duration was 1.5 months (range: 5 days to 25+ months). Immune-mediated pneumonitis led to permanent discontinuation of YERVOY with nivolumab in 5% of patients and withholding of YERVOY with nivolumab in 3.6% of patients.

Systemic corticosteroids were required in 100% of patients with pneumonitis followed by a corticosteroid taper. Pneumonitis resolved in 72% of the patients. Approximately 13% (2/16) of patients had recurrence of pneumonitis after re-initiation of YERVOY with nivolumab.

YERVOY 3 mg/kg with 1 mg/kg Nivolumab

Immune-mediated pneumonitis occurred in 7% (31/456) of patients who received YERVOY 3 mg/kg with nivolumab for the treatment of HCC or melanoma, including Grade 4 (0.2%), Grade 3 (2.0%), and Grade 2 (4.4%). Immune-mediated pneumonitis led to permanent discontinuation or withholding of treatment in 2.9% and 3.9% of patients, respectively.

Systemic corticosteroids were required in 100% of patients with pneumonitis. Pneumonitis resolved in 94% of the patients. Of the 13 patients in whom YERVOY or nivolumab was withheld

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 15 of 81

for pneumonitis, 13 received additional treatment after symptom improvement, and 4 had recurrence of pneumonitis.

Immune-Mediated Nephritis with Renal Dysfunction

YERVOY 1 mg/kg with 3 mg/kg Nivolumab

Immune-mediated nephritis with renal dysfunction occurred in 4.1% (27/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 4 (0.6%), Grade 3 (1.1%), and Grade 2 (2.2%). Nephritis with renal dysfunction led to permanent discontinuation of YERVOY and nivolumab in 1.2% and withholding of nivolumab and YERVOY in 1.8% of patients.

In patients who received YERVOY 1 mg/kg with nivolumab, use of systemic corticosteroids was one of the diagnostic criteria required to identify immune-mediated nephritis with renal dysfunction. Systemic corticosteroids were therefore required in 100% (27/27) of patients with immune-mediated nephritis with renal dysfunction. Nephritis with renal dysfunction resolved in 67% of the 27 patients. Of the 12 patients in whom YERVOY or nivolumab was withheld for nephritis, 10 received additional treatment after symptom improvement; of these, 4 had recurrence of nephritis.

Other Immune-Mediated Adverse Reactions

Across clinical trials of YERVOY administered as a single agent or in combination with nivolumab, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified, as shown below:

Nervous System: Autoimmune neuropathy (2%), meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nerve paresis, motor dysfunction

Cardiovascular: Angiopathy, myocarditis, pericarditis, temporal arteritis, vasculitis

Ocular: Blepharitis, episcleritis, iritis, orbital myositis, scleritis, uveitis. Some cases can be associated with retinal detachment. 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 corticosteroids to reduce the risk of permanent vision loss.

Gastrointestinal: Duodenitis, gastritis, pancreatitis (1.3%)

Musculoskeletal and Connective Tissue: Arthritis, myositis, polymyalgia rheumatica, polymyositis, rhabdomyolysis

Other (hematologic/immune): Aplastic anemia, conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), hypersensitivity vasculitis, meningitis, neurosensory hypoacusis, psoriasis, sarcoidosis, systemic inflammatory response syndrome, and solid organ transplant rejection.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 16 of 81

5.2 Infusion-Related Reactions

Severe infusion-related reactions can occur 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 (2.3)]*. Infusion-related reactions occurred in 0.6% (3/511) of patients who received single-agent YERVOY 3 mg/kg for the unresectable or metastatic treatment of melanoma. Infusion-related reactions occurred in 5% (33/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or CRC. Infusion-related reactions occurred in 8% (4/49) of patients who received YERVOY 3 mg/kg with nivolumab for the treatment of HCC. Infusion-related reactions occurred in 12% (37/300) of patients with malignant pleural mesothelioma who received YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks.

5.3 Complications of Allogeneic Hematopoietic Stem Cell Transplant after YERVOY

Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive YERVOY either before or after allogeneic hematopoietic stem cell transplantation (HSCT). These complications may occur despite intervening therapy between CTLA-4 receptor blocking antibody and allogeneic HSCT.

Follow patients closely for evidence of GVHD and intervene promptly *[see Adverse Reactions (6.2)]*. Consider the benefit versus risks of treatment with YERVOY after allogeneic HSCT.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, YERVOY can cause fetal harm when administered to a pregnant woman. 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. The effects of ipilimumab 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 *[see Use in Specific Populations (8.1, 8.3)]*.

5.5 Risks Associated When Administered in Combination with Nivolumab

YERVOY is indicated for use in combination with nivolumab for patients with advanced RCC, MSI-H or dMMR mCRC, HCC, and NSCLC. Refer to the nivolumab Full Prescribing Information for additional risk information that applies to the combination use treatment.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Severe and fatal immune-mediated adverse reactions *[see Warnings and Precautions (5.1)]*.
- Infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 17 of 81

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described in the Warnings and Precautions section reflect exposure to YERVOY 3 mg/kg as a single agent (or in combination with an investigational gp100 peptide vaccine) in 511 patients in Study MDX010-20; YERVOY 1 mg/kg administered with nivolumab 3 mg/kg in 1,362 patients in CHECKMATE-214, CHECKMATE-142, CHECKMATE-227, and CHECKMATE-743; YERVOY 3 mg/kg administered with nivolumab 1 mg/kg in 456 patients enrolled in CHECKMATE-067, CHECKMATE-040, and another randomized trial; and to YERVOY 1 mg/kg, administered in combination with nivolumab and platinum-doublet chemotherapy in CHECKMATE-9LA.

Unresectable or Metastatic Melanoma

The safety of YERVOY was evaluated in 643 previously treated patients with unresectable or metastatic melanoma in Study MDX010-20 *[see Clinical Studies (14.1)]*. Study MDX010-20 excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. Patients received YERVOY 3 mg/kg by intravenous infusion for 4 doses as a single agent (n=131), YERVOY with an investigational gp100 peptide vaccine (n=380), or gp100 peptide vaccine as a single agent (n=132). Patients in the trial received a median of 4 doses (range: 1 to 4 doses).

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 4 presents adverse reactions from Study MDX010-20.

Table 4: Selected Adverse Reactions (≥5%) in Patients Receiving YERVOY with a Difference Between Arms of >5% for All Grades and >1% for Grades 3 to 5 Compared to gp100 Peptide Vaccine in Study MDX010-20

Adverse Reactions	YERVOY 3 mg/kg n=131		YERVOY 3 mg/kg and gp100 n=380		gp100 n=132	
	All Grades (%)	Grade 3 to 5 (%)	All Grades (%)	Grade 3 to 5 (%)	All Grades (%)	Grade 3 to 5 (%)
General and Administration-Site Conditions						
Fatigue	41	7	34	5	31	3
Gastrointestinal						
Diarrhea	32	5	37	4	20	1
Colitis	8	5	5	3	2	0
Dermatologic						
Pruritus	31	0	21	<1	11	0
Rash	29	2	25	2	8	0

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 18 of 81

Unresectable or Metastatic Melanoma: In Combination with Nivolumab

The safety of YERVOY, administered with nivolumab or as a single agent, was evaluated in CHECKMATE-067, a randomized (1:1:1), double-blind trial in 937 patients with previously untreated, unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*. The trial excluded patients with autoimmune disease, a medical condition requiring systemic treatment with corticosteroids (more than 10 mg daily prednisone equivalent) or other immunosuppressive medication within 14 days of the start of study therapy, a positive test result for hepatitis B or C, or a history of HIV.

Patients were randomized to receive:

- YERVOY 3 mg/kg by intravenous infusion over 90 minutes with nivolumab 1 mg/kg by intravenous infusion every 3 weeks for 4 doses followed by nivolumab as a single agent at a dose of 3 mg/kg by intravenous infusion every 2 weeks (YERVOY and nivolumab arm; n=313), or
- Nivolumab 3 mg/kg by intravenous infusion every 2 weeks (nivolumab arm; n=313), or
- YERVOY 3 mg/kg by intravenous infusion over 90 minutes every 3 weeks for up to 4 doses (YERVOY arm; n=311).

The median duration of exposure to nivolumab was 2.8 months (range: 1 day to 36.4 months) for the YERVOY and nivolumab arm. In the YERVOY and nivolumab arm, 39% were exposed to nivolumab for ≥6 months and 30% exposed for >1 year.

Serious adverse reactions (74%), adverse reactions leading to permanent discontinuation (47%) or to dosing delays (58%), and Grade 3 or 4 adverse reactions (72%) occurred in patients treated with YERVOY and nivolumab.

The most frequent (≥10%) serious adverse reactions in the YERVOY and nivolumab arm were diarrhea (13%), colitis (10%), and pyrexia (10%). The most frequent adverse reactions leading to discontinuation of both drugs in the YERVOY and nivolumab arm were colitis (10%), diarrhea (8%), increased ALT (4.8%), increased AST (4.5%), and pneumonitis (1.9%).

The most common (≥20%) adverse reactions in the YERVOY and nivolumab arm were fatigue, diarrhea, rash, nausea, pyrexia, pruritus, musculoskeletal pain, vomiting, decreased appetite, cough, headache, dyspnea, upper respiratory tract infection, arthralgia, and increased transaminases.

Tables 5 and 6 summarize the incidence of adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-067.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 19 of 81

Table 5: Adverse Reactions Occurring in ≥10% of Patients on the YERVOY and Nivolumab Arm or the Nivolumab Arm and at a Higher Incidence than in the YERVOY Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-067

Adverse Reaction	YERVOY and Nivolumab (n=313)		Nivolumab (n=313)		YERVOY (n=311)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General						
Fatigue[a]	62	7	59	1.6	51	4.2
Pyrexia	40	1.6	16	0	18	0.6
Gastrointestinal						
Diarrhea	54	11	36	5	47	7
Nausea	44	3.8	30	0.6	31	1.9
Vomiting	31	3.8	20	1.0	17	1.6
Skin and Subcutaneous Tissue						
Rash[b]	53	6	40	1.9	42	3.5
Vitiligo	9	0	10	0.3	5	0
Musculoskeletal and Connective Tissue						
Musculoskeletal pain[c]	32	2.6	42	3.8	36	1.9
Arthralgia	21	0.3	21	1.0	16	0.3
Metabolism and Nutrition						
Decreased appetite	29	1.9	22	0	24	1.3
Respiratory, Thoracic and Mediastinal						
Cough/productive cough	27	0.3	28	0.6	22	0
Dyspnea/exertional dyspnea	24	2.9	18	1.3	17	0.6
Infections						
Upper respiratory tract infection[d]	23	0	22	0.3	17	0
Endocrine						
Hypothyroidism	19	0.6	11	0	5	0
Hyperthyroidism	11	1.3	6	0	1	0
Investigations						
Decreased weight	12	0	7	0	7	0.3
Vascular						
Hypertension[e]	7	2.2	11	5	9	2.3

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia and fatigue.

[b] Includes pustular rash, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, exfoliative dermatitis, psoriasiform dermatitis, drug eruption, exfoliative rash, erythematous rash, generalized rash, macular rash, maculopapular rash, morbilliform rash, papular rash, papulosquamous rash, and pruritic rash.

[c] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.

[d] Includes upper respiratory tract infection, nasopharyngitis, pharyngitis, and rhinitis.

[e] Includes hypertension and blood pressure increased.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 20 of 81

Clinically important adverse reactions in <10% of patients who received YERVOY with nivolumab:

Gastrointestinal Disorders: stomatitis, intestinal perforation

Skin and Subcutaneous Tissue Disorders: vitiligo

Musculoskeletal and Connective Tissue Disorders: myopathy, Sjogren's syndrome, spondyloarthropathy, myositis (including polymyositis)

Nervous System Disorders: neuritis, peroneal nerve palsy

Table 6: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥20% of Patients Treated with YERVOY with Nivolumab or Single-Agent Nivolumab and at a Higher Incidence than in the YERVOY Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-067

Laboratory Abnormality	YERVOY and Nivolumab		Nivolumab		YERVOY	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Chemistry						
Increased ALT	55	16	25	3.0	29	2.7
Hyperglycemia	53	5	46	7	26	0
Increased AST	52	13	29	3.7	29	1.7
Hyponatremia	45	10	22	3.3	26	7
Increased lipase	43	22	32	12	24	7
Increased alkaline phosphatase	41	6	27	2.0	23	2.0
Hypocalcemia	31	1.1	15	0.7	20	0.7
Increased amylase	27	10	19	2.7	15	1.6
Increased creatinine	26	2.7	19	0.7	17	1.3
Hematology						
Anemia	52	2.7	41	2.6	41	6
Lymphopenia	39	5	41	4.9	29	4.0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: YERVOY and nivolumab (range: 75 to 297); nivolumab (range: 81 to 306); YERVOY (range: 61 to 301)

Adjuvant Treatment of Melanoma

The safety of YERVOY was evaluated in Study E1609, an open-label, multicenter, randomized trial for the adjuvant treatment of patients with completely resected node positive cutaneous melanoma *[see Clinical Studies (14.2)]*. Patients received YERVOY 3 mg/kg intravenously every 3 weeks for 4 doses followed by 3 mg/kg every 12 weeks for up to 4 additional doses, or high-dose interferon-α2b (HDI). Among patients who received YERVOY, 55% were exposed for 6 months or longer and 42% were exposed for greater than 1 year.

Fatal adverse reactions occurred in 1.4% of patients who received YERVOY, including gastric perforation (0.2%), and cardiac arrest (0.2%). Permanent discontinuation of YERVOY due to an adverse reaction occurred in 35% of patients.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 21 of 81

The most common adverse reactions (≥20%) in the YERVOY arm were fatigue, diarrhea, rash, pruritus, nausea, and headache. Table 7 summarizes adverse reactions in E1609.

Table 7: Adverse Reactions (>10%) in Patients Receiving YERVOY 3 mg/kg in E1609

Adverse Reaction	YERVOY 3 mg/kg n=516		HDI n=520	
	All Grades (%)	Grade 3 to 4 (%)	All Grades (%)	Grade 3 to 4 (%)
General disorders and administration site conditions				
Fatigue	56	3	87	22
Decreased appetite	14	0.6	53	2.1
Pyrexia	10	0	31	0.8
Gastrointestinal				
Diarrhea	49	10	34	0.8
Nausea	29	1.2	66	4.2
Abdominal Pain	19	1	9	0.4
Vomiting	11	0.6	26	2.3
Colitis	10	8	1	0.4
Dermatologic				
Rash	46	4	18	1
Pruritus	41	2	15	0
Nervous System Disorders				
Headache	25	2	45	3
Endocrine				
Endocrine disorders, other	19	4.1	2	0
Hypothyroidism	11	0.6	10	0.2
Adrenal insufficiency	10	2	0.6	0

Other Clinical Experience

Across clinical studies in which patients received YERVOY as a single agent at doses ranging from 0.3 to 10 mg/kg, the following adverse reactions were also reported (incidence <1% unless otherwise noted): urticaria (2%), large intestinal ulcer, esophagitis, acute respiratory distress syndrome, renal failure, and infusion reaction.

Advanced Renal Cell Carcinoma: In Combination with Nivolumab

The safety of YERVOY in combination with nivolumab was evaluated in 1082 patients with previously untreated advanced RCC in CHECKMATE-214 *[see Clinical Studies (14.3)]*. Patients received YERVOY 1 mg/kg with nivolumab 3 mg/kg intravenously every 3 weeks for 4 doses followed by nivolumab as a single agent at a dose of 3 mg/kg every 2 weeks (n=547) or sunitinib 50 mg orally daily for first 4 weeks of each 6-week cycle (n=535). The median duration of treatment was 7.9 months (range: 1 day to 21.4+ months) in YERVOY and nivolumab arm. In this trial, 57% of patients in the YERVOY and nivolumab arm were exposed to treatment for greater than 6 months and 38% of patients were exposed to treatment for greater than 1 year.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 22 of 81

Serious adverse reactions occurred in 59% of patients receiving YERVOY with nivolumab. The most frequent serious adverse reactions reported in ≥2% of patients treated with YERVOY and nivolumab were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis.

In patients who received YERVOY with nivolumab, study therapy was discontinued for adverse reactions in 31% and delayed for adverse reactions in 54%.

The most common adverse reactions (≥20%) in the YERVOY and nivolumab arm were fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, vomiting, dyspnea, and decreased appetite. Table 8 summarizes adverse reactions in CHECKMATE-214.

Table 8: Adverse Reactions (>15%) in Patients Receiving YERVOY and Nivolumab in CHECKMATE-214

Adverse Reaction	YERVOY 1 mg/kg and Nivolumab n=547		Sunitinib n=535	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
General and Administration Site Conditions				
Fatigue[a]	58	8	69	13
Pyrexia	25	0.7	17	0.6
Edema[b]	16	0.5	17	0.6
Skin and Subcutaneous Tissue				
Rash[c]	39	3.7	25	1.1
Pruritus/generalized pruritus	33	0.5	11	0
Gastrointestinal				
Diarrhea	38	4.6	58	6
Nausea	30	2.0	43	1.5
Vomiting	20	0.9	28	2.1
Abdominal pain	19	1.6	24	1.9
Constipation	17	0.4	18	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	37	4.0	40	2.6
Arthralgia	23	1.3	16	0
Respiratory, Thoracic, and Mediastinal				
Cough/productive cough	28	0.2	25	0.4
Dyspnea/exertional dyspnea	20	2.4	21	2.1
Metabolism and Nutrition				
Decreased appetite	21	1.8	29	0.9
Nervous System				
Headache	19	0.9	23	0.9
Endocrine				
Hypothyroidism	18	0.4	27	0.2

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

[b] Includes peripheral edema, peripheral swelling.

[c] 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.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 23 of 81

[d] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.

Table 9 summarizes the laboratory abnormalities in CHECKMATE-214.

Table 9: Laboratory Abnormalities (>15%) Worsening from Baseline in Patients Receiving YERVOY and Nivolumab in CHECKMATE-214

Laboratory Abnormality	YERVOY 1 mg/kg and Nivolumab[a]		Sunitinib[a]	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Increased lipase	48	20	51	20
Increased creatinine	42	2.1	46	1.7
Increased ALT	41	7	44	2.7
Increased AST	40	4.8	60	2.1
Increased amylase	39	12	33	7
Hyponatremia	39	10	36	7
Increased alkaline phosphatase	29	2.0	32	1.0
Hyperkalemia	29	2.4	28	2.9
Hypocalcemia	21	0.4	35	0.6
Hypomagnesemia	16	0.4	26	1.6
Hematology				
Anemia	43	3.0	64	9
Lymphopenia	36	5	63	14

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

In addition, among patients with TSH ≤ ULN at baseline, a lower proportion of patients experienced a treatment-emergent elevation of TSH > ULN in the YERVOY with nivolumab group compared to the sunitinib group (31% and 61%, respectively).

MSI-H or dMMR Metastatic Colorectal Cancer

Treatment of MSI -H or dMMR mCRC: In Combination with Nivolumab

The safety of YERVOY in combination with nivolumab was evaluated in CHECKMATE-8HW, a randomized, open-label, three arm trial in immunotherapy naïve patients with MSI-H or dMMR mCRC *[see Clinical Studies (14.4)]*. Patients received one of the following:

- YERVOY 1 mg/kg every 3 weeks and nivolumab 240 mg every 3 weeks for a maximum of 4 doses, then nivolumab 480 mg every 4 weeks.
- Nivolumab 240 mg every 2 weeks for 6 doses, then nivolumab 480 mg every 4 weeks.
- Investigator's choice chemotherapy: mFOLFOX or FOLFIRI *[see Clinical Studies (14.4)]*.

