PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr OPDIVO®

nivolumab for injection

Intravenous Infusion, 10 mg nivolumab /mL
40 mg and 100 mg single-use vials

Antineoplastic

Pr OPDIVO® has been issued marketing authorization **with conditions**, pending the results of trials to verify its clinical benefit, for the treatment of adult patients with:

- Previously untreated unresectable or metastatic BRAF V600 mutation-positive melanoma. An improvement in survival has not yet been established.
- Previously untreated unresectable or metastatic melanoma when used in combination with ipilimumab.

  Relative to OPDIVO monotherapy, an increase in progression-free survival (PFS) for the combination of OPDIVO with ipilimumab is established only in patients with low tumour PD-L1 expression (based on the predefined expression level of < 5%)**.**

  An improvement in survival has not yet been established.
- Classical Hodgkin Lymphoma (cHL) that has relapsed or progressed after:
  - autologous stem cell transplantation (ASCT) and brentuximab vedotin, or
  - 3 or more lines of systemic therapy including ASCT.

  An improvement in survival or disease-related symptoms has not yet been established.
- As a monotherapy in patients with advanced (not amenable to curative therapy or local therapeutic measures) or metastatic hepatocellular carcinoma (HCC) who are intolerant to or have progressed on sorafenib therapy.
  The marketing authorization with conditions is primarily based on tumour objective response rate and duration of response. An improvement in survival or disease-related symptoms has not yet been established.
- In combination with ipilimumab, for the treatment of adult patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer after:
  - prior fluoropyrimidine-based therapy in combination with oxaliplatin or irinotecan.

  An improvement in survival has not yet been established.

Patients should be advised of the nature of the authorization. For further information for Pr OPDIVO® please refer to Health Canada's Notice of Compliance with conditions - drug products web site: http://www.hc-sc.gc.ca/dhpmps/prodpharma/notices-avis/conditions/index-eng.php.

[Pr] OPDIVO® has been issued marketing authorization **without conditions** for the treatment of adult patients with:

- Previously untreated unresectable or metastatic BRAF V600 wild-type melanoma.
- Unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.
- Melanoma with regional lymph node involvement, in transit metastases/satellites without metastatic nodes, or distant metastases, as adjuvant therapy after complete resection.
- Locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving OPDIVO.
- Metastatic NSCLC, expressing PD-L1 ≥ 1% as determined by a validated test, with no EGFR or ALK genomic tumour aberrations and no prior systemic treatment for metastatic NSCLC, when used in combination with ipilimumab.
- Metastatic NSCLC with no EGFR or ALK genomic tumour aberrations and no prior systemic therapy for metastatic NSCLC, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy.
- Advanced or metastatic renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.
- Intermediate/poor-risk advanced or metastatic RCC when used in combination with ipilimumab.
- Recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) progressing on or after platinum-based therapy.

Bristol-Myers Squibb Canada Co.
Montreal, Canada

Submission Control No: 239474

Date of Initial Approval:
September 25, 2015

Date of Revision:
February 11, 2021

This product has been authorized under the Notice of Compliance with Conditions (NOC/c)

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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- Melanoma with regional lymph node involvement, in transit metastases/satellites without metastatic nodes, or distant metastases, as adjuvant therapy after complete resection.
- Locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour

aberrations should have disease progression on a therapy for these aberrations prior to receiving OPDIVO.
- Metastatic NSCLC, expressing PD-L1 ≥ 1% as determined by a validated test with no EGFR or ALK genomic tumour aberrations, and no prior systemic treatment for metastatic NSCLC, when used in combination with ipilimumab.
- Metastatic NSCLC with no EGFR or ALK genomic tumour aberrations and no prior systemic therapy for metastatic NSCLC, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy.
- Advanced or metastatic renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.
- Intermediate/poor-risk advanced or metastatic RCC when used in combination with ipilimumab.
- Recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) progressing on or after platinum-based therapy.

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous Infusion	40 mg nivolumab /4 mL (10 mg/mL) 100 mg nivolumab /10 mL (10 mg/mL)	None *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

DESCRIPTION

OPDIVO (nivolumab) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) developed by recombinant deoxyribonucleic acid (DNA) technology. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. Nivolumab has a calculated molecular mass of 146,221 Da.

INDICATIONS AND CLINICAL USE

Unresectable or Metastatic Melanoma:

OPDIVO (nivolumab) is indicated for the treatment of unresectable or metastatic BRAF V600 wild-type melanoma in previously untreated adults.

NOC/c OPDIVO is indicated for the treatment of unresectable or metastatic BRAF V600 mutation-positive melanoma in previously untreated adults.

An improvement in survival has not yet been established.

NOC/c OPDIVO in combination with ipilimumab is indicated for the treatment of unresectable or metastatic melanoma in previously untreated adults.

Relative to OPDIVO monotherapy, an increase in progression-free survival (PFS) for the combination of OPDIVO with ipilimumab is established only in patients with low tumour PD-L1 expression (based on the predefined expression level of < 5%).

An improvement in survival has not yet been established.

OPDIVO is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation-positive, a BRAF inhibitor.

Adjuvant Treatment of Melanoma:

OPDIVO, as monotherapy, is indicated for the adjuvant treatment of adult patients after complete resection of melanoma with regional lymph node involvement, in transit metastases/satellites without metastatic nodes, or distant metastases.

Metastatic Non-Small Cell Lung Cancer (NSCLC):

OPDIVO, as monotherapy, is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving OPDIVO.

OPDIVO, in combination with ipilimumab, is indicated for the treatment of adult patients with metastatic NSCLC, expressing PD-L1 ≥ 1% as determined by a validated test, with no EGFR or ALK genomic tumour aberrations, and no prior systemic therapy for metastatic NSCLC. (See **CLINICAL TRIALS** *for the treatment benefit by PD-L1 tumour expression.*)

OPDIVO, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the treatment of adult patients with metastatic NSCLC with no EGFR or ALK genomic tumour aberrations, and no prior systemic therapy for metastatic NSCLC.

Metastatic Renal Cell Carcinoma (RCC):

OPDIVO, as monotherapy, is indicated for the treatment of adult patients with advanced or metastatic renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

OPDIVO, in combination with ipilimumab, is indicated for the treatment of adult patients with intermediate/poor-risk advanced or metastatic RCC.

Squamous Cell Carcinoma of the Head and Neck (SCCHN):

OPDIVO is indicated for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) in adults progressing on or after platinum-based therapy.

NOC/c **Classical Hodgkin Lymphoma (cHL)**:

OPDIVO, as monotherapy, is indicated for the treatment of adult patients with classical Hodgkin Lymphoma (cHL) that has relapsed or progressed after:

- autologous stem cell transplantation (ASCT) and brentuximab vedotin, or
- 3 or more lines of systemic therapy including ASCT.

An improvement in survival or disease-related symptoms has not yet been established.

NOC/c **Hepatocellular Carcinoma (HCC):**

OPDIVO is indicated as a monotherapy for the treatment of adult patients with advanced (not amenable to curative therapy or local therapeutic measures) or metastatic hepatocellular carcinoma (HCC) who are intolerant to or have progressed on sorafenib therapy.

The marketing authorization with conditions is primarily based on tumour objective response rate and duration of response. An improvement in survival or disease-related symptoms has not yet been established.

NOC/c **Microsatellite Instability-High (MSI-H)/ Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer:**

OPDIVO, in combination with ipilimumab, is indicated for the treatment of adult patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer after prior fluoropyrimidine-based therapy in combination with oxaliplatin or irinotecan.

The marketing authorization with conditions is primarily based on tumour objective response rate and durability of response. An improvement in survival has not yet been established. (see **CLINICAL TRIALS**)

Geriatrics (> 65 years of age):

No overall differences in safety or efficacy were reported between elderly patients (≥ 65 years) and younger patients (< 65 years). Limited safety and efficacy information is available for OPDIVO in cHL ≥ 65 years of age (n=7/266). (see **WARNINGS AND PRECAUTIONS**, ***Special Populations***)

Pediatrics (< 18 years of age):

The safety and effectiveness of OPDIVO have not been established in pediatric patients.

NOC/c CONTRAINDICATIONS

OPDIVO (nivolumab) is contraindicated in patients who are hypersensitive to nivolumab or to any ingredient in the formulation or component of the container. (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**)

NOC/c WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

OPDIVO as monotherapy or in combination with ipilimumab can cause severe and fatal immune-mediated adverse reactions, including pneumonitis, interstitial lung disease, encephalitis, myocarditis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and autoimmune hemolytic anemia [see WARNINGS AND PRECAUTIONS, Immune-mediated adverse reactions].

Immune-mediated adverse reactions may involve any organ system. While most of these reactions occurred during treatment, onset months after the last dose has been reported [see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS].

Early diagnosis and appropriate management are essential to minimize potential life-threatening complications. Patients should be monitored for signs and symptoms suggestive of immune-mediated adverse reactions [see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION for management guidelines for these adverse reactions]. OPDIVO or OPDIVO in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction.

Healthcare professionals should consult the ipilimumab Product Monograph prior to initiation of OPDIVO in combination with ipilimumab.

General

OPDIVO (nivolumab) should be administered under the supervision of physicians experienced in the treatment of cancer.

When OPDIVO is administered in combination with ipilimumab, refer to the product monograph for ipilimumab prior to initiation of treatment.

Immune-mediated adverse reactions

Adverse reactions observed with immunotherapies such as OPDIVO may differ from those observed with non-immunotherapies, can be severe and life-threatening, and may require immunosuppression. Early identification of adverse reactions and intervention are essential to minimize potential life-threatening complications. Immune-mediated adverse reactions have occurred at higher frequencies when OPDIVO was administered in combination with ipilimumab compared with OPDIVO as monotherapy. Most immune-mediated adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications.

Patients should be monitored for signs and symptoms suggestive of immune-mediated adverse reactions and appropriately managed with treatment modification. OPDIVO or OPDIVO in combination with ipilimumab must be permanently discontinued for any severe immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction.

Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with OPDIVO or OPDIVO in combination with ipilimumab may occur at any time during

or after discontinuation of therapy. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening of the adverse reaction. Non-corticosteroid immunosuppressive medications should be added if there is worsening or no improvement despite corticosteroid use.

Do not resume OPDIVO or OPDIVO in combination with ipilimumab while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive medications. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive medications.

Immune-Mediated Endocrinopathies

OPDIVO can cause severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency (including secondary adrenocortical insufficiency), hypophysitis (including hypopituitarism), diabetes mellitus (including fulminant type I diabetes), and diabetic ketoacidosis. These have been observed with OPDIVO monotherapy and OPDIVO in combination with ipilimumab. Monitor patients for signs and symptoms of endocrinopathies such as fatigue, weight change, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease, changes in blood glucose levels and thyroid function. If signs or symptoms are present, complete endocrine function evaluation. (see **ADVERSE REACTIONS**)

For Grade 2 or 3 hypothyroidism, withhold OPDIVO or OPDIVO in combination with ipilimumab and initiate thyroid hormone replacement therapy. For Grade 2 or 3 hyperthyroidism, withhold OPDIVO or OPDIVO in combination with ipilimumab and initiate antithyroid therapy. For Grade 4 hypothyroidism, or Grade 4 hyperthyroidism, permanently discontinue OPDIVO or OPDIVO in combination with ipilimumab. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered, as clinically indicated. Upon improvement, for Grade 2 or 3, resume OPDIVO or OPDIVO in combination with ipilimumab after corticosteroid taper. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilized.

For Grade 2 adrenal insufficiency, withhold OPDIVO or OPDIVO in combination with ipilimumab, and initiate physiologic corticosteroid replacement. For Grade 3 or 4 (life-threatening) adrenal insufficiency, permanently discontinue OPDIVO or OPDIVO in combination with ipilimumab. Monitoring of adrenal function and hormone levels should continue to ensure appropriate corticosteroid replacement is utilized.

For Grade 2 hypophysitis, withhold OPDIVO or OPDIVO in combination with ipilimumab and initiate appropriate hormone therapy. For Grade 3 or 4 hypophysitis, permanently discontinue OPDIVO or OPDIVO in combination with ipilimumab. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered, as clinically indicated. Upon improvement, for Grade 2, resume OPDIVO or OPDIVO in combination with ipilimumab after corticosteroid taper. Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilized.

For Grade 3 diabetes, OPDIVO or OPDIVO in combination with ipilimumab should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised. For Grade 4 diabetes, permanently discontinue OPDIVO.

Immune-Mediated Gastrointestinal Adverse Reactions

OPDIVO can cause severe diarrhea or colitis. This has been observed with OPDIVO monotherapy and OPDIVO in combination with ipilimumab. Monitor patients for diarrhea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Rule out infectious and disease-related etiologies. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Stool infections work-up (including CMV, other viral etiology, culture, Clostridium difficile, ova, and parasite) should be performed upon presentation of diarrhea or colitis to exclude infectious or other alternate etiologies. (see **ADVERSE REACTIONS**)

For Grade 4 diarrhea or colitis, permanently discontinue OPDIVO or OPDIVO in combination with ipilimumab and initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 3 diarrhea or colitis, withhold OPDIVO and initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents. Upon improvement, resume OPDIVO after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, permanently discontinue OPDIVO. Grade 3 diarrhea observed with OPDIVO in combination with ipilimumab also requires permanent discontinuation of treatment and initiation of corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 diarrhea or colitis, withhold OPDIVO or OPDIVO in combination with ipilimumab and start immediate corticosteroid treatment at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, resume OPDIVO or OPDIVO in combination with ipilimumab after corticosteroid taper if needed. If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day methylprednisolone equivalents and permanently discontinue OPDIVO or OPDIVO in combination with ipilimumab.

Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-related colitis if other causes are excluded (including CMV infection/reactivation evaluated with viral PCR on biopsy, and other viral, bacterial, and parasitic etiology).

Immune-Mediated Hepatic Adverse Reactions

OPDIVO can cause severe hepatotoxicity, including hepatitis. This has been observed with OPDIVO monotherapy and OPDIVO in combination with ipilimumab. Monitor patients for signs

and symptoms of hepatotoxicity, such as transaminase and total bilirubin elevations. Rule out infectious and disease-related etiologies. (see **ADVERSE REACTIONS**)

For Grade 3 or 4 transaminase or total bilirubin elevation, permanently discontinue OPDIVO or OPDIVO in combination with ipilimumab and initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 transaminase or total bilirubin elevation, withhold OPDIVO or OPDIVO in combination with ipilimumab and start immediate corticosteroid treatment at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, resume OPDIVO or OPDIVO in combination with ipilimumab after corticosteroid taper if needed. If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day methylprednisolone equivalents and permanently discontinue OPDIVO or OPDIVO in combination with ipilimumab.

HCC patients (see **DOSAGE AND ADMINISTRATION**):

In patients with HCC, OPDIVO monotherapy should be withheld or permanently discontinued based on the following criteria and corticosteroids initiated at a dose of 1 to 2 mg/kg methylprednisolone equivalent.

- For Grade 1 transaminase levels at baseline (>1to 3 times ULN) and on-treatment transaminase elevation at >5 to10 times ULN, OPDIVO should be withheld.
- For Grade 2 transaminase levels at baseline (>3 to 5 times ULN) and on-treatment transaminase elevation at >8 to 10 times ULN, OPDIVO should be withheld.
- Regardless of baseline transaminase levels, OPDIVO must be permanently discontinued for on-treatment transaminase increases >10 times ULN or Grade 3 or 4 total bilirubin increases.

Immune-Mediated Pulmonary Adverse Reactions

OPDIVO can cause severe pneumonitis or interstitial lung disease, including fatal cases. These have been observed with OPDIVO monotherapy and OPDIVO in combination with ipilimumab. Monitor patients for signs and symptoms of pneumonitis, such as radiographic changes (eg, focal ground glass opacities, patchy filtrates), dyspnea, and hypoxia. Rule out infectious and disease-related etiologies. (see **ADVERSE REACTIONS**)

For Grade 3 or 4 pneumonitis, permanently discontinue OPDIVO or OPDIVO in combination with ipilimumab and initiate corticosteroids at a dose of 2 to 4 mg/kg/day methylprednisolone equivalents.

For Grade 2 (symptomatic) pneumonitis, withhold OPDIVO or OPDIVO in combination with ipilimumab and initiate corticosteroids at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, resume OPDIVO or OPDIVO in combination with ipilimumab after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 2 to 4 mg/kg/day methylprednisolone equivalents and permanently discontinue OPDIVO or OPDIVO in combination with ipilimumab.

Immune-Mediated Renal Adverse Reactions

OPDIVO can cause severe nephrotoxicity, including nephritis and renal failure. This has been observed with OPDIVO monotherapy and OPDIVO in combination with ipilimumab. Monitor patients for signs and symptoms of nephrotoxicity. Most patients present with asymptomatic increase in serum creatinine. Rule out disease-related etiologies. (see **ADVERSE REACTIONS**)

For Grade 3 or 4 serum creatinine elevation, permanently discontinue OPDIVO or OPDIVO in combination with ipilimumab and initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 serum creatinine elevation, withhold OPDIVO or OPDIVO in combination with ipilimumab and initiate corticosteroid treatment at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, resume OPDIVO or OPDIVO in combination with ipilimumab after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day methylprednisolone equivalents and permanently discontinue OPDIVO or OPDIVO in combination with ipilimumab.

Immune-Mediated Skin Adverse Reactions

OPDIVO can cause severe rash. This has been observed with OPDIVO monotherapy and OPDIVO in combination with ipilimumab.

Monitor patients for rash. Withhold OPDIVO or OPDIVO in combination with ipilimumab for Grade 3 rash and permanently discontinue OPDIVO or OPDIVO in combination with ipilimumab for Grade 4 rash. Administer corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents for severe or life-threatening rash.

Rare cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been observed. If symptoms or signs of SJS or TEN appear, OPDIVO or OPDIVO in combination with ipilimumab should be withheld and the patient referred to a specialized unit for assessment and treatment. If the patient has confirmed SJS or TEN, permanent discontinuation of OPDIVO or OPDIVO in combination with ipilimumab is recommended.

Immune-Mediated Encephalitis

OPDIVO can cause immune-mediated encephalitis. This has been observed in less than 1% of patients treated with OPDIVO monotherapy and OPDIVO in combination with ipilimumab in clinical trials across doses and tumour types, including one fatal case of limbic encephalitis.

Withhold OPDIVO or OPDIVO in combination with ipilimumab in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. Evaluation may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue OPDIVO or OPDIVO in combination with ipilimumab for immune-mediated encephalitis (see **DOSAGE AND ADMINISTRATION**).

Other Immune-Mediated Adverse Reactions

OPDIVO can cause other clinically significant and potentially fatal immune-mediated adverse reactions. Across clinical trials of OPDIVO and OPDIVO in combination with ipilimumab investigating various doses and tumour types, the following immune-mediated adverse reactions were reported in less than 1% of patients: uveitis, Guillain-Barré syndrome, pancreatitis, autoimmune neuropathy (including facial and abducens nerve paresis), demyelination, myasthenic syndrome, myasthenia gravis, aseptic meningitis, gastritis, sarcoidosis, duodenitis, myositis, myocarditis, and rhabdomyolysis. Cases of Vogt-Koyanagi-Harada syndrome and hypoparathyroidism have been reported during post approval use of OPDIVO or OPDIVO in combination with ipilimumab (see **ADVERSE REACTIONS**).

For suspected immune-mediated adverse reactions, perform adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold OPDIVO or OPDIVO in combination with ipilimumab and administer corticosteroids. Upon improvement, resume OPDIVO or OPDIVO in combination with ipilimumab after corticosteroid taper. Permanently discontinue OPDIVO or OPDIVO in combination with ipilimumab for any severe immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction.

Cases of autoimmune hemolytic anemia, some with fatal outcome, have been reported with OPDIVO or OPDIVO in combination with ipilimumab (see **ADVERSE REACTIONS**). Patients with signs and symptoms of anemia should undergo a prompt diagnostic workup to evaluate for autoimmune hemolytic anemia. If autoimmune hemolytic anemia is suspected, hematology consultation should be initiated. Based on the severity of anemia as defined by hemoglobin level, withhold or permanently discontinue OPDIVO or OPDIVO in combination with ipilimumab. Red blood cell transfusion may be necessary in severe cases.

Cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with OPDIVO or OPDIVO in combination with ipilimumab. Some cases of myocarditis can be asymptomatic, so a diagnosis of myocarditis requires a high index of suspicion. Therefore, patients with cardiac or cardio-pulmonary symptoms should undergo a prompt diagnostic workup to evaluate for myocarditis with close monitoring. If myocarditis is suspected, prompt initiation of a high dose of steroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day), and prompt cardiology consultation with diagnostic workup including electrocardiogram, troponin assay, and echocardiogram should be initiated. Additional testing may be warranted, as guided by the cardiologist, and may include cardiac magnetic resonance imaging. Once a diagnosis is established, OPDIVO or OPDIVO in combination with ipilimumab should be withheld. For grade 3 myocarditis, OPDIVO or OPDIVO in combination with ipilimumab therapy should be permanently discontinued (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with OPDIVO. Treatment with OPDIVO may increase the risk of rejection in solid organ

transplant recipients. Consider the benefit of treatment with OPDIVO versus the risk of possible organ rejection in these patients.

Rapid-onset and severe graft-versus-host disease (GVHD), some with fatal outcome, has been reported in the post-marketing setting in patients who had undergone prior allogeneic stem cell transplant and subsequently received OPDIVO (see **ADVERSE REACTIONS**).

Complications, including fatal events, occurred in patients who received allogeneic hematopoietic stem cell transplantation (HSCT) after OPDIVO

Preliminary results from the follow-up of patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) after previous exposure to nivolumab showed a higher than expected number of cases of acute GVHD and transplant related mortality (TRM).

These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT.

Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease (VOD), and other immune-mediated adverse reactions, and intervene promptly. (see **ADVERSE REACTIONS**)

Increased mortality in patients with multiple myeloma [not an approved indication] when OPDIVO is added to a thalidomide analogue and dexamethasone

In randomized clinical trials in patients with multiple myeloma, the addition of a PD-1 blocking antibody, including OPDIVO, to a thalidomide analogue plus dexamethasone, a use for which no PD-1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Haemophagocytic lymphohistiocytosis (HLH)

Haemophagocytic lymphohistiocytosis (HLH) has been reported in relation to the use of OPDIVO either as monotherapy, or in combination with ipilimumab. Patients should be closely monitored. If HLH is suspected, OPDIVO or OPDIVO in combination with ipilimumab should be withheld. If HLH is confirmed, OPDIVO or OPDIVO in combination with ipilimumab should be discontinued and treatment for HLH should be initiated, as deemed medically appropriate (see **ADVERSE REACTIONS**).

Carcinogenesis and Mutagenesis

The mutagenic and carcinogenic potential of nivolumab have not been evaluated. Fertility studies have not been performed with nivolumab.

Infusion Reactions

OPDIVO can cause severe infusion reactions. These have been reported in clinical trials of OPDIVO and OPDIVO in combination with ipilimumab. In case of a severe or life-threatening infusion reaction (Grade 3 or 4), OPDIVO or OPDIVO in combination with ipilimumab infusion

must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive OPDIVO or OPDIVO in combination with ipilimumab with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.

Patients on controlled sodium diet

Each mL of this medicinal product contains 0.1 mmol (or 2.30 mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet.

Special Populations

Pregnant Women:

There are no adequate and well-controlled studies of OPDIVO in pregnant women. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death (see **PART II, TOXICOLOGY**). Human IgG4 is known to cross the placental barrier and nivolumab is an immunoglobulin G4 (IgG4); therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. OPDIVO is not recommended during pregnancy unless the clinical benefit outweighs the potential risk to the fetus. Advise women of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months after the last dose of OPDIVO.

Nursing Women:

It is unknown whether nivolumab is secreted in human milk. Because antibodies are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from nivolumab, a decision should be made whether to discontinue nursing or to discontinue OPDIVO, taking into account the importance of OPDIVO to the mother.

Pediatrics (< 18 years of age):

The safety and effectiveness of OPDIVO have not been established in pediatric patients.

Geriatrics (> 65 years of age):

No overall differences in safety or efficacy were reported between elderly patients (≥ 65 years) and younger patients (< 65 years). Limited safety and efficacy information is available for OPDIVO in cHL ≥ 65 years of age (n=7/266).

Unresectable or Metastatic Melanoma:

Of the 210 patients randomized to OPDIVO in CHECKMATE-066, 50% were 65 years of age or older. Of the 272 patients randomized to OPDIVO in CHECKMATE-037, 35% were 65 years of age or older. Of the 316 patients randomized to OPDIVO in CHECKMATE-067, 37% were 65 years of age or older and of the 314 patients randomized to OPDIVO administered with ipilimumab, 41% were 65 years of age or older.

Adjuvant Treatment of Melanoma:

Of the 523 patients randomized to OPDIVO in CHECKMATE-238, 26% were 65 years of age or older and 3% were 75 years or older. Data from patients 75 years of age or older are too limited to draw conclusions.

Metastatic NSCLC:

Of the 427 patients randomized with OPDIVO in NSCLC Studies CHECKMATE-057 and CHECKMATE-017, 38% of patients were 65 years or older and 7% were 75 years or older. Data from patients 75 years of age or older are too limited to draw conclusions on this population.

Of the 576 patients randomized to OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks in CHECKMATE-227, 48% were 65 years or older and 10% were 75 years or older. Data from patients 75 years of age or older are too limited to draw conclusions on this population. However, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (29.3%) relative to all patients who received OPDIVO with ipilimumab (18.1%). For patients who received treatment with chemotherapy, the discontinuation rate was 7.0% in patients aged 75 years or older compared with a discontinuation rate of 9.1% for all patients.

Of the 361 patients randomized to OPDIVO 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and platinum-doublet chemotherapy every 3 weeks (for 2 cycles) in CHECKMATE-9LA, 51% were 65 years or older and 10% were 75 years or older. For patients treated with OPDIVO in combination with ipilimumab and chemotherapy, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (43%) relative to all patients (28%). For patients who received treatment with chemotherapy only, the discontinuation rate was 16% in patients aged 75 years or older compared with a discontinuation rate of 17% for all patients.

Metastatic RCC:

Of the 410 patients randomized to OPDIVO in CHECKMATE-025, 37% were 65 years of age or older and 8% were 75 years or older. Data from patients 75 years of age or older are too limited to draw conclusions on this population. Of the 550 patients randomized to OPDIVO in combination with ipilimumab in CHECKMATE-214, 38% were 65 years or older and 8% were 75 years or older.

Recurrent or Metastatic SCCHN:

Of the 240 patients randomized to OPDIVO in CHECKMATE-141, 28% were 65 years or older and 5% were 75 years or older.

Hepatocellular Carcinoma:

Of the 145 patients randomized to OPDIVO in CHECKMATE-040, 44% were 65 years or older and 11% were 75 years or older.

MSI-H/dMMR mCRC:

Of the 119 patients randomized to OPDIVO in combination with ipilimumab in CHECKMATE-

142, 32% were 65 years or older and 9% were 75 years or older. Data from patients 65 years of age or older are too limited to draw conclusions on this population.

Renal Impairment

No dose adjustment is needed in patients with mild or moderate renal impairment based on a population PK analysis. Data are not sufficient for drawing a conclusion on patients with severe renal impairment. (see **ACTION AND CLINICAL PHARMACOLOGY**)

Hepatic Impairment

No dose adjustment is needed for patients with mild hepatic impairment (total bilirubin [TB] >1.0 to 1.5 times the upper limit of normal [ULN] or AST >ULN) based on a population PK analysis. OPDIVO has not been studied in patients with moderate (TB >1.5 to 3.0 times ULN and any AST) or severe (TB >3 times ULN and any AST) hepatic impairment. (see **ACTION AND CLINICAL PHARMACOLOGY**)

Hepatocellular Carcinoma:

In advanced hepatocellular carcinoma, there are limited safety and efficacy data available for Child-Pugh Class B patients. No clinical data are available for Child-Pugh Class C patients. (see **CLINICAL TRIALS**)

Monitoring and Laboratory Tests

Liver function tests, thyroid function tests, blood glucose and electrolytes should be monitored prior to and periodically during treatment. Patients should be closely monitored during treatment for signs and symptoms of immune-mediated adverse reactions, including but not limited to, dyspnea, hypoxia; increased frequency of bowel movements, diarrhea; elevated transaminase and bilirubin levels; elevated creatinine levels; rash pruritis; headache, fatigue, hypotension, mental status changes; visual disturbances; muscle pain or weakness; paresthesias.

Metastatic NSCLC and SCCHN:

In the clinical trials, PD-L1 testing was conducted using the Health Canada approved PD-L1 IHC 28-8 pharmDx assay. However, the role of the PD-L1 expression status has not been fully elucidated.

In patients with metastatic non-squamous NSCLC or SCCHN and no measurable tumour PD-L1 expression or in those deemed non-quantifiable, close monitoring for unequivocal progression during the first months of treatment with OPDIVO may be clinically prudent.

NOC/c

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Unresectable or Metastatic Melanoma:

In CHECKMATE-066, OPDIVO was administered at 3 mg/kg every 2 weeks in patients with advanced (unresectable or metastatic) treatment-naive, BRAF V600 wild-type melanoma (n=206) or dacarbazine at 1000 mg/m^2 every 3 weeks (n=205) (see **CLINICAL TRIALS**). OPDIVO patients in this study received a median of 12 doses. The median duration of therapy was 6.51 months (95% CI: 4.86, NA) for OPDIVO and 2.10 months (95% CI: 1.87, 2.40) for chemotherapy. In this trial, 47% of patients received OPDIVO for greater than 6 months and 12% of patients received OPDIVO for greater than 1 year.

In CHECKMATE-067, OPDIVO as a single agent at 3 mg/kg every 2 weeks (n=313) or OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by OPDIVO 3 mg/kg as a single agent every 2 weeks (n=313) or ipilimumab as a single agent at 3 mg/kg every 3 weeks for 4 doses (n=311) was administered in patients with advanced (unresectable or metastatic) treatment-naive melanoma (see **CLINICAL TRIALS**). The median duration of therapy was 2.8 months (95% CI: 2.40, 3.91) with a median of 4 doses (range: 1-39 for OPDIVO; 1-4 for ipilimumab) for OPDIVO in combination with ipilimumab, 6.6 months (95% CI: 5.16, 9.69) with a median of 15 doses (range: 1-38) for single-agent OPDIVO, and 3.0 months (95% CI: 2.56, 3.71) with a median of 4 doses (range: 1-4) in ipilimumab. In the OPDIVO in combination with ipilimumab arm, 39% of patients received treatment for greater than 6 months and 24% received treatment for greater than 1 year. In the single-agent OPDIVO arm, 53% received treatment for greater than 6 months and 32% received treatment for greater than 1 year.

In CHECKMATE-037, OPDIVO was administered at 3 mg/kg every 2 weeks in patients with advanced (unresectable or metastatic) melanoma (n=268) or investigator's choice of chemotherapy (n=102), either dacarbazine 1000 mg/m^2 every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m^2 every 3 weeks (see **CLINICAL TRIALS**). Patients were required to have progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. Patients treated with OPDIVO in this study received a median of eight doses. The median duration of therapy was 5.3 months (range: 1 day-13.8+ months) for OPDIVO and 2 months (range: 1 day-9.6+ months) for chemotherapy. In this ongoing trial, 24% of patients received OPDIVO for greater than 6 months and 3% of patients received OPDIVO for greater than 1 year.

Adjuvant Treatment of Melanoma:

The safety of OPDIVO as a single agent was evaluated in CHECKMATE-238, a randomized (1:1), double-blind Phase 3 trial in which 905 patients with completely resected Stage IIIB/C or Stage IV melanoma received OPDIVO 3 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks (n=452) or ipilimumab 10 mg/kg (n=453) administered as an intravenous infusion every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to a 1 year (see **CLINICAL TRIALS**). The median duration of exposure was 11.5 months (95% CI: 11.47, 11.53) in OPDIVO-treated patients and was 2.7 months (95% CI: 2.33, 3.25) in ipilimumab-treated patients. In this ongoing trial, 74% of patients received OPDIVO for greater than 6 months.

Metastatic NSCLC (previously treated):

Second-line Treatment of Metastatic NSCLC:

OPDIVO 3 mg/kg has been administered to approximately 535 patients with metastatic NSCLC, from two Phase 3 randomized trials in patients with metastatic squamous NSCLC (CHECKMATE-017) and non-squamous NSCLC (CHECKMATE-057), and a Phase 2 single-arm trial in squamous NSCLC (CHECKMATE-063).

CHECKMATE-017 was conducted in patients with metastatic squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen (see **CLINICAL TRIALS**). Patients received 3 mg/kg of OPDIVO (n=131) administered intravenously over 60 minutes every 2 weeks or docetaxel (n=129) administered intravenously at 75 mg/m^2 every 3 weeks. The median duration of therapy was 3.3 months (range: 1 day-21.65+ months) with a median of 8 doses (range: 1-48) in OPDIVO-treated patients and was 1.4 months (range: 1 day-20.01+ months) in docetaxel-treated patients. Therapy was discontinued due to adverse reactions in 3% of patients receiving OPDIVO and 10% of patients receiving docetaxel.

CHECKMATE-057 was conducted in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen (see **CLINICAL TRIALS**). Patients received 3 mg/kg of OPDIVO (n=287) administered intravenously over 60 minutes every 2 weeks or docetaxel (n=268) administered intravenously at 75 mg/m^2 every 3 weeks. The median duration of therapy was 2.6 months (range: 0-24.0+ months) with a median of 6 doses (range: 1-52) in OPDIVO-treated patients and was 2.3 months (range: 0-15.9 months) in docetaxel-treated patients. Therapy was discontinued due to adverse reactions in 5% of patients receiving OPDIVO and 15% of patients receiving docetaxel.

CHECKMATE-063 was a single-arm multinational, multicenter trial in 117 patients with metastatic squamous NSCLC and progression on both a prior platinum-based therapy and at least one additional systemic therapy (see **CLINICAL TRIALS***)*. The median duration of therapy was 2.3 months (range: 1 day-16.1+ months). Patients received a median of 6 doses (range: 1-34).

Metastatic NSCLC (previously untreated):

First-line Treatment of Metastatic NSCLC:

CHECKMATE-227:

The safety of OPDIVO in combination with ipilimumab 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 tumour aberrations (see **CLINICAL TRIALS**). Patients received OPDIVO 3 mg/kg by intravenous infusion over 30 minutes every 2 weeks and ipilimumab 1 mg/kg by intravenous infusion over 30 minutes every 6 weeks (N = 576) or platinum-doublet chemotherapy every 3 weeks for 4 cycles (N = 570). The median duration of therapy in OPDIVO and ipilimumab-treated patients was 4.2 months (range: 1 day to 25.5 months): 39% of patients received OPDIVO and ipilimumab for >6 months and 23% of patients received OPDIVO and ipilimumab for >1 year. The median duration of therapy in

platinum-doublet chemotherapy treated patients was 2.6 months (range: 1 day to 37.6+ months): 24% of patients received platinum-doublet chemotherapy for >6 months and 8% of patients received platinum-doublet chemotherapy for >1 year.

Serious adverse events occurred in 52% of patients treated with OPDIVO in combination with ipilimumab compared with 36% of patients treated with platinum-doublet chemotherapy. Adverse events leading to discontinuation of study therapy were reported in 24% of patients treated with OPDIVO in combination with ipilimumab and in 15% of patients treated with platinum-doublet chemotherapy. In addition, 54% of patients treated with OPDIVO in combination with ipilimumab compared with 49% of patients treated with platinum-doublet chemotherapy had at least one dose withheld for an adverse event (dose delay or dose reduction).

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

CHECKMATE-9LA:

The safety of OPDIVO in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy was evaluated in CHECKMATE-9LA, a randomized, multicenter, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK tumour aberrations (see **CLINICAL TRIALS**). Patients received either OPDIVO 360 mg administered intravenously over 30 minutes every 3 weeks in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 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 for OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was 6.1 months (range: 1 day to 19.1 months): 50% of patients received OPDIVO and ipilimumab for > 6 months and 13% of patients received OPDIVO and ipilimumab for > 1 year.

Serious adverse events occurred in 56.7% of patients treated with OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy compared with 41.3% of patients treated with platinum-doublet chemotherapy. The most frequent (≥2%) serious adverse events reported in patients treated with OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis and respiratory failure. Fatal adverse reactions occurred in 7 patients treated with OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy and included hepatic toxicity, hepatitis, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia. Adverse events leading to discontinuation of study therapy were reported in 27.9% of patients treated with OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy and 16.9% of patients treated with platinum-doublet chemotherapy. In addition, 56.4% of patients treated with

OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy compared with 45.8% of patients treated with platinum-doublet chemotherapy had at least one dose withheld for an adverse event (dose delay or dose reduction).

Metastatic RCC:

Advanced RCC (previously treated):

The safety of OPDIVO was evaluated in a randomized open-label Phase 3 trial (CHECKMATE-025) in which 803 patients with advanced RCC who had experienced disease progression during or after 1 or 2 anti-angiogenic treatment regimens, received OPDIVO 3 mg/kg intravenously every 2 weeks (n=406) or everolimus 10 mg po daily (n=397) (see **CLINICAL TRIALS**). The median duration of treatment was 5.5 months (range: 0-29.6+ months) with a median of 12 doses (range: 1-65) in OPDIVO-treated patients and was 3.7 months (range: 6 days-25.7+ months) in everolimus-treated patients.

Study therapy was discontinued for adverse reactions in 8% of patients receiving OPDIVO and 13% of patients receiving everolimus. Serious adverse reactions occurred in 12% of patients receiving OPDIVO and 13% of patients receiving everolimus. The most frequent serious adverse reactions reported in at least 1% of patients in the OPDIVO arm were pneumonitis and diarrhea.

No treatment related deaths were associated with OPDIVO versus two with everolimus.

Advanced RCC (untreated):

The safety of OPDIVO 3 mg/kg, administered with ipilimumab 1 mg/kg was evaluated in CHECKMATE-214, a randomized open-label trial in which 1082 patients with previously untreated advanced RCC received OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by OPDIVO monotherapy at the 3 mg/kg dose (n=547) every 2 weeks or sunitinib administered orally 50 mg daily for 4 weeks followed by 2 weeks off, every cycle (n=535) (see **CLINICAL TRIALS**). The median duration of treatment was 7.9 months (range: 1 day to 21.4+ months) in OPDIVO plus ipilimumab treated patients and 7.8 months (range: 1 day to 20.2+ months) in sunitinib-treated patients.

Study therapy was discontinued for adverse reactions in 22% of OPDIVO plus ipilimumab patients and 12% of sunitinib patients. Serious adverse reactions occurred in 30% of patients receiving OPDIVO plus ipilimumab and 15% of patients receiving sunitinib. The most frequent serious adverse reactions reported in at least 1% of patients were diarrhea, pneumonitis, hypophysitis, adrenal insufficiency, colitis, hyponatremia, increased ALT, pyrexia and nausea.

In CHECKMATE-214, Grade 3-4 adverse reactions were reported in 46% of OPDIVO plus ipilimumab patients and in 63% of sunitinib patients. Among the patients treated with OPDIVO in combination with ipilimumab, 169/547 (31%) had the first onset of Grade 3 or 4 adverse reactions during the initial combination phase. Among the 382 patients in this group who continued treatment in the single-agent phase, 144 (38%) experienced at least one Grade 3 or 4 adverse reaction during the single-agent phase.

There were seven treatment-related deaths associated with OPDIVO in combination with ipilimumab versus four in patients treated with sunitinib.

Recurrent or Metastatic SCCHN:

The safety of OPDIVO was evaluated in a randomized, open-label, Phase 3 trial (CHECKMATE-141) in patients with recurrent or metastatic SCCHN and progression during or after one prior platinum-based therapy. Patients received 3 mg/kg of OPDIVO (n=236) administered intravenously over 60 minutes every 2 weeks or investigator's choice of either cetuximab (n=13), 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly, or methotrexate (n=46) 40 to 60 mg/m^2 weekly, or docetaxel (n=52) 30 to 40 mg/m^2 weekly (see **CLINICAL TRIALS**). The median duration of therapy was 1.9 months (range: 0.03-16.1+ months) in OPDIVO-treated patients and was 1.9 months (range: 0.03-9.1 months) in patients receiving investigator's choice. In this trial, 18% of patients received OPDIVO for greater than 6 months and 2.5% of patients received OPDIVO for greater than 1 year.

In CHECKMATE-141, therapy was discontinued for adverse reactions in 4% of patients receiving OPDIVO and in 10% of patients receiving investigator's choice. Twenty-four percent (24%) of OPDIVO-treated patients had a drug delay for an adverse reaction. Serious adverse reactions occurred in 7% of OPDIVO-treated patients and in 15% receiving investigator's choice.

There were two treatment-related deaths associated with OPDIVO (pneumonitis and hypercalcemia) versus none in patients treated with investigator's choice therapy.

cHL:

The safety of OPDIVO 3 mg/kg every 2 weeks was evaluated in 266 adult patients with cHL (243 patients in CHECKMATE-205 and 23 patients in CHECKMATE-039) (see **CLINICAL TRIALS**). The median duration of therapy was 18.6 months (range: 12.1 to 20.5 months). Patients received a median of 23 doses (range: 1 to 48).

OPDIVO was discontinued due to adverse reactions in 6.4% of patients. Serious adverse reactions occurred in 10.9% of patients receiving nivolumab. The most frequent serious adverse reactions reported in at least 1% of patients were infusion-related reaction and pneumonitis.

HCC:

The safety of OPDIVO was evaluated in an open-label trial (CHECKMATE-040) in which 145 patients with advanced HCC previously treated with sorafenib (patients either progressed on or were intolerant to sorafenib) received OPDIVO at 3 mg/kg every 2 weeks (see **CLINICAL TRIALS**). The median duration of exposure was 5.26 months [range: 0 to 31.8 (censored value)]. In this trial, 46% of patients received OPDIVO for greater than 6 months and 22.8% of patients received OPDIVO for greater than 1 year.

In CHECKMATE-040, OPDIVO therapy was discontinued in 7% of patients and the dose was delayed in 44% of patients for an adverse reaction. The most common adverse event leading to discontinuation was ascites (1.4%). The most common adverse events leading to dose delay were ALT increased (5.5%), AST increased (4.8%), diarrhea (2.8%), and fatigue (2.8%). Grade 3 or 4

adverse events identified as treatment related by the investigator occurred in 17% of patients. The most common Grade 3 or 4 treatment related adverse events were lipase increased (3.4%), platelet count decreased (2.8%), AST increased (2.8%), ALT increased (2.1%), and fatigue (2.1%). Serious adverse reactions occurred in 46% of patients. The most frequent serious adverse reactions reported in at least 2% of patients were abdominal pain, pyrexia, pneumonia, pneumonitis, and back pain. There was one treatment-related death (pneumonitis) associated with OPDIVO.

In CHECKMATE-040, the safety profile of OPDIVO was generally similar to that observed in other tumour types, with the exception of a higher frequency of pruritus (18.6%), abdominal pain (6.2%), and hepatic and pancreatic laboratory abnormalities, including increased AST (59.2%), increased ALT (47.9%), increased total bilirubin (36.4%), increased lipase (37.1%), and increased amylase (32.1%).

MSI-H/dMMR mCRC:

The safety of OPDIVO administered in combination with ipilimumab was evaluated in CHECKMATE-142, a multicenter, non-randomized, multiple parallel-cohort, open-label trial (see **CLINICAL TRIALS**).