In the YERVOY and nivolumab arm, the median duration of exposure to YERVOY was 2.1 months (range 1 day to 3.7 months); patients received a median of 4 doses (range 1-4). The median duration of treatment in the YERVOY and nivolumab arm was 20.5 months (range: 1 day to 35.9 months); 70% were exposed to treatment for >6 months, and 63% were exposed for >1 year. The

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 24 of 81

median duration of treatment was 16.4 months (range: 1 day to 36 months) in the nivolumab-only arm; 64% were exposed to treatment for >6 months, and 54% were exposed for >1 year.

Serious adverse reactions occurred in 46% of patients receiving YERVOY in combination with nivolumab, and 39% of patients receiving nivolumab alone. The most frequent serious adverse reactions reported in ≥1% of patients who received YERVOY with nivolumab were adrenal insufficiency (2.8%), hypophysitis (2.8%), diarrhea (2.0%), abdominal pain (2.0%), small intestinal obstruction (2.0%), pneumonia (1.7%), acute kidney injury (1.4%), immune-mediated enterocolitis (1.4%), pneumonitis (1.4%), colitis (1.1%), large intestinal obstruction (1.1%), and urinary tract infection (1.1%). The most frequent serious adverse reactions reported in >1% of patients who received OPDIVO, as a single agent, were intestinal obstruction (2.3%), acute kidney injury (1.7%), COVID-19 (1.7%), abdominal pain (1.4%), diarrhea (1.4%), ileus (1.4%), subileus (1.4%), pulmonary embolism (1.4%), adrenal insufficiency (1.1%) and pneumonia (1.1%).

Fatal adverse reactions occurred in 2 (0.6%) patients who received YERVOY in combination with nivolumab; these included myocarditis, and pneumonitis (1 each).

YERVOY and/or nivolumab were permanently discontinued in 19% of patients receiving the combination. The most frequent adverse reactions (>1%) leading to permanent discontinuation were adrenal insufficiency (1.4%), immune-mediated enterocolitis (1.1%), and pneumonitis (1.1%). Nivolumab was permanently discontinued in 13% of patients receiving single agent nivolumab. Adverse reactions leading to the delay of YERVOY and/or nivolumab occurred in 48% of patients receiving the combination; single agent nivolumab was delayed in 37% of patients due to adverse reactions.

The most common adverse reactions reported in ≥20% of patients treated with YERVOY in combination with nivolumab were fatigue, diarrhea, pruritus, abdominal pain, musculoskeletal pain, and nausea. The most common adverse reactions reported in ≥20% of patients treated with nivolumab as a single agent, were fatigue, diarrhea, abdominal pain, pruritus, and musculoskeletal pain.

Tables 10 and 11 summarize the adverse reactions and selected laboratory abnormalities, for YERVOY in combination with nivolumab and nivolumab arms respectively, in CHECKMATE-8HW.

Table 10: Adverse Reactions in ≥10% in Patient and a Difference Between Arms of >5% for All Grades in - CHECKMATE-8HW

Adverse Reaction	YERVOY and Nivolumab (n=352)		Nivolumab (n=351)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Gastrointestinal				
Diarrhea[a]	35	4.5	30	3.4
Skin and Subcutaneous Tissue				
Pruritus	30	0	23	0
Musculoskeletal and Connective Tissue				

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 25 of 81

Table 10: Adverse Reactions in ≥10% in Patient and a Difference Between Arms of >5% for All Grades in - CHECKMATE-8HW

Adverse Reaction	YERVOY and Nivolumab (n=352)		Nivolumab (n=351)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Arthralgia	20	0.6	15	0.6
Endocrine				
Hypothyroidism	18	0.6	10	0
Hyperthyroidism	12	0	5	0

Toxicity was graded per NCI CTCAE v5.

[a] Includes colitis, diarrhea, enterocolitis, immune-mediated enterocolitis

Table 11: Laboratory Values Worsening from Baseline[a] in ≥10% of Patients and a Difference Between Arms of >5% for All Grades - CHECKMATE-8HW

Laboratory Abnormality[a]	YERVOY and Nivolumab (n=352)		Nivolumab (n=351)	
	All Grades (%)	Grades 3-or 4 (%)	All Grades (%)	Grades 3 or -4 (%)
Hematology				
Lymphocytes decreased	30	5	37	4
Neutrophils decreased	21	1.7	12	0.6
Chemistry				
Lipase increased	44	10	32	11
Amylase increased	41	4.6	33	5
ALT increased	39	3.5	32	1.4
AST increased	38	3.2	29	1.4
Sodium decreased	36	3.2	30	2.3
Creatinine increased	32	2	25	1.4
Potassium increased	29	1.2	35	0.9
Glucose decreased	17	0	12	0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: YERVOY and nivolumab group (range: 108 to 343 patients) or nivolumab group (range: 102 to 348 patients).

Hepatocellular Carcinoma: In Combination with Nivolumab

Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

The safety of YERVOY in combination with nivolumab was evaluated in CHECKMATE-9DW, a randomized, open-label trial in adult patients with unresectable or metastatic HCC *[see Clinical Studies (14.5)]*. Patients received YERVOY in combination with nivolumab (n=332) or investigator's choice of lenvatinib (n=275) or sorafenib (n=50) at the following dosage:

- YERVOY 3 mg/kg administered intravenously over 30 minutes in combination with nivolumab 1 mg/kg administered intravenously over 30 minutes every 3 weeks, for a maximum of 4 doses, followed by single agent nivolumab at 480 mg administered intravenously over 30 minutes every 4 weeks, or

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 26 of 81

- Investigator's choice:
  - Lenvatinib 8 mg orally daily (if body weight <60 kg) or 12 mg orally daily (if body weight ≥60 kg), or
  - Sorafenib 400 mg orally twice daily

In the YERVOY and nivolumab arm, the median duration of exposure to nivolumab was 4.7 months (range: <0.1 to 24.4 months), 45% were exposed for >6 months and 30% were exposed for >1 year.

Serious adverse reactions occurred in 53% of patients treated with YERVOY in combination with nivolumab. The most frequent non-liver-related serious adverse reactions reported in ≥2% were diarrhea/colitis (4.5%), gastrointestinal hemorrhage (3%), and rash (2.4%).

Liver-related serious adverse reactions occurred in 17% of patients treated with YERVOY in combination with nivolumab, including Grade 3-4 events in 16% of patients. The most frequently reported all grade liver-related serious adverse reactions occurring in ≥1% of patients were immune-mediated hepatitis (3%), increased AST/ALT (3%), hepatic failure (2.4%), ascites (2.4%), and hepatotoxicity (1.2%).

Fatal adverse reactions occurred in 12 (3.6%) patients who received YERVOY in combination with nivolumab; these included 4 (1.2%) patients who died due to immune-mediated or autoimmune hepatitis and 4 (1.2%) patients who died of hepatic failure.

Permanent discontinuation due to an adverse reaction occurred in 27% of patients treated with YERVOY in combination with nivolumab. Adverse reactions leading to permanent discontinuation in >1% of patients included immune-mediated hepatitis (1.8%), diarrhea/colitis (1.8%), and hepatic failure (1.2%).

Dosage interruptions due to an adverse reaction occurred in 62% of patients treated with YERVOY in combination with nivolumab. Adverse reactions which required dosage interruption in >5% of patients included increased AST (13%), increased ALT (11%), and diarrhea/colitis (8%).

The most common (>20%) adverse reactions were rash, pruritus, fatigue, and diarrhea.

Tables 12 and 13 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9DW.

Table 12: Adverse Reactions Occurring in ≥10% of YERVOY in combination with Nivolumab-Treated Patients - CHECKMATE-9DW

Adverse Reaction	YERVOY and Nivolumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash[a]	36	3.6	15	1.2
Pruritus	34	1.5	7	0.3
General				
Fatigue[a]	33	2.4	39	4
Pyrexia[a]	15	0.6	9	1.5
Edema[a]	13	1.2	13	1.5

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 27 of 81

Table 12: Adverse Reactions Occurring in ≥10% of YERVOY in combination with Nivolumab-Treated Patients - CHECKMATE-9DW

Adverse Reaction	YERVOY and Nivolumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Diarrhea	25	6	39	3.4
Abdominal pain[a]	14	1.2	27	2.5
Nausea	10	0.3	16	0.9
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[a]	17	0.6	23	0.3
Arthralgia	12	0.3	13	0.6
Metabolism and Nutrition				
Decreased appetite	16	1.2	28	1.8
Endocrine				
Hypothyroidism[a]	14	0	27	0
Hyperthyroidism	11	0.6	1.5	0
Respiratory, Thoracic and Mediastinal				
Cough[a]	13	0	8	0

Toxicity was graded per NCI CTCAE v5

[a] Represents a composite of multiple related terms.

Clinically important adverse reactions reported in <10% of patients who received YERVOY with nivolumab were hyperglycemia (8%), adrenal insufficiency (4.2%), pneumonitis (2.7%), and pancreatitis (2.4%).

Table 13: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of YERVOY in combination with Nivolumab-Treated Patients - CHECKMATE-9DW

Laboratory Abnormality	YERVOY and Nivolumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Increased AST	62	29	51	14
Increased ALT	61	17	46	9
Increased lipase	58	16	39	5
Decreased albumin	48	0.9	57	0.6
Hyponatremia	45	6	42	3.8
Hyperglycemia	44	15	32	2.1
Increased bilirubin	44	10	44	8
Increased amylase	41	6	26	1
Increased alkaline phosphatase	36	1.2	38	5
Hypocalcemia	29	0.9	46	0
Increased creatinine	26	2.4	23	0.6
Hypokalemia	21	2.1	20	2.6
Hematology				
Anemia	44	5	40	3.8
Lymphopenia	40	6.1	40	8

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 28 of 81

Table 13: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of YERVOY in combination with Nivolumab-Treated Patients - CHECKMATE-9DW

Laboratory Abnormality	YERVOY and Nivolumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Thrombocytopenia	27	4	44	4.8
Neutropenia	24	4	32	3.5

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: YERVOY and nivolumab group (range: 168 to 331 patients) and lenvatinib or sorafenib group (range: 145 to 315 patients).

Previously Treated Hepatocellular Carcinoma

The safety of YERVOY 3 mg/kg in combination with nivolumab 1 mg/kg was evaluated in a subgroup of 49 patients with HCC and Child-Pugh Class A cirrhosis who progressed on or were intolerant to sorafenib enrolled in Cohort 4 of CHECKMATE-040. YERVOY and nivolumab were administered every 3 weeks for four doses, followed by single-agent nivolumab 240 mg every 2 weeks until disease progression or unacceptable toxicity.

During the YERVOY and nivolumab combination period, 33 of 49 (67%) patients received all four planned doses of YERVOY and nivolumab. During the entire treatment period, the median duration of exposure to YERVOY was 2.1 months (range: 0 to 4.5 months) and to nivolumab was 5.1 months (range: 0 to 35+ months). Forty-seven percent of patients were exposed to treatment for >6 months, and 35% of patients were exposed to treatment for >1 year. Serious adverse reactions occurred in 59% of patients. Treatment was discontinued in 29% of patients and delayed in 65% of patients for an adverse reaction.

Serious adverse reactions reported in ≥4% of patients were pyrexia, diarrhea, anemia, increased AST, adrenal insufficiency, ascites, esophageal varices hemorrhage, hyponatremia, increased blood bilirubin, and pneumonitis.

Table 14 summarizes the adverse reactions and Table 15 summarizes the laboratory abnormalities of YERVOY in combination with nivolumab in CHECKMATE-040.

Table 14: Adverse Reactions Occurring in ≥10% of Patients Receiving YERVOY in Combination with Nivolumab in Cohort 4 of CHECKMATE-040

Adverse Reaction	YERVOY and Nivolumab (n=49)	
	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue		
Rash	53	8
Pruritus	53	4
Musculoskeletal and Connective Tissue		
Musculoskeletal pain	41	2
Arthralgia	10	0
Gastrointestinal		

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 29 of 81

Table 14: Adverse Reactions Occurring in ≥10% of Patients Receiving YERVOY in Combination with Nivolumab in Cohort 4 of CHECKMATE-040

Adverse Reaction	YERVOY and Nivolumab (n=49)	
	All Grades (%)	Grades 3-4 (%)
Diarrhea	39	4
Abdominal pain	22	6
Nausea	20	0
Ascites	14	6
Constipation	14	0
Dry mouth	12	0
Dyspepsia	12	2
Vomiting	12	2
Stomatitis	10	0
Respiratory, Thoracic and Mediastinal		
Cough	37	0
Dyspnea	14	0
Pneumonitis	10	2
Metabolism and Nutrition		
Decreased appetite	35	2
General		
Fatigue	27	2
Pyrexia	27	0
Malaise	18	2
Edema	16	2
Influenza-like illness	14	0
Chills	10	0
Nervous System		
Headache	22	0
Dizziness	20	0
Endocrine		
Hypothyroidism	20	0
Adrenal insufficiency	18	4
Investigations		
Weight decreased	20	0
Psychiatric		
Insomnia	18	0
Blood and Lymphatic System		
Anemia	10	4
Infections		
Influenza	10	2
Vascular		
Hypotension	10	0

Clinically important adverse reactions reported in <10% of patients receiving YERVOY with nivolumab were hyperglycemia (8%), colitis (4%), and increased blood creatine phosphokinase (2%).

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 30 of 81

Table 15: Select Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients Receiving YERVOY in Combination with Nivolumab in Cohort 4 of CHECKMATE-040

Laboratory Abnormality	YERVOY and Nivolumab (n=47)	
	All Grades (%)	Grades 3-4 (%)
Hematology		
Lymphopenia	53	13
Anemia	43	4.3
Neutropenia	43	9
Leukopenia	40	2.1
Thrombocytopenia	34	4.3
Chemistry		
Increased AST	66	40
Increased ALT	66	21
Increased bilirubin	55	11
Increased lipase	51	26
Hyponatremia	49	32
Hypocalcemia	47	0
Increased alkaline phosphatase	40	4.3
Increased amylase	38	15
Hypokalemia	26	2.1
Hyperkalemia	23	4.3
Increased creatinine	21	0
Hypomagnesemia	11	0

In patients who received YERVOY with nivolumab, virologic breakthrough occurred in 4 of 28 (14%) patients and 2 of 4 (50%) patients with active HBV or HCV at baseline, respectively. HBV virologic breakthrough was defined as at least a 1 log increase in HBV DNA for those patients with detectable HBV DNA at baseline. HCV virologic breakthrough was defined as a 1 log increase in HCV RNA from baseline.

First-line Treatment of Metastatic NSCLC: In Combination with Nivolumab

The safety of YERVOY in combination with nivolumab was evaluated in CHECKMATE-227, a randomized, multicenter, multi-cohort, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations *[see Clinical Studies (14.6)]*. The trial excluded patients with untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients received YERVOY 1 mg/kg by intravenous infusion over 30 minutes every 6 weeks and nivolumab 3 mg/kg by intravenous infusion over 30 minutes every 2 weeks or platinum-doublet chemotherapy every 3 weeks for 4 cycles. The median duration of therapy in YERVOY and nivolumab-treated patients was 4.2 months (range: 1 day to 25.5 months): 39% of patients received YERVOY and nivolumab for >6 months and 23% of patients received YERVOY and nivolumab for >1 year. The population characteristics were: median age 64 years (range: 26 to 87); 48% were ≥65 years of age, 76% White, and 67% male. Baseline ECOG performance status was 0 (35%) or 1 (65%), 85% were former/current smokers, 11% had brain metastases, 28% had squamous histology and 72% had non-squamous histology.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 31 of 81

Serious adverse reactions occurred in 58% of patients. YERVOY and nivolumab were discontinued for adverse reactions in 24% of patients and 53% had at least one dose withheld for an adverse reaction.

The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure. The most common (≥20%) adverse reactions were fatigue, rash, decreased appetite, musculoskeletal pain, diarrhea/colitis, dyspnea, cough, hepatitis, nausea, and pruritus.

Tables 16 and 17 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-227.

Table 16: Adverse Reactions in ≥10% of Patients Receiving YERVOY and Nivolumab - CHECKMATE-227

Adverse Reaction	YERVOY and Nivolumab (n=576)		Platinum-Doublet Chemotherapy (n=570)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	44	6	42	4.4
Pyrexia	18	0.5	11	0.4
Edema[b]	14	0.2	12	0.5
Skin and Subcutaneous Tissue				
Rash[c]	34	4.7	10	0.4
Pruritus[d]	21	0.5	3.3	0
Metabolism and Nutrition				
Decreased appetite	31	2.3	26	1.4
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[e]	27	1.9	16	0.7
Arthralgia	13	0.9	2.5	0.2
Gastrointestinal				
Diarrhea/colitis[f]	26	3.6	16	0.9
Nausea	21	1.0	42	2.5
Constipation	18	0.3	27	0.5
Vomiting	13	1.0	18	2.3
Abdominal pain[g]	10	0.2	9	0.7
Respiratory, Thoracic, and Mediastinal				
Dyspnea[h]	26	4.3	16	2.1
Cough[i]	23	0.2	13	0
Hepatobiliary				
Hepatitis[j]	21	9	10	1.2
Endocrine				
Hypothyroidism[k]	16	0.5	1.2	0
Hyperthyroidism[l]	10	0	0.5	0
Infections and Infestations				
Pneumonia[m]	13	7	8	4.0

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 32 of 81

Table 16: Adverse Reactions in ≥10% of Patients Receiving YERVOY and Nivolumab - CHECKMATE-227

Adverse Reaction	YERVOY and Nivolumab (n=576)		Platinum-Doublet Chemotherapy (n=570)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Nervous System				
Headache	11	0.5	6	0

[a] Includes fatigue and asthenia.

[b] Includes eyelid edema, face edema, generalized edema, localized edema, edema, edema peripheral, and periorbital edema.

[c] Includes autoimmune dermatitis, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, dermatitis psoriasiform, granulomatous dermatitis, rash generalized, drug eruption, dyshidrotic eczema, eczema, exfoliative rash, nodular rash, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic skin eruption.

[d] Includes pruritus and pruritus generalized.

[e] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, and pain in extremity.

[f] Includes colitis, colitis microscopic, colitis ulcerative, diarrhea, enteritis infectious, enterocolitis, enterocolitis infectious, and enterocolitis viral.

[g] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness.

[h] Includes dyspnea and dyspnea exertional.

[i] Includes cough and productive cough.

[j] Includes alanine aminotransferase increased, aspartate aminotransferase increased, autoimmune hepatitis, blood bilirubin increased, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatitis, hepatitis E, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test abnormal, liver function test increased, transaminases increased.

[k] Includes autoimmune thyroiditis, blood thyroid stimulating hormone increased, hypothyroidism, primary hypothyroidism, thyroiditis, and tri-iodothyronine free decreased.

[l] Contains blood thyroid stimulating hormone decreased, hyperthyroidism, and tri-iodothyronine free increased.

[m] Includes lower respiratory tract infection, lower respiratory tract infection bacterial, lung infection, pneumonia, pneumonia adenoviral, pneumonia aspiration, pneumonia bacterial, pneumonia klebsiella, pneumonia influenzal, pneumonia viral, atypical pneumonia, organizing pneumonia.

Other clinically important adverse reactions in CHECKMATE-227 were:

Skin and Subcutaneous Tissue: urticaria, alopecia, erythema multiforme, vitiligo

Gastrointestinal: stomatitis, pancreatitis, gastritis

Musculoskeletal and Connective Tissue: arthritis, polymyalgia rheumatica, rhabdomyolysis

Nervous System: peripheral neuropathy, autoimmune encephalitis

Blood and Lymphatic System: eosinophilia

Eye Disorders: blurred vision, uveitis

Cardiac: atrial fibrillation, myocarditis

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 33 of 81

Table 17: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on YERVOY and Nivolumab - CHECKMATE-227

Laboratory Abnormality	YERVOY and Nivolumab		Platinum-doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	46	3.6	78	14
Lymphopenia	46	5	60	15
Chemistry				
Hyponatremia	41	12	26	4.9
Increased AST	39	5	26	0.4
Increased ALT	36	7	27	0.7
Increased lipase	35	14	14	3.4
Increased alkaline phosphatase	34	3.8	20	0.2
Increased amylase	28	9	18	1.9
Hypocalcemia	28	1.7	17	1.3
Hyperkalemia	27	3.4	22	0.4
Increased creatinine	22	0.9	17	0.2

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: YERVOY and nivolumab group (range: 494 to 556 patients) and chemotherapy group (range: 469 to 542 patients).

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Nivolumab and Platinum-Doublet Chemotherapy

The safety of YERVOY in combination with nivolumab and platinum-doublet chemotherapy was evaluated in CHECKMATE-9LA *[see Clinical Studies (14.6)]*. Patients received either YERVOY 1 mg/kg administered every 6 weeks in combination with nivolumab 360 mg administered every 3 weeks and platinum-doublet chemotherapy administered every 3 weeks for 2 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 4 cycles. The median duration of therapy in YERVOY in combination with nivolumab and platinum-doublet chemotherapy was 6 months (range: 1 day to 19 months): 50% of patients received YERVOY and nivolumab for >6 months and 13% of patients received YERVOY and nivolumab for >1 year.

Serious adverse reactions occurred in 57% of patients who were treated with YERVOY in combination with nivolumab and platinum-doublet chemotherapy. The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia.

Study therapy with YERVOY in combination with nivolumab and platinum-doublet chemotherapy was permanently discontinued for adverse reactions in 24% of patients and 56% had at least one treatment withheld for an adverse reaction. The most common (>20%) adverse reactions were fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 34 of 81

Tables 18 and 19 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9LA.

Table 18: Adverse Reactions in >10% of Patients Receiving YERVOY and Nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Adverse Reaction	YERVOY and Nivolumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	49	5	40	4.9
Pyrexia	14	0.6	10	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[b]	39	4.5	27	2.0
Gastrointestinal				
Nausea	32	1.7	41	0.9
Diarrhea[c]	31	6	18	1.7
Constipation	21	0.6	23	0.6
Vomiting	18	2.0	17	1.4
Abdominal pain[d]	12	0.6	11	0.9
Skin and Subcutaneous Tissue				
Rash[e]	30	4.7	10	0.3
Pruritus[f]	21	0.8	2.9	0
Alopecia	11	0.8	10	0.6
Metabolism and Nutrition				
Decreased appetite	28	2.0	22	1.7
Respiratory, Thoracic and Mediastinal				
Cough[g]	19	0.6	15	0.9
Dyspnea[h]	18	4.7	14	3.2
Endocrine				
Hypothyroidism[i]	19	0.3	3.4	0
Nervous System				
Headache	11	0.6	7	0
Dizziness[j]	11	0.6	6	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes fatigue and asthenia.

[b] Includes myalgia, back pain, pain in extremity, musculoskeletal pain, bone pain, flank pain, muscle spasms, musculoskeletal chest pain, musculoskeletal disorder, osteitis, musculoskeletal stiffness, non-cardiac chest pain, arthralgia, arthritis, arthropathy, joint effusion, psoriatic arthropathy, synovitis.

[c] Includes colitis, ulcerative colitis, diarrhea, and enterocolitis.

[d] Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, and gastrointestinal pain.

[e] Includes acne, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, generalized exfoliative dermatitis, eczema, keratoderma blennorrhagica, palmar-plantar erythrodysesthesia syndrome, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, morbilliform rash, papular rash, pruritic rash, skin exfoliation, skin reaction, skin toxicity, Stevens-Johnson syndrome, urticaria.

[f] Includes pruritus and generalized pruritus.

[g] Includes cough, productive cough, and upper-airway cough syndrome.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 35 of 81

[h] Includes dyspnea, dyspnea at rest, and exertional dyspnea.

[i] Includes autoimmune thyroiditis, increased blood thyroid stimulating hormone, hypothyroidism, thyroiditis, and decreased free tri-iodothyronine.

[j] Includes dizziness, vertigo and positional vertigo

Table 19: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on YERVOY and Nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Laboratory Abnormality	YERVOY and Nivolumab and Platinum-Doublet Chemotherapy		Platinum-Doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	70	9	74	16
Lymphopenia	41	6	40	11
Neutropenia	40	15	42	15
Leukopenia	36	10	40	9
Thrombocytopenia	23	4.3	24	5
Chemistry				
Hyperglycemia	45	7	42	2.6
Hyponatremia	37	10	27	7
Increased ALT	34	4.3	24	1.2
Increased lipase	31	12	10	2.2
Increased alkaline phosphatase	31	1.2	26	0.3
Increased amylase	30	7	19	1.3
Increased AST	30	3.5	22	0.3
Hypomagnesemia	29	1.2	33	0.6
Hypocalcemia	26	1.4	22	1.8
Increased creatinine	26	1.2	23	0.6
Hyperkalemia	22	1.7	21	2.1

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: YERVOY and nivolumab and platinum-doublet chemotherapy group (range: 197 to 347 patients) and platinum-doublet chemotherapy group (range: 191 to 335 patients).

First-line Treatment of Unresectable Malignant Pleural Mesothelioma: In Combination with Nivolumab

The safety of YERVOY in combination with nivolumab was evaluated in CHECKMATE-743, a randomized, open-label trial in patients with previously untreated unresectable malignant pleural mesothelioma *[see Clinical Studies (14.7)]*. Patients received either YERVOY 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks and nivolumab 3 mg/kg over 30 minutes by intravenous infusion every 2 weeks for up to 2 years; or platinum-doublet chemotherapy for up to 6 cycles. The median duration of therapy in YERVOY and nivolumab-treated patients was 5.6 months (range: 0 to 26.2 months); 48% of patients received YERVOY and nivolumab for >6 months and 24% of patients received YERVOY and nivolumab for >1 year.

Serious adverse reactions occurred in 54% of patients who were treated with YERVOY in combination with nivolumab. The most frequent (≥2%) serious adverse reactions were pneumonia, pyrexia, diarrhea, pneumonitis, pleural effusion, dyspnea, acute kidney injury, infusion-related reaction, musculoskeletal pain, and pulmonary embolism. Fatal adverse reactions occurred in 4 (1.3%) patients and included pneumonitis, acute heart failure, sepsis, and encephalitis.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 36 of 81

Both YERVOY and nivolumab were permanently discontinued due to adverse reactions in 23% of patients and 52% had at least one dose withheld due to an adverse reaction. An additional 4.7% of patients permanently discontinued YERVOY alone due to adverse reactions.

The most common (≥20%) adverse reactions were fatigue, musculoskeletal pain, rash, diarrhea, dyspnea, nausea, decreased appetite, cough, and pruritus.

Tables 20 and 21 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-743.

Table 20: Adverse Reactions in ≥10% of Patients Receiving YERVOY and Nivolumab - CHECKMATE-743

Adverse Reaction	YERVOY and Nivolumab (n=300)		Chemotherapy (n=284)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	43	4.3	45	6
Pyrexia[b]	18	1.3	4.6	0.7
Edema[c]	17	0	8	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	38	3.3	17	1.1
Arthralgia	13	1.0	1.1	0
Skin and Subcutaneous Tissue				
Rash[e]	34	2.7	11	0.4
Pruritus[f]	21	1.0	1.4	0
Gastrointestinal				
Diarrhea[g]	32	6	12	1.1
Nausea	24	0.7	43	2.5
Constipation	19	0.3	30	0.7
Abdominal pain[h]	15	1	10	0.7
Vomiting	14	0	18	2.1
Respiratory, Thoracic, and Mediastinal				
Dyspnea[i]	27	2.3	16	3.2
Cough[j]	23	0.7	9	0
Metabolism and Nutrition				
Decreased appetite	24	1.0	25	1.4
Endocrine				
Hypothyroidism[k]	15	0	1.4	0
Infections and Infestations				
Upper respiratory tract infection[l]	12	0.3	7	0
Pneumonia[m]	10	4.0	4.2	2.1

[a] Includes fatigue and asthenia.

[b] Includes pyrexia and tumor-associated fever.

[c] Includes edema, generalized edema, peripheral edema, and peripheral swelling.

[d] Includes musculoskeletal pain, back pain, bone pain, flank pain, involuntary muscle contractions, muscle spasms, muscle twitching, musculoskeletal chest pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, polymyalgia rheumatica, and spinal pain.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 37 of 81

[e] Includes rash, acne, acneiform dermatitis, allergic dermatitis, atopic dermatitis, autoimmune dermatitis, bullous dermatitis, contact dermatitis, dermatitis, drug eruption, dyshidrotic eczema, eczema, erythematous rash, exfoliative rash, generalized exfoliative dermatitis, generalized rash, granulomatous dermatitis, keratoderma blennorrhagica, macular rash, maculopapular rash, morbilliform rash, nodular rash, papular rash, psoriasiform dermatitis, pruritic rash, pustular rash, skin exfoliation, skin reaction, skin toxicity, Stevens-Johnson syndrome, toxic skin eruption, and urticaria.

[f] Includes pruritus, allergic pruritus, and generalized pruritus.

[g] Includes diarrhea, colitis, enteritis, infectious enteritis, enterocolitis, infectious enterocolitis, microscopic colitis, ulcerative colitis, and viral enterocolitis.

[h] Includes abdominal pain, abdominal discomfort, abdominal tenderness, gastrointestinal pain, lower abdominal pain, and upper abdominal pain.

[i] Includes dyspnea, dyspnea at rest, and exertional dyspnea.

[j] Includes cough, productive cough, and upper-airway cough syndrome.

[k] Includes hypothyroidism, autoimmune thyroiditis, decreased free tri-iodothyronine, increased blood thyroid stimulating hormone, primary hypothyroidism, thyroiditis, and autoimmune hypothyroidism.

[l] Includes upper respiratory tract infection, nasopharyngitis, pharyngitis, and rhinitis.

[m] Includes pneumonia, lower respiratory tract infection, lung infection, aspiration pneumonia, and Pneumocystis jirovecii pneumonia.

Table 21: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on YERVOY and Nivolumab - CHECKMATE-743

Laboratory Abnormality	YERVOY and Nivolumab		Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Hyperglycemia	53	3.7	34	1.1
Increased AST	38	7	17	0
Increased ALT	37	7	15	0.4
Increased lipase	34	13	9	0.8
Hyponatremia	32	8	21	2.9
Increased alkaline phosphatase	31	3.1	12	0
Hyperkalemia	30	4.1	16	0.7
Hypocalcemia	28	0	16	0
Increased amylase	26	5	13	0.9
Increased creatinine	20	0.3	20	0.4
Hematology				
Lymphopenia	43	8	57	14
Anemia	43	2.4	75	15

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: YERVOY and nivolumab group (range: 109 to 297 patients) and chemotherapy group (range: 90 to 276 patients).

First-line Treatment of Unresectable Advanced or Metastatic ESCC: In Combination with Nivolumab

The safety of YERVOY in combination with nivolumab was evaluated in CHECKMATE-648, a randomized, active-controlled, multicenter, open-label trial in patients with previously untreated

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 38 of 81

unresectable advanced, recurrent or metastatic ESCC *[see Clinical Studies (14.8)]*. Patients received one of the following treatments:

- YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 3 mg/kg every 2 weeks.
- 5-FU (fluorouracil) 800 mg/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 intravenously on day 1 (of a 4-week cycle).

Among patients who received YERVOY and nivolumab, the median duration of exposure was 2.8 months (range: 0 to 24 months).

Serious adverse reactions occurred in 69% of patients receiving YERVOY in combination with nivolumab.

The most frequent serious adverse reactions reported in ≥2% of patients who received YERVOY with nivolumab were pneumonia (10%), pyrexia (4.3%), pneumonitis (4.0%), aspiration pneumonia (3.7%), dysphagia (3.7%), hepatic function abnormal (2.8%), decreased appetite (2.8%), adrenal insufficiency (2.5%), and dehydration (2.5%).

Fatal adverse reactions occurred in 5 (1.6%) patients who received YERVOY in combination with nivolumab; these included pneumonitis, interstitial lung disease, pulmonary embolism, and acute respiratory distress syndrome.

YERVOY and/or nivolumab were discontinued in 23% of patients and delayed in 46% of patients for an adverse reaction.

The most common adverse reactions reported in ≥20% of patients treated with YERVOY in combination with nivolumab were rash, fatigue, pyrexia, nausea, diarrhea, and constipation.

Tables 22 and 23 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-648.

Table 22: Adverse Reactions in ≥10% of Patients Receiving YERVOY and Nivolumab - CHECKMATE-648

Adverse Reaction	YERVOY and Nivolumab (n=322)		Cisplatin and 5-FU (n=304)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash[a]	31	3.1	7	0
Pruritis	17	0.9	3.6	0
General				
Fatigue[c]	28	2.5	41	4.9
Pyrexia[b]	23	0.9	12	0.3
Gastrointestinal				
Nausea	22	0.6	56	2.6
Diarrhea	22	1.9	20	2.0
Constipation	20	0.3	43	1.0
Vomiting	15	1.6	19	3.0
Dysphagia	12	5	12	4.9
Stomatitis[d]	11	0.6	35	3.0

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 39 of 81

Table 22: Adverse Reactions in ≥10% of Patients Receiving YERVOY and Nivolumab - CHECKMATE-648

Adverse Reaction	YERVOY and Nivolumab (n=322)		Cisplatin and 5-FU (n=304)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Abdominal pain[e]	10	0.9	11	0.7
Metabolism and Nutrition				
Decreased appetite	17	4.0	50	6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[f]	14	0.6	8	0.3
Infections and Infestations				
Pneumonia[g]	14	8	10	2.6
Endocrine				
Hypothyroidism	14	0	0.3	0
Respiratory, Thoracic and Mediastinal				
Cough[h]	13	0.3	13	0.3
Investigations				
Weight decreased	12	1.9	11	1.0

Toxicity was graded per NCI CTCAE v4.

[a] Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, drug eruption, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, and rash pruritic.

[b] Includes tumor associated fever.

[c] Includes asthenia and malaise.

[d] Includes aphthous ulcer, mouth ulceration, and mucosal inflammation.

[e] Includes abdominal discomfort, abdominal pain lower, and abdominal pain upper.

[f] Includes back pain, bone pain, musculoskeletal chest pain, myalgia, neck pain, pain in extremity, and spinal pain.

[g] Includes organizing pneumonia, pneumonia bacterial, and pneumonia pseudomonal.

[h] Includes productive cough.

Table 23: Laboratory Values Worsening from Baseline[a] Occurring in ≥10% of Patients on YERVOY and Nivolumab - CHECKMATE-648

Laboratory Abnormality	YERVOY and Nivolumab (n=322)		Cisplatin and 5-FU (n=304)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	52	7	66	14
Lymphopenia	50	13	44	8
Neutropenia	13	1.3	48	13
Thrombocytopenia	12	1.0	29	2.8
Chemistry				
Hyponatremia	45	11	40	8
Hyperglycemia	43	4.3	36	0.8
Increased AST	39	6	11	1.4
Increased ALT	33	6	8	0.7
Hypocalcemia	32	0	23	0.7

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 40 of 81

Table 23: Laboratory Values Worsening from Baseline[a] Occurring in ≥10% of Patients on YERVOY and Nivolumab - CHECKMATE-648

Laboratory Abnormality	YERVOY and Nivolumab (n=322)		Cisplatin and 5-FU (n=304)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Increased alkaline phosphatase	31	3.3	15	0
Hyperkalemia	23	1.6	24	0.7
Hypokalemia	19	5	17	6
Hypercalcemia	15	2.0	8	0
Hypoglycemia	15	1.2	7	0
Increased creatinine	15	0.7	31	0.7
Hypomagnesemia	15	0	25	1.8

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: YERVOY and nivolumab group (range: 59 to 307 patients) or Cisplatin and 5-FU group (range: 56 to 283 patients).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval 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.

Blood and lymphatic system disorders: hemophagocytic lymphohistiocytosis (HLH)

Immune System: graft-versus-host disease, solid organ transplant rejection

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, YERVOY can cause fetal harm when administered to a pregnant woman. There is insufficient human data for YERVOY exposure in pregnant women. 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. Advise pregnant women of the potential risk to a fetus. Report pregnancies to Bristol-Myers Squibb at 1-844-593-7869.

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.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 41 of 81

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 humans exposure based on area under the curve at a dose of 3 mg/kg). 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 multiorgan 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

There are no data on the presence of YERVOY in human milk or its effects on the breastfed child or milk production. In monkeys, ipilimumab was present in milk *(see Data)*. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with YERVOY and for 3 months following the last 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

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating YERVOY *[see Use in Specific Populations (8.1)]*.

Contraception

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.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 42 of 81

8.4 Pediatric Use

The safety and effectiveness of YERVOY have been established in pediatric patients aged 12 years and older for the following indications: as a single agent and in combination with nivolumab for unresectable or metastatic melanoma, in combination with nivolumab for the treatment of MSI-H or dMMR unresectable and metastatic CRC, and in combination with nivolumab for MSI-H or dMMR mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of YERVOY for these indications is supported by evidence from adequate and well-controlled studies in adults with melanoma or MSI-H or dMMR mCRC and additional pharmacokinetic data in pediatric patients. Ipilimumab exposures in pediatric patients 12 years and older are comparable to that of adults, and the courses of melanoma and MSI-H or dMMR mCRC are similar in pediatric patients aged 12 years and older to that of adults to allow extrapolation of safety and efficacy *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.4)]*.

The safety and effectiveness of YERVOY have not been established in pediatric patients younger than 12 years old with unresectable or metastatic melanoma or MSI-H or dMMR mCRC.

The safety and effectiveness of YERVOY have not been established in pediatric patients for the adjuvant treatment of melanoma or for the treatment of advanced renal cell carcinoma, hepatocellular carcinoma, metastatic non-small cell lung cancer, malignant pleural mesothelioma and esophageal cancer.

In a dose-finding trial (NCT01445379), 33 patients aged 2 to 21 years (median 13 years) with relapsed or refractory solid tumors were evaluated including unresectable stage IIIc or stage IV melanoma (12), progressive or refractory sarcomas (17), renal or bladder carcinoma (3), and neuroblastoma (1). No responses in the patients with non-melanoma solid tumors and no new safety signals were observed in pediatric patients in this study.

8.5 Geriatric Use

Single Agent

Of the 511 patients treated with YERVOY in Study MDX010-20 (unresectable or metastatic melanoma), 28% were 65 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients.