In CHECKMATE-142, 119 patients with mCRC received a combination therapy of OPDIVO 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks for 4 doses, then OPDIVO 3 mg/kg every 2 weeks until disease progression or until unacceptable toxicity. The median duration of therapy was 24.9 months (range: 0 to 44+ months). Patients received a median of 51.0 doses (range: 1 to 93) of OPDIVO and 4.0 doses (range: 1-4) of ipilimumab.

In this ongoing trial, 64.7% of patients received OPDIVO in combination with ipilimumab for greater than 1 year.

OPDIVO was discontinued due to adverse reactions in 13% of patients on the combination therapy. Serious adverse reactions occurred in 22.7% of patients receiving nivolumab in combination with ipilimumab. The most frequent (≥1%) serious adverse reactions were colitis (2.5%), abdominal pain (1.7%), hypophysitis (1.7%), pyrexia (2.5%), increased transaminase (1.7%), anemia (1.7%) and acute kidney injury (1.7%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

OPDIVO is most commonly associated with adverse reactions resulting from increased or excessive immune activity (see **WARNINGS AND PRECAUTIONS** for guidance on management of immune-mediated adverse reactions). Most of these adverse reactions, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of OPDIVO (see **WARNINGS AND PRECAUTIONS**).

Unresectable or Metastatic Melanoma:

CHECKMATE-066:

In CHECKMATE-066 (monotherapy), the most frequently reported adverse reactions (occurring at ≥15%) were fatigue, nausea, diarrhea, pruritus and rash. The majority of adverse reactions were mild to moderate (Grade 1 or 2). OPDIVO therapy was discontinued for adverse reactions in 2.4% of patients. Fifteen percent (15%) of OPDIVO-treated patients had a drug delay for an adverse reaction.

Table 1 lists adverse reactions that occurred in at least 1% of patients in CHECKMATE-066.

Table 1: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-066

	OPDIVO (n=206)		Dacarbazine (n=205)	
System Organ Class Preferred Term	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[a]			
General Disorders and Administration Site Conditions				
Fatigue	30.1	0	25.4	1.5
Pyrexia	7.3	0	5.4	0.5
Edema	3.4	0.5	1.0	0
Gastrointestinal Disorders				
Nausea	16.5	0	41.5	0
Diarrhea	16.0	1.0	15.6	0.5
Constipation	10.7	0	12.2	0
Vomiting	6.3	0.5	21.0	0.5
Abdominal pain	4.4	0	2.4	0
Skin and Subcutaneous Tissue Disorders				
Rash	20.9	1.0	4.9	0
Pruritus	17.0	0.5	5.4	0
Vitiligo	10.7	0	0.5	0
Erythema	6.3	0	2.0	0
Dry Skin	4.4	0	1.0	0
Alopecia	3.4	0	1.0	0
Nervous System Disorders				
Headache	4.4	0	7.3	0
Peripheral Neuropathy	2.9	0	5.4	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain	8.7	0.5	2.9	0
Arthralgia	5.8	0	1.5	0
Metabolism and Nutrition Disorders				
Decreased appetite	5.3	0	9.3	0
Hyperglycemia	1.5	1.0	0	0
Endocrine Disorders				
Hypothyroidism	4.4	0	0.5	0
Hyperthyroidism	3.4	0.5	0	0
Hypopituitarism	1.5	0	0	0
Injury, Poisoning, and Procedural Complications				
Infusion-related reaction	4.4	0	3.9	0

Table 1: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-066

System Organ Class Preferred Term	OPDIVO (n=206)		Dacarbazine (n=205)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[a]			
Infections and Infestations				
Upper respiratory tract infection	1.9	0	0	0
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	2.9	0	1.0	0
Dyspnea	1.9	0	2.0	0
Pneumonitis	1.5	0	0	0
Renal and Urinary Disorders				
Renal Failure	1.5	0.5	0	0

[a] Incidences presented in this table are based on reports of drug-related adverse events.

The following additional adverse reactions were reported in less than 1% of patients treated with OPDIVO 3 mg/kg monotherapy every two weeks in CHECKMATE-066. Adverse reactions presented elsewhere in this section are excluded.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Skin and subcutaneous tissue disorder: psoriasis, rosacea.

Gastrointestinal disorders: stomatitis, colitis.

Nervous system disorder: dizziness, Guillain-Barré syndrome.

Metabolism and nutrition disorders: diabetes mellitus, diabetic ketoacidosis.

Endocrine disorders: hypophysitis.

Eye disorders: uveitis.

Vascular disorders: hypertension.

Abnormal Hematologic and Clinical Chemistry Findings

The incidence of worsening laboratory abnormalities in CHECKMATE-066 is shown in Table 2.

Table 2: Laboratory Abnormalities (CHECKMATE-066)

Test	Number (%) of Patients with Worsening Laboratory Test from Baseline					
	OPDIVO			Dacarbazine		
	N[a]	Grades 1-4	Grades 3-4	N[a]	Grades 1-4	Grades 3-4
Decreased hemoglobin[b]	195	72 (36.9)	3 (1.5)	189	78 (41.3)	12 (6.3)
Decreased platelet count	203	23 (11.3)	1 (0.5)	195	65 (33.3)	13 (6.7)
Decreased lymphocytes	195	56 (28.7)	11 (5.6)	186	87 (46.8)	13 (7.0)
Decreased absolute neutrophil count	196	15 (7.7)	1 (0.5)	190	47 (24.7)	17 (8.9)

Table 2: Laboratory Abnormalities (CHECKMATE-066)

	Number (%) of Patients with Worsening Laboratory Test from Baseline					
	OPDIVO			Dacarbazine		
Test	N[a]	Grades 1-4	Grades 3-4	N[a]	Grades 1-4	Grades 3-4
Increased alkaline phosphatase[c]	194	41 (21.1)	5 (2.6)	186	26 (14.0)	3 (1.6)
Increased AST[c]	195	47 (24.1)	7 (3.6)	191	37 (19.4)	1 (0.5)
Increased ALT[c]	197	49 (24.9)	6 (3.0)	193	37 (19.2)	1 (0.5)
Increased total bilirubin[c]	194	26 (13.4)	6 (3.1)	190	12 (6.3)	0
Increased creatinine	199	21 (10.6)	1 (0.5)	197	19 (9.6)	1 (0.5)

[a] The total number of patients who had both baseline and on-study laboratory measurements available.

[b] Grade 4 for hemoglobin is not applicable per anemia criteria in CTCAE v4.0.

[c] Laboratory Abnormalities Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% [Grades 1-4] or ≥2% [Grades 3-4]).

CHECKMATE-067:

In CHECKMATE-067 (monotherapy and combination therapy), the most common adverse reactions (reported in at least 20% of patients) in either the OPDIVO in combination with ipilimumab arm or the single-agent OPDIVO arm were fatigue, rash, diarrhea, nausea and pruritis. The overall frequency of serious adverse events (SAEs) was higher in the OPDIVO in combination with ipilimumab group (69.3%) compared to the OPDIVO monotherapy (36.1%) and ipilimumab monotherapy groups (52.1%). The overall frequency of drug-related SAEs was higher in the OPDIVO in combination with ipilimumab group (47.9%) compared to the OPDIVO monotherapy (8.0%) and ipilimumab monotherapy groups (22.2%). The overall frequency of AEs leading to discontinuation was higher in the OPDIVO in combination with ipilimumab group (43.1%) compared to the OPDIVO monotherapy (13.7%) and ipilimumab monotherapy (22.5%) groups.

A total of 85 (27.2%), 86 (27.5%), and 114 (36.7%) deaths were reported in the OPDIVO, OPDIVO in combination with ipilimumab, and ipilimumab groups, respectively prior to database lock. Disease progression was the most common cause of death in all 3 groups (72 [23.0%], 70 [22.4%], and 102 [32.8%]). There were no treatment-related deaths in patients receiving OPDIVO in combination with ipilimumab. One patient treated with single-agent OPDIVO died due to neutropenia, and one patient treated with ipilimumab died due to cardiac arrest. Thirteen subjects in the OPDIVO in combination with ipilimumab group had death classified as 'other' by the investigator, these included: pulmonary embolus (3 events), dyspnea due to emphysema, pneumonia (2 events), intercurrent illness, likely infection leading to multi organ failure, euthanasia, respiratory failure (2 events), accident, sudden cardiac death, and worsening of general condition.

Among the patients treated with OPDIVO in combination with ipilimumab, 193/313 (62%) had the first onset of Grade 3 or 4 adverse reactions during the initial combination phase. Among the

147 patients in this group who continued treatment in the single-agent phase, 53 (36%) experienced at least one Grade 3 or 4 adverse reaction during the single-agent phase.

As compared to the overall study population, no meaningful differences in safety were observed based on BRAF status or PD-L1 expression level.

Table 3 summarizes the adverse reactions that occurred in at least 1% of patients in either OPDIVO-containing arm or in the ipilimumab arm in CHECKMATE-067.

Table 3: Adverse Reactions Reported in at Least 1% of Patients (CHECKMATE-067)

	OPDIVO + ipilimumab (n=313)		OPDIVO (n=313)		ipilimumab (n=311)	
System Organ Class **Preferred Term**	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[a]					
General Disorders and Administration Site Conditions						
Fatigue	42.5	4.2	39.3	1.6	32.5	1.6
Pyrexia	18.5	0.6	6.1	0	6.8	0.3
Chills	6.4	0	3.5	0	3.2	0
Influenza-like Illness	2.6	0	3.2	0	3.5	0.3
Edema[b]	3.2	0	2.2	0	3.5	0.3
Malaise	1.9	0.3	1.0	0.3	0.6	0
Pain	1.6	0	0.6	0	1.6	0
General physical health deterioration	1.0	0.3	0	0	0.3	0.3
Thirst	1.0	0	0	0	0	0
Gastrointestinal Disorders						
Diarrhea	44.1	9.3	19.2	2.2	33.1	6.1
Nausea	25.9	2.2	13.1	0	16.1	0.6
Vomiting	15.3	2.6	6.4	0.3	7.4	0.3
Abdominal pain	11.8	0.3	7.3	0	10.3	1.0
Colitis	11.8	7.7	1.3	0.6	11.6	8.7
Dry Mouth	5.1	0	4.2	0	2.3	0
Constipation	3.8	0	6.1	0	5.1	0
Stomatitis	3.5	0.3	2.2	0	1.6	0
Dyspepsia	2.6	0	2.6	0	1.6	0
Gastritis	1.6	1.0	0	0	0.3	0
Abdominal distension	1.3	0	1.3	0	1.0	0
Skin and Subcutaneous Tissue Disorders						
Rash	46.3	5.1	30.0	1.3	36.7	2.9
Pruritus	33.2	1.9	18.8	0	35.4	0.3
Vitiligo	6.7	0	7.3	0.3	3.9	0
Dry Skin	3.2	0	4.8	0	3.2	0
Hyperhidrosis	3.8	0	0.6	0	1.0	0
Night sweats	2.6	0	1.0	0	1.6	0
Eczema	1.9	0	1.6	0	0.6	0
Alopecia	1.6	0	1.9	0	0	0
Skin hypopigmentation	1.6	0	1.9	0	0.6	0
Hair colour changes	1.3	0	1.3	0	0	0
Photosensitivity	1.0	0	0.3	0	0.3	0

Table 3: Adverse Reactions Reported in at Least 1% of Patients (CHECKMATE-067)

System Organ Class Preferred Term	OPDIVO + ipilimumab (n=313)		OPDIVO (n=313)		ipilimumab (n=311)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[a]					
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	10.5	0.3	8.0	0	6.4	0
Musculoskeletal Pain	7.3	0.3	9.6	0.3	7.4	0
Muscular weakness	1.9	0.3	1.3	0	0.6	0
Muscle spams	1.6	0.3	1.3	0	1.0	0
Musculoskeletal stiffness	1.0	0	0.6	0	0.3	0
Metabolism and Nutrition Disorders						
Decreased appetite	17.9	1.3	10.9	0	12.5	0.3
Dehydration	4.2	1.3	0.3	0	1.6	0.6
Hyperglycaemia	2.6	1.0	0.3	0.3	0.6	0
Hyponatremia	2.6	1.0	0.6	0.3	1.0	0.6
Hypoalbuminemia	1.9	0	0.6	0	1.0	0.3
Hypokalemia	1.9	0.3	0.3	0.3	0.6	0.3
Hypomagnesemia	1.0	0	0.3	0	0.6	0
Endocrine Disorders						
Hypothyroidism	15.0	0.3	8.9	0	4.2	0
Hyperthyroidism	9.9	1.0	4.2	0	1.0	0
Hypophysitis	7.7	1.6	0.6	0.3	3.9	1.9
Thyroiditis	4.5	1.0	1.0	0	0.3	0
Adrenal Insufficiency	2.6	1.6	0.6	0.3	1.3	0.3
Hypopituitarism	1.6	1.0	0.3	0.3	1.3	0.6
Respiratory, Thoracic, and Mediastinal Disorders						
Dyspnea	10.2	0.6	5.8	0.3	4.8	0
Cough	7.0	0	5.4	0.3	4.8	0
Pneumonitis	7.0	1.0	1.6	0.3	1.9	0.3
Wheezing	1.0	0	0.6	0	0.3	0
Nervous System Disorders						
Headache	10.2	0.3	7.3	0	7.7	0.3
Dizziness	4.8	0	4.5	0	3.2	0
Neuropathy Peripheral	4.8	0.6	2.9	0.3	1.6	0
Dysgeusia	4.5	0	5.4	0	2.9	0
Lethargy	2.9	0	1.3	0	1.9	0
Paresthesia	1.3	0	2.2	0	2.3	0
Syncope	1.3	0.3	0	0	0	0
Somnolence	1.0	0.3	0	0	0	0
Tremor	1.0	0	0	0	0.3	0
Injury, Poisoning, and Procedural Complications						
Infusion-related reaction	2.9	0	2.2	0.3	2.3	0.3
Blood and Lymphatic System Disorders						
Eosinophilia	2.2	0	0.3	0	0.3	0
Thrombocytopenia	1.9	0.6	1.6	0.3	0	0
Neutropenia	1.3	0.3	1.3	1.0[c]	0.6	0.3
Hepatobiliary Disorders						

Table 3: Adverse Reactions Reported in at Least 1% of Patients (CHECKMATE-067)

System Organ Class Preferred Term	OPDIVO + ipilimumab (n=313)		OPDIVO (n=313)		ipilimumab (n=311)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[a]					
Hepatitis	4.5	4.2	0.6	0.6	0.6	0.3
Hyperbilirubinaemia	3.2	0	0.6	0	1.0	0
Hepatotoxicity	3.2	2.6	0.3	0.3	0.3	0
Hepatocellular injury	1.0	0.6	0.6	0.3	0	0
Eye Disorders						
Blurred vision	1.9	0	1.9	0	1.9	0
Dry eye	1.0	0	2.2	0	1.6	0
Uveitis	1.0	0	0.6	0	1.0	0.3
Psychiatric Disorders						
Sleep disorder	2.2	0.3	2.9	0.3	1.9	0
Anxiety	1.3	0	0.3	0	0.3	0
Confusional state	1.0	0	0.6	0.3	0	0
Depression	1.0	0	0.6	0	0.3	0
Infections and Infestations						
Upper respiratory tract infection	1.3	0	0.6	0	0.6	0
Conjunctivitis	1.3	0	0.3	0	0.6	0
Vascular Disorders						
Hypotension	1.9	0.6	0.3	0.3	0.6	0
Hypertension	1.3	0.3	1.3	0.6	0.3	0.3
Flushing	1.0	0	1.0	0	1.9	0
Renal and Urinary Disorders						
Renal failure	1.6	1.3	0.6	0.3	1.0	0
Nephritis	1.0	0.6	0	0	0.3	0.3
Immune System Disorders						
Hypersensitivity	1.3	0	1.9	0	0.3	0
Cardiac Disorders						
Tachycardia	1.3	0	0	0	0.6	0
Palpitations	1.0	0	0.3	0	0.6	0

[a] Incidences presented in this table are based on reports of drug-related adverse events.
[b] Including peripheral edema.
[c] Includes one Grade 5 event (refer to **Blood and Lymphatic System Disorders** - Neutropenia).

The following additional adverse reactions were reported in less than 1% of patients treated with either OPDIVO as a single agent at 3 mg/kg every two weeks or OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by OPDIVO 3 mg/kg as a single agent every two weeks in CHECKMATE-067. Adverse reactions presented elsewhere in this section are excluded.

Less Common Clinical Trial Adverse Drug Reactions (<1%) OPDIVO + Ipilimumab

Gastrointestinal Disorders: intestinal perforation.

Musculoskeletal and Connective Tissue Disorders: polymyalgia rheumatica, Sjogren's syndrome, spondyloarthropathy.

Nervous System Disorders: neuritis, peroneal nerve palsy.

Respiratory, Thoracic and Mediastinal Disorders: pleural effusion.

Cardiac Disorders: atrial fibrillation.

Less Common Clinical Trial Adverse Drug Reactions (<1%) OPDIVO

Musculoskeletal and Connective Tissue Disorders: myopathy.

Respiratory, Thoracic and Mediastinal Disorders: pleural effusion.

Cardiac Disorders: atrial fibrillation.

Abnormal Hematologic and Clinical Chemistry Findings

Table 4 presents selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of patients in either OPDIVO-containing arm or in the ipilimumab arm in CHECKMATE-067.

Table 4: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients treated with OPDIVO in Combination with Ipilimumab or Single-Agent OPDIVO and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (CHECKMATE-067)

	Percentage (%) of Patients[a]					
	OPDIVO + ipilimumab (n=313)		OPDIVO (n=313)		ipilimumab (n=311)	
Test	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Decreased hemoglobin[b]	50	2.7	39	2.6	40	5.6
Decreased platelet count	11	1.4	9	0.3	5	0.3
Decreased leukocytes	12	0.3	16	0.3	6	0.3
Decreased lymphocytes (absolute)	35	4.8	39	4.3	27	3.4
Decreased absolute neutrophil count	12	0.7	14	0.3	6	0.3
Increased alkaline phosphatase	40	5.5	24	2.0	22	2.0
Increased ALT	53	14.8	23	3.0	28	2.7
Increased AST	47	12.7	27	3.7	27	1.7
Bilirubin, total	12	1.0	10	1.3	5	0
Increased creatinine	23	2.7	16	0.3	16	1.3
Increased amylase	25	9.1	15	1.9	14	1.6
Increased lipase	41	19.9	29	8.6	23	7.0
Hyponatremia	42	9.2	20	3.3	25	6.7
Hypocalcemia	29	1.1	13	0.7	21	0.7
Hypokalemia	17	4.4	7	1.0	10	1.0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO+ipilimumab (range: 241-297); single-agent OPDIVO (range: 260-306); ipilimumab (range: 253-304).

[b] Grade 4 for hemoglobin is not applicable per anemia criteria in CTCAE v4.0.

CHECKMATE-037:

In CHECKMATE-037 (monotherapy), the most frequently reported adverse reactions (occurring at ≥15%) were fatigue, nausea, diarrhea, pruritus and rash. The majority of adverse reactions were mild to moderate (Grade 1 or 2). OPDIVO was discontinued due to adverse reactions in 2% of patients receiving OPDIVO and in 8% of patients receiving chemotherapy. Ten percent (10%) of OPDIVO-treated patients had a drug delay for an adverse reaction. Serious adverse reactions occurred in 6% of patients receiving OPDIVO. Grade 3 and 4 adverse reactions occurred in 5% of patients receiving OPDIVO.

The frequency of adverse events in the cardiac disorders system organ class regardless of causality was higher in the OPDIVO group (27/268; 10.1% all grades, 4.1% grade 3-5) than in the chemotherapy group (1/102; 1% all grades) in post-CTLA4/BRAF inhibitor metastatic melanoma population (CHECKMATE-037). Incidence rates of cardiac events per 100 person-years of exposure were 13.4 in the OPDIVO group vs none in the chemotherapy group. Serious cardiac events were reported by 4.5% patients in the OPDIVO group vs none in the chemotherapy group. One serious cardiac adverse event (ventricular arrhythmia) was considered related to OPDIVO by investigators.

At the final analysis for CHECKMATE-037, there were no new safety signals observed and therefore with additional follow-up, no meaningful changes occurred in the safety profile of OPDIVO.

Table 5 lists adverse reactions that occurred in at least 1% of patients in CHECKMATE-037.

Table 5: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-037

	OPDIVO (n=268)		Chemotherapy (n=102)	
System Organ Class **Preferred Term**	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[a]			
General Disorders and Administration Site Conditions				
Fatigue	29.5	0.7	40.2	3.9
Pyrexia	3.4	0	4.9	1.0
Edema	3.0	0	1.0	0

Table 5: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-037

System Organ Class Preferred Term	OPDIVO (n=268)		Chemotherapy (n=102)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[a]			
Gastrointestinal Disorders				
Diarrhea	11.2	0.4	14.7	2.0
Nausea	9.3	0	37.3	2.0
Vomiting	3.4	0.4	19.6	2.0
Abdominal pain	2.6	0.4	2.9	0
Constipation	2.2	0	13.7	1.0
Stomatitis	1.1	0	2.9	0
Colitis	1.1	0.7	0	0
Skin and Subcutaneous Tissue Disorders				
Rash	16.8	0.4	6.9	0
Pruritus	16.0	0	2.0	0
Vitiligo	5.2	0	0	0
Dry Skin	4.9	0	0	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	5.6	0.4	11.8	1.0
Musculoskeletal Pain	5.2	0	9.8	0
Metabolism and Nutrition Disorders				
Decreased appetite	5.2	0	15.7	0
Hyperglycemia	1.1	0.7	0	0
Endocrine Disorders				
Hypothyroidism	5.6	0	0	0
Hyperthyroidism	1.9	0	1.0	0
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea	3.7	0	7.8	0
Cough	2.6	0	0	0
Pneumonitis	2.2	0	0	0
Nervous System Disorders				
Peripheral Neuropathy	2.6	0.4	22.5	2.0
Headache	2.6	0	2.9	0
Dizziness	1.5	0	2.9	0
Investigations				
Lipase increased	1.5	1.1	2.0	1.0
Amylase increased	1.1	0.7	0	0
Injury, Poisoning, and Procedural Complications				
Infusion-related reaction	1.1	0.4	6.9	0
Infections and Infestations				
Upper respiratory tract infection	1.1	0	0	0
Eye Disorders				
Uveitis	1.5	0.4	0	0

[a] Incidences presented in this table are based on reports of drug-related adverse events.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Skin and subcutaneous tissue disorder: alopecia, urticaria, erythema multiforme.