In Combination with Nivolumab

Of the 314 patients randomized to YERVOY administered with nivolumab in CHECKMATE-067, 41% were 65 years or older and 11% were 75 years or older. No overall differences in safety or effectiveness were reported between elderly patients and younger patients.

Of the 576 patients randomized to YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-227 (NSCLC), 48% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (29%) relative to all patients who received YERVOY with nivolumab (18%). Of the 396 patients in the primary efficacy population (PD-L1 ≥1%) randomized to YERVOY

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 43 of 81

1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-227, the hazard ratio for overall survival was 0.70 (95% CI: 0.55, 0.89) in the 199 patients younger than 65 years compared to 0.91 (95% CI: 0.72, 1.15) in the 197 patients 65 years or older *[see Clinical Studies (14.6)]*.

Of the 303 patients randomized to YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-743 (malignant pleural mesothelioma), 77% were 65 years old or older and 26% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there were higher rates of serious adverse reactions and discontinuation rate due to adverse reactions in patients aged 75 years or older (68% and 35%, respectively) relative to all patients who received YERVOY with nivolumab (54% and 28%, respectively). For patients aged 75 years or older who received chemotherapy, the rate of serious adverse reactions was 34% and discontinuation due to adverse reactions was 26% relative to 28% and 19% respectively for all patients. The hazard ratio for overall survival was 0.76 (95% CI: 0.52, 1.11) in the 71 patients younger than 65 years compared to 0.74 (95% CI: 0.59, 0.93) in the 232 patients 65 years or older randomized to YERVOY in combination with nivolumab.

Of the 550 patients randomized to YERVOY 1 mg/kg with nivolumab in CHECKMATE-214 (renal cell carcinoma), 38% were 65 years or older and 8% were 75 years or older. No overall difference in safety was observed between these patients and younger patients. In geriatric patients with intermediate or poor risk, no overall difference in effectiveness was observed.

Of the 354 patients with dMMR or MSI-H metastatic CRC (mCRC) who were randomized to YERVOY in combination with nivolumab, 44% were 65 years or older and 14% were 75 years or older. Of the 353 patients randomized to nivolumab, as a single agent, 45% were 65 years or older and 13% were 75 years or older. There was a higher incidence of any Grade 3 or 4 adverse reactions (55%) in patients aged 65 years or older receiving YERVOY in combination with nivolumab compared to those younger than 65 receiving the combination (42%). There was a higher incidence of adverse reactions leading to discontinuation in patients aged 65 years or older receiving YERVOY in combination with nivolumab (23%) compared to those younger than 65 receiving the combination (15%). No overall differences in effectiveness were reported between elderly patients and younger patients receiving YERVOY in combination with nivolumab *[see Clinical Studies (14.4)]*.

Of the 335 patients with unresectable hepatocellular carcinoma who were randomized to YERVOY in combination with nivolumab, 52% were 65 years or older and 14% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients.

Of the 49 patients who received YERVOY 3 mg/kg with nivolumab in Cohort 4 of CHECKMATE-040 (previously treated hepatocellular carcinoma), 29% were between 65 years and 74 years of age and 8% were 75 years or older. Clinical studies of YERVOY in combination with nivolumab did not include sufficient numbers of patients with hepatocellular carcinoma aged 65 and over to determine whether they respond differently from younger patients.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 44 of 81

Of the 325 patients who received YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-648 (ESCC), 43% were 65 years old or older and 7% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (38%) relative to all patients who received YERVOY with nivolumab (23%). For patients aged 75 years or older who received chemotherapy, the discontinuation rate due to adverse reactions was 33% relative to 23% for all patients.

Study CA184-029 (adjuvant treatment of melanoma) and CHECKMATE-142 (metastatic colorectal cancer) did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

In Combination with Nivolumab and Platinum-Doublet Chemotherapy

Of the 361 patients randomized to YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 360 mg every 3 weeks and platinum-doublet chemotherapy every 3 weeks (for 2 cycles) in CHECKMATE-9LA (NSCLC), 51% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (43%) relative to all patients who received YERVOY with nivolumab and chemotherapy (24%). For patients aged 75 years or older who received chemotherapy only, the discontinuation rate due to adverse reactions was 16% relative to all patients who had a discontinuation rate of 13%. Based on an updated analysis for overall survival, of the 361 patients randomized to YERVOY in combination with nivolumab and platinum-doublet chemotherapy in CHECKMATE-9LA, the hazard ratio for overall survival was 0.61 (95% CI: 0.47, 0.80) in the 176 patients younger than 65 years compared to 0.73 (95% CI: 0.56, 0.95) in the 185 patients 65 years or older.

11 DESCRIPTION

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

YERVOY (ipilimumab) injection, for intravenous use is a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. It is supplied in single-dose vials of 50 mg/10 mL or 200 mg/40 mL. Each milliliter 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), tris hydrochloride (3.15 mg), and Water for Injection, USP at a pH of 7.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CTLA-4 is a negative regulator of T-cell activity. 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

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 45 of 81

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.

12.3 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 once every 3 weeks for 4 doses. The PK of ipilimumab is linear in the dose range of 0.3 mg/kg to 10 mg/kg. Following 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 minimum concentration (C_{min}) at steady state was 19.4 mcg/mL at 3 mg/kg and 58.1 mcg/mL at 10 mg/kg every 3 weeks.

Elimination

The mean (percent coefficient of variation) terminal half-life ($t_{1/2}$) was 15.4 days (34%) and then mean (percent coefficient of variation) clearance (CL) was 16.8 mL/h (38%).

The CL of ipilimumab was unchanged in presence of anti-ipilimumab antibodies.

Specific Populations

The CL of ipilimumab increased with increasing body weight supporting the 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 (glomerular filtration rate ≥15 mL/min/1.73 m^2), mild hepatic impairment (total bilirubin [TB] >1 to 1.5 times the upper limit of normal [ULN] or AST > ULN), previous cancer therapy, and baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined due to limited data available in non-White racial groups. YERVOY has not been studied in patients with moderate (TB >1.5 to 3 times ULN and any AST) or severe (TB >3 times ULN and any AST) hepatic impairment.

Pediatric Patients

The exposures of ipilimumab in pediatric patients 12 years and older are comparable to those in adult patients at the recommended dosage.

Drug Interaction Studies

Ipilimumab with Nivolumab

When YERVOY 1 mg/kg was administered with nivolumab 3 mg/kg every 3 weeks, the CL of ipilimumab was unchanged compared to when YERVOY was administered alone.

When YERVOY 3 mg/kg every 3 weeks was administered in combination with nivolumab 1 mg/kg every 3 weeks, the CL of ipilimumab was unchanged compared to ipilimumab administered alone and the CL of nivolumab was increased by 29% compared to nivolumab administered alone.

When YERVOY 1 mg/kg every 6 weeks was administered in combination with nivolumab 3 mg/kg every 2 weeks, the CL of ipilimumab increased by 30% compared to YERVOY

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 46 of 81

administered alone and the CL of nivolumab was unchanged compared to nivolumab administered alone.

When YERVOY 1 mg/kg every 6 weeks was administered in combination with nivolumab 360 mg every 3 weeks and chemotherapy, the CL of ipilimumab increased by 22% compared to YERVOY administered alone and the CL of nivolumab was unchanged compared to nivolumab administered alone.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of YERVOY or of other ipilimumab products.

Eleven (1.1%) of 1024 evaluable patients with unresectable or metastatic melanoma tested positive for treatment-emergent binding antibodies against ipilimumab 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 developed anti-ipilimumab antibodies and 7 (4.5%) of 156 patients receiving placebo for the adjuvant treatment of melanoma tested positive for anti-ipilimumab antibodies 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 anti-ipilimumab antibodies.

Of the 499 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-214 and CHECKMATE-142, 27 (5.4%) were positive for anti-ipilimumab antibodies; there were no patients with neutralizing antibodies against ipilimumab. There was no evidence of increased incidence of infusion reactions to YERVOY in patients with anti-ipilimumab antibodies.

Of 483 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-227 Part 1, 8.5% were positive for treatment-emergent anti-ipilimumab antibodies. No patients had neutralizing antibodies against ipilimumab. In Part 1 of the same study, of 491 patients evaluable for anti-nivolumab antibodies, 36.7% were positive for anti-nivolumab antibodies and 1.4% had neutralizing antibodies against nivolumab.

Of 305 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-9LA, 8% were positive for anti-ipilimumab antibodies and 1.6% were positive for anti-ipilimumab neutralizing antibodies. There was no evidence of increased incidence of infusion reactions to YERVOY in patients with anti-ipilimumab antibodies. Of 308 patients evaluable for anti-nivolumab antibodies in CHECKMATE-9LA, 34% were positive for anti-nivolumab antibodies and 2.6% had neutralizing antibodies against nivolumab.

Of 271 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-743, 13.7% were positive for anti-ipilimumab antibodies and 0.4% were positive for anti-ipilimumab neutralizing antibodies. Of 269 patients evaluable for anti-nivolumab antibodies in CHECKMATE-743, 25.7% were positive for anti-nivolumab antibodies and 0.7% had neutralizing antibodies against nivolumab.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 47 of 81

Anti-drug antibody and neutralizing antibody responses were monitored throughout the treatment period where the benefit to risk ratio was assessed. Incidence of anti-drug antibodies and neutralizing antibodies are presented in Table 24.

Table 24: YERVOY Anti-Drug Antibody (ADA) and Neutralizing Antibody (NAb) Incidence

Treatment Regimen[a]	Indication(s)	ADA	NAb[b]
YERVOY as a single agent	Melanoma	1.1% (11/1024)	0 (0/11)
	Adjuvant Melanoma	4.9 (7/144)	0 (0/7)
YERVOY with nivolumab for 4 doses followed by nivolumab as a single agent	Melanoma	8.4% (33/391)	3% (1/33)
	HCC	5.3% (13/244)	0 (0/13)
	RCC and CRC	5.4% (27/499)	0% (0/27)
YERVOY with nivolumab	Malignant Pleural Mesothelioma	13.7% (37/271)	2.7% (1/37)
	NSCLC	8.5% (41/483)	0 (0/41)
YERVOY with nivolumab and 2 cycles of platinum-doublet chemotherapy	NSCLC	7.5% (23/305)	21.7% (5/23)

[a] Details of each treatment regimen are described in Section 14 *[see Clinical Studies (14)]*.
[b] NAb incidence is reported among the subset of patients positive for ADA.
ADA = treatment-emergent anti-ipilimumab antibodies, NAb = neutralizing antibodies, HCC = hepatocellular carcinoma, RCC = renal cell carcinoma, CRC = colorectal cancer, NSCLC = non-small cell lung cancer.

Effects of Anti-Drug Antibodies

Presence of treatment-emergent anti-ipilimumab antibodies did not affect ipilimumab clearance after administration of ipilimumab as monotherapy or in combination with nivolumab. These anti-drug antibody-associated pharmacokinetic changes were not considered to be clinically significant. There was no identified clinically significant effect of anti-drug antibodies on incidence of infusion-related reactions. In hepatocellular carcinoma, there was no identified clinically significant effect of anti-drug antibodies on efficacy for ipilimumab in combination with nivolumab. For other indications, the effects of anti-drug antibodies on effectiveness have not been fully characterized.

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.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 48 of 81

Fertility studies have not been performed with ipilimumab.

14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

The efficacy of YERVOY was investigated in a Study MDX010-20, a randomized (3:1:1), double-blind, double-dummy trial (NCT00094653) that included patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. 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. Patients were randomized to YERVOY administered at a dose of 3 mg/kg as an intravenous infusion every 3 weeks for 4 doses with an investigational peptide vaccine with incomplete Freund's adjuvant - gp100 administered at a dose of 2 mg peptide by deep subcutaneous injection every 3 weeks for 4 doses; gp100 administered at a dose of 2 mg by deep subcutaneous injection every 3 weeks for 4 doses as a single agent with a placebo; or YERVOY administered at a dose of 3 mg/kg by intravenous infusion every 3 weeks for 4 doses with a placebo. The major efficacy outcome measure was overall survival (OS) in the YERVOY and gp100 arm compared to that in the single-agent gp100 arm. Secondary efficacy outcome measures were OS in the YERVOY and gp100 arm compared to the YERVOY arm, OS in the YERVOY arm compared to the gp100 arm, best overall response rate (BORR) as assessed by the investigator at week 24 between each of the trial arms, and duration of response. Assessment of tumor response was conducted 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.

A total of 676 patients were randomized, 403 to YERVOY and gp100 arm, 137 to YERVOY single agent arm and 136 to gp100 single agent arm. Of the randomized patients, 61%, 59%, and 54% in the YERVOY and gp100, YERVOY, and gp100 arms, respectively, were male. 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, 98% had ECOG performance status of 0 and 1, 23% had received aldesleukin, and 38% had elevated LDH level. Sixty-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 efficacy results are shown in Table 25 and Figure 1.

Table 25: Efficacy Results for Study MDX010-20

	YERVOY 3 mg/kg n=137	**YERVOY 3 mg/kg and gp100 n=403**	**gp100 n=136**
Overall Survival			
Median in months (95% CI)	10 (8.0, 13.8)	10 (8.5, 11.5)	6 (5.5, 8.7)
Hazard ratio (vs. gp100) (95% CI)	0.66 (0.51, 0.87)	0.68 (0.55, 0.85)	
p-value	p=0.0026[a]	p=0.0004	

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 49 of 81

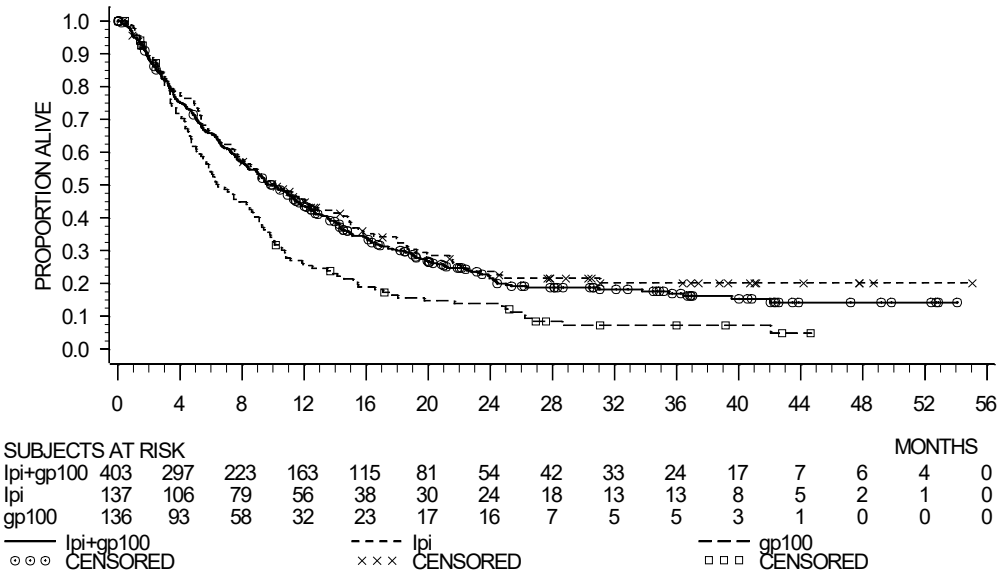
Table 25: Efficacy Results for Study MDX010-20

	YERVOY 3 mg/kg n=137	YERVOY 3 mg/kg and gp100 n=403	gp100 n=136
Hazard ratio (vs. YERVOY) (95% CI)		1.04 (0.83, 1.30)	
Best Overall Response Rate (BORR) (95% CI)	10.9% (6.3%, 17.4%)	5.7% (3.7%, 8.4%)	1.5% (0.2%, 5.2%)
Median duration of response in months	NR[b]	11.5	NR[b]

[a] Not adjusted for multiple comparisons.

[b] Not Reached

Figure 1: Kaplan-Meier Curves for Overall Survival in Study MDX010-20



Previously Untreated Metastatic Melanoma: In Combination with Nivolumab

CHECKMATE-067 (NCT01844505) was a multicenter, randomized (1:1:1), double-blind trial in which 945 patients with previously untreated, unresectable or metastatic melanoma were randomized to one of the following arms: YERVOY and nivolumab, nivolumab, or YERVOY. Patients were required to have completed adjuvant or neoadjuvant treatment at least 6 weeks prior to randomization and have no prior treatment with anti-CTLA-4 antibody and no evidence of active brain metastasis, ocular melanoma, autoimmune disease, or medical conditions requiring systemic immunosuppression.

Patients were randomized to receive:

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 50 of 81

- YERVOY 3 mg/kg with nivolumab 1 mg/kg intravenously every 3 weeks for 4 doses, followed by nivolumab as a single agent at a dose of 3 mg/kg by intravenous infusion every 2 weeks (YERVOY and nivolumab arm),
- Nivolumab 3 mg/kg by intravenous infusion every 2 weeks (nivolumab arm), or
- YERVOY 3 mg/kg intravenously every 3 weeks for 4 doses followed by placebo every 2 weeks (YERVOY arm)

Randomization was stratified by PD-L1 expression (≥5% vs. <5% tumor cell membrane expression) as determined by a clinical trial assay, BRAF V600 mutation status, and M stage per the AJCC staging system (M0, M1a, M1b vs. M1c). Tumor assessments were conducted 12 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter. The major efficacy outcome measures were investigator-assessed PFS per RECIST v1.1 and OS. Additional efficacy outcome measures were confirmed ORR and duration of response.

The trial population characteristics were: median age 61 years (range: 18 to 90); 65% male; 97% White; ECOG performance score 0 (73%) or 1 (27%). Disease characteristics were: AJCC Stage IV disease (93%); M1c disease (58%); elevated LDH (36%); history of brain metastases (4%); BRAF V600 mutation-positive melanoma (32%); PD-L1 ≥5% tumor cell membrane expression as determined by the clinical trials assay (46%); and prior adjuvant therapy (22%).

CHECKMATE-067 demonstrated statistically significant improvements in OS and PFS for patients randomized to either nivolumab-containing arm as compared with the YERVOY arm. The trial was not designed to assess whether adding YERVOY to nivolumab improves PFS or OS compared to nivolumab as a single agent. Efficacy results are shown in Table 26 and Figure 2.

Table 26: Efficacy Results - CHECKMATE-067

	YERVOY and Nivolumab (n=314)	**Nivolumab (n=316)**	**YERVOY (n=315)**
Overall Survival[a]			
Deaths (%)	128 (41)	142 (45)	197 (63)
Hazard ratio[b] (vs. YERVOY) (95% CI)	0.55 (0.44, 0.69)	0.63 (0.50, 0.78)	
p-value[c, d]	<0.0001	<0.0001	
Progression-free Survival[a]			
Disease progression or death	151 (48%)	174 (55%)	234 (74%)
Median (months) (95% CI)	11.5 (8.9, 16.7)	6.9 (4.3, 9.5)	2.9 (2.8, 3.4)
Hazard ratio[b] (vs. YERVOY) (95% CI)	0.42 (0.34, 0.51)	0.57 (0.47, 0.69)	
p-value[c, e]	<0.0001	<0.0001	
Confirmed Overall Response Rate[a]	50%	40%	14%
(95% CI)	(44, 55)	(34, 46)	(10, 18)
p-value[f]	<0.0001	<0.0001	
Complete response	8.9%	8.5%	1.9%
Partial response	41%	31%	12%
Duration of Response			

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 51 of 81

Table 26: Efficacy Results - CHECKMATE-067

	YERVOY and Nivolumab (n=314)	Nivolumab (n=316)	YERVOY (n=315)
Proportion ≥6 months in duration	76%	74%	63%
Range (months)	1.2+ to 15.8+	1.3+ to 14.6+	1.0+ to 13.8+

[a] OS results are based on final OS analysis with 28 months of minimum follow-up; PFS (co-primary endpoint) and ORR (secondary endpoint) results were based on primary analysis with 9 months of minimum follow-up.

[b] Based on a stratified proportional hazards model.

[c] Based on stratified log-rank test.

[d] If the maximum of the two OS p-values is less than 0.04 (a significance level assigned by the Hochberg procedure), then both p-values are considered significant.

[e] p-value is compared with 0.005 of the allocated alpha for final PFS treatment comparisons.

[f] Based on the stratified Cochran-Mantel-Haenszel test.

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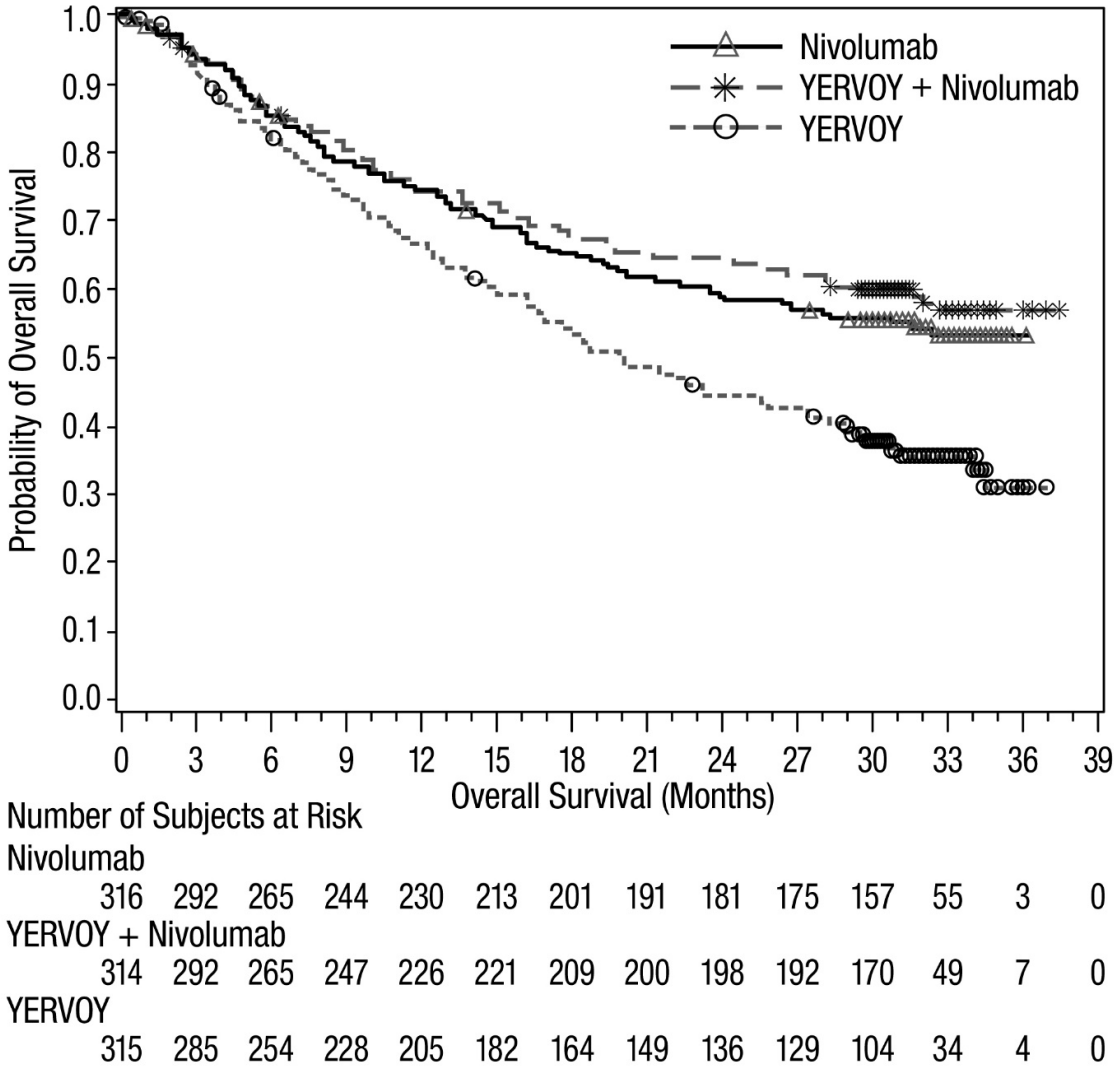
Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 52 of 81

Figure 2: Overall Survival - CHECKMATE-067



Based on a minimum follow-up of 48 months, the median OS was not reached (95% CI: 38.2, NR) in the YERVOY and nivolumab arm. The median OS was 36.9 months (95% CI: 28.3, NR) in the nivolumab arm and 19.9 months (95% CI: 16.9, 24.6) in the YERVOY arm.

Based on a minimum follow-up of 28 months, the median PFS was 11.7 months (95% CI: 8.9, 21.9) in the YERVOY and nivolumab arm, 6.9 months (95% CI: 4.3, 9.5) in the nivolumab arm, and 2.9 months (95% CI: 2.8, 3.2) in the YERVOY arm. Based on a minimum follow-up of 28 months, the proportion of responses lasting ≥24 months was 55% in the YERVOY and nivolumab arm, 56% in the nivolumab arm, and 39% in the YERVOY arm.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 53 of 81

14.2 Adjuvant Treatment of Melanoma

The efficacy of YERVOY was evaluated in Study E1609 (NCT01274338), an open-label, multicenter, randomized trial for the adjuvant treatment of cutaneous melanoma in patients with completely resected node positive disease (either clinically detectable or any size with ulceration or mitosis ≥1/mm^2), in transit metastasis, satellites, or metastatic disease. The trial excluded patients with a history of prior therapy for melanoma and autoimmune disease requiring steroid treatment. Patients were randomized to receive one of the following regimens:

- YERVOY 3 mg/kg intravenously every 3 weeks for 4 doses, followed by the same dose every 12 weeks for up to 4 additional doses,
- High-dose interferon α-2b (HDI) intravenously at 20 million units/m^2 per day, 5 days per week, for 4 weeks (induction), followed by 10 million units/m^2 per day SC every other day, 3 days per week, for 48 weeks (maintenance), or
- YERVOY 10 mg/kg intravenously every 3 weeks for 4 doses, followed by the same dose every 12 weeks for up to 4 additional doses.

Randomization was stratified by AJCC 7th edition stage (IIIB, IIIC, M1a, or M1b). Tumor assessments were conducted every 3 months in patients <2 years from study entry, then every 6 months in patients 2-5 years from study entry, and every 12 months in patients >5 years from study entry for up to 20 years. Treatment continued for a maximum of 60 weeks with ipilimumab or 52 weeks with HDI, or until unacceptable toxic effects, disease progression, or withdrawal of consent. The major efficacy outcome measures were investigator-assessed recurrence-free survival (RFS) by imaging (for CNS lesions) or imaging and positive cytology or histology (for non-CNS lesions) and overall survival (OS). Only the efficacy results for the recommended starting dose of 3 mg/kg YERVOY are described below.

A total of 1051 patients were randomized to YERVOY 3 mg/kg (n=523) and HDI (n=528). The median age was 54 years (range: 18 to 83), 62% were male, 97% were white, 0.3% were Asian, and 0.4% were Black. Regarding disease stage, 53% had Stage IIIB, 40% had Stage IIIC (with no in-transit metastases), and 7% had Stage IV disease.

The efficacy results are in Table 27 and Figure 3.

Table 27: Efficacy Results for E1609

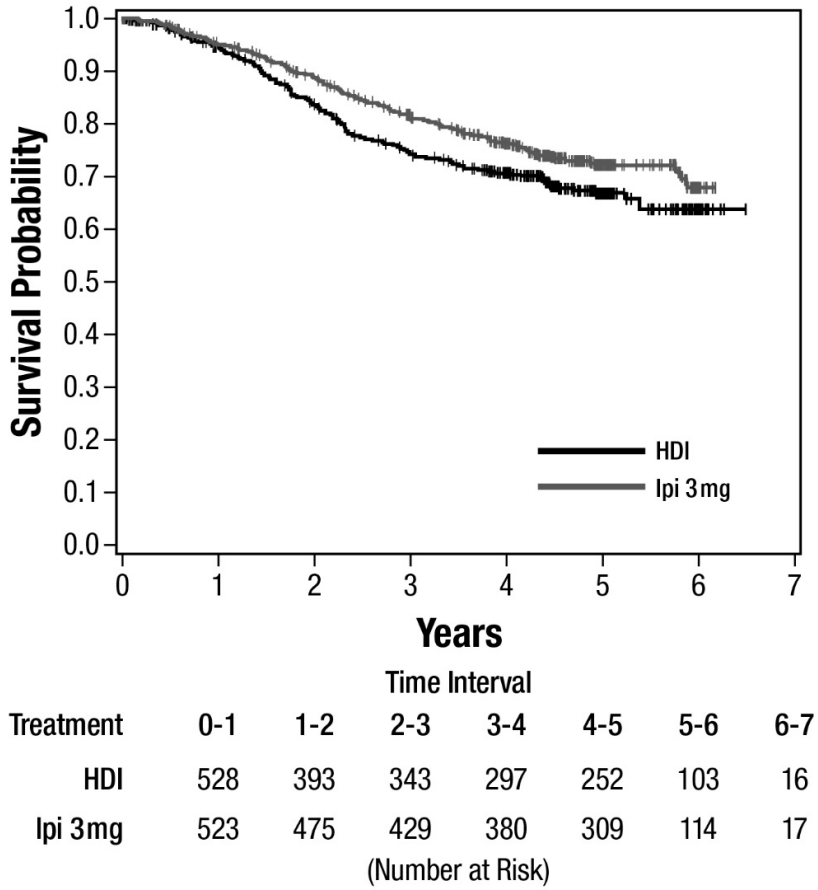
	YERVOY 3 mg/kg n=523	**HDI n=528**
Overall Survival		
Number of deaths (%)	130 (25)	134 (25)
Hazard ratio (95% CI)	0.78 (0.61, 0.99)	
p-value (stratified log-rank[a])	0.044	
5-year OS Rates (95% CI)	72 (68, 76)	67 (62, 71)
Recurrence-Free Survival		
Number of events (%)	246 (47)	232 (44)
Median in years (95% CI)	4.5 (2.7, NA)	2.5 (1.8, 3.5)
Hazard ratio (95% CI)	0.85 (0.71, 1.02)	

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 54 of 81

[a] Two-sided p-value from log-rank test stratified by AJCC stage.

Figure 3: Kaplan-Meier Curves for Overall Survival with Ipilimumab 3 mg/kg vs. HDI in Study E1609



14.3 Advanced Renal Cell Carcinoma

The efficacy of YERVOY with nivolumab was evaluated in CHECKMATE-214 (NCT02231749), 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 randomized to nivolumab 3 mg/kg and YERVOY 1 mg/kg administered intravenously every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every two weeks or to sunitinib administered orally 50 mg daily for the first 4 weeks of each 6-week cycle. Treatment continued until disease progression or unacceptable toxicity. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region. The major efficacy outcome measures were OS, PFS (IRRC-assessed), and confirmed ORR (IRRC-assessed) in intermediate/poor risk patients. Intermediate/poor risk

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 55 of 81

patients had at least 1 or more of 6 prognostic risk factors as per the IMDC criteria: less than one year from time of initial RCC diagnosis to randomization, Karnofsky performance status (KPS) <80%, hemoglobin less than the lower limit of normal, corrected calcium >10 mg/dL, platelet count >ULN, and absolute neutrophil count >ULN.

A total of 847 patients were randomized, 425 to YERVOY with nivolumab and 422 to sunitinib. 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.

Efficacy results from CHECKMATE-214 are presented in Table 28 and Figure 4. In intermediate/poor risk patients, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to YERVOY and nivolumab arm as compared with sunitinib arm. OS benefit was observed regardless of PD-L1 expression level. The trial did not demonstrate a statistically significant improvement in PFS.

Table 28: Efficacy Results for CHECKMATE-214

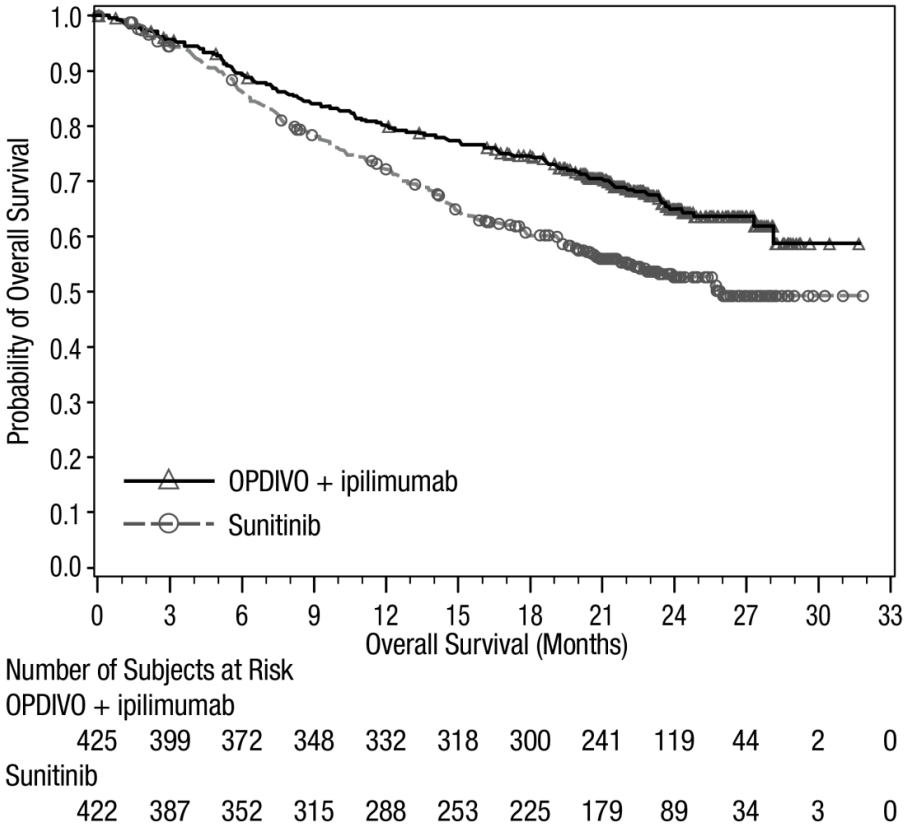
Efficacy Parameter	**Intermediate/Poor-Risk**	
	YERVOY 1 mg/kg and Nivolumab n=425	**Sunitinib n=422**
Overall Survival		
Number of deaths	140 (32.9%)	188 (44.5%)
Median in months	NE	25.9
Hazard ratio (99.8% CI)[a]	0.63 (0.44, 0.89)	
p-value[b,c]	<0.0001	
Confirmed Objective Response Rate (95% CI)	41.6% (36.9%, 46.5%)	26.5% (22.4%, 31.0%)
Complete Response	40 (9.4%)	5 (1.2%)
Partial Response	137 (32.2%)	107 (25.4%)
Median duration of response in months (95% CI)	NE (21.8, NE)	18.2 (14.8, NE)
p-value[d,e]	<0.0001	
Progression-free Survival		
Number of events (progression or death)	228 (53.6%)	228 (54.0%)
Median in months	11.6	8.4
Hazard ratio (99.1% CI)[a]	0.82 (0.64, 1.05)	
p-value[b]	NS[f]	

[a] Based on a stratified proportional hazards model.
[b] Based on a stratified log-rank test.
[c] p-value is compared to alpha 0.002 in order to achieve statistical significance.
[d] Based on the stratified DerSimonian-Laird test.
[e] p-value is compared to alpha 0.001 in order to achieve statistical significance.
[f] Not Significant at alpha level of 0.009.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 56 of 81

Figure 4: Kaplan-Meier Curves for Overall Survival (Intermediate/Poor Risk Population) in CHECKMATE-214



CHECKMATE-214 also randomized 249 favorable risk patients as per IMDC criteria to nivolumab and 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 and YERVOY compared to sunitinib has a hazard ratio of 1.45 (95% CI: 0.75, 2.81). The efficacy of nivolumab and YERVOY in previously untreated renal cell carcinoma with favorable risk disease has not been established.

14.4 Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer

Treatment of MSI-H or dMMR mCRC In Combination with Nivolumab

CHECKMATE-8HW (NCT03143153) was a randomized, 3-arm, open-label trial in immunotherapy-naive patients across all lines of therapy with unresectable or metastatic CRC with known tumor MSI-H or dMMR (MSI-H/dMMR) status as determined in accordance with local standard of practice using PCR, NGS or IHC, assays. Central assessment of MSI-H status using PCR (Idylla MSI) test and dMMR status using IHC (Omnis MMR) test was conducted retrospectively on patient tumor specimens used for local MSI-H/dMMR status determination. Patients with confirmed MSI-H/dMMR status by either central test comprised the primary study population.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 57 of 81

The trial excluded patients with brain metastasis that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or had been treated with checkpoint inhibitors.

Patients were randomized to receive one of the following treatments:

- YERVOY 1 mg/kg every 3 weeks and nivolumab 240 mg every 3 weeks for a maximum of 4 doses, then nivolumab 480 mg every 4 weeks
- Nivolumab 240 mg every 2 weeks for 6 doses, then nivolumab 480 mg every 4 weeks.
- Investigator's choice chemotherapy
  - mFOLFOX6 (oxaliplatin, leucovorin, and FU) with or without either bevacizumab or cetuximab: Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 bolus followed by FU 2400 mg/m^2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg or cetuximab 500 mg/m^2 administered prior to mFOLFOX6 every 2 weeks.
  - FOLFIRI (irinotecan, leucovorin, and FU) with or without either bevacizumab or cetuximab: Irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 bolus and FU 2400 mg/m^2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg on or cetuximab 500 mg/m^2 administered prior to FOLFIRI every 2 weeks.

Randomization was stratified by tumor location (right vs left) and by prior lines of therapy (0, 1, 2L+). Patients randomized to the chemotherapy arm could receive YERVOY plus nivolumab combination upon progression assessed by BICR.

Study treatment was administered until disease progression, unacceptable toxicity, or for up to 2 years for patients who received YERVOY plus nivolumab or nivolumab monotherapy. Patients who discontinued combination therapy because of an adverse reaction attributed to YERVOY were permitted to continue nivolumab as a single agent. Nivolumab with or without YERVOY could be administered beyond RECIST 1.1-assessed progressive disease if there was a clinical benefit as determined by investigator and therapy was tolerated. Tumor assessments per RECIST v1.1 were conducted every 6 weeks for the first 24 weeks, then every 8 weeks thereafter up until week 96, then every 16 weeks thereafter up until week 144, and then every 24 weeks.

The evaluation of efficacy relied on the comparison of patients with centrally confirmed MSI-H/dMMR mCRC randomized to YERVOY in combination with nivolumab versus chemotherapy in the first-line (1L) setting and the comparison of patients with centrally confirmed MSI-H/dMMR mCRC randomized to YERVOY in combination with nivolumab vs nivolumab in all lines setting.