Endocrine disorders: thyroiditis.

Renal and urinary disorders: tubulointerstitial nephritis.

Cardiac disorders: ventricular arrhythmia.

Abnormal Hematologic and Clinical Chemistry Findings

The incidence of worsening laboratory abnormalities for CHECKMATE-037 is shown in Table 6.

Table 6: Laboratory Abnormalities (CHECKMATE-037)

	Number (%) of Patients with Worsening Laboratory Test from Baseline					
	OPDIVO			Chemotherapy		
Test	N[a]	Grades 1-4	Grades 3-4	N[a]	Grades 1-4	Grades 3-4
Decreased hemoglobin[b]	259	94 (36.3)	16 (6.2)	99	59 (59.6)	9 (9.1)
Decreased platelet count	257	24 (9.3)	0	99	40 (40.4)	9 (9.1)
Leukopenia	257	22 (8.6)	1 (0.4)	100	53 (53.0)	14 (14.0)
Decreased lymphocytes	256	112 (43.8)	17 (6.6)	99	52 (52.5)	15 (15.2)
Decreased absolute neutrophil count	256	20 (7.8)	3 (1.2)	99	44 (44.4)	21 (21.2)
Increased alkaline phosphatase[c]	252	55 (21.8)	6 (2.4)	94	12 (12.8)	1 (1.1)
Increased AST[c]	253	70 (27.7)	6 (2.4)	96	11 (11.5)	1 (1.0)
Increased ALT[c]	253	41 (16.2)	4 (1.6)	96	5 (5.2)	0
Increased total bilirubin	249	24 (9.6)	1 (0.4)	94	0	0
Increased creatinine	254	34 (13.4)	2 (0.8)	94	8 (8.5)	0
Hyponatremia[c]	256	63 (24.6)	13 (5.1)	95	17 (17.9)	1 (1.1)
Hyperkalemia[c]	256	39 (15.2)	5 (2.0)	95	6 (6.3)	0

[a] The total number of patients who had both baseline and on-study laboratory measurements available.

[b] Grade 4 for hemoglobin is not applicable per anemia criteria in CTCAE v4.0.

[c] Laboratory Abnormalities Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% [Grades 1-4] or ≥2% [Grades 3-4]).

Overall, there were no differences in the types or frequencies of adverse drug reactions reported in CHECKMATE-066 and CHECKMATE-037. The frequency of cardiac adverse events was lower in the OPDIVO group than in the dacarbazine group in the metastatic melanoma without prior treatment population (CHECKMATE-066).

The safety profile of OPDIVO in combination with ipilimumab in CHECKMATE-069 was consistent with that observed in CHECKMATE-067.

Adjuvant Treatment of Melanoma:

In CHECKMATE-238, the most frequently reported adverse reactions (occurring at ≥10%) in the OPDIVO group were fatigue, rash, diarrhea, pruritus, nausea, arthralgia, musculoskeletal pain, and hypothyroidism. The majority of adverse reactions were mild to moderate (Grade 1 or 2). Grade 3-4 adverse reactions were reported in 14% of OPDIVO patients and 46% of ipilimumab patients.

Study therapy was discontinued for adverse reactions in 8% of OPDIVO patients and 42% of ipilimumab patients. In the OPDIVO group, the most frequently reported adverse reactions (occurring at ≥1%) leading to discontinuation were diarrhea (1.5%) and colitis (1.1%). Twenty percent (20%) of OPDIVO-treated patients had a drug delay (dose omission or reduction) for an adverse reaction. The most frequently reported adverse reactions (occurring at ≥1%) leading to dose delay were diarrhea (3.3%), ALT increased (2.9%), AST increased (2.4%), hypothyroidism (2.0%), hyperthyroidism (1.8%), arthralgia (1.5%), increased lipase (1.3%) and increased amylase (1.1%).

Serious adverse reactions occurred in 5% of OPDIVO patients and 31% of ipilimumab patients. The most frequently reported serious adverse reactions (occurring at ≥0.5%) in OPDIVO patients were diarrhea (0.7%) and pneumonitis (0.7%).

Table 7 lists adverse reactions that occurred in at least 1% of patients in CHECKMATE-238.

Table 7: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-238

	OPDIVO (n=452)		Ipilimumab (n=453)	
System Organ Class **Preferred Term**	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[a]			
General Disorders and Administration Site Conditions				
Fatigue[b]	46.5	0.7	44.4	1.8
Influenza like illness	2.0	0	2.4	0.2
Pyrexia	1.5	0	11.9	0.4
Chest pain	1.1	0	0.4	0
Pain	1.1	0.2	1.5	0
Gastrointestinal Disorders				
Diarrhea	24.3	1.5	45.9	9.5
Nausea	15.0	0.2	20.1	0
Abdominal pain[c]	9.3	0	13.0	0.2
Dry mouth	5.3	0	3.1	0
Stomatitis	3.3	0.2	1.8	0
Dyspepsia	2.9	0	3.8	0
Vomiting	2.7	0.2	9.7	0.4
Constipation	2.4	0	2.2	0
Colitis	2.0	0.7	11.3	8.6
Abdominal distension	1.8	0	2.0	0
Flatulence	1.1	0	0.7	0
Skin and Subcutaneous Tissue Disorders				
Rash[d]	28.5	1.1	42.8	4.9
Pruritus	23.2	0	33.6	1.1

Table 7: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-238

System Organ Class Preferred Term	OPDIVO (n=452)		Ipilimumab (n=453)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[a]			
Erythema	4.4	0	3.5	0
Vitiligo	4.2	0	1.8	0
Eczema	2.9	0	1.8	0.2
Alopecia	1.8	0	2.9	0
Dry Skin	1.8	0	1.5	0.4
Generalized pruritus	1.8	0	1.5	0
Nervous System Disorders				
Headache	9.7	0.2	17.4	1.5
Dizziness	3.5	0	3.5	0
Dysgeusia	2.7	0	2.6	0
Paraesthesia	2.7	0	2.2	0
Neuropathy peripheral	1.1	0	3.3	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	12.6	0.2	10.8	0.4
Musculoskeletal pain[e]	11.3	0.4	9.5	0.2
Musculoskeletal stiffness	1.1	0	0.9	0
Tendonitis	1.1	0	0	0
Metabolism and Nutrition Disorders				
Decreased appetite	4.0	0	8.6	0.2
Hyponatremia	1.1	0	1.5	0.7
Endocrine Disorders				
Hypothyroidism[f]	11.1	0.2	6.8	0.4
Hyperthyroidism	8.4	0.2	4.0	0.2
Thyroiditis	2.2	0	1.8	0.2
Hypophysitis	1.5	0.4	10.6	2.4
Adrenal insufficiency	1.1	0.2	2.6	0.7
Injury, Poisoning, and Procedural Complications				
Infusion-related reaction	2.0	0	1.5	0
Eye Disorders				
Dry eye	2.2	0	1.5	0
Vision blurred	1.3	0	2.2	0
Psychiatric Disorders				
Insomnia	1.8	0	1.8	0
Vascular Disorders				
Flushing	1.5	0	3.3	0
Cardia Disorders				
Palpitations	1.3	0	0.2	0
Immune System Disorders				
Sarcoidosis	1.1	0.2	0.2	0
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea	4.2	0.4	5.3	0
Cough	2.2	0	5.1	0
Pneumonitis	1.3	0	2.4	0.9
Blood and Lymphatic System Disorders				
Anemia	1.1	0	2.2	0.2

[a] Incidences presented in this table are based on reports of drug-related adverse events (CTCAE v4.0).
b Includes asthenia.
c Includes abdominal discomfort, lower abdominal pain, upper abdominal pain, and abdominal tenderness.
d Includes dermatitis also described as acneiform, allergic, bullous, or exfoliative and rash described as generalized, erythematous, macular, papular, maculopapular, pruritic, pustular, vesicular, or butterfly, and drug eruption.
e Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, spinal pain, and pain in extremity.
f Includes secondary hypothyroidism and autoimmune hypothyroidism.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following other clinically important adverse reactions were reported in less than 1% of patients in the OPDIVO group in CHECKMATE-238. Adverse reactions presented elsewhere are excluded.

Endocrine disorders: fulminant type I diabetes

Abnormal Hematologic and Clinical Chemistry Findings

The incidence of worsening laboratory abnormalities in CHECKMATE-238 is shown in Table 8.

Table 8: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients (CHECKMATE-238)

	Number (%) of Patients with Worsening Laboratory Test from Baseline					
	OPDIVO			Ipilimumab		
Test	N[a]	Grades 1-4	Grades 3-4	N[a]	Grades 1-4	Grades 3-4
Decreased hemoglobin[b]	447	25.5	0	440	33.6	0.5
Decreased Leukocytes	447	13.9	0	440	2.7	0.2
Decreased lymphocytes	446	26.7	0.4	439	12.3	0.9
Decreased absolute neutrophil count	447	12.5	0	439	5.9	0.5
Increased ALT	445	23.6	1.3	440	32.7	8.6
Increased AST	447	25.3	1.8	443	39.5	11.7
Increased creatinine	446	12.1	0	440	12.7	0
Increased amylase	400	17.0	3.3	392	13.3	3.1
Increased lipase	438	24.9	7.1	427	23.2	8.7
Hyponatremia	446	16.1	1.1	438	21.7	3.2
Hyperkalemia	445	12.4	0.2	439	8.9	0.5
Hypocalcemia	434	10.6	0.7	422	17.3	0.5

[a] The total number of patients who had both baseline and on-study laboratory measurements available.
[b] Grade 4 for hemoglobin is not applicable per anemia criteria in CTCAE v4.0.

Metastatic NSCLC (previously treated):

In patients who received 3 mg/kg OPDIVO monotherapy in CHECKMATE-017 and CHECKMATE-057, the most frequently reported adverse drug reactions (occurring at ≥10%) were fatigue, nausea, rash, and decreased appetite (Table 9). The majority of adverse drug reactions were mild to moderate (Grade 1 or 2).

Table 9 summarizes adverse drug reactions that occurred in at least 1% of patients receiving OPDIVO in CHECKMATE-017 and CHECKMATE-057.

Table 9: Adverse Drug Reactions Reported in at Least 1% of Patients in CHECKMATE-017 and CHECKMATE-057

Adverse Reaction	OPDIVO (n=418)		Docetaxel (n=397)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	Percentage (%) of Patients			
General Disorders and Administration Site Conditions				
Fatigue[a]	26	1	45	8
Pyrexia	3	0	7	0.3
Edema[b]	3	0	11	0.3
Gastrointestinal Disorders				
Nausea	11	0.5	25	1
Diarrhea	8	0.5	22	2
Vomiting	5	0	9	0.3
Constipation	4	0	7	0.5
Stomatitis	3	0	14	2
Skin and Subcutaneous Tissue Disorders				
Rash[c]	11	0.7	10	0.8
Pruritus	7	0	1	0
Urticaria	1	0	0.5	0
Metabolism and Nutrition Disorders				
Decreased appetite	11	0.2	17	1
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[d]	6	0.2	18	1
Arthralgia[e]	6	0	6	0
Respiratory, Thoracic, and Mediastinal Disorders				
Pneumonitis	4	1	0.5[f]	0.3
Cough	4	0.2	1	0
Dyspnea	3	0.5	3	0.3
Nervous System Disorders				
Peripheral neuropathy	4	0	22	2
Headache	1	0	2	0
Endocrine Disorders				

Table 9: Adverse Drug Reactions Reported in at Least 1% of Patients in CHECKMATE-017 and CHECKMATE-057

Adverse Reaction	OPDIVO (n=418)		Docetaxel (n=397)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	Percentage (%) of Patients			
Hypothyroidism	6	0	0	0
Hyperthyroidism	1	0	0	0
Injury, Poisoning and Procedural Complications				
Infusion-related reaction	2	0	2	0.3

[a] Includes asthenia.

[b] Includes face edema, peripheral edema, local swelling, localized edema, orbital edema, generalized edema, peripheral swelling, swelling face.

[c] Includes maculopapular rash, rash erythematous, rash macular, rash papular, rash pustular, rash pruritic, rash generalized, dermatitis, dermatitis exfoliative, dermatitis acneiform, dermatitis bullous, drug eruption, toxic skin eruption, and erythema.

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

[e] Includes arthritis and osteoarthritis.

[f] Includes 1 Grade 5 event.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following other clinically important adverse drug reactions were reported in less than 1% of patients treated with OPDIVO 3 mg/kg monotherapy in CHECKMATE-017 and CHECKMATE-057. Adverse reactions presented elsewhere are excluded.

Gastrointestinal Disorders: pancreatitis.

Musculoskeletal and Connective Tissue Disorders: polymyalgia rheumatica.

Endocrine Disorders: hyperglycaemia.

Eye Disorders: blurred vision.

Neoplasms Benign, Malignant and Unspecified: histocytic necrotising lymphadenitis (Kikuchi lymphadenitis).

Investigations: lipase increased, amylase increased.

Respiratory, Thoracic, and Mediastinal Disorders: pleural effusion.

Infections and Infestations: pneumonia.

Abnormal Hematologic and Clinical Chemistry Findings

The incidence of worsening laboratory abnormalities is shown in Table 10.

Table 10: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients (CHECKMATE-017 and CHECKMATE-057)

	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	OPDIVO		Docetaxel	
Test	**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**
Chemistry				
Hyponatremia	35	7	34	4.9
Increased AST	27	1.9	13	0.8
Increased alkaline phosphatase	26	0.7	18	0.8
Hyperkalemia	23	1.7	20	2.6
Increased ALT	22	1.7	17	0.5
Hypomagnesemia	21	1.2	17	0.3
Hypocalcemia	20	0.2	23	0.3
Increased creatinine	18	0	12	0.5
Hypokalemia	15	1.4	13	2.1
Hypercalcemia	12	1.2	8	0.5
Hematology				
Lymphopenia	48	10	59	24
Anemia	34	2.4	57	5
Thrombocytopenia	12	0.7	12	0
Leukopenia	11	1.2	78	50

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 405-417 patients) and docetaxel group (range: 372-390 patients).

Metastatic Squamous NSCLC Trial:

The most common adverse drug reactions (reported in at least 10% of patients) in CHECKMATE-063 were fatigue, decreased appetite, nausea, diarrhea, and rash.

Metastatic NSCLC (previously untreated):

CHECKMATE-227:

Table 11 lists adverse reactions that occurred in at least 1% of OPDIVO plus ipilimumab treated patients in CHECKMATE-227.

Table 11: Adverse Reactions Reported in at Least 1% of Patients Receiving OPDIVO and Ipilimumab in CHECKMATE-227

	OPDIVO + ipilimumab (n=576)		Platinum-doublet chemotherapy (n=570)	
System Organ Class Preferred Term	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[a]			
Skin and Subcutaneous Tissue Disorders				
Rash[b]	28.0	3.1	8.4	0.2
Pruritus	14.2	0.5	1.1	0

Table 11: Adverse Reactions Reported in at Least 1% of Patients Receiving OPDIVO and Ipilimumab in CHECKMATE-227

System Organ Class Preferred Term	OPDIVO + ipilimumab (n=576)		Platinum-doublet chemotherapy (n=570)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[a]			
Dry skin	5.4	0.2	1.1	0
Erythema	1.9	0.2	0.5	0
Eczema[c]	1.4	0.5	0	0
Generalised pruritus	1.0	0	0.2	0
General Disorders and Administration Site Conditions				
Fatigue[d]	23.8	3.0	31.1	2.3
Pyrexia	7.5	0.3	3.2	0
Edema[e]	2.8	0	5.8	0
Malaise	1.6	0	3.9	0
Chills	1.2	0	0.2	0
Xerosis	1.0	0	0	0
Gastrointestinal Disorders				
Diarrhea	17.0	1.7	9.6	0.7
Nausea	9.9	0.5	36.1	2.1
Vomiting	4.9	0.3	13.5	2.3
Constipation	4.5	0	14.9	0.4
Stomatitis[f]	3.5	0.2	8.9	1.1
Abdominal pain[g]	2.8	0.2	2.6	0
Dry Mouth	2.8	0	0.4	0
Colitis	2.3	0.7	0	0
Pancreatitis[h]	1.0	0.7	0	0
Endocrine Disorders				
Hypothyroidism	12.5	0.3	0	0
Hyperthyroidism	8.3	0	0	0
Adrenal insufficiency	3.3	1.7	0	0
Hypophysitis	2.1	1.0	0	0
Hypopituitarism	1.2	0.5	0	0
Metabolism and Nutrition Disorders				
Decreased appetite	13.2	0.7	19.6	1.2
Hyponatremia	3.1	1.7	1.9	0.5
Dehydration	1.2	0.5	1.2	0.2
Hypoalbuminemia	1.2	0	1.1	0.2
Hypokalemia	1.2	0.3	1.1	0.4
Diabetes mellitus	1.0	0.7	0	0
Respiratory, Thoracic, and Mediastinal Disorders				
Pneumonitis[i]	8.3[o]	3.3	1.1	0.5
Dyspnea	2.6	0.2	1.4	0
Cough	2.1	0.2	0.4	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	5.0	0.7	0.4	0
Musculoskeletal pain[j]	4.2	0.2	2.6	0
Arthritis[k]	1.4	0.7	0	0
Immune System Disorders				
Infusion-related reaction	3.3	0	0.9	0.2

Table 11: Adverse Reactions Reported in at Least 1% of Patients Receiving OPDIVO and Ipilimumab in CHECKMATE-227

System Organ Class Preferred Term	OPDIVO + ipilimumab (n=576)		Platinum-doublet chemotherapy (n=570)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[a]			
Investigations				
Increased transaminases[l]	11.5	4.5	5.8	0.2
Increased lipase	7.5	4.0	0.9	0.4
Increased amylase	6.3	3.0	0.9	0.2
Increased blood creatinine	2.4	0	3.3	0
Increased blood alkaline phosphatase	2.3	0.7	1.1	0
Weight decreased	2.1	0.2	1.8	0.2
Decreased white blood cell count	1.6	0	0.2	0
Increased thyroid stimulating hormone	1.0	0	0	0
Hepatobiliary Disorders				
Hepatitis	2.1	1.9	0	0
Nervous System Disorders				
Dysgeusia	2.1	0	5.1	0
Headache	1.9	0	1.4	0
Paresthesia	1.4	0	1.9	0
Renal and Urinary Disorders				
Renal failure (including acute kidney injury)	1.4	0.3	1.4	0.4
Blood and Lymphatic System Disorders				
Anemia[m]	4.0	1.4	33.3	11.6
Thrombocytopenia[n]	1.4	0.3	17.9	7.7
Infections and Infestations				
Conjunctivitis	1.0	0	1.8	0
Immune System Disorders				
Infusion-related reaction	3.3	0	0.9	0.2
Hepatobiliary Disorders				
Hepatitis	2.1	1.9	0	0
Eye Disorders				
Dry eye	1.6	0	1.2	0

[a] Incidences presented in this table are based on reports of drug-related adverse events (CTCAE v4.0).

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

[c] Includes eczema, dyshidrotic eczema, and eczema nummular.

[d] Includes fatigue and asthenia.

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

[f] Includes stomatitis, mouth ulceration and mucosal inflammation.

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

[h] Includes pancreatitis, autoimmune pancreatitis, and acute pancreatitis.

[i] Includes pneumonitis and Interstitial lung disease.

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

[k] Includes arthritis, autoimmune arthritis and polyarthritis .

[l] Includes increase transaminases, increased alanine aminotransferase and increased aspartate aminotransferase.

[m] Includes anemia, increased hemoglobin, and iron deficiency anemia.

[n] Includes thrombocytopenia and decreased platelet counts.

[o] Includes 4 Grade 5 events.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following other clinically important adverse drug reactions were reported in less than 1% of patients treated with OPDIVO plus ipilimumab in CHECKMATE-227. Adverse reactions presented elsewhere are excluded.

Musculoskeletal and Connective Tissue: rhabdomyolysis, myositis (including polymyositis) and polymyalgia rheumatica.

Nervous System: autoimmune encephalitis.

Cardiac Disorders: atrial fibrillation and myocarditis.

Eye Disorders: blurred vision and uveitis.

Skin Disorders: urticaria, alopecia and vitiligo.

Immune System Disorders: hypersensitivity.

Abnormal Hematologic and Clinical Chemistry Findings

The incidence of worsening laboratory abnormalities is shown in Table 12.

Table 12: Laboratory Abnormalities Worsening from Baseline Occurring in >15% of Patients on OPDIVO plus ipilimumab (CHECKMATE-227)

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	OPDIVO plus ipilimumab		Platinum-doublet chemotherapy	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Hematology				
Anemia	46	3.6	78	14
Lymphopenia	46	5.2	60	15.4
Chemistry				
Hyponatremia	41	11.6	26	4.9
Increased AST	39	5.4	26	0.4
Increased ALT	36	7.0	27	0.7
Increased lipase	35	13.9	14	3.4
Increased alkaline phosphatase	34	3.8	20	0.2
Hypocalcemia	28	1.7	18	1.3
Increased amylase	28	9.3	18	1.9
Hyperkalemia	27	3.4	22	0.4
Increased creatinine	22	0.9	17	0.2
Hypomagnesemia	21	0.6	28	0.8
Hypokalemia	15	4.0	10	2.3

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

CHECKMATE-9LA:

In CHECKMATE-9LA, the most frequently reported adverse reactions (occurring at ≥ 10%) in patients who received OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy were fatigue, nausea, rash, anemia, diarrhea, pruritus, decreased appetite, hypothyroidism, neutropenia, and vomiting.

Table 13 lists adverse reactions that occurred in at least 1% of patients treated with OPDIVO and ipilimumab and platinum-doublet chemotherapy in CHECKMATE-9LA.

Table 13: Adverse Reactions Reported in at Least 1% of Patients Receiving OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy in CHECKMATE-9LA

	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
System Organ Class **Preferred Term**	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[a]			
Gastrointestinal Disorders				
Nausea	26.3	1.4	36.1	0.9
Diarrhea	20.4[n]	3.9	12.0	1.1
Vomiting	13.1	1.7	14.6	1.4
Constipation	8.9	0	10.9	0
Stomatitis	6.4	0.6	4.6	0.9
Abdominal pain[b]	4.2	0.3	4.0	0
Colitis	3.4	1.4	0.3	0
Dry Mouth	2.2	0	0	0
Pancreatitis	1.1	0.8	0	0
Skin and Subcutaneous Tissue Disorders				
Rash[c]	25.4	3.6	4.9	0.3
Pruritus	18.4	0.8	1.1	0
Alopecia	8.9	0.8	8.9	0.6
Dry skin	3.6	0	0.3	0
Erythema	1.7	0	0.6	0
Urticaria	1.4	0	0.3	0
Night sweats	1.1	0	0	0
Skin toxicity	1.1	0	0.3	0
General Disorders and Administration Site Conditions				
Fatigue[d]	36.0	3.1	28.1	2.9
Pyrexia	5.6	0	3.2	0.3
Malaise	2.5	0	4.3	0
Edema[e]	1.7	0	5.2	0
Blood and Lymphatic System Disorders				
Anemia[f]	22.6	5.6	37.5	13.8
Neutropenia[g]	13.7	8.7	20.3	11.5
Thrombocytopenia[h]	6.7	3.1	13.5	3.4
Febrile neutropenia	3.9	3.9	3.2	2.9
Lymphopenia[i]	2.0	0.3	1.4	0.3

Table 13: Adverse Reactions Reported in at Least 1% of Patients Receiving OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy in CHECKMATE-9LA

System Organ Class Preferred Term	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[a]			
Metabolism and Nutrition Disorders				
Decreased appetite	15.6	1.1	15.2	1.1
Dehydration	3.1	1.4	2.0	0.6
Hypomagnesemia	2.8	0	3.2	0
Hypoalbuminemia	1.7	0	0.9	0
Hypokalemia	1.4	0	1.4	0.3
Hyponatremia	1.4	0.6	1.1	1.1
Hypophosphatemia	1.1	0.3	0	0
Endocrine Disorders				
Hypothyroidism	14.5	0.3	1	0
Hyperthyroidism	7.5	0	0	0
Adrenal insufficiency	3.6	1.4	0	0
Hypophysitis	1.4	0.8	0	0
Thyroiditis	1.4	0	0	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[j]	8.9	0.3	6.3	0
Arthralgia	7.3	0.3	3.4	0.3
Arthritis[k]	1.7	0.6	0.3	0
Nervous System Disorders				
Dysgeusia	3.9	0	2.6	0
Peripheral neuropathy	3.9	0	6.9	0.3
Dizziness	3.1	0	0.9	0
Headache	2.0	0.3	0.6	0
Paresthesia	1.1	0	3.7	0
Respiratory, Thoracic, and Mediastinal Disorders				
Pneumonitis	5.3	1.4	1.1	0.3
Dyspnea	2.5	0.6	1.1	0
Cough	1.4	0	0.3	0
Infections and Infestations				
Conjunctivitis	2.2	0	2.3	0
Pneumonia	1.7	0.6	0.9	0.9
Folliculitis	1.1	0	0	0
Oral candidiasis	1.1	0	0.9	0
Respiratory tract infection[l]	1.1	0.8	0.9	0.3
Hepatobiliary Disorders				
Hepatotoxicity	2.8	1.4	0.6	0
Hepatitis	1.7	1.4	0	0
Hepatocellular injury	1.4	0.8	0.3	0
Immune System Disorders				
Infusion-related reaction	3.4	0.6	0.9	0.6
Hypersensitivity	1.7	0	0.3	0
Investigations				
Increased transaminases[m]	8.1	2.0	4.3	0.6
Increased amylase	5.0	2.2	1.4	0

Table 13: Adverse Reactions Reported in at Least 1% of Patients Receiving OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy in CHECKMATE-9LA

System Organ Class Preferred Term	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[a]			
Increased lipase	5.0	3.6	0.9	0.3
Increased blood creatinine	4.5	0.3	4.0	0
Decreased weight	3.9	0	2.3	0
Increased blood alkaline phosphatase	2.8	0	2.6	0
Decreased white blood cell count	2.8	0.8	2.3	0.6
Increased thyroid stimulating hormone	2.0	0	0	0
Renal and Urinary Disorders				
Acute kidney injury	1.7	1.4	1.4	0.6
Renal failure	1.7	0.3	0.6	0.6
Eye Disorders				
Dry eye	1.7	0	1.4	0

[a] Incidences presented in this table are based on reports of drug-related adverse events (CTCAE v4.0).

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

[c] Includes rash, maculopapular rash, rash erythematous, rash macular, rash papular, rash pruritic, rash generalized, rash morbilliform, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, drug eruption.

[d] Includes fatigue and asthenia.

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

[f] Includes anemia, increased hemoglobin, and iron deficiency anemia.

[g] Includes neutropenia and decreased neutrophil count.

[h] Includes thrombocytopenia and decreased platelet counts.

[i] Includes lymphopenia and decreased lymphocyte count.

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

[k] Includes arthritis and polyarthritis.

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

[m] Includes increase transaminases, increased alanine aminotransferase and increased aspartate aminotransferase.

[n] Includes 1 Grade 5 event.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following other clinically important adverse drug reactions were reported in less than 1% of patients treated with OPDIVO and ipilimumab and platinum-doublet chemotherapy in CHECKMATE-9LA.

Blood and Lymphatic System Disorder: Eosinophilia.

Cardiac Disorders: Arrhythmia (including tachycardia, atrial fibrillation, and bradycardia).

Endocrine Disorders: Hypopituitarism, hypoparathyroidism.

Eye Disorders: Blurred vision, episcleritis.

General Disorders and Administration Site Conditions: Chills, chest pain.

Investigations: Increased total bilirubin, increased gamma-glutamyltransferase.

Musculoskeletal and Connective Tissue Disorders: Muscular weakness, muscle spasms, polymyalgia rheumatica.

Nervous System Disorders: Polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis.

Renal and Urinary Disorders: Nephritis.

Respiratory, Thoracic and Mediastinal Disorders: Pleural effusion.

Skin and Subcutaneous Tissue Disorders: Psoriasis, Stevens-Johnson syndrome, vitiligo.

Vascular Disorders: Hypertension.

Abnormal Hematologic and Clinical Chemistry Findings

The incidence of worsening laboratory abnormalities is shown in Table 14.

Table 14: Laboratory Abnormalities Worsening from Baseline Occurring in >15% of Patients on OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (CHECKMATE-9LA)

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy		Platinum-Doublet Chemotherapy	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Hematology				
Anemia	70	9.2	74	16.4
Lymphopenia	41	5.8	40	10.8
Neutropenia	41	14.7	42	14.8
Leukopenia	36	9.8	40	9.0
Thrombocytopenia	23	4.3	24	5.1
Chemistry				
Hyperglycemia	45	7.1	42	2.6
Hyponatremia	37	10.7	28	6.9
Increased ALT	34	4.3	24	1.2
Hypomagnesemia	32	1.2	36	0.9
Increased lipase	31	11.9	10	2.2
Increased alkaline phosphatase	31	1.2	26	0.3
Increased amylase	30	6.7	19	1.3
Increased AST	30	3.5	22	0.3
Hypocalcemia	28	1.4	23	1.8
Increased creatinine	26	1.2	23	0.6
Hyperkalemia	22	1.7	21	2.7
Hypokalemia	15	3.5	10	1.2

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

Metastatic RCC:

Advanced RCC (previously treated):

Table 15 lists adverse reactions that occurred in at least 1% of patients in pivotal renal cell carcinoma trial CHECKMATE-025:

Table 15: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-025

	OPDIVO (n=406)		Everolimus (n=397)	
System Organ Class **Preferred Term**	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[a]			
General Disorders and Administration Site Conditions				
Fatigue	36.7	2.7	39.0	4.0
Pyrexia	8.6	0	9.3	0.5
Edema	5.7	0	15.4	0.5
Chills	4.9	0	2.8	0
Chest Pain	2.2	0	1.5	0
Influenza-Like Illness	1.7	0.5	1.0	0
Malaise	1.5	0	1.8	0
Pain	1.2	0.5	0.8	0
Gastrointestinal Disorders				
Nausea	14.0	0.2	16.6	0.8
Diarrhea	12.3	1.2	21.2	1.3
Constipation	5.9	0.2	5.3	0
Vomiting	5.9	0	9.1	0.3
Stomatitis	4.7	0	45.6	7.3
Abdominal pain	3.9	0	4.0	0
Dry Mouth	3.9	0	3.5	0
Dyspepsia	2.0	0	2.5	0
Colitis	1.7	0.7	0	0
Abdominal Distention	1.5	0	0	0
Skin and Subcutaneous Tissue Disorders				
Rash	18.2	1.0	30.7	1.0
Pruritus	14.0	0	9.8	0
Dry Skin	6.4	0	8.3	0
Erythema	2.7	0	1.5	0.3
Alopecia	1.2	0	1.0	0
Hyperhydrosis	1.2	0	0.3	0
Night Sweats	1.0	0	1.0	0
Palmar-Plantar Erythrodysaesthesia Syndrome	1.0	0	5.5	0
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	9.6	0	20.7	0
Dyspnea	9.1	1.0	15.6	0.5
Pneumonitis	4.4	1.5	17.6	3.3
Dysphonia	1.7	0	0.8	0

Table 15: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-025

System Organ Class Preferred Term	OPDIVO (n=406)		Everolimus (n=397)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[a]			
Nasal Congestion	1.0	0	0.5	0
Wheezing	1.0	0	0.5	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain	9.4	0.5	5.5	0
Arthralgia	6.7	0.2	3.5	0
Arthritis	1.7	0.2	0.3	0
Joint Swelling	1.7	0	0.5	0
Muscle Spasms	1.7	0	0.8	0
Muscular Weakness	1.0	0.2	0	0
Musculoskeletal Stiffness	1.0	0.2	0	0
Metabolism and Nutrition Disorders				
Decreased appetite	11.8	0.5	20.7	1.0
Hyperglycemia	2.2	1.2	11.6	3.8
Hypertriglyceridemia	1.2	0	19.1	5.8
Hyponatremia	1.2	0.5	0.5	0.3
Nervous System Disorders				
Headache	5.9	0	4.8	0.3
Dizziness	3.2	0	3.0	0
Dysgeugia	2.7	0	12.8	0
Peripheral Neuropathy	2.0	0	2.3	0
Blood and Lymphatic Disorders				
Anemia	8.4	1.7	24.9	7.8
Lymphopenia	2.7	0.7	2.0	0.5
Thrombocytopenia	1.2	0.2	6.5	1.0
Neutropenia	1.0	0	2.3	0.5
Endocrine Disorders				
Hypothyroidism	5.9	0.2	0.5	0
Hyperthyroidism	1.7	0	0.3	0
Adrenal Insufficiency	1.5	0.5	0	0
Infections and Infestations				
Upper respiratory tract infection	2.2	0	2.0	0
Pneumonia	1.0	0	3.5	1.5
Eye Disorders				
Dry Eye	1.5	0	1.3	0
Lacrimation Increased	1.2	0	1.5	0
Vascular Disorders				
Hypertension	2.0	0.7	2.3	1.0
Flushing	1.7	0	0.5	0
Hypotension	1.7	0	0	0
Injury, Poisoning, and Procedural Complications				
Infusion-related reaction	3.2	0	0	0
Immune System Disorders				
Hypersensitivity	2.2	0.2	0.3	0
Psychiatric Disorders				
Insomnia	1.0	0	1.3	0
Renal and Urinary Disorders				
Pollakiuria	1.0	0	0.3	0

[a] Incidences presented in this table are based on reports of drug-related adverse events.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following other clinically important adverse drug reactions were reported in less than 1% of patients treated with OPDIVO 3 mg/kg monotherapy in CHECKMATE-025. Adverse reactions presented elsewhere are excluded.

Immune System Disorders: anaphylactic reaction.

Metabolism & Nutrition Disorders: diabetic ketoacidosis.

Renal and Urinary Disorders: tubulointerstitial nephritis.

Respiratory, Thoracic, and Mediastinal Disorders: hemoptysis.

Table 16: Laboratory Abnormalities Reported in CHECKMATE-025

	Number (%) of Patients with Worsening Laboratory Test from Baseline					
	OPDIVO			everolimus		
Test	N[a]	Grades 1-4	Grades 3-4	N[a]	Grades 1-4	Grades 3-4
Decreased hemoglobin[b]	395	153 (38.7)	33 (8.4)	383	264 (68.9)	60 (15.7)
Decreased platelet count	391	39 (10.0)	1 (0.3)	379	104 (27.4)	7 (1.8)
Decreased lymphocytes	390	163 (41.8)	25 (6.4)	376	198 (52.7)	42 (11.2)
Decreased absolute neutrophil count	391	28 (7.2)	0	377	56 (14.9)	3 (0.8)
Increased alkaline phosphatase	400	127 (31.8)	9 (2.3)	374	119 (31.8)	3 (0.8)
Increased AST	399	131 (32.8)	11 (2.8)	374	146 (39.0)	6 (1.6)
Increased ALT	401	87 (21.7)	13 (3.2)	376	115 (30.6)	3 (0.8)
Increased total bilirubin	401	37 (9.2)	2 (0.5)	376	13 (3.5)	2 (0.5)
Increased creatinine	398	168 (42.2)	8 (2.0)	379	170 (44.9)	6 (1.6)

[a] The total number of patients who had both baseline and on-study laboratory measurements available.

[b] Grade 4 for hemoglobin is not applicable per anemia criteria in CTCAE v4.0.

Advanced RCC (untreated):

Table 17 lists adverse reactions that occurred in at least 1% of OPDIVO plus ipilimumab-treated patients in CHECKMATE-214.

Table 17: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-214

System Organ Class Preferred Term	OPDIVO + ipilimumab (n=547)		Sunitinib (n=535)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[a]			
General Disorders and Administration Site Conditions				
Fatigue	47.5	5.5	62.1	11.2
Pyrexia	14.4	0.4	6.2	0.2
Edema	4.9	0.2	8.6	0.4
Influenza-like illness	4.8	0.4	2.4	0.2
Chills	3.3	0	3.7	0.2
Pain	2.0	0	3.2	0
Chest pain	1.8	0	1.9	0.2
Malaise	1.5	0	4.7	0
Gastrointestinal Disorders				
Diarrhea	26.5	3.8	52.0	5.2
Nausea	19.9	1.5	37.8	1.1
Vomiting	10.8	0.7	20.6	1.9
Abdominal pain	9.0	0.4	14.4	0.2
Stomatitis	6.8	0	53.1	5.4
Constipation	6.4	0	7.3	0
Dry Mouth	5.7	0	6.0	0
Dyspepsia	3.8	0.2	27.1	0
Colitis	3.7	2.2	0.4	0
Dysphagia	1.5	0	1.7	0.2
Pancreatitis	1.3	0.4	1.3	0.7
Abdominal distention	1.1	0	3.9	0
Skin and Subcutaneous Tissue Disorders				
Rash	33.8	3.5	19.8	0.6
Pruritus	28.2	0.5	9.2	0
Dry skin	7.3	0	8.6	0
Erythema	2.7	0	0.9	0
Hyperhydrosis	1.5	0	1.3	0
Night sweats	1.5	0	0.4	0
Urticaria	1.5	0.2	0.4	0
Generalized pruritus	1.5	0	0.4	0
Endocrine Disorders				
Hypothyroidism	15.7	0.4	25.0	0.2
Hyperthyroidism	11.2	0.7	2.2	0
Adrenal insufficiency	5.3	2.0	0	0
Hypophysitis	4.0	2.7	0	0
Thyroiditis	3.3	0.2	0	0
Metabolism and Nutrition Disorders				
Decreased appetite	13.7	1.3	24.9	0.9
Hyperglycemia	5.1	1.5	1.9	0
Hyponatremia	4.4	2.9	3.7	2.2
Dehydration	3.1	1.1	3.6	1.5
Hyperkalemia	2.6	0.7	2.2	0.4
Diabetes mellitus	1.8	1.1	0	0
Hypomagnesemia	1.8	0.2	3.6	0.6
Hypoalbuminemia	1.3	0	1.7	0
Hypokalemia	1.3	0.4	1.7	0.2

Table 17: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-214

System Organ Class Preferred Term	OPDIVO + ipilimumab (n=547)		Sunitinib (n=535)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[a]			
Hypophosphatemia	1.3	0.2	3.4	0.4
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain	14.8	1.5	14.0	0.4
Arthralgia	13.9	0.9	7.3	0
Muscle spasms	4.0	0	3.2	0
Arthritis	2.0	0.2	0.4	0
Muscular weakness	1.8	0	1.3	0.4
Nervous System Disorders				
Headache	9.7	0.7	12.1	0.2
Dizziness	6.0	0.4	6.0	0.4
Dysgeusia	5.7	0	33.5	0.2
Peripheral neuropathy	4.0	0.2	5.8	0.4
Paresthesia	3.3	0.4	3.9	0
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	8.4	0	6.2	0
Dyspnea	6.8	0.2	8.2	0.4
Pneumonitis	6.2	1.1	0.2	0
Dysphonia	1.3	0	3.9	0.2
Pleural effusion	1.3	0	0.2	0.2
Oropharyngeal pain	1.1	0	2.4	0.2
Blood and Lymphatic Disorders				
Anemia	6.4	0.4	15.9	4.5
Lymphopenia	1.5	0.4	4.5	2.4
Neutropenia	1.1	0.4	19.3	10.3
Thrombocytopenia	1.1	0.2	29.5	11.2
Infections and Infestations				
Conjunctivitis	1.5	0	0.7	0
Pneumonia	1.5	0.2	0.4	0
Upper respiratory tract infection	1.5	0.2	0.6	0
Eye Disorders				
Vision Blurred	1.6	0	0.4	0
Dry Eye	1.5	0	1.1	0
Vascular Disorders				
Hypertension	2.2	0.7	40.7	16.1
Hypotension	2.2	0.7	0.7	0.2
Flushing	1.6	0	1.3	0
Renal and Urinary Disorders				
Acute kidney injury	1.8	0.7	1.7	0.6
Psychiatric Disorders				
Insomnia	1.6	0	2.1	0
Confusional state	1.1	0	0	0
Injury, Poisoning, and Procedural Complications				
Infusion-related reaction	2.6	0	0	0
Hepatobiliary Disorders				
Hepatitis	1.3	0.9	0.2	0.2
Cardiac Disorders				

Table 17: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-214

System Organ Class Preferred Term	OPDIVO + ipilimumab (n=547)		Sunitinib (n=535)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[a]			
Palpitations	1.3	0	0.9	0
Tachycardia	1.3	0	0.4	0
Immune System Disorders				
Hypersensitivity	1.6	0	1.1	0.4

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following other clinically important adverse drug reactions were reported in less than 1% of patients treated with OPDIVO plus ipilimumab in CHECKMATE-214. Adverse reactions presented elsewhere are excluded.

Infections and Infestations: Aseptic meningitis.

Nervous System Disorder: Myasthenia gravis.

Abnormal Hematologic and Clinical Chemistry Findings

The incidence of worsening laboratory abnormalities is shown in Table 18.

Table 18: Laboratory Abnormalities Worsening from Baseline Occurring in >15% of Patients on OPDIVO plus ipilimumab (CHECKMATE-214)

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	OPDIVO plus ipilimumab		Sunitinib	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Hematology				
Anemia	43	3.0	64	8.8
Lymphopenia	36	5.1	63	14.3
Chemistry				
Increased lipase	48	20.1	51	20.2
Increased creatinine	43	2.1	46	1.5
Increased ALT	41	6.5	44	2.7
Increased AST	40	4.8	60	2.1
Increased amylase	39	12.2	33	7.2
Hyponatremia	39	9.9	36	7.3
Increased alkaline phosphatase	29	2.0	32	1.0
Hyperkalemia	29	2.4	28	2.9
Hypocalcemia	22	0.4	36	0.6
Hypomagnesemia	19	0.4	28	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: OPDIVO plus ipilimumab group (range: 490 to 538 patients) and sunitinib group (range: 485 to 523 patients).