The major efficacy outcome measure was BICR-assessed PFS per RECIST 1.1. Additional efficacy measures included ORR and duration of response assessed by BICR and OS.

The baseline characteristics of the total of 839 patients randomized were: the median age was 63 years (range: 20 to 87), with 46% ≥65 years of age and 14% ≥75 years of age; 50% were male and 87% were White, 9.3% were Asian, 1.5% Black or African American, and 2.3% other race; 9.2% were Hispanic or Latino, 50% Not Hispanic or Latino, 41% ethnicity unknown. Baseline ECOG performance status was 0 (52%) and (48%); number of prior lines of therapy was 0 (56%) and 1

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 58 of 81

(24%), and ≥2 (19%); tumor location was right-sided or left-sided for 69% and 31% of patients. The baseline characteristics in patients with centrally confirmed MSI-H/dMMR is consistent with all randomized patients.

First Line YERVOY in combination with nivolumab

Among 303 patients in the first-line setting were randomly assigned to YERVOY in combination with nivolumab (202) and to chemotherapy (101), 171 and 84 patients had centrally confirmed MSI-H/dMMR status in YERVOY in combination with nivolumab arm and chemotherapy arm, respectively.

In the 1L setting, 200 of 202 patients assigned to receive YERVOY in combination with nivolumab and 88 of 101 patients assigned to received chemotherapy received at least 1 dose of study treatment. Among the 88 patients who received chemotherapy, 58% and 42% of patients received oxaliplatin-containing regimens and irinotecan-containing regimens, respectively, and 66 (75%) patients received a targeted agent, either bevacizumab (64%) or cetuximab (11%).

The BICR-assessed PFS efficacy results for patients with centrally confirmed MSI-H/dMMR randomized to the YERVOY and nivolumab arm compared with chemotherapy in the 1L setting are presented in Table 29 and Figure 5. The comparative results of ORR and OS between arms were not available at the time of the PFS analysis due to statistical testing strategy.

Table 29: Efficacy Results - CHECKMATE-8HW

	YERVOY and Nivolumab (n=171)	**Chemotherapy (n=84)**
Progression-free Survival		
Disease progression or death (%)	48 (28)	52 (62)
Median in months[b] (95% CI)	NR (38.4, NE)	5.8 (4.4, 7.8)
Hazard ratio[c] (95% CI)	0.21 (0.14, 0.32)	
p-value[a]	<0.0001	

NR: Not Reached; NE: Not Estimable.
Minimum follow-up was 6.1 months at data cutoff date 12Oct2023.

[a] Based on log-rank test stratified by the same factors as used in the Cox proportional hazards model. The p-value threshold for statistical significance was 0.0209.

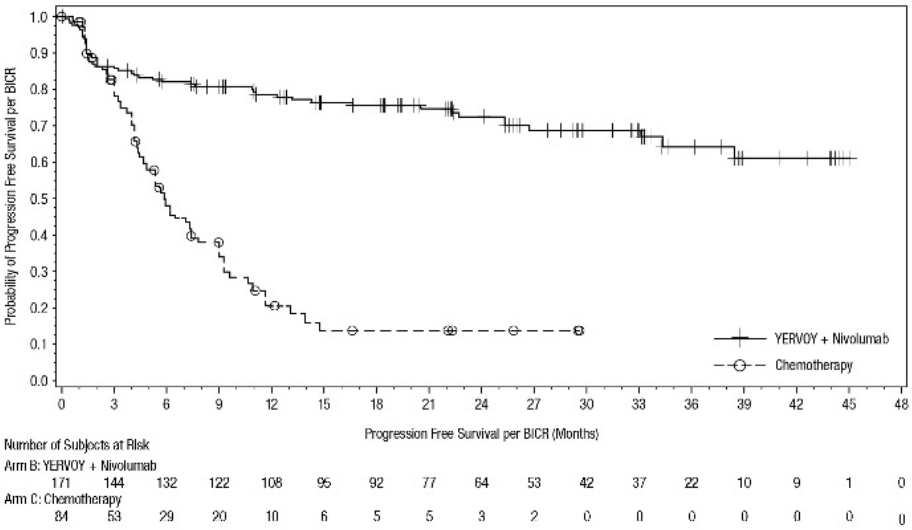
[b] Based on Kaplan-Meier estimates.

[c] HR from a Cox proportional hazards model stratified by tumor sidedness (left vs right) per IRT

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 59 of 81

Figure 5: Progression-free Survival, (First line YERVOY + nivolumab vs Chemotherapy)- CHECKMATE-8HW



All Lines YERVOY in combination with nivolumab

Among 707 patients across all treatment lines who were randomly assigned to YERVOY in combination with nivolumab (354) and to nivolumab (353) single agent, 296 and 286 patients had centrally confirmed MSI-H/dMMR status in the YERVOY in combination with nivolumab arm and in the nivolumab arm, respectively. Patients receiving at least 1 dose of study treatment included 352 of 354 patients randomized to OPDIVO in combination with ipilimumab, and 351 of 353 patients randomized to single agent OPDIVO.

The BICR-assessed PFS and ORR efficacy results for patients with centrally confirmed MSI-H/dMMR randomized to the YERVOY in combination with nivolumab compared with nivolumab single agent across all treatment lines setting are presented in Table 30 and Figure 6. At the time of PFS analysis OS between arms were not available due to statistical testing strategy.

Table 30: Efficacy Results All Lines - CHECKMATE-8HW

	YERVOY and Nivolumab (n=296)	**Nivolumab (n=286)**
Progression-free Survival		
Disease progression or death n (%)	101 (34)	136 (48)
Median (months)[b] (95% CI)	NR (53.82, NE)	39.3 (22.1, NE)
Hazard ratio[c] (95% CI)	0.62 (0.48, 0.81)	
p-value[a]	0.0003	
Objective Response Rate (ORR)		
Response Rate, n (%) (95% CI)	209 (71%) (65, 76)	165 (58%) (52, 63)
Complete Response Rate, n (%)	90 (30%)	80 (28%)
Partial Response, n (%)	119 (40%)	65 (30%)

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 60 of 81

Table 30: Efficacy Results All Lines - CHECKMATE-8HW

	YERVOY and Nivolumab (n=296)	Nivolumab (n=286)
p-value[d]	0.0011	

NR: Not Reached; NE: Not Estimable.
Minimum follow-up was 16.7 months at data cutoff date 28Aug2024.

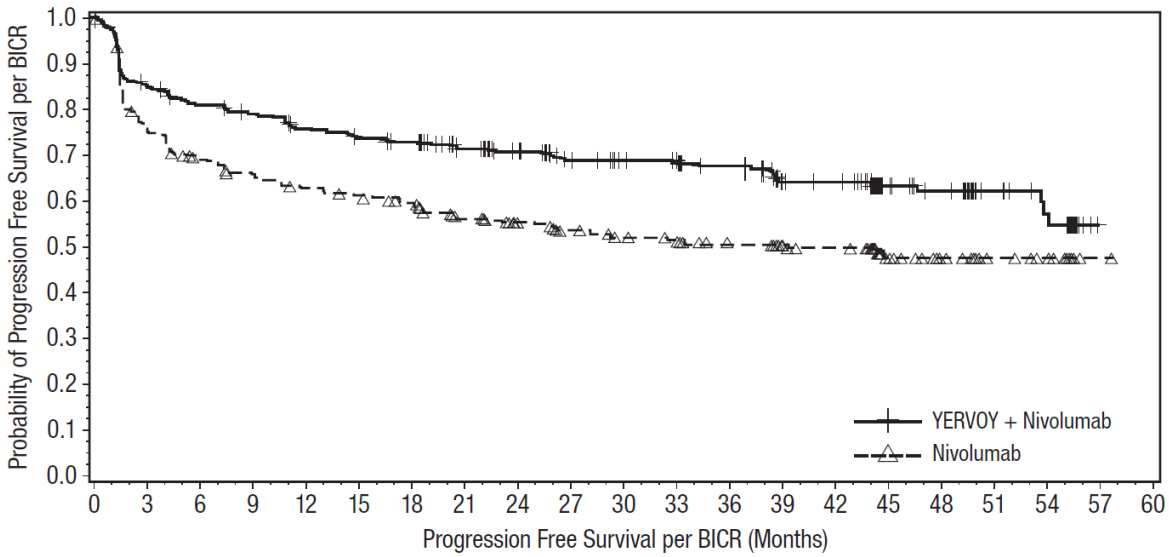
[a] Based on log-rank test stratified by the same factors as used in the Cox proportional hazards model. The p-value threshold for statistical significance was 0.0095.

[b] Based on Kaplan-Meier estimates.

[c] HR from a Cox proportional hazards model stratified by tumor sidedness (left vs right) and prior lines of therapy (0, 1, ≥2) per IRT.

[d] Based on Cochran-Mantel-Haenszel test stratified by the same factors as used in the Cox proportional hazards model. The p-value threshold for statistical significance was 0.006.

Figure 6: Progression-free Survival (All lines (YERVOY + Nivolumab vs Nivolumab)- CHECKMATE-8HW



Number of Subjects at Risk

Arm A: Nivolumab
286 210 191 179 169 164 158 141 124 109 98 95 81 72 69 39 31 15 12 1 0

Arm B: YERVOY + Nivolumab
296 248 234 225 214 207 200 180 164 146 136 134 121 102 100 61 54 29 23 0 0

14.5 Hepatocellular Carcinoma

Treatment of Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

CHECKMATE-9DW (NCT04039607) was a randomized (1:1), open-label trial in adults (18 years of age or older) with unresectable or metastatic HCC. Patients had histologically confirmed HCC, Child Pugh Class A, ECOG performance status 0 or 1, and no prior systemic therapy for advanced disease. Esophagogastroduodenoscopy was not mandated prior to enrollment. The trial excluded patients with active autoimmune disease, brain or leptomeningeal metastases, a history of hepatic

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 61 of 81

encephalopathy (within 12 months of randomization), a platelet count <60,000, clinically significant ascites, medical conditions requiring systemic immunosuppression, infection with HIV, or active co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV).

Patients were randomized to receive either:

- YERVOY 3 mg/kg administered intravenously over 30 minutes in combination with nivolumab 1 mg/kg administered intravenously over 30 minutes every 3 weeks, for a maximum of 4 doses, followed by single agent nivolumab at 480 mg administered intravenously over 30 minutes every 4 weeks, or
- Investigator's choice:
  - Lenvatinib 8 mg orally daily (if body weight <60 kg) or 12 mg orally daily (if body weight ≥60 kg), or
  - Sorafenib 400 mg orally twice daily

Randomization was stratified by etiology (HBV vs. HCV vs. non-viral), macrovascular invasion and/or extrahepatic spread (present or absent), and alpha-fetoprotein levels (≥400 or <400 ng/mL). Study treatment for YERVOY in combination with nivolumab continued until disease progression, unacceptable toxicity, or up to 2 years. Patients who discontinued combination therapy because of an adverse reaction attributed to YERVOY were permitted to continue nivolumab as a single agent. Treatment beyond RECIST 1.1 defined disease progression was permitted if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Tumor assessments were performed at baseline, after randomization at week 9 and week 16, then every 8 weeks up to 48 weeks, and then every 12 weeks thereafter until disease progression, treatment discontinuation, or initiation of subsequent therapy. The primary efficacy outcome measure was OS in all randomized patients. Additional efficacy measures included BICR-assessed ORR and DOR based on RECIST 1.1 criteria.

A total of 668 patients were randomized to receive YERVOY in combination with nivolumab (n=335) or investigator's choice (n=333) of lenvatinib or sorafenib. In the investigator arm, 85% and 15% of treated patients received lenvatinib or sorafenib, respectively. The trial population characteristics were: median age was 66 years (range: 20 to 89), with 53% ≥65 years old; 82% male; 53% White, 44% Asian, 2.2% Black; 12% Hispanic or Latino, 48% Not Hispanic or Latino, 40% not reported. Baseline ECOG performance status was 0 (71%) or 1 (29%). Thirty-four percent (34%) of patients had HBV infection, 28% had HCV infection, and 36% had no evidence of HBV or HCV infection.

Nineteen percent (19%) of patients had alcoholic liver disease and 11% had non-alcoholic fatty liver disease. The majority of patients had BCLC stage C (73%) disease at baseline, 19% had stage B, and 6% had stage A. Patients with Child-Pugh scores of 5, 6, and 7 were 77%, 20%, and 3%, respectively; 1 patient with Child Pugh 8 was enrolled. A total of 54% of patients had extrahepatic spread; 25% had macrovascular invasion; and 33% had AFP levels ≥400 μg/L.

CHECKMATE-9DW demonstrated a statistically significant improvement in OS and ORR. The minimum follow-up was 26.8 months. Efficacy results are shown in Table 31 and Figure 7.

Reference ID: 5595665

Table 31: Efficacy Results - CHECKMATE-9DW

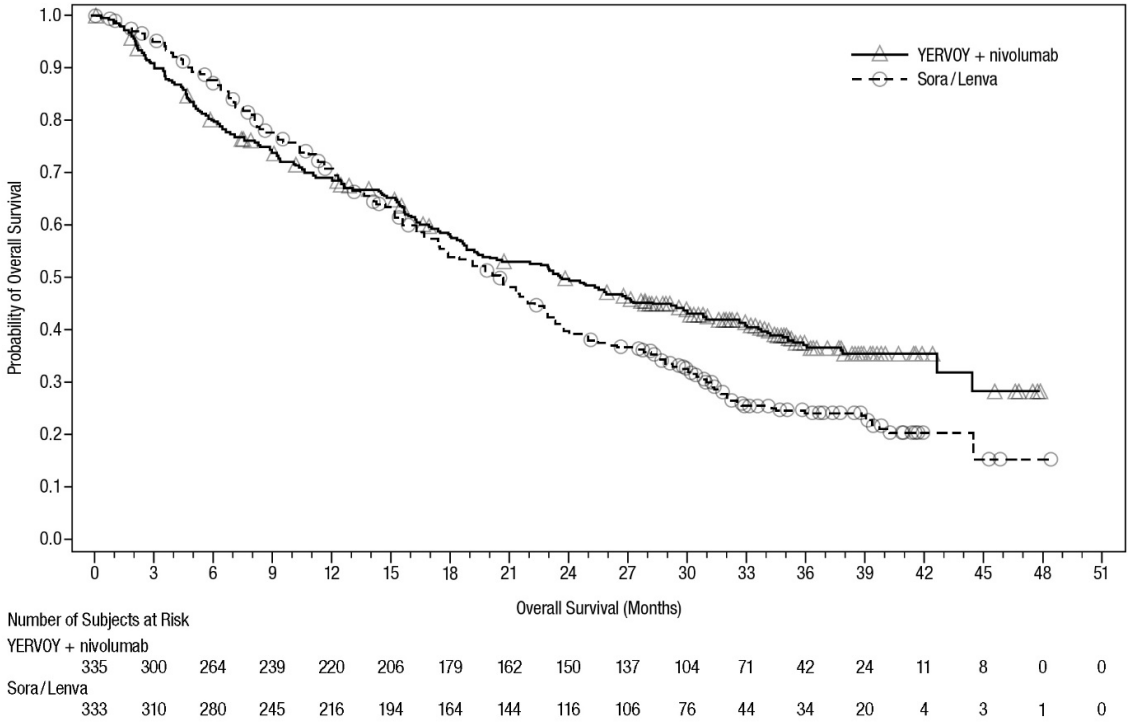
	YERVOY and Nivolumab (n=335)	Lenvatinib or Sorafenib (n=333)
Overall Survival		
Deaths (%)	194 (58%)	228 (68%)
Median (months) (95% CI)	23.7 (18.8, 29.4)	20.6 (17.5, 22.5)
Hazard ratio (95% CI) [a]	0.79 (0.65, 0.96)	
p-value [b]	0.0180	
Overall Response Rate, n (%)[c]	121 (36.1)	44 (13.2)
(95% CI)	(31.0, 41.5)	(9.8, 17.3)
p-value [d]	<0.0001	
Complete response (%)	23 (6.9)	6 (1.8)
Partial response (%)	98 (29.3)	38 (11.4)
Duration of Response (months) [c]		
Median (95% CI)	30.4 (21.2, NR[e])	12.9 (10.2, 31.2)
Range	1.5+, 36.9+	2.1+, 32.5+

[a] Based on stratified Cox proportional hazard model.
[b] Based on a 2-sided stratified log-rank test. Boundary for statistical significance: p-value ≤0.0257
[c] Assessed by BICR using RECIST 1.1
[d] Based on a 2-sided stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: p-value ≤0.025
[e] NR: Not Reached
+ Censored observation

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 63 of 81

Figure 7: Overall Survival - CHECKMATE-9DW



Previously Treated Hepatocellular Carcinoma

CHECKMATE-040 (NCT01658878) was a multicenter, multiple cohort, open-label trial conducted in patients with HCC who progressed on or were intolerant to sorafenib. Additional eligibility criteria included histologic confirmation of HCC and Child-Pugh Class A cirrhosis. The trial excluded patients with active autoimmune disease, brain metastasis, a history of hepatic encephalopathy, clinically significant ascites, infection with HIV, or active co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV); however, patients with only active HBV or HCV were eligible.

The efficacy of YERVOY 3 mg/kg in combination with nivolumab 1 mg/kg was evaluated in Cohort 4 of CHECKMATE-040. A total of 49 patients received the combination regimen, which was administered every 3 weeks for four doses, followed by single-agent nivolumab at 240 mg every 2 weeks until disease progression or unacceptable toxicity.

The median age was 60 years (range: 18 to 80); 88% were male; 74% were Asian, and 25% were White. Baseline ECOG performance status was 0 (61%) or 1 (39%). Fifty-seven percent (57%) of patients had active HBV infection, 8% had active HCV infection, and 35% had no evidence of active HBV or HCV. The etiology for HCC was alcoholic liver disease in 16% and non-alcoholic liver disease in 6% of patients. Child-Pugh class and score was A5 for 82% and A6 for 18%; 80% of patients had extrahepatic spread; 35% had vascular invasion; and 51% had alfa-fetoprotein (AFP) levels ≥400 µg/L. Prior treatment history included surgery (74%), radiotherapy (29%), or

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 64 of 81

local treatment (59%). All patients had received prior sorafenib, of whom 10% were unable to tolerate sorafenib; 29% of patients had received 2 or more prior systemic therapies.

Efficacy results are shown in Table 32.

Table 32: Efficacy Results - Cohort 4 of CHECKMATE-040

	YERVOY and Nivolumab (Cohort 4) (n=49)
Overall Response Rate per BICR,[a] n (%), RECIST v1.1	16 (33%)
(95% CI)[b]	(20, 48)
Complete response	4 (8%)
Partial response	12 (24%)
Duration of Response per BICR,[a] RECIST v1.1	n=16
Range (months)	4.6, 30.5+
Percent with duration ≥6 months	88%
Percent with duration ≥12 months	56%
Percent with duration ≥24 months	31%
Overall Response Rate per BICR,[a] n (%), mRECIST	17 (35%)
(95% CI)[b]	(22, 50)
Complete response	6 (12%)
Partial response	11 (22%)

[a] Confirmed by BICR.

[b] Confidence interval is based on the Clopper and Pearson method.

14.6 Metastatic Non-Small Cell Lung Cancer

First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) Expressing PD-L1 (≥1%): In Combination with Nivolumab

CHECKMATE-227 (NCT02477826) was a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC. The study included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer [ASLC] classification), ECOG performance status 0 or 1, and no prior anticancer therapy. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents.