Recurrent or Metastatic SCCHN:

Table 19 lists adverse reactions that occurred in at least 1% of patients in pivotal squamous cell cancer of the head and neck CHECKMATE-141:

Table 19: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-141

	OPDIVO (n=236)		Investigator Choice[a] (n=111)	
System Organ Class **Preferred Term**	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[b]			
General Disorders and Administration Site Conditions				
Fatigue	17.8	2.5	31.5	4.5
Pyrexia	1.7	0	3.6	1.8
Edema	2.5	0	1.8	0
Gastrointestinal Disorders				
Nausea	8.5	0	20.7	0.9
Diarrhea	6.8	0	13.5	1.8
Stomatitis	3.8	0.4	21.6	4.5
Vomiting	3.4	0	7.2	0
Dysphagia	1.7	0.4	0	0
Constipation	1.3	0	3.6	0
Skin and Subcutaneous Tissue Disorders				
Rash	10.6	0	12.6	1.8
Pruritus	7.2	0	0	0
Dry Skin	3.0	0	9.0	0
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	2.5	0.4	0	0
Pneumonitis	2.1	0.8	0.9	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	2.1	0	0	0
Metabolism and Nutrition Disorders				
Decreased appetite	7.2	0	7.2	0
Hyponatremia	1.7	0.8	3.6	2.7
Hypomagnesaemia	1.3	0	3.6	0
Investigations				
Lipase Increased	2.5	1.7	0	0
Transaminase Increased	1.7	0.8	2.7	0.9
Weight Decreased	1.7	0	5.4	0
Thyroid stimulating hormone	1.3	0	0	0
Nervous System Disorders				
Headache	1.7	0.4	0.9	0
Blood and Lymphatic System Disorders				
Anemia	5.1	1.3	16.2	4.5
Lymphopenia	2.5	1.3	3.6	3.6
Thrombocytopenia	2.5	0	6.3	2.7
Endocrine Disorders				
Hypothyroidism	4.2	0.4	0.9	0
Vascular Disorders				
Hypertension	1.7	0.4	0	0

Table 19: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-141

System Organ Class Preferred Term	OPDIVO (n=236)		Investigator Choice[a] (n=111)	
	Any Grade	Grades 3-4	Any Grade	Grades 3-4
	Percentage (%) of Patients[b]			
Injury, Poisoning, and Procedural Complications				
Infusion-related reaction	1.3	0	1.8	0.9

[a] Cetuximab, methotrexate or docetaxel.

[b] Incidences presented in this table are based on reports of drug-related adverse events.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following other clinically important adverse drug reactions were reported in less than 1% of patients treated with OPDIVO 3 mg/kg monotherapy in CHECKMATE-141. Adverse reactions presented elsewhere are excluded.

Skin and Subcutaneous: urticaria.

Eye Disorders: vision blurred.

Infections and Infestations: bronchitis.

Endocrine: hypophysitis.

Metabolism and Nutrition: hyperglycemia, hypercalcemia.

Respiratory, Thoracic and Mediastinal: dyspnea, pulmonary embolism, pneumonia aspiration.

Table 20: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of OPDIVO-Treated Patients for all NCI CTCAE Grades and at a Higher Incidence than Comparator (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (Trial CHECKMATE-141)

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	OPDIVO		Investigator Choice[b]	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Chemistry				
Increased alkaline phosphatase	23	1.8	15	0
Increased amylase	12	3.2	8	1.1
Hypercalcemia	15	2.2	10	1.0
Hyperkalemia	17	0.4	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: OPDIVO group (range: 186-225 patients) and investigator's choice group (range: 92-104 patients).

[b] Cetuximab, methotrexate or docetaxel.

cHL:

CHECKMATE-205 and CHECKMATE-039:

The most common adverse reactions (reported in at least 10% of patients) were fatigue, diarrhea, nausea, rash, pruritus, and infusion-related reactions. At the final analysis for CHECKMATE-205, there were no new safety signals observed and therefore with additional follow-up, no meaningful changes occurred in the safety profile of OPDIVO. Table 21 summarizes adverse reactions that occurred in at least 1% of patients in studies CHECKMATE-205 and CHECKMATE-039:

Table 21: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-205 and CHECKMATE-039

	OPDIVO (n=266)	
	Percentage (%) of Patients	
System Organ Class **Preferred Term**	**Any Grade**	**Grades 3-4**
General Disorders and Administration Site Conditions		
Fatigue [a]	22.9	0.8
Pyrexia	9.4	0
Chills	3.0	0
Edema	2.3	0
Pain	1.5	0
Chest Pain	1.1	0
Malaise	1.1	0
Gastrointestinal Disorders		
Diarrhea	14.7	0.8
Nausea	10.5	0
Vomiting	7.9	0.4
Abdominal Pain [b]	6.0	0.8
Stomatitis	4.9	0.4
Constipation	4.1	0
Dry Mouth	1.5	0
Dyspepsia	1.5	0
Colitis	1.1	0.8
Pancreatitis	1.1	0.4
Skin and Subcutaneous Tissue Disorders		
Rash[c]	14.7	1.1
Pruritus	10.2	0
Alopecia	2.6	0
Urticaria	1.1	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Pain [d]	7.9	0
Arthralgia	7.5	0
Arthritis	1.9	0.4
Muscle Spasms	1.5	0

Table 21: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-205 and CHECKMATE-039

	OPDIVO (n=266)	
	Percentage (%) of Patients	
System Organ Class **Preferred Term**	**Any Grade**	**Grades 3-4**
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	6.0	0
Pneumonitis	4.5	0
Dyspnea [e]	4.1	0.8
Oropharyngeal Pain	1.9	0
Endocrine Disorders		
Hypothyroidism	9.4	0
Hyperthyroidism	1.9	0
Nervous System Disorders		
Headache	5.6	0
Peripheral Neuropathy [e]	4.9	0.4
Amnesia	1.1	0
Dysgeusia	1.1	0
Syncope	1.1	0.8
Injury, Poisoning, and Procedural Complications		
Infusion related reaction	13.2	0.4
Metabolism and Nutrition Disorders		
Decreased Appetite	3.4	0
Hyperglycemia	2.3	0
Hypercalcemia	1.5	0.4
Hypophosphatemia	1.1	0.4
Infections and Infestations		
Upper Respiratory Tract Infection	3.0	0
Pneumonia	1.5	0.8
Respiratory Tract Infection [f]	1.1	0
Urinary Tract Infection	1.1	0
Investigations		
Weight Increased	1.1	0
Immune System Disorders		
Hypersensitivity	2.3	0.4
Hepatobiliary Disorders		
Hepatitis	1.9	1.5
Vascular Disorders		
Flushing	1.1	0
Neoplasms Benign, Malignant and Unspecified		
Tumour Pain	1.1	0

[a] Includes asthenia.

[b] Includes abdominal discomfort and upper abdominal pain.

[c] Includes dermatitis, dermatitis acneiform, dermatitis exfoliative, rash macular, rash maculopapular, rash papular, and rash pruritic.

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

[e] Includes hyperaesthesia, hypoaesthesia, peripheral motor neuropathy, and peripheral sensory neuropathy.

f Includes nasopharyngitis, pharyngitis, and rhinitis.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following other clinically important adverse drug reactions were reported in less than 1% of patients treated with nivolumab 3 mg/kg monotherapy in CHECKMATE-205 and CHECKMATE-039. Adverse reactions presented elsewhere are excluded.

Cardiac Disorders: pericardial effusion.

Metabolism and Nutrition Disorders: glucose tolerance impairment.

Neoplasm Benign, Malignant and Unspecified: myelodysplastic syndrome.

Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO

In 40 evaluated patients from two cHL studies who underwent allogeneic HSCT after discontinuing OPDIVO, Grade 3 or 4 acute GVHD was reported in 7/40 patients (17.5%). Hyperacute GVHD, defined as acute GVHD occurring within 14 days after stem cell infusion, was reported in two patients (5%). A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in six patients (15%) within the first 6 weeks post-transplantation, with five patients responding to steroids. Hepatic VOD occurred in one patient, who died of GVHD and multi-organ failure. Six of 40 patients (15%) died from complications of allogeneic HSCT after OPDIVO. The 40 patients had a median follow-up from subsequent allogeneic HSCT of 2.9 months (range: 0-17 months).

Further to a subsequent update of safety information from the final analysis (median 5.6 months (range 0-19 months)) for CHECKMATE-205, 9 additional patients underwent allogeneic HSCT resulting in higher rates of Grade 3 or 4 acute GVHD (13/49 patients, 26.5%) and of hyperacute GVHD (3/49 patients, 6%). Also, from the CHECKMATE-205 final study report, the number of deaths reported due to complications of allogeneic HSCT after OPDIVO was updated to 9 of 49 patients (18.4%).

Laboratory Abnormalities:

The incidence of worsening laboratory abnormalities is shown in Table 22.

Table 22: Laboratory Abnormalities Worsening from Baseline in ≥10% of Patients in CHECKMATE-205 and CHECKMATE-039

	Percentage (%) of Patients [a]	
	Grades 1-4	**Grades 3-4**
Hematology		
Leukopenia	38.1	4.5
Thrombocytopenia	36.6	3.0
Neutropenia	36.6	5.3
Lymphopenia	32.1	11.3
Anemia [b]	26.4	2.6
Chemistry		
Hyperglycemia	36.2	0

Table 22: Laboratory Abnormalities Worsening from Baseline in ≥10% of Patients in CHECKMATE-205 and CHECKMATE-039

	Percentage (%) of Patients [a]	
	Grades 1-4	**Grades 3-4**
Increased alkaline phosphatase	20.0	1.5
Increased AST	32.5	2.6
Increased ALT	31.3	3.4
Increased Lipase	21.8	8.6
Hyponatremia	19.9	1.1
Hypomagnesemia	16.8	0.4
Increased Creatinine	16.2	0.8
Hypokalemia	15.8	1.9
Hypocalcemia	15.4	0.8
Hyperkalemia	15.0	1.5
Hypoglycemia	14.5	0
Increased Total Bilirubin	11.3	1.5

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available. Hyperglycemia and hypoglycemia are based on 69 patients, and all other laboratory parameters are based on a range of 238-266 patients.

[b] Grade 4 for hemoglobin is not applicable per anemia criteria in CTCAE v4.0.

Hepatocellular Carcinoma

Table 23 lists adverse reactions that occurred in at least 1% of patients in the Expansion Phase of CHECKMATE-040:

Table 23: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-040

	OPDIVO (n=145)	
System Organ Class Preferred Term	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients[a]	
General Disorders and Administration Site Conditions		
Fatigue	40 (27.6)	3 (2.1)
Pyrexia	6 (4.1)	0
Malaise	5 (3.4)	0
Edema	4 (2.8)	0
Chills	3 (2.1)	0
Pain	3 (2.1)	0
Chest Pain	2 (1.4)	0
Xerosis	2 (1.4)	0
Gastrointestinal Disorders		
Diarrhea	23 (15.9)	2 (1.4)
Nausea	13 (9.0)	0
Dry Mouth	8 (5.5)	0
Abdominal Pain	9 (6.2)	1 (0.7)
Stomatitis	6 (4.1)	0
Constipation	5 (3.4)	0

Table 23: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-040

System Organ Class Preferred Term	OPDIVO (n=145) Any Grade	OPDIVO (n=145) Grades 3-4
	Percentage (%) of Patients[a]	
Vomiting	5 (3.4)	0
Abdominal distension	5 (3.4)	0
Dyspepsia	3 (2.1)	1 (0.7)
Colitis	2 (1.4)	1 (0.7)
Skin and Subcutaneous Tissue Disorders		
Rash	29 (20.0)	1 (0.7)
Pruritus	28 (19.3)	1 (0.7)
Dry Skin	6 (4.1)	0
Hyperhidrosis	3 (2.1)	0
Skin exfoliation	3 (2.1)	0
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	3 (2.1)	0
Dyspnea	3 (2.1)	0
Pneumonitis	2 (1.4)	1 (0.7)
Epistaxis	2 (1.4)	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Pain	12 (8.3)	0
Arthralgia	5 (3.4)	0
Metabolism and Nutrition Disorders		
Decreased appetite	11 (7.6)	1 (0.7)
Hypoalbuminaema	3 (2.1)	0
Hypophosphataemia	3 (2.1)	0
Hyponatraemia	2 (1.4)	2 (1.4)
Hyperglycemia	2 (1.4)	2 (1.4)
Investigations		
Transaminase Increased	11 (7.6)	5 (3.4)
Lipase Increased	6 (4.1)	6 (4.1)
Amylase Increased	5 (4.3)	2 (1.4)
Blood thyroid stimulating hormone increased	4 (2.8)	0
Blood Bilirubin Increased	3 (2.1)	0
Blood Alkaline Phosphatase Increased	3 (2.1)	0
Weight Decreased	2 (1.4)	0
C-reactive protein decreased	2 (1.4)	0
Nervous System Disorders		
Dizziness	5 (3.4)	0
Dysgeusia	2 (1.4)	0
Headache	4 (2.8)	0
Blood and Lymphatic System Disorders		
Thrombocytopenia	12 (8.3)	4 (2.8)
Anemia	8 (5.5)	1 (0.7)
Neutropenia	4 (2.8)	1 (0.7)
Leukopenia	2 (1.4)	0
Endocrine Disorders		
Hypothyroidism	5 (3.4)	0
Hepatobiliary Disorders		

Table 23: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-040

System Organ Class Preferred Term	OPDIVO (n=145) Any Grade	OPDIVO (n=145) Grades 3-4
	Percentage (%) of Patients[a]	
Hyperbilirubinemia	2 (1.4)	0
Infections and Infestations		
Pneumonia	2 (1.4)	0
Eye Disorders		
Vision Blurred	2 (1.4)	0
Vascular Disorders		
Flushing	2 (1.4)	0
Renal and Urinary Disorders		
Nocturia	2 (1.4)	0
Psychiatric Disorders		
Insomnia	3 (2.1)	0
Cardiac Disorders		
Tachycardia	3 (2.1)	0
Injury, Poisoning, and Procedural Complications		
Infusion-related reaction	4 (2.8)	0

[a] Incidences presented in this table are based on reports of drug-related adverse events.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Other clinically important adverse drug reactions reported in less than 1% of patients in the Expansion Phase of CHECKMATE-040 have been reported previously in OPDIVO clinical studies and are presented elsewhere. (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**)

Laboratory Abnormalities:

The incidence of worsening laboratory abnormalities is shown in Table 24.

Table 24: Laboratory Abnormalities Reported in CHECKMATE-040 - Expansion phase

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a] OPDIVO Grades 1-4	OPDIVO Grades 3-4
Decreased hemoglobin[b]	52.1	6.3
Decreased platelet count	36.6	7.0
Decreased leukocytes	26.6	3.5
Decreased lymphocytes (absolute)	57.7	14.8
Decreased absolute neutrophil count	20.4	2.8
Increased alkaline phosphatase	46.2	7.0
Increased AST	59.2	16.9
Increased ALT	48.6	10.6
Increased bilirubin, total	37.1	7.7

Table 24: Laboratory Abnormalities Reported in CHECKMATE-040 - Expansion phase

	Percentage of Patients with Worsening Laboratory Test from Baseline[a]	
	OPDIVO	
Laboratory Abnormality	**Grades 1-4**	**Grades 3-4**
Increased creatinine	19.0	1.4
Increased amylase, total	32.8	6.9
Increased lipase, total	37.1	14.3
Hypernatremia	2.8	0
Hyponatremia	41.5	9.9
Hyperkalemia	20.4	2.8
Hypokalemia	12.0	0.7
Hypercalcemia	7.7	0
Hypocalcemia	30.3	0
Hypermagnesemia	8.5	0
Hypomagnesemia	13.5	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 (range: 131-143).

[b] Per Anemia criteria in CTC version 4.0 there is no grade 4 for hemoglobin.

MSI-H/dMMR mCRC:

In the dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in CRC (n =119), the most frequent adverse reactions (≥ 10%) were fatigue (28.6%), rash (25.3%), diarrhea (25.2%), pruritus (20.2%), hypothyroidism (17.6%), pyrexia (15.1%), hyperthyroidism (14.3%), nausea (13.4%), decreased appetite (10.9%) and anemia (10.1%). The majority of adverse reactions were mild to moderate (Grade 1 or 2) with 31.9% Grade 3-4 adverse reactions.

Table 25, lists the adverse reactions that occurred in at least 1% of patients treated with OPDIVO in combination with ipilimumab in CHECKMATE-142.

Table 25: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-142

	OPDIVO + ipilimumab[a] (n=119)	
System Organ Class Preferred Term	**Any Grade**	**Grades 3-4**
	Percentage (%) of Patients	
General Disorders and Administration Site Conditions		
Fatigue	34 (28.6)	3 (2.5)
Pyrexia	18 (15.1)	0
Influenza like illness	6 (5.0)	0
Chills	5 (4.2)	0
Face edema	2 (1.7)	0
Edema	2 (1.7)	0
Pain	2 (1.7)	0
Gastrointestinal Disorders		
Diarrhea	30 (25.2)	3 (2.5)
Nausea	16 (13.4)	1 (0.8)
Vomiting	8 (6.7)	1 (0.8)
Abdominal pain	8 (6.7)	2 (1.7)
Stomatitis	5 (4.2)	0

Table 25: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-142

System Organ Class Preferred Term	OPDIVO + ipilimumab[a] (n=119) Any Grade	 Grades 3-4
	Percentage (%) of Patients	
Dry mouth	7 (5.9)	0
Dyspepsia	4 (3.4)	0
Constipation	4 (3.4)	0
Colitis	3 (2.5)	3 (2.5)
Skin and Subcutaneous Tissue Disorders		
Rash	30 (25.3)	2 (2.5)
Pruritus	24 (20.2)	2 (1.7)
Dry skin	11 (9.2)	0
Erythema	4 (3.4)	0
Alopecia	2 (1.7)	0
Endocrine Disorders		
Hypothyroidism	21 (17.6)	1 (0.8)
Hyperthyroidism	17 (14.3)	0
Adrenal Insufficiency	8 (6.7)	1 (0.8)
Hypophysitis	4 (3.4)	2 (1.7)
Thyroiditis	4 (3.4)	2 (1.7)
Autoimmune thyroid disorder	2 (1.7)	1 (0.8)
Blood and Lymphatic System Disorders		
Anemia	12 (10.1)	3 (2.5)
Neutropenia	5 (4.2)	0
Thrombocytopenia	10 (8.4)	1 (0.8)
Lymphopenia	3 (2.5)	0
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	10 (8.4)	1 (0.8)
Musculoskeletal pain[b]	10 (8.4)	1 (0.8)
Joint stiffness	2 (1.7)	0
Metabolism and Nutrition Disorders		
Decreased appetite	13 (10.9)	2 (1.7)
Hypomagneaemia	3 (2.5)	0
Dehydration	2 (1.7)	1 (0.8)
Hypocalcaemia	2 (1.7)	0
Hyponatraemia	2 (1.7)	2 (1.7)
Nervous System Disorders		
Dizziness	4 (3.4)	0
Headache	7 (5.9)	0
Neuropathy peripheral	4 (3.4)	0
Respiratory, Thoracic, and Mediastinal Disorders		
Pneumonitis	7 (5.9)	1 (0.8)
Dyspnoea	3 (2.5)	2 (1.7)
Hepatobiliary Disorders		
Hepatitis	3 (2.5)	3 (2.5)
Injury, Poisoning, and Procedural Complications		

Table 25: Adverse Reactions Reported in at Least 1% of Patients in CHECKMATE-142

System Organ Class Preferred Term	OPDIVO + ipilimumab[a] (n=119)	
	Any Grade	Grades 3-4
	Percentage (%) of Patients	
Infusion releated reaction	4 (3.4)	0
Renal and Urinary Disorders		
Acute kidney injury	2 (1.7)	2 (1.7)
Immune System Disorders		
Sarcoidosis	2 (1.7)	0
Eye disorders		
Vision blurred	2 (1.7)	0

[a] Nivolumab in combination with ipilimumab for the first 4 doses then followed by nivolumab monotherapy.

[b] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.

The following adverse reactions were reported in less than 1% of MSI-H patients treated with OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for 4 doses in CHECKMATE-142. Adverse reactions presented elsewhere in this section are excluded.

Less Common Clinical Trial Adverse Drug Reactions (<1%) OPDIVO + Ipilimumab

Skin and Subcutaneous Tissue Disorders: Psoriasis, Urticaria.

General Disorders and Administration Site Conditions: Chest pain.

Gastrointestinal Disorders: Pancreatitis.

Endocrine Disorders: Secondary adrenocortical insufficiency.

Musculoskeletal and Connective Tissue Disorders: Arthritis, Myositis, Necrotising myositis.

Nervous System Disorders: paraesthesia.

Respiratory, Thoracic and Mediastinal Disorders: Cough.

Infections and Infestations: Upper respiratory tract infection.

Vascular Disorders: Flushing, Hypertension, Hypotension.

Eye Disorders: Dry eye.

Table 26: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Reported in CHECKMATE-142 (OPDIVO in Combination with Ipilimumab) with MSI-H/dMMR mCRC

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a]	
	OPDIVO + Ipilimumab (n=119)	
	Grades 1-4	Grades 3-4
Decreased hemoglobin[b]	50 (43.5)	11 (9.6)
Thrombocytopenia	33 (28.9)	1 (0.9)
Leukopenia	24 (20.9)	0
Lymphopenia	37 (32.7)	7 (6.2)
Neutropenia	33 (28.9)	0
Increased alkaline phosphatase	36 (31.9)	6 (5.3)
Increased AST	51 (44.3)	15 (13.0)
Increased ALT	45 (39.1)	13 (11.3)
Increased total bilirubin	31 (27.2)	6 (5.3)
Increased creatinine	31 (27.2)	4 (3.5)
Increased total amylase	34 (38.6)	3 (3.4)
Increased total lipase	50 (44.6)	19 (17.0)
Hypercalcemia	7 (10.0)	0
Hypocalcemia	31 (27.7)	1 (0.9)
Hyperkalemia	33 (28.9)	1 (0.9)
Hypokalemia	21 (18.4)	4 (3.5)
Hypomagnesemia	27 (24.1)	0
Hyponatremia	35 (30.4)	7 (6.1)

[a] Each test incidence is based on the number of patients who had both baseline and on-treatment laboratory measurement available. All laboratory parameters are based on a range of 88-115 patients for OPDIVO in combination with ipilimumab.

[b] Per anemia criteria in CTC version 4.0, there is no Grade 4 for hemoglobin.

Other Adverse Reactions Reported in Clinical Trials:

The following additional adverse reactions have been reported in clinical trials of OPDIVO monotherapy or OPDIVO in combination with ipilimumab across tumour types:

OPDIVO monotherapy:

Metabolism and Nutrition Disorders: metabolic acidosis.

Nervous System Disorders: polyneuropathy.

Vascular Disorders: vasculitis.

Respiratory, Thoracic and Mediastinal Disorders: lung infiltration.