Primary efficacy results were based on Part 1a of the study, which was limited to patients with PD-L1 tumor expression ≥1%. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. Randomization was stratified by tumor histology (non-squamous versus squamous). The evaluation of efficacy relied on the comparison between:

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 65 of 81

- YERVOY 1 mg/kg administered intravenously over 30 minutes every 6 weeks in combination with nivolumab 3 mg/kg administered intravenously over 30 minutes every 2 weeks; or
- Platinum-doublet chemotherapy

Chemotherapy regimens consisted of pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) or pemetrexed (500 mg/m^2) and carboplatin (AUC 5 or 6) for non-squamous NSCLC or gemcitabine (1000 or 1250 mg/m^2) and cisplatin (75 mg/m^2) or gemcitabine (1000 mg/m^2) and carboplatin (AUC 5) (gemcitabine was administered on Days 1 and 8 of each cycle) for squamous NSCLC.

Study treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Treatment continued beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse event attributed to YERVOY were permitted to continue nivolumab as a single agent. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR.

In Part 1a, a total of 793 patients were randomized to receive either YERVOY in combination with nivolumab (n=396) or platinum-doublet chemotherapy (n=397). The median age was 64 years (range: 26 to 87) with 49% of patients ≥65 years and 10% of patients ≥75 years, 76% White, and 65% male. Baseline ECOG performance status was 0 (34%) or 1 (65%), 50% with PD-L1 ≥50%, 29% with squamous and 71% with non-squamous histology, 10% had brain metastases, and 85% were former/current smokers.

The study demonstrated a statistically significant improvement in OS for PD-L1 ≥1% patients randomized to the YERVOY and nivolumab arm compared to platinum-doublet chemotherapy arm. The OS results are presented in Table 33 and Figure 8.

Table 33: Efficacy Results (PD-L1 ≥1%) - CHECKMATE-227 Part 1a

	YERVOY and Nivolumab (n=396)	**Platinum-Doublet Chemotherapy (n=397)**
Overall Survival		
Events (%)	258 (65%)	298 (75%)
Median (months)[a] (95% CI)	17.1 (15, 20.1)	14.9 (12.7, 16.7)
Hazard ratio (95% CI)[b]	0.79 (0.67, 0.94)	
Stratified log-rank p-value	0.0066	

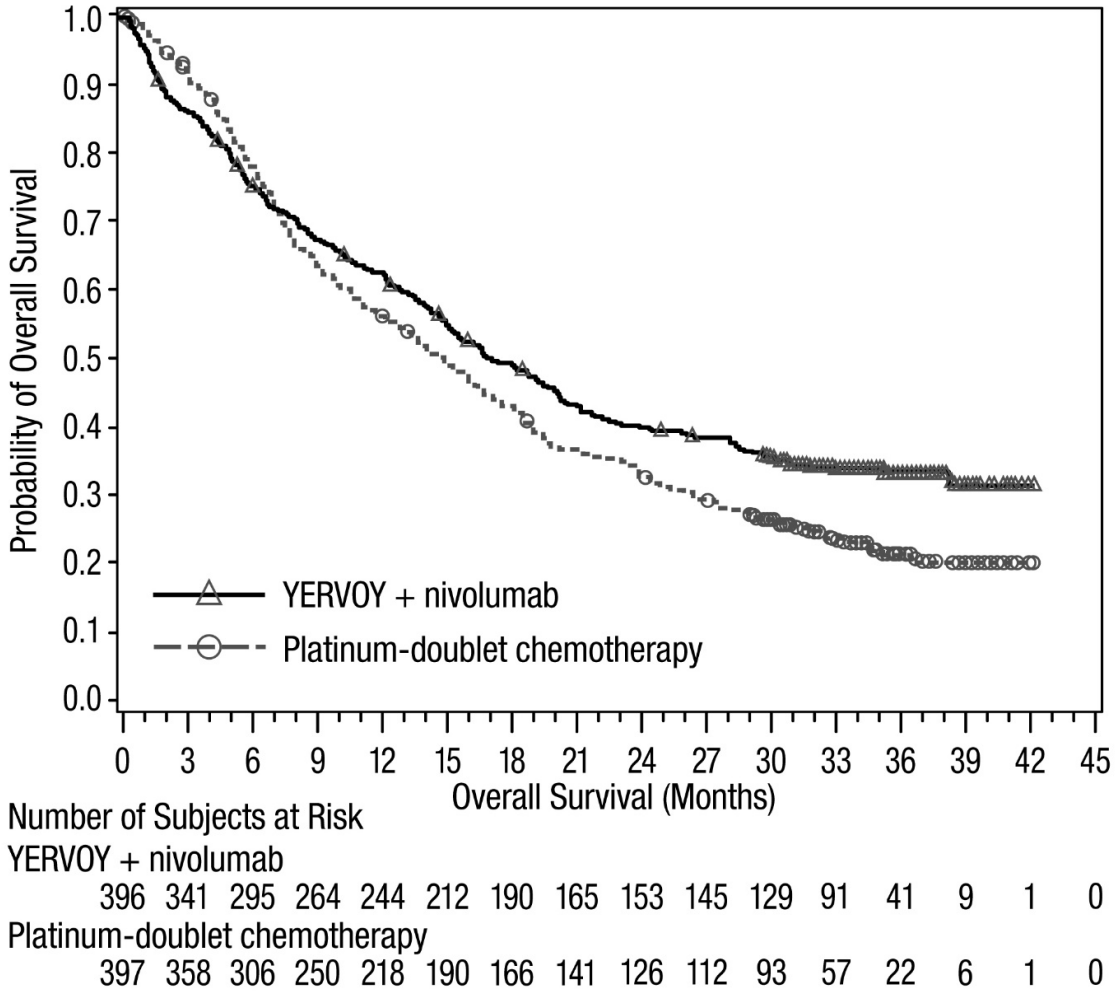
[a] Kaplan-Meier estimate.

[b] Based on a stratified Cox proportional hazard model.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 66 of 81

Figure 8: Overall Survival (PD-L1 ≥1%) - CHECKMATE-227



BICR-assessed PFS showed a HR of 0.82 (95% CI: 0.69, 0.97), with a median PFS of 5.1 months (95% CI: 4.1, 6.3) in the YERVOY and nivolumab arm and 5.6 months (95% CI: 4.6, 5.8) in the platinum-doublet chemotherapy arm. The BICR-assessed confirmed ORR was 36% (95% CI: 31, 41) in the YERVOY and nivolumab arm and 30% (95% CI: 26, 35) in the platinum-doublet chemotherapy arm. Median duration of response observed in the YERVOY and nivolumab arm was 23.2 months and 6.2 months in the platinum-doublet chemotherapy arm.

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Nivolumab and Platinum-Doublet Chemotherapy

CHECKMATE-9LA (NCT03215706) was a randomized, open-label trial in patients with metastatic or recurrent NSCLC. The trial included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification [IASLC]), ECOG performance status 0 or 1, and no prior

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 67 of 81

anticancer therapy (including EGFR and ALK inhibitors) for metastatic disease. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with stable brain metastases were eligible for enrollment.

Patients were randomized 1:1 to receive either:

- YERVOY 1 mg/kg administered intravenously over 30 minutes every 6 weeks, nivolumab 360 mg administered intravenously over 30 minutes every 3 weeks, and platinum-doublet chemotherapy administered intravenously every 3 weeks for 2 cycles, or
- platinum-doublet chemotherapy administered every 3 weeks for 4 cycles.

Platinum-doublet chemotherapy consisted of either carboplatin (AUC 5 or 6) and pemetrexed 500 mg/m^2, or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 for non-squamous NSCLC; or carboplatin (AUC 6) and paclitaxel 200 mg/m^2 for squamous NSCLC. Patients with non-squamous NSCLC in the control arm could receive optional pemetrexed maintenance therapy. Stratification factors for randomization were tumor PD-L1 expression level (≥1% versus <1% or non-quantifiable), histology (squamous versus non-squamous), and sex (male versus female). Study treatment continued until disease progression, unacceptable toxicity, or for up to 2 years. Treatment could continue beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse reaction attributed to YERVOY were permitted to continue nivolumab as a single agent as part of the study. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR.

A total of 719 patients were randomized to receive either YERVOY in combination with nivolumab and platinum-doublet chemotherapy (n=361) or platinum-doublet chemotherapy (n=358). The median age was 65 years (range: 26 to 86) with 51% of patients ≥65 years and 10% of patients ≥75 years. The majority of patients were White (89%) and male (70%). Baseline ECOG performance status was 0 (31%) or 1 (68%), 57% had tumors with PD-L1 expression ≥1% and 37% had tumors with PD-L1 expression that was <1%, 32% had tumors with squamous histology and 68% had tumors with non-squamous histology, 17% had CNS metastases, and 86% were former or current smokers.

The study demonstrated a statistically significant benefit in OS, PFS, and ORR. Efficacy results from the prespecified interim analysis when 351 events were observed (87% of the planned number of events for final analysis) are presented in Table 34.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 68 of 81

Table 34: Efficacy Results - CHECKMATE-9LA

	YERVOY and Nivolumab and Platinum-Doublet Chemotherapy (n=361)	Platinum-Doublet Chemotherapy (n=358)
Overall Survival		
Events (%)	156 (43.2)	195 (54.5)
Median (months) (95% CI)	14.1 (13.2, 16.2)	10.7 (9.5, 12.5)
Hazard ratio (96.71% CI)[a]	0.69 (0.55, 0.87)	
Stratified log-rank p-value[b]	0.0006	
Progression-free Survival per BICR		
Events (%)	232 (64.3)	249 (69.6)
Hazard ratio (97.48% CI)[a]	0.70 (0.57, 0.86)	
Stratified log-rank p-value[c]	0.0001	
Median (months)[d] (95% CI)	6.8 (5.6, 7.7)	5.0 (4.3, 5.6)
Overall Response Rate per BICR (%)	38	25
(95% CI)[e]	(33, 43)	(21, 30)
Stratified CMH test p-value[f]	0.0003	
Duration of Response per BICR		
Median (months) (95% CI)[d]	10.0 (8.2, 13.0)	5.1 (4.3, 7.0)

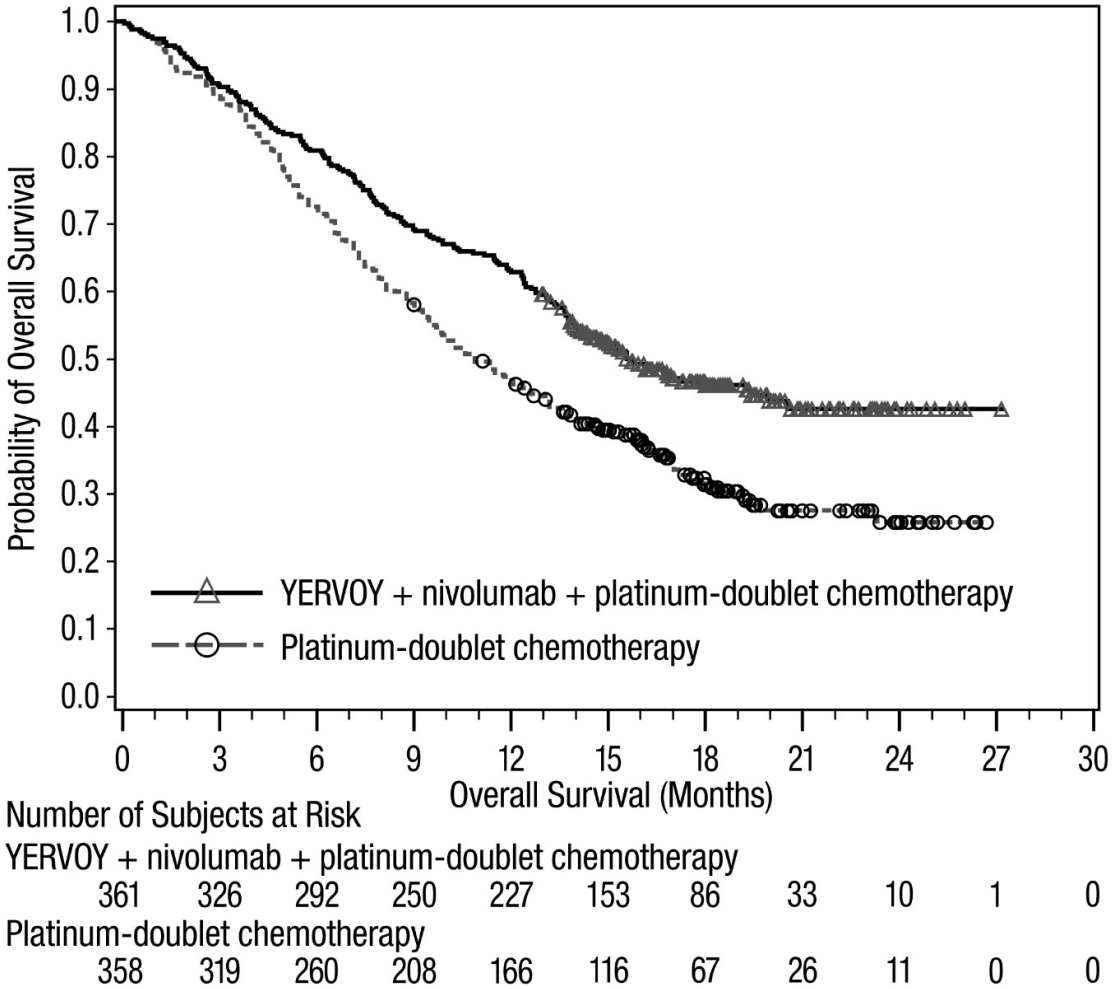
[a] Based on a stratified Cox proportional hazard model.
[b] p-value is compared with the allocated alpha of 0.033 for this interim analysis.
[c] p-value is compared with the allocated alpha of 0.0252 for this interim analysis.
[d] Kaplan-Meier estimate.
[e] Confidence interval based on the Clopper and Pearson Method.
[f] p-value is compared with the allocated alpha of 0.025 for this interim analysis.

With an additional 4.6 months of follow-up the hazard ratio for overall survival was 0.66 (95% CI: 0.55, 0.80) and median survival was 15.6 months (95% CI: 13.9, 20.0) and 10.9 months (95% CI: 9.5, 12.5) for patients receiving YERVOY and nivolumab and platinum-doublet chemotherapy or platinum-doublet chemotherapy, respectively (Figure 9).

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 69 of 81

Figure 9: Overall Survival - CHECKMATE-9LA



14.7 Malignant Pleural Mesothelioma

CHECKMATE-743 (NCT02899299) was a randomized, open-label trial in patients with unresectable malignant pleural mesothelioma. The trial included patients with histologically confirmed and previously untreated malignant pleural mesothelioma with no palliative radiotherapy within 14 days of initiation of therapy. Patients with interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, or active brain metastasis were excluded from the trial. Patients were randomized 1:1 to receive either:

- YERVOY 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks and nivolumab 3 mg/kg over 30 minutes by intravenous infusion every 2 weeks for up to 2 years, or
- cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2, or carboplatin 5 AUC and pemetrexed 500 mg/m^2 administered every 3 weeks for 6 cycles.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 70 of 81

Stratification factors for randomization were tumor histology (epithelioid vs. sarcomatoid or mixed histology subtypes) and sex (male vs. female). Study treatment continued for up to 2 years, or until disease progression or unacceptable toxicity. Patients who discontinued combination therapy because of an adverse reaction attributed to YERVOY were permitted to continue nivolumab as a single agent. Treatment could continue beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR utilizing modified RECIST criteria.

A total of 605 patients were randomized to receive either YERVOY in combination with nivolumab (n=303) or chemotherapy (n=302). The median age was 69 years (range: 25 to 89), with 72% of patients ≥65 years and 26% ≥75 years; 85% were White, 11% were Asian, and 77% were male. Baseline ECOG performance status was 0 (40%) or 1 (60%), 35% had Stage III and 51% had Stage IV disease, 75% had epithelioid and 25% had non-epithelioid histology, 75% had tumors with PD-L1 expression ≥1%, and 22% had tumors with PD-L1 expression <1%.

The trial demonstrated a statistically significant improvement in OS for patients randomized to YERVOY in combination with nivolumab compared to chemotherapy. Efficacy results from the prespecified interim analysis are presented in Table 35 and Figure 10.

Table 35: Efficacy Results - CHECKMATE-743

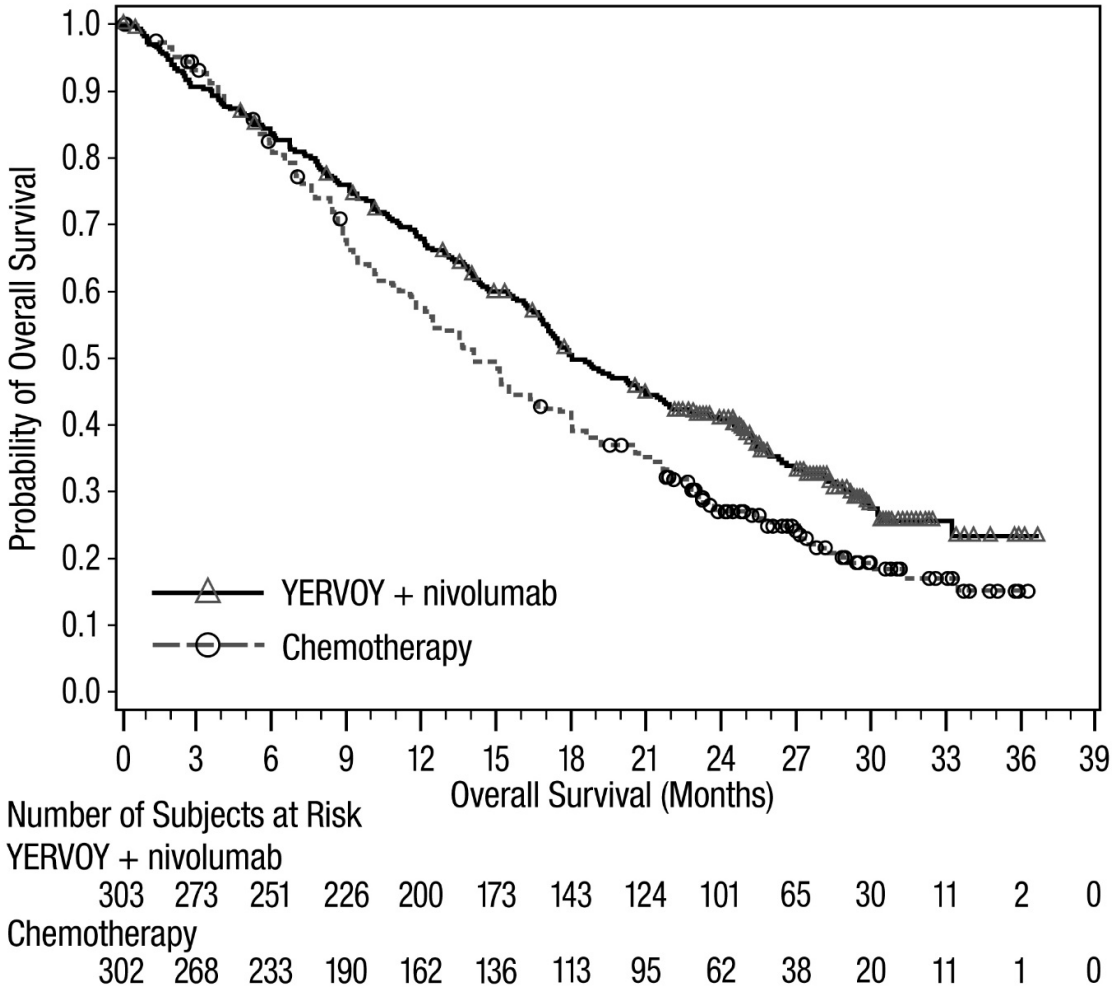
	YERVOY and Nivolumab (n=303)	**Chemotherapy (n=302)**
Overall Survival[a]		
Events (%)	200 (66)	219 (73)
Median (months)[b] (95% CI)	18.1 (16.8, 21.5)	14.1 (12.5, 16.2)
Hazard ratio (95% CI)[c]	0.74 (0.61, 0.89)	
Stratified log-rank p-value[d]	0.002	
Progression-free Survival		
Events (%)	218 (72)	209 (69)
Hazard ratio (95% CI)[c]	1.0 (0.82, 1.21)	
Median (months)[b] (95% CI)	6.8 (5.6, 7.4)	7.2 (6.9, 8.1)
Overall Response Rate[e]	40%	43%
(95% CI)	(34, 45)	(37, 49)
Duration of Response		
Median (months)[a] (95% CI)	11.0 (8.1, 16.5)	6.7 (5.3, 7.1)

[a] At the time of the interim analysis, 419 deaths (89% of the deaths needed for the final analysis) had occurred.
[b] Kaplan-Meier estimate.
[c] Stratified Cox proportional hazard model.
[d] p-value is compared with the allocated alpha of 0.0345 for this interim analysis.
[e] Based on confirmed response by BICR.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 71 of 81

Figure 10: Overall Survival - CHECKMATE-743



In a prespecified exploratory analysis based on histology, in the subgroup of patients with epithelioid histology, the hazard ratio (HR) for OS was 0.85 (95% CI: 0.68, 1.06), with median OS of 18.7 months in the YERVOY and nivolumab arm and 16.2 months in the chemotherapy arm. In the subgroup of patients with non-epithelioid histology, the HR for OS was 0.46 (95% CI: 0.31, 0.70), with median OS of 16.9 months in the YERVOY and nivolumab arm and 8.8 months in the chemotherapy arm.