Gastrointestinal Disorders: duodenal ulcer.

Hepatobiliary Disorders: cholestasis.

Cardiac Disorders: tachycardia.

OPDIVO in combination with ipilimumab:

Infections and Infestations: bronchitis, pneumonia.

Nervous System Disorders: polyneuropathy.

Skin and Subcutaneous Tissue Disorders: erythema, urticaria, psoriasis.

Musculoskeletal and Connective Tissue Disorders: arthritis, myopathy.

Renal and Urinary Disorders: tubulointerstitial nephritis.

General Disorders and Administration Site Conditions: chest pain.

Cardiac Disorders: arrhythmia (including ventricular arrhythmia).

Investigations: weight decreased.

Description of Immune-Mediated Adverse Reactions

Data for the following immune-mediated adverse reactions are based on patients who received OPDIVO monotherapy or OPDIVO in combination with ipilimumab in clinical studies across tumour types (melanoma, NSCLC, RCC, SCCHN, cHL, HCC and CRC), and include the melanoma indication based on CHECKMATE-067, the cHL indication based on CHECKMATE-205 and CHECKMATE-039, the HCC indication based on CHECKMATE-040, as well as the CRC indication based on CHECKMATE-142, approved with conditions. Analyses also include safety data from completed studies in other tumour types. Rates of immune-mediated adverse reactions were generally similar across tumour types for patients who received OPDIVO monotherapy. In each tumour type, the most commonly reported immune-mediated adverse reactions were:

- RCC: hepatic (11.3%), renal (6.9%) and pulmonary (specifically pneumonitis) (3.9%);
- Metastatic melanoma: gastrointestinal (17.7%) and skin (38.4%);
- Adjuvant treatment of melanoma: skin (44.5%) and gastrointestinal (25.2%);
- NSCLC: pulmonary (specifically pneumonitis) (3.6%);
- SCCHN: endocrine (11.0%) and gastrointestinal (14.8%).

The frequency of immune-mediated adverse reactions observed in HCC are consistent with that established across tumour types for OPDIVO.

For patients receiving OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, there was a higher frequency of liver and thyroid test abnormalities reported in the OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg group compared with the monotherapy groups. Grade 3-4 abnormalities in liver were also reported with higher frequency in the OPDIVO in combination with ipilimumab group (19.8%) compared with the monotherapy OPDIVO (5.1%) and monotherapy ipilimumab (4.5%) groups.

For patients receiving OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, skin, endocrine, and gastrointestinal adverse reactions were the most common (48.8%, 32.5%, and 28.2%, respectively).

For patients receiving OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, skin, endocrine, gastrointestinal and hepatic adverse reactions were the most common (34.0%, 23.8%, 18.2% and 15.8%, respectively).

For patients receiving OPDIVO 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy in NSCLC, skin, endocrine, gastrointestinal and hepatic adverse reactions were the most common (37.7%, 24.0%, 22.3% and 13.4%, respectively).

For patients receiving OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in CRC, skin, endocrine, gastrointestinal and hepatic adverse reactions were the most common (35.3%, 31.9%, 25.2% and 23.5% respectively).

The management guidelines for these adverse reactions are described in Table 30.

Immune-Mediated Endocrinopathies

OPDIVO monotherapy:

In patients treated with OPDIVO monotherapy, the incidence of endocrinopathies (thyroid disorders, adrenal disorders, pituitary disorders and diabetes) was 9.9% (293/2950). The incidence of thyroid disorders, including hypothyroidism or hyperthyroidism, was 9.0% (265/2950). The majority of cases were Grade 1 or 2 in severity reported in 4.0% (117/2950) and 4.9% (145/2950) of patients, respectively. Grade 3 thyroid disorders were reported in 0.1% (3/2950) of patients. Hypophysitis (one Grade 1; two Grade 2, five Grade 3, and one Grade 4), hypopituitarism (four Grade 2 and two Grade 3), adrenal insufficiency including secondary adrenocortical insufficiency (one Grade 1; nine Grade 2; and five Grade 3), diabetes mellitus including (fulminant) Type 1 diabetes mellitus (three Grade 2 and three Grade 3), and diabetic ketoacidosis (three Grade 3 and one Grade 4) were reported. No Grade 5 cases were reported in these studies.

The median time to onset was 2.8 months (range: 0.3-29.1). Nineteen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 2.7 weeks (range 0.1-51.1). Two patients with Grade 3 and one with Grade 4 endocrinopathies required permanent discontinuation of OPDIVO. Resolution of endocrinopathies occurred in 123 patients (42%). Time to resolution ranged from 0.4 to 144.1+; + denotes a censored observation.

OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma:

In patients treated with OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of endocrinopathies (thyroid disorders, adrenal disorders, pituitary disorders and

diabetes) was 29.2% (131/448). The incidence of thyroid disorders was 23.7% (106/448). Grade 2 and Grade 3 thyroid disorders were reported in 13.4% (60/448) and 1.6% (7/448) of patients, respectively. Grade 2 and Grade 3 hypophysitis occurred in 6.0% (27/448) and 1.8% (8/448) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency each occurred in 1.1% (5/448), and Grade 4 adrenal insufficiency occurred in 0.2% (1/448) of patients. Grade 1 and Grade 2 diabetes mellitus and Grade 4 diabetic ketoacidosis were each reported in 0.2% (1/448) of patients. No Grade 5 endocrinopathy was reported.

Median time to onset of these endocrinopathies was 1.5 months (range: 0.0-10.1). Eleven patients (2.5%) required discontinuation of OPDIVO in combination with ipilimumab. Thirty-six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 2.9 weeks (range: 0.1-12.7). Resolution occurred in 59 patients (45.0%). Time to resolution ranged from 0.4-74.4+ weeks.

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of endocrinopathies (thyroid disorders, adrenal disorders, pituitary disorders and diabetes) was 32.5% (178/547). The incidence of thyroid disorders was 27.2% (149/547). Grade 2 and Grade 3 thyroid disorders were reported in 15.7% (86/547) and 1.3% (7/547) of patients, respectively. Hypophysitis occurred in 4.0% (22/547) of patients. Grade 2, Grade 3, and Grade 4 cases were reported in 0.5% (3/547), 2.4% (13/547), and 0.4% (2/547) of patients, respectively. Grade 2 hypopituitarism occurred in 0.4% (2/547) of patients. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 2.9% (16/547), 2.2% (12/547) and 0.4% (2/547) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus (three Grade 2, two Grade 3, and three Grade 4), and diabetic ketoacidosis (one Grade 4) were reported. No Grade 5 endocrinopathy was reported.

The median time to onset was 1.9 months (range: 0.0-22.3). Sixteen (2.9%) patients required permanent discontinuation. Forty-five patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 2.1 weeks (range 0.1-24.3). Resolution of endocrinopathies occurred in 76 patients (43%) with a time to resolution ranging from 0.4-130.3+.

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of endocrinopathies (thyroid disorders, adrenal disorders, pituitary disorders and diabetes) was 23.8% (137/576). The incidence of thyroid disorders was 20.0% (115/576). Grade 2, Grade 3, and Grade 4 thyroid disorders were reported in 10.6% (61/576), 0.3% (2/576) and 0.2% (1/576) of patients, respectively. Hypophysitis occurred in 2.1% (12/576) of patients. Grade 2, Grade 3 and Grade 4 cases were reported in 0.7% (4/576), 0.9% (5/576) and 0.2% (1/576) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.2% (1/576) and 0.5% (3/576) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency occurred in 1.0% (6/576) and 1.7% (10/576) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus (one Grade 2, three Grade 3, and one Grade 4) were reported. No Grade 5 endocrinopathy was reported.

The median time to onset was 2.3 months (range: 0.5-16.1). Nine (1.6%) patients required permanent discontinuation. Twenty-three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 1.9 weeks (range 0.1-6.1). Resolution of endocrinopathies occurred in 57 patients (42%) with a time to resolution ranging from 0.7-176.6+ weeks.

OPDIVO 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy in NSCLC:

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy in NSCLC, the incidence of endocrinopathies (thyroid disorders, adrenal disorders, pituitary disorders and diabetes) was 24.0% (86/358). The incidence of thyroid disorders was 21% (74/358). Grade 2 and Grade 3 thyroid disorders were reported in 12.3% (44/358) and 0.3% (1/358) of patients, respectively. Hypophysitis occurred in 1.4% (5/358) of patients. Grade 2 and Grade 3 cases were reported in 0.6% (2/358) and 0.8% (3/358) of patients, respectively. Grade 2 hypopituitarism occurred in 0.3% (1/358) of patients. Grade 2 and Grade 3 adrenal insufficiency occurred in 1.7% (6/358) and 1.4% (5/358) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus was not reported. No Grade 5 endocrinopathy was reported.

Median time to onset of these endocrinopathies was 12.1 weeks (range:1.9-58.3). Seven patients (2.0%) required permanent discontinuation. Seven patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 2.0 weeks (range: 0.1-4.4). Resolution occurred in 30 patients (35.3%). Time to resolution ranged from 1.4 to 72.4+ weeks.

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in CRC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in CRC, the incidence of endocrinopathies (thyroid disorders, adrenal disorders, pituitary disorders and diabetes) was 31.9% (38/119). The incidence of thyroid disorders was 25.2% (30/119). Grade 2 and Grade 3 thyroid disorders were reported in 13.4% (16/119) and 3.4% (4/119) of patients, respectively. Hypophysitis occurred in 3.4% (4/119) of patients. Grade 2 and Grade 3 cases were reported in 1.7% (2/119) and 1.7% (2/119) of patients, respectively. Grade 2 hypopituitarism occurred in 0.8% (1/119) of patients. No Grade 3 events were reported. Grade 2 and Grade 3 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 5.9% (7/119) and 1.7% (2/119) of patients, respectively. Diabetes mellitus was not reported. No Grade 5 endocrinopathy was reported. Median time to onset of these endocrinopathies was 2.6 months (range: 0.7-27.2). No patients required permanent discontinuation. Seven patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 2.29 weeks (range 0.3-4.0). Resolution occurred in 3 patients (33%) with a range of 1.3-126.7^{+} weeks to resolution. (see **WARNINGS AND PRECAUTIONS**)

Immune-Mediated Gastrointestinal Adverse Reactions

OPDIVO monotherapy:

In patients treated with OPDIVO monotherapy, the incidence of diarrhea, colitis and frequent bowel movements was 12.5% (369/2950) [colitis: 1.2%]. The majority of cases were Grade 1 or 2 in severity reported in 8.0% (236/2950) and 3.0% (88/2950) of patients, respectively. Grade 3 cases were reported in 1.5% (45/2950) of patients. No Grade 4 or 5 cases were reported in these studies.

The median time to onset was 1.6 months (range: 0.0-26.6). Fifty-two patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 2.4 weeks (range: 0.1-30.7). Fifteen patients (0.6%) with Grade 3, five (0.2%) with Grade 2, and one (<0.1%) with Grade 1 diarrhea or colitis required permanent discontinuation of OPDIVO. Resolution occurred in 319 patients (87%) with a median time to resolution of 2.3 weeks (range: 0.1-124.4+).

OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma:

In patients treated with OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of diarrhea, and colitis, was 45.5% (204/448) [colitis: 13.8% and enterocolitis: 0.4%]. Grade 2, Grade 3, and Grade 4 cases were reported in 13.2% (59/448), 15.4% (69/448), and 0.4% (2/448) of patients, respectively. No Grade 5 cases were reported.

Median time to onset was 1.1 months (range: 0.0-10.4). Seventy-one patients (15.8%) required permanent discontinuation of OPDIVO in combination with ipilimumab. Ninety-six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 4.6 weeks (range: 0.1-50.7). Resolution occurred in 184 patients (90.6%) with a median time to resolution of 3.0 weeks (range: 0.1-78.7+).

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of diarrhea, and colitis was 28.2% (154/547) [colitis: 3.7%, enterocolitis: 0.2%, and ulcerative colitis: 0.2%]. Grade 2 and Grade 3 cases were reported in 10.4% (57/547) and 4.9% (27/547) of patients, respectively. No Grade 4 or 5 cases were reported.

The median time to onset was 1.2 months (range: 0.0-24.7). Twenty-two (4.0%) patients required permanent discontinuation. Forty patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 3.1 weeks (range: 0.1-99.6). Resolution occurred in 140 patients (92%) with a median time to resolution of 2.4 weeks (range: 0.1-103.0+).

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of diarrhea, and colitis was 18.2% (105/576) [colitis: 2.3% and enterocolitis: 0.5%]. Grade 2, Grade 3 and Grade 4 cases were reported in 7.5% (43/576), 2.1% (12/576) and 0.3% (2/576) of patients, respectively. No Grade 5 cases were reported.

The median time to onset was 2.0 months (range: 0.0-22.5). Eighteen (3.1%) patients required permanent discontinuation. Thirty eight patients received high-dose corticosteroids (at least 40 mg

prednisone equivalents) for a median duration of 1.6 weeks (range: 0.1-11.1). Resolution occurred in 98 patients (94%) with a median time to resolution of 2.1 weeks (range: 0.1-149.3+).

OPDIVO 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy in NSCLC:

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy in NSCLC, the incidence of diarrhea or colitis was 22.3% (80/358) [colitis: 3.4%, and ulcerative colitis: 0.3%]. Grade 2, Grade 3, and Grade 4 cases were reported in 7% (25/358), 5% (18/358), and 0.3% (1/358) of patients, respectively. One Grade 5 case of diarrhea was reported.

Median time to onset was 5.1 weeks (range: 0.1-53.9). Fifteen patients (4.2%) required permanent discontinuation. Sixteen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 3.0 weeks (range: 0.1-7.3). Resolution occurred in 70 patients (87.5%) with a median time to resolution of 1.4 weeks (range: 0.1-76.9+).

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in CRC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in CRC, the incidence of diarrhea or colitis was 25.2% (30/119). Grade 2 and Grade 3 cases were reported in 5.0% (6/119) and 3.4% (4/119) of patients, respectively. No Grade 4 or 5 cases were reported.

Median time to onset was 2.2 months (range: 0.1-30.6). Two (1.7%) patients required permanent discontinuation. Four patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 2.64 weeks (range 2.0-6.0). Resolution occurred in 28 patients (97%) with a median time to resolution of 1.43 weeks (range: 0.1-77.4^{+}). (see **WARNINGS AND PRECAUTIONS**)

Immune-Mediated Hepatic Adverse Reactions

OPDIVO monotherapy:

In patients treated with OPDIVO monotherapy, the incidence of liver function test abnormalities was 6.5% (193/2950) [hepatitis: 0.3%]. The majority of cases were Grade 1 or 2 in severity reported in 3.4% (101/2950) and 1.2% (35/2950) of patients, respectively. Grade 3 and 4 cases were reported in 1.6% (48/2950) and 0.3% (9/2950) of patients, respectively. No Grade 5 cases were reported in these studies.

The median time to onset was 1.9 months (range: 0.0-27.6). Thirty-eight patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 2.7 weeks (range: 0.1-22.1). Twenty-eight patients (0.9%), nineteen with Grade 3, five with Grade 4, three with Grade 2 and one with Grade 1 liver function test abnormalities, required permanent discontinuation of OPDIVO. Resolution occurred in 146 patients (76%) with a median time to resolution of 6.1 weeks (range: 0.1-82.6+).

OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma:

In patients treated with OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of liver function test abnormalities was 27.9% (125/448) [hepatitis: 3.6%]. Grade 2, Grade 3, and Grade 4 cases were reported in 6.3% (28/448), 15.0% (67/448), and 1.8% (8/448) of patients, respectively. No Grade 5 cases were reported.

Median time to onset was 1.4 months (range: 0.0-11.0). Forty-one patients (9.2%) required permanent discontinuation of OPDIVO in combination with ipilimumab. Fifty-eight patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 3.8 weeks (range: 0.1-57.6). Resolution occurred in 116 patients (92.8%) with a median time to resolution of 5.0 weeks (range: 0.1-53.1).

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of liver function test abnormalities was 18.5% (101/547) [hepatitis: 1.3%]. Grade 2, Grade 3, and Grade 4 cases were reported in 4.8% (26/547), 6.6% (36/547), and 1.6% (9/547) of patients, respectively. No Grade 5 cases were reported.

The median time to onset was 2.0 months (range: 0.4-26.8). Twenty-four patients (4.4%) required permanent discontinuation. Thirty-five patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 4.0 weeks (range: 0.1-9.7). Resolution occurred in 86 patients (85%) with a median time to resolution of 6.1 weeks (range: 0.1+-82.9+).

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of liver function test abnormalities was 15.8% (91/576) [hepatitis: 2.1%]. Grade 2, Grade 3, and Grade 4 cases were reported in 2.8% (16/576), 7.5% (43/576) and 0.7% (4/576) of patients, respectively. No Grade 5 cases were reported.

The median time to onset was 2.4 months (range: 0.2-20.3). Seventeen patients (3.0%) required permanent discontinuation. Thirty-nine patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 2.0 weeks (range: 0.3-11.3). Resolution occurred in 82 patients (90%) with a median time to resolution of 5.3 weeks (range: 0.4-155.1+).

OPDIVO 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy in NSCLC:

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy in NSCLC, the incidence of liver function test abnormalities was 13.4% (48/358) [hepatitis: 1.7%]. Grade 2, Grade 3, and Grade 4 cases were reported in 3.1% (11/358), 3.4% (12/358), and 1.1% (4/358) of patients, respectively. One case of Grade 4 hepatitis subsequently worsened with fatal outcome, and one case of Grade 3 hepatotoxicity resulted in a fatal outcome.

Median time to onset was 10.6 weeks (range: 1.1-68.3). Twelve patients (3.4%) required permanent discontinuation. Fourteen patients received high-dose corticosteroids (at least 40 mg

prednisone equivalents) for a median duration of 2.9 weeks (range: 0.1-9.6). Resolution occurred in 37 patients (80.4%) with a median time to resolution of 5 weeks (range: 0.3+-45.0+).

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in CRC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in CRC, the incidence of liver function test abnormalities was 23.5% (28/119). Grade 2 and Grade 3 cases were reported in 3.4% (4/119) and 11.8% (14/119) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 2.2 months (range: 0.3-15.2). Six (5%) patients required permanent discontinuation. Twelve patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 3.07 weeks (range 0.4-52.7). Resolution occurred in 22 patients (79%) with a median time to resolution of 9.43 weeks (range: 0.3-130.7^{+}). (see **WARNINGS AND PRECAUTIONS**)

Immune-Mediated Pulmonary Adverse Reactions

Across the clinical trial program, fatal immune-mediated pneumonitis occurred in 5 patients receiving OPDIVO in a dose-finding study at doses of 1 mg/kg (two patients), 3 mg/kg (two patients), and 10 mg/kg (one patient). One patient with Grade 3 pulmonary embolism and Grade 3 pneumonitis subsequently died in the SCCHN clinical trial. In patients treated with OPDIVO 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks in NSCLC, four patients died due to pneumonitis.

OPDIVO monotherapy:

In patients treated with OPDIVO monotherapy, the incidence of pneumonitis, including interstitial lung disease, was 3.3% (96/2950). The majority of cases were Grade 1 or 2 in severity reported in 0.9% (26/2950) and 1.6% (46/2950) of patients, respectively. Grade 3 and 4 cases were reported in 0.7% (21/2950) and <0.1% (1/2230) of patients, respectively. Grade 5 cases were reported <0.1% (2/2950) of patients.

The median time to onset was 3.6 months (range: 0.2-19.6). Sixty-four patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 3.4 weeks (range: 0.1-13.1). Six with Grade 1, eight with Grade 2, eighteen patients with Grade 3 and two with Grade 4, and one with Grade 5 required permanent discontinuation of OPDIVO. Resolution occurred in 67 patients (70%); with a median time to resolution of 6.1 weeks (range: 0.1-96.7+).

OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma:

In patients treated with OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of pneumonitis including interstitial lung disease, was 7.4% (33/448). Grade 2, Grade 3, and Grade 4 cases were reported in 4.5% (20/448), 1.1% (5/448), and 0.2% (1/448) of patients, respectively. One of the Grade 3 pneumonitis cases worsened over 11 days with a fatal outcome.

Median time to onset was 2.3 months (range: 0.7-6.7). Nine patients (2.0%) required permanent discontinuation of OPDIVO in combination with ipilimumab. Twenty-one patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 4.3 weeks

(range: 0.7-51.1). Resolution occurred in 29 patients (87.9%) with a median time to resolution of 6.1 weeks (range: 0.3-46.9+).

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of pneumonitis including interstitial lung disease was 6.2% (34/547). Grade 2 and Grade 3 cases were reported in 3.1% (17/547) and 1.1% (6/547), of patients, respectively. No Grade 4 or 5 cases were reported in this study.

The median time to onset was 2.6 months (range: 0.25-20.6). Twelve patients (2.2%) required permanent discontinuation. Twenty patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 2.4 weeks (range: 0.6-14.0). Resolution occurred in 31 patients (91%) with a median time to resolution of 6.1 weeks (range: 0.7-85.9+).

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of pneumonitis including interstitial lung disease was 8.0% (48/576). Grade 2, Grade 3 and Grade 4 cases were reported in 4.0% (23/576), 3.0% (17/576) and 0.3% (2/576) of patients, respectively. Grade 5 cases of pneumonitis were reported in 4 patients (4/576).

The median time to onset was 3.6 months (range: 0.9-23.7). Twenty-seven patients (4.7%) required permanent discontinuation. Forty-three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 2.9 weeks (range: 0.3-22.1). Resolution occurred in 41 patients (85%) with a median time to resolution of 6.0 weeks (range: 0.7-109.4+).

OPDIVO 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy in NSCLC:

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy in NSCLC, the incidence of pneumonitis including interstitial lung disease was 5.3% (19/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 1.1% (4/358), 0.6% (2/358) and of patients, respectively. One case of Grade 4 pneumonitis resulted in a fatal outcome.