14.8 Esophageal Cancer

CHECKMATE-648 (NCT03143153) was a randomized, active-controlled, open-label trial in patients with previously untreated unresectable advanced, recurrent or metastatic ESCC (squamous or adenosquamous histology). The trial enrolled patients whose tumor was evaluable for tumor cell (TC) PD-L1 expression [also called PD-L1 tumor proportion score (TPS)], which was evaluated using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. Patients were not

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 72 of 81

amenable to chemoradiation or surgery with curative intent. A retrospective scoring of a patient's tumor PD-L1 status using Combined Positive Score (CPS) was also conducted using the PD-L1-stained tumor specimens used for randomization. Prior treatment with curative intent was allowed if completed more than six months prior to trial enrollment. The trial excluded patients with brain metastasis that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or patients at high risk of bleeding or fistula due to apparent invasion of tumor to organs adjacent to the esophageal tumor. Patients were randomized to receive one of the following treatments:

- YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 3 mg/kg every 2 weeks.
- Fluorouracil 800 mg/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 intravenously on day 1 (of a 4-week cycle).

Patients were treated until disease progression, unacceptable toxicity, or up to 2 years. Patients who discontinued combination therapy because of an adverse reaction attributed to YERVOY were permitted to continue nivolumab as a single agent.

Randomization was stratified by TC PD-L1 expression (≥1% vs. <1% or indeterminate), region (East Asia vs. Rest of Asia vs. Rest of World), ECOG performance status (0 vs. 1), and number of organs with metastases (≤1 vs. ≥2). The major efficacy outcome measures were OS and BICR-assessed PFS in patients with TC PD-L1 expression ≥1%. Additional efficacy measures included OS in all randomized patients, BICR-assessed PFS in all randomized patients, and ORR assessed by BICR in TC PD-L1 expression ≥1% and in all randomized patients. The tumor assessments per RECIST v1.1 were conducted every 6 weeks up to and including week 48, then every 12 weeks thereafter.

A total of 649 patients were randomized in Arms A and C of the CHECKMATE-648 study, among whom 644 and 601 patients had quantifiable TC PD-L1 expression and CPS at baseline, respectively; 84% (546/649) had tumors with PD-L1 CPS ≥1. The trial population characteristics in patients with PD-L1 CPS ≥1 were: median age 63 years (range: 26 to 81), 45% were ≥65 years of age, 84% were male, 71% were Asian, 25% were White, and 1.6% were Black or African American. Patients had histological confirmation of squamous cell carcinoma (99%) or adenosquamous cell carcinoma (1.3%) in the esophagus. Baseline ECOG performance status was 0 (46%) or 1 (54%).

A statistically significant improvement in OS was demonstrated in patients randomized to YERVOY in combination with nivolumab compared with chemotherapy; however, an exploratory analysis of OS in patients with PD-L1 CPS <1 showed a HR of 1.0 (95% CI 0.52, 1.94), including that the improvement in the ITT population was primarily attributed to the results observed in the subgroup of patients with PD-L1 CPS ≥1. Efficacy results are shown in Table 36 and Figures 11 and 12.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 73 of 81

Table 36: Efficacy Results - Arms A and C of CHECKMATE-648

	YERVOY and Nivolumab (n=158)	Cisplatin and Fluorouracil (n=157)	YERVOY and Nivolumab (n=266)	Cisplatin and Fluorouracil (n=280)
	TC PD-L1 expression ≥1%		PD-L1 CPS ≥1	
Overall Survival				
Deaths (%)	106 (67)	121 (77)	179 (67)	205 (73)
Median (months) (95% CI)	13.7 (11.2, 17.0)	9.1 (7.7, 10)	12.7 (10.9, 15.5)	9.8 (8.8, 11.6)
Hazard ratio (95% CI)[b]	0.64 (0.49, 0.84)		0.76 (0.62, 0.93)	
p-value[c]	0.0010[S1]		-	
Progression-free Survival[a]				
Disease progression or death (%)	123 (78)	100 (64)	206 (77)	184 (66)
Median (months) (95% CI)	4.0 (2.4, 4.9)	4.4 (2.9, 5.8)	2.8 (2.6, 4.2)	5.6 (4.2, 5.9)
Hazard ratio (95% CI)[b]	1.02 (0.78, 1.34)		1.2 (1.0, 1.5)	
p-value[c]	NS		-	
Overall Response Rate, n (%)[a], NT	56 (35.4)	31 (19.7)	74 (28)	76 (27)
(95% CI)	(28.0, 43.4)	(13.8, 26.8)	(22.5, 33.6)	(22.0, 32.8)
Complete response (%)	28 (17.7)	8 (5.1)	32 (12.0)	18 (6.4)
Partial response (%)	28 (17.7)	23 (14.6)	42 (15.8)	58 (20.7)
Median (95% CI)	11.8 (7.1, 27.4)	5.7 (4.4, 8.7)	11.8 (7.1, 23.6)	6.9 (5.7, 8.2)
Range	1.4+, 34.5+	1.4+, 31.8+	1.4+, 34.5+	1.4+, 31.8+

[a] Assessed by BICR.

[b] Based on stratified Cox proportional hazard model. Hazard ratios are reported for each nivolumab- containing arm compared to chemotherapy within each analysis population.

[c] Based on a stratified 2-sided log-rank test.

[S1] Significant p-value compared to stopping boundary of 0.014.

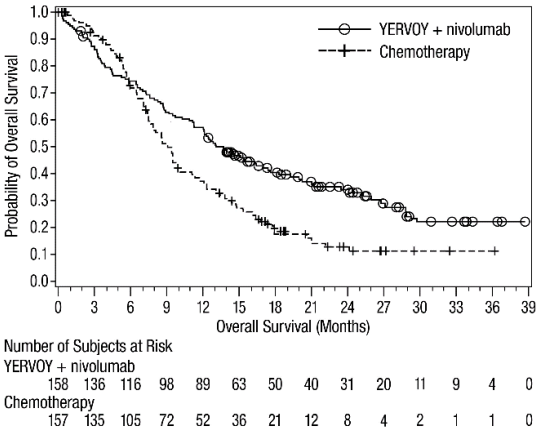
NS: Not Statistically significant, NT: Not evaluated for statistical significance as per pre-specified hierarchical testing procedure.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 74 of 81

Figure 11: Overall Survival - CHECKMATE-648

(A) OS in TC PD-L1 ≥1% (B) OS in PD-L1 CPS ≥1



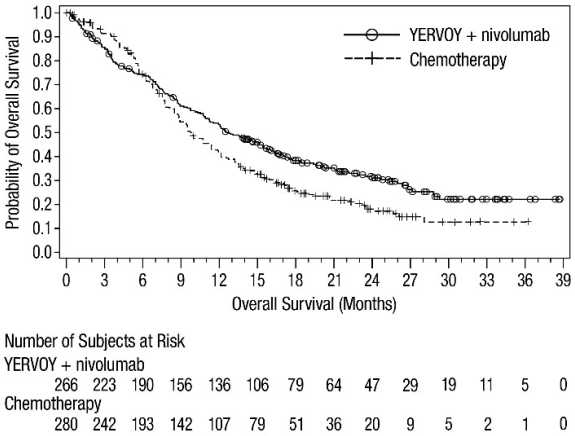
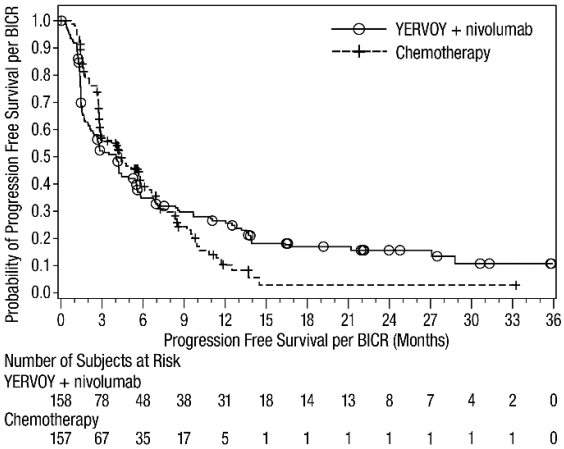
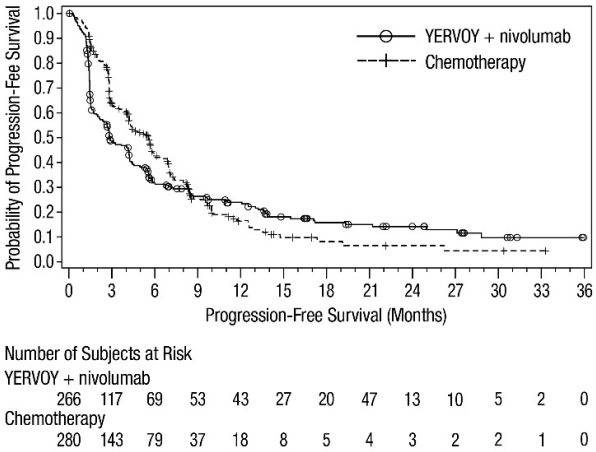


Figure 12: Progression-free Survival – CHECKMATE-648

(A) PFS in TC PD-L1 ≥1% (B) PFS in PD-L1 CPS ≥1





16 HOW SUPPLIED/STORAGE AND HANDLING

YERVOY (ipilimumab) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution. YERVOY is available as follows:

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 75 of 81

Carton Contents	NDC
One 50 mg/10 mL (5 mg/mL), single-dose vial	NDC 0003-2327-11
One 200 mg/40 mL (5 mg/mL), single-dose vial	NDC 0003-2328-22

Store YERVOY under refrigeration at 2°C to 8°C (36°F to 46°F). Protect YERVOY from light by storing in the original carton until time of use. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Advise patients that YERVOY can cause immune-mediated adverse reactions including the following *[see Warnings and Precautions (5.1)]*:

- Immune-Mediated Diarrhea or Colitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of diarrhea or colitis.
- Immune-Mediated Hepatitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatitis.
- Immune-Mediated Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately if they develop a new rash.
- Immune-Mediated Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus.
- Immune-Mediated Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening symptoms of pneumonitis.
- Immune-Mediated Nephritis with Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.

Infusion-Related Reactions

- Advise patients who are receiving YERVOY of the potential risk of an infusion-related reaction *[see Warnings and Precautions (5.2)]*.

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.4), Use in Specific Populations (8.3)]*.
- 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 patients who may have been exposed to YERVOY during pregnancy to contact Bristol-Myers Squibb at 1-844-593-7869 *[see Use in Specific Populations (8.1)]*.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 76 of 81

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)]*.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
U.S. License No. 1713

[print code]

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 77 of 81

MEDICATION GUIDE
YERVOY® (yur-voi)
(ipilimumab)
injection

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 is a medicine that may treat certain cancers by working with your immune system. YERVOY can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. You may have more than one of these problems at the same time. These problems may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when YERVOY is used in combination with nivolumab.

Call or see your healthcare provider right away if you develop any new or worse signs or symptoms, including:

Intestinal problems.

- diarrhea (loose stools) or more frequent bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdominal) pain or tenderness

Liver problems.

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach-area (abdomen)
- dark urine (tea colored)
- bleeding or bruising more easily than normal

Skin problems.

- rash
- itching
- skin blistering or peeling
- painful sores in mouth or nose, throat, or genital area

Hormone gland problems.

- headache that will not go away or unusual headaches
- eye sensitivity to light
- eye problems
- rapid heartbeat
- increased sweating
- extreme tiredness
- weight gain or weight loss
- feeling more hungry or thirsty than usual
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- dizziness or fainting
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Lung problems.

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

Kidney problems.

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

Eye problems.

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

Problems can also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that can happen with YERVOY. Call or see your healthcare provider right away for any new or worsening signs or symptoms.

- Chest pain, irregular heartbeat, shortness of breath or swelling of ankles
- Confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- Double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- Persistent or severe muscle pain or weakness, muscle cramps
- Low red blood cells, bruising

Getting medical treatment right away may help keep these problems from becoming more serious. Your healthcare provider will check you for these problems during your treatment with YERVOY. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also 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.**

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 78 of 81

- YERVOY may be used alone or in combination with nivolumab in adults and children 12 years of age and older when melanoma has spread or cannot be removed by surgery.
- YERVOY may be used alone in adults to help prevent melanoma from coming back after it and lymph nodes that contain cancer have been removed by surgery.

- **in adults 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 may be used in combination with nivolumab when your colon or rectal cancer:
    - cannot be removed with surgery, or has spread, **and**
    - is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).
- **in adults with liver cancer (hepatocellular carcinoma).**
  - YERVOY may be used in combination with nivolumab as your first treatment when your liver cancer:
    - cannot be removed by surgery, **or**
    - has spread.
  - YERVOY may be used in combination with nivolumab when your liver cancer:
    - cannot be removed by surgery, **or**
    - has spread, **and**
    - you have received prior treatment with sorafenib.
- **in adults with a type of lung cancer called non-small cell lung cancer (NSCLC).**
  - YERVOY may be used in combination with nivolumab as your first treatment for NSCLC:
    - when your lung cancer has spread to other parts of your body (metastatic), **and**
    - your tumors are positive for PD-L1, but do not have an abnormal EGFR or ALK gene.
  - YERVOY may be used in combination with nivolumab and 2 cycles of chemotherapy that contains platinum and another chemotherapy medicine, as the first treatment of your NSCLC when your lung cancer:
    - has spread or grown, or comes back, **and**
    - your tumor does not have an abnormal EGFR or ALK gene.
- **in adults with a type of cancer that affects the lining of the lungs and chest wall called malignant pleural mesothelioma.**
  - YERVOY may be used in combination with nivolumab as your first treatment for malignant pleural mesothelioma that cannot be removed by surgery.
- **in adults with cancer of the tube that connects your throat to your stomach (esophageal cancer).**
  - YERVOY may be used in combination with nivolumab as your first treatment when your esophageal cancer:
    - is a type called squamous cell carcinoma, **and**
    - cannot be removed with surgery (advanced), or has spread to the other parts of the body (metastatic), **and**
    - your tumors are positive for PD-L1.

It is not known if YERVOY is safe and effective in children younger than 12 years of age with melanoma that has spread or cannot be removed by surgery, or with MSI-H or dMMR metastatic colorectal cancer.
It is not known if YERVOY is safe and effective in children for the treatment of any other cancers.

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

- have immune system problems such as ulcerative colitis, Crohn's disease, or lupus
- have received an organ transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are pregnant or plan to become pregnant. YERVOY can harm your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider will give you a pregnancy test before you start treatment with YERVOY.
  - You should use an effective method of birth control during treatment and for 3 months after your last dose of YERVOY. Talk to your healthcare provider about birth control methods that you can use during this time.
  - Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with YERVOY. You or your healthcare provider should contact Bristol-Myers Squibb at 1-844-593-7869 as soon as you become aware of a pregnancy.
- are breastfeeding or plan to breastfeed. It is not known if YERVOY passes into your breast milk. Do not breastfeed during treatment and for 3 months after your 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?

- Your healthcare provider will give you YERVOY into your vein through an intravenous (IV) line.
- YERVOY is usually given over **30** minutes.
- If you are receiving YERVOY as treatment for melanoma that has been removed by surgery to help prevent it from coming back, YERVOY will be given over **30** minutes.

Reference ID: 5595665

BMS EX2003
Amgen v. BMS, IPR2025-00601
Page 79 of 81

- In combination with nivolumab, YERVOY is usually given every 3 weeks for up to 4 doses. After that, nivolumab alone is usually given every 2 or 4 weeks.
- For NSCLC that has spread to other parts of your body, YERVOY is given every 6 weeks and nivolumab is given every 3 weeks for up to 2 years. Your healthcare provider will determine if you will also need to receive chemotherapy every 3 weeks for 2 cycles.
- For malignant pleural mesothelioma that cannot be removed by surgery, YERVOY is given every 6 weeks and nivolumab is given every 3 weeks for up to 2 years.
- When YERVOY is used in combination with nivolumab for esophageal squamous cell carcinoma (ESCC), YERVOY is given every 6 weeks and nivolumab is given every 2 or 3 weeks for up to 2 years.
- 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.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

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-related reactions.** Tell your healthcare provider or nurse right away if you get these symptoms during an infusion of YERVOY:
  - chills or shaking
  - itching or rash
  - flushing
  - shortness of breath or wheezing
  - dizziness
  - feel like passing out
  - fever
  - back or neck pain
- **Complications, including graft-versus-host disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic).** These complications can be severe and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with YERVOY. Your healthcare provider will monitor you for these complications.

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
- diarrhea
- rash
- itching
- nausea
- pain in muscles, bones, and joints
- fever
- cough
- decreased appetite
- vomiting
- stomach-area (abdominal) pain
- shortness of breath
- upper respiratory tract infection
- headache
- low thyroid hormone levels (hypothyroidism)
- constipation
- decreased weight
- dizziness

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

- feeling tired
- pain in muscles, bones, and joints
- nausea
- diarrhea
- rash
- decreased appetite
- constipation
- itching

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. If you would like more information about YERVOY, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about YERVOY that is written for health professionals.

What are the ingredients of YERVOY?

Active ingredient: ipilimumab

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

Manufactured by: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
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For more information, call 1-800-321-1335

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: May 2025