Median time to onset was 18.1 weeks (range: 0.6-52.4). Eight patients (2.2%) required permanent discontinuation. Thirteen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 3.0 weeks (range: 0.1-6.0). Resolution occurred in 14 patients (74%) with a median time to resolution of 4.3 weeks (range: 0.7-27.9+).

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in CRC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in CRC, the incidence of pneumonitis was 5.9% (7/119). Grade 2 and Grade 3 cases were reported in 2.5% (3/119) and 0.8% (1/119) of patients, respectively. No Grade 4 or 5 cases were reported in this study. Median time to onset was 2.7 months (range: 0.9-25.5). One (0.8%) patients required permanent discontinuation. Three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 2.14 weeks (range 1.7-12.3). Resolution occurred

in 6 patients (86%) with a median time to resolution of 5.43 weeks (range: 1.0-110.3+). (see **WARNINGS AND PRECAUTIONS**)

Immune-Mediated Renal Adverse Reactions

OPDIVO monotherapy:

In patients treated with OPDIVO monotherapy, the incidence of nephritis and renal dysfunction was 2.4% (72/2950) [nephritis: < 0.1%, and tubulointerstitial nephritis: 0.1%]. The majority of cases were Grade 1 or 2 in severity reported in 1.4% (41/2950) and 0.6% (19/2950) of patients, respectively. Grade 3 and 4 cases were reported in 0.4% (11/2950) and <0.1% (1/2950) of patients, respectively. No Grade 5 nephritis or renal dysfunction was reported in these studies.

The median time to onset was 2.3 months (range: 0.0-18.2). Nineteen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 2.9 weeks (range: 0.1-67.0). Seven patients (0.2%), four with Grade 2, two with Grade 3 and one with Grade 4 nephritis or renal dysfunction required permanent discontinuation of OPDIVO. Resolution occurred in 42 patients (61%) with a median time to resolution of 12.1 weeks (range: 0.3-79.1+).

OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma:

In patients treated with OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of nephritis and renal dysfunction was 4.2% (19/448) [nephritis: 0.4%, and tubulointerstitial nephritis: 0.2%]. Grade 2, Grade 3, and Grade 4 cases were reported in 1.1% (5/448), 0.9% (4/448), and 0.7% (3/448) of patients, respectively. No Grade 5 cases were reported.

Median time to onset was 2.6 months (range: 0.5-14.7). Four patients (0.9%) required permanent discontinuation of OPDIVO in combination with ipilimumab. Four patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 2.5 weeks (range: 0.1-4.1). Resolution occurred in 17 patients (89.5%) with a median time to resolution of 1.9 weeks (range: 0.4-42.6+).

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of nephritis and renal dysfunction was 8.8% (48/547) [nephritis 0.9%, and tubulointerstitial nephritis: 0.2%]. Grade 2, Grade 3, and Grade 4 cases were reported in 4.4% (24/547), 0.7% (4/547), and 0.5% (3/547) of patients, respectively. No Grade 5 cases were reported.

The median time to onset was 2.1 months (range: 0.0-16.1). Seven patients (1.3%) required permanent discontinuation. Thirteen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 2.1 weeks (range: 0.6-25.7). Resolution occurred in 37 patients (77%) with a median time to resolution of 13.2 weeks (range: 0.1+-106.0+).

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of nephritis and renal dysfunction was 4.3% (25/576) [nephritis 0.3%, and

tubulointerstitial nephritis: 0.2%]. Grade 2, Grade 3 and Grade 4 cases were reported in 1.4% (8/576), 0.5% (3/576) and 0.2% (1/576) of patients, respectively. No Grade 5 cases were reported.

The median time to onset was 4.9 months (range: 0.5-21.2). Two patients (0.3%) required permanent discontinuation. Five patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 3.3 weeks (range: 1.1-5.1). Resolution occurred in 23 patients (92%) with a median time to resolution of 2.4 weeks (range: 0.3-152.4+).

OPDIVO 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy in NSCLC:

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy in NSCLC, the incidence of nephritis or renal dysfunction was 7% (25/358) [nephritis: 0.3%]. Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 1.7% (6/358), and 0.6 (2/358) of patients, respectively. No Grade 5 cases were reported.

Median time to onset was 10.6 weeks (range: 0.1-51.3). Five patients (1.4%) required permanent discontinuation. Six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 1.7 weeks (range: 0.7-7.9). Resolution occurred in 14 patients (56%) with a median time to resolution of 6.3 weeks (range: 0.1+-82.9+).

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in CRC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in CRC, the incidence of nephritis or renal dysfunction was 5.9% (7/119). Grade 4 cases were reported in 1.7% (2/119) of patients. No Grade 2, 3, or 5 cases were reported. Median time to onset was 4.2 months (range: 0.3-11.8). Two (1.7%) patients required permanent discontinuation. Two patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 7.36 weeks (range 4.4-10.3). Resolution occurred in 6 patients (86%) with a median time to resolution of 6.71 weeks (range: 2.7-27.3). (see **WARNINGS AND PRECAUTIONS**)

Immune-Mediated Skin Adverse Reactions

OPDIVO monotherapy:

In patients treated with OPDIVO monotherapy, the incidence of rash was 25.1% (741/2950). The majority of cases were Grade 1 in severity reported in 19.2% (567/2950) of patients. Grade 2 and Grade 3 cases were reported in 4.7% (140/2950) and 1.2% (34/2950) of patients, respectively. No Grade 4 or 5 cases were reported in these studies.

Median time to onset was 1.4 months (range: 0.0-27.9). Twenty-nine patients received high dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 2.0 weeks (range: 0.1-122.6). Seven patients (0.2%) with Grade 3, three with Grade 2, and one with Grade 1 rash required permanent discontinuation of OPDIVO. Resolution occurred in 465 patients (64%) with a median time to resolution of 17.0 weeks (0.1-150.0+).

OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma:

In patients treated with OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, the incidence of rash was 63.4% (284/448). Grade 2 and Grade 3 cases were reported in 19.2% (86/448) and 7.4% (33/448) of patients, respectively. No Grade 4 or 5 cases were reported.

Median time to onset was 0.5 months (range: 1 day-9.7 months). Three patients (0.7%) required permanent discontinuation of OPDIVO in combination with ipilimumab. Twenty patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 1.6 weeks (range: 0.3-15.6). Resolution occurred in 192 patients (67.6%) with a median time to resolution of 10.4 weeks (range: 0.1-74.0+).

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of rash was 48.8% (267/547). Grade 2 and Grade 3 cases were reported in 13.7% (75/547) and 3.7% (20/547) of patients, respectively. No Grade 4 or 5 cases were reported.

The median time to onset was 0.9 months (range: 0.0-17.9). Eight patients (1.5%) required permanent discontinuation. Nineteen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 2.3 weeks (range: 0.1-100.3). Resolution occurred in 192 patients (72%) with a median time to resolution of 11.6 weeks (range: 0.1-126.7+).

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in NSCLC, the incidence of rash was 34.0% (196/576). Grade 2 and Grade 3 cases were reported in 10.6% (61/576) and 4.2% (24/576) of patients, respectively. No Grade 4 or 5 cases were reported.

The median time to onset was 1.0 month (range: 0.0-17.9). Four patients (0.7%) required permanent discontinuation. Twenty-eight patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 1.2 weeks (range: 0.1-7.9). Resolution occurred in 148 patients (76%) with a median time to resolution of 9.9 weeks (range: 0.1-165.0+).

OPDIVO 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy in NSCLC:

In patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and platinum-doublet chemotherapy in NSCLC, the incidence of rash was 37.7% (135/358). Grade 2, Grade 3, and Grade 4 cases were reported in 11.5% (41/358), 4.2% (14/358), and 0.3% (1/358) of patients, respectively. No Grade 5 cases were reported.

Median time to onset was 3.3 weeks (range: 0.1-83.1). Four patients (1.1%) required permanent discontinuation. Fourteen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 1.0 weeks (range: 0.1-3.9). Resolution occurred in 96 patients (71.6%) with a median time to resolution of 9.4 weeks (range: 0.1+-84.1+).

OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in CRC:

In patients treated with OPDIVO 3 mg/kg in combination with ipilimumab 1 mg/kg in CRC, the incidence of rash was 35.3% (42/119). Grade 2 and Grade 3 cases were reported in 11.8% (14/119) and 4.2% (5/119) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 1.4 months (range: 0.1-15.9). No patients required permanent discontinuation. Four patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 1.86 weeks (range 1.1-3.3). Resolution occurred in 32 patients (76%) with a median time to resolution of 11.50 weeks (range: 0.4-187.4^{+}). (see **WARNINGS AND PRECAUTIONS**)

Post-Market Adverse Reactions:

The following events have been identified during post approval use of OPDIVO or OPDIVO in combination with ipilimumab. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made.

Blood and lymphatic system disorders: haemophagocytic lymphohistiocytosis (HLH), autoimmune hemolytic anemia.

Cardiac disorders: pericarditis.

Endocrine: hypoparathyroidism.

Eye disorders: Vogt-Koyanagi-Harada syndrome.

Immune system disorders: solid organ transplant rejection, graft-versus-host-disease.

Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response to nivolumab.

Of 2085 patients who were treated with OPDIVO 3 mg/kg every 2 weeks and evaluable for the presence of anti-product antibodies, 233 patients (11.2%) tested positive for treatment-emergent anti-product antibodies by an electrochemiluminescent (ECL) assay. Neutralizing antibodies were detected in 15 infusion patients (0.7% of the total). There was no evidence of altered pharmacokinetic profile or toxicity profile associated with anti-product antibody development. Neutralizing antibodies were not associated with loss of efficacy.

Of patients who were treated with OPDIVO in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26.0% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 36.7% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, and 37.8% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. Of the patients who were treated with OPDIVO 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and platinum-doublet chemotherapy every 3 weeks, and were evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 33.8%. The incidence of neutralizing antibodies against nivolumab was 0.5% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 1.4% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, and 4.6%

with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks, and 2.6% with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and platinum-doublet chemotherapy every 3 weeks. Of patients evaluable for the presence of anti-ipilimumab antibodies, the incidence of anti-ipilimumab antibodies ranged from 6.3 to 8.3% and neutralizing antibodies against ipilimumab ranged from 0 to 1.6%. Overall, there was no evidence of altered toxicity profile associated with anti-product antibody development. Neutralizing antibodies were not associated with loss of efficacy.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to nivolumab with the incidences of antibodies to other products may be misleading.

DRUG INTERACTIONS

No formal drug-drug interaction studies have been conducted with nivolumab. Nivolumab is considered to have low potential to affect pharmacokinetics of other drugs based on the lack of effect on cytokines in peripheral circulation.

Systemic Immunosuppression

The use of systemic corticosteroids and other immunosuppressants at baseline, before starting OPDIVO, should be avoided because of their potential interference with the pharmacodynamic activity. However, systemic corticosteroids and other immunosuppressants can be used after starting OPDIVO to treat immune-related adverse reactions. The preliminary results show that systemic immunosuppression after starting OPDIVO treatment does not appear to preclude the response on nivolumab.

NOC/c DOSAGE AND ADMINISTRATION

Patient Selection

For treatment of MSI-H/dMMR mCRC:
Patients should be selected for treatment based on MSI-H or dMMR tumor status as determined by an experienced laboratory using validated testing methods **(**see **CLINICAL TRIALS).**

Recommended Dose

OPDIVO as monotherapy:

The recommended dose of OPDIVO as monotherapy is either:

- 3 mg/kg every 2 weeks or
- 240 mg every 2 weeks or
- 480 mg every 4 weeks

administered as an intravenous infusion over 30 minutes.

Continue treatment as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

The maximum treatment duration with OPDIVO as monotherapy for adjuvant treatment of melanoma is 12 months.

If patients need to be switched from the 3mg/kg or 240 mg every 2 weeks schedule to the 480 every 4 weeks schedule, the first 480 mg dose should be administered two weeks after the last 3mg/kg or 240 mg dose. Conversely, if patients need to be switched from the 480 mg every 4 weeks schedule to the 3 mg/kg or 240 mg every 2 weeks schedule, the first 3 mg/kg or 240 mg dose should be administered four weeks after the last 480 mg dose (see **ACTION AND CLINICAL PHARMACOLOGY; Pharmacokinetics/Pharmacodynamics**).

OPDIVO in combination with ipilimumab:

Unresectable or metastatic melanoma

The recommended dose of OPDIVO during the combination phase is 1 mg/kg administered as an intravenous infusion over 30 minutes, followed by ipilimumab 3 mg/kg administered as an intravenous infusion over 90 minutes on the same day, every 3 weeks for the first 4 doses or until unacceptable toxicity, whichever occurs earlier. After the completion of the combination phase, administer OPDIVO as a single agent, either:

- 3 mg/kg every 2 weeks or
- 240 mg every 2 weeks or
- 480 mg every 4 weeks

as an intravenous infusion over 30 minutes (Table 27). Continue treatment as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

Table 27: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab

	Combination phase, every 3 weeks for 4 dosing cycles	**Monotherapy phase**
Nivolumab	1 mg/kg over 30 minutes	3 mg/kg every 2 weeks over 30 minutes[a] or 240 mg every 2 weeks over 30 minutes[a] or 480 mg every 4 weeks over 30 minutes[b]
Ipilimumab	3 mg/kg over 90 minutes	-

[a:] 3 weeks after the last dose of the combination of nivolumab and ipilimumab
[b:] 6 weeks after the last dose of the combination of nivolumab and ipilimumab

Metastatic renal cell carcinoma and colorectal cancer

The recommended dose of OPDIVO during the combination phase is 3 mg/kg nivolumab administered as an intravenous infusion over 30 minutes, followed by ipilimumab 1 mg/kg administered as an intravenous infusion over 30 minutes on the same day, every 3 weeks for the

first 4 doses. After completion of the combination phase, administer OPDIVO as a single agent, either:

- 3 mg/kg every 2 weeks or
- 240 mg every 2 weeks or
- 480 mg every 4 weeks

as an intravenous infusion over 30 minutes (Table 28). Continue treatment as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

Table 28: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab

	Combination phase, every 3 weeks for 4 dosing cycles	**Monotherapy phase**
Nivolumab	3 mg/kg over 30 minutes	3 mg/kg every 2 weeks over 30 minutes[a] or 240 mg every 2 weeks over 30 minutes[a] or 480 mg every 4 weeks over 30 minutes[b]
Ipilimumab	1 mg/kg over 30 minutes	-

[a:] 3 weeks after the last dose of the combination of nivolumab and ipilimumab
[b:] 6 weeks after the last dose of the combination of nivolumab and ipilimumab

Metastatic NSCLC

For previously untreated metastatic NSCLC, select patients for OPDIVO in combination with ipilimumab treatment based on the presence of positive PD-L1 expression as determined by an experienced laboratory using a validated test. A test authorized by Health Canada which is equivalent to that used in clinical trials should be required (see **CLINICAL TRIALS**).

The recommended dose of OPDIVO in combination with ipilimumab for previously untreated metastatic NSCLC is 3 mg/kg every 2 weeks (30-minute intravenous infusion) in combination with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion) until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.

OPDIVO in combination with ipilimumab and chemotherapy:

Metastatic NSCLC

The recommended dose is OPDIVO 360 mg administered as a 30-minute intravenous infusion every 3 weeks in combination with ipilimumab 1 mg/kg administered as a 30-minute intravenous infusion every 6 weeks, and platinum-doublet chemotherapy administered every 3 weeks for 2 cycles. After completion of 2 cycles of chemotherapy, treatment is continued with OPDIVO 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression (Table 29).

Table 29: Recommended doses and infusion times for intravenous administration of OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy

	Recommended Dose	Duration
OPDIVO	360 mg over 30 minutes every 3 weeks	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression
Ipilimumab	1 mg/kg over 30 minutes every 6 weeks	In combination with OPDIVO until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression
Chemotherapy	histology-based platinum doublet chemotherapy every 3 weeks	2 cycles of histology-based platinum-doublet chemotherapy

Recommended Dosage Adjustment

For treatment with OPDIVO, OPDIVO in combination with ipilimumab, or OPDIVO in combination with ipilimumab and chemotherapy, dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.

Treatment with OPDIVO or OPDIVO in combination with ipilimumab may be continued for clinically stable patients with initial evidence of disease progression until disease progression is confirmed. Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed.

Table 30: Recommended Treatment Modifications for OPDIVO Monotherapy or in Combination with other therapeutic agents

Target Organ/System	Adverse Reaction[a]	Treatment Modification
Endocrine	Grade 2 or 3 hypothyroidism, Grade 2 or 3 hyperthyroidism, and Grade 2 hypophysitis Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold dose(s) until symptoms resolve and acute management with corticosteroids, if needed, is complete[b]
	Grade 3 or 4 hypophysitis Grade 4 hypothyrodism Grade 4 hyperthyroidism Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment[c]
Gastrointestinal	Grade 2 or 3 diarrhea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 3 diarrhea or colitis	Permanently discontinue treatment

Table 30: Recommended Treatment Modifications for OPDIVO Monotherapy or in Combination with other therapeutic agents

Target Organ/System	Adverse Reaction[a]	Treatment Modification
	OPDIVO in combination with ipilimumab	
	Grade 4 diarrhea or colitis	Permanently discontinue treatment[c]
Hepatic	*Patients with normal AST/ALT/bilirubin at baseline:*	
	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue treatment[c]
	HCC patients with elevated AST/ALT at baseline:	
	Grade 1 elevation in AST/ALT at baseline (>1 to 3 times upper limit of normal [ULN]) and on-treatment AST/ALT elevation at .>5-10 times the ULN	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids is complete
	Grade 2 elevation in AST/ALT at baseline (>3 to 5 times ULN) and on-treatment AST/ALT elevation at >8-10 times ULN	
	AST/ALT >10 times ULN (regardless of baseline) or Grade 3 or 4 elevation in total bilirubin	Permanently discontinue treatment[c]
Pulmonary	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment[c]
Renal	Grade 2 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete
	Grade 3 or 4 creatinine elevation	Permanently discontinue treatment[c]
Skin	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose(s)
	Grade 4 rash Confirmed SJS/TEN	Permanently discontinue treatment[c]
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete

Table 30: Recommended Treatment Modifications for OPDIVO Monotherapy or in Combination with other therapeutic agents

Target Organ/System	Adverse Reaction[a]	Treatment Modification
	Immune-mediated encephalitis	Permanently discontinue treatment[c]
Myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete. Retreatment may be considered after recovery.
	Grade 3 myocarditis	Permanently discontinue treatment[c]
Other	Grade 3	Withhold dose(s) until symptoms resolve or improve and management with corticosteroids is complete
	Grade 4 or recurrent Grade 3, Grade 3 or 4 infusion reaction, persistent Grade 2 or 3 despite treatment modification, inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day	Permanently discontinue treatment[c]

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

[b] May resume treatment while receiving physiologic replacement therapy.

[c] See WARNINGS & PRECAUTIONS for treatment recommendations.

When OPDIVO is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either the combination treatment or OPDIVO monotherapy could be resumed based on the evaluation of the individual patient.

Administration

OPDIVO is to only be administered by intravenous infusion.

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

Administer the infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2-1.2 micrometer).

OPDIVO should not be infused concomitantly in the same intravenous line with other agents. Physical or biochemical compatibility studies have not been conducted to evaluate the coadministration of OPDIVO with other agents.

Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.

When OPDIVO is administered in combination with ipilimumab or with ipilimumab and chemotherapy, OPDIVO should be given first followed by ipilimumab and then chemotherapy (if applicable), on the same day. Use separate infusion bags and filters for each infusion.

Preparation for Administration

OPDIVO can be used for intravenous administration either:

- without dilution: withdraw the required volume of OPDIVO injection, 10 mg/mL, and aseptically transfer into a sterile intravenous container (PVC container, non-PVC container, or glass bottle); or
- after diluting with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, according to the following instructions:

  -the final infusion concentration should range between 1 to 10 mg/mL.

  -the total volume of infusion must not exceed 160 mL. For patients weighing less than 40 kg, the total volume of infusion must not exceed 4 mL per kilogram of patient weight.

Mix diluted solution by gentle inversion of the infusion container, do not shake.

The OPDIVO infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions: 2°C to 8°C and protected from light for up to 24 hours (a maximum of 8 hours of the total 24 can be at room temperature 20°C to 25°C and room light).

Discard partially used vials or empty vials of OPDIVO.

OVERDOSAGE

There is no information on overdosage with OPDIVO (nivolumab).

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumours and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumour responses in metastatic melanoma. In murine syngeneic tumour models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumour activity.

Pharmacokinetics

Nivolumab pharmacokinetics (PK) was assessed using a population PK approach for both single agent OPDIVO and OPDIVO in combination with ipilimumab.

OPDIVO as a single agent: The pharmacokinetics (PK) of nivolumab is linear in the dose range of 0.1 to 20 mg/kg. The geometric mean clearance (CL), volume of distribution at steady state (Vss), and terminal half-life ($t_{1/2}$) of nivolumab were 9.5 mL/h, 8.0 L and 26.7 days, respectively.

The metabolic pathway of nivolumab has not been characterized. As a fully human IgG4 monoclonal antibody, nivolumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

OPDIVO in combination with ipilimumab: When nivolumab was administered at 1 mg/kg every 3 weeks in combination with ipilimumab 3 mg/kg every 3 weeks, in the respective population PK models, the CL parameter of nivolumab was increased by 35%, whereas there was no effect on the CL parameter of ipilimumab.

When nivolumab was administered at 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks, the nivolumab CL parameter was unchanged compared to nivolumab administered alone (< 20%) and the ipilimumab CL parameter was increased by 30% compared to ipilimumab administered alone.

OPDIVO in combination with ipilimumab and platinum-based chemotherapy:

When nivolumab 360 mg every 3 weeks was administered in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy, the CL parameter of nivolumab decreased approximately 10% and the CL parameter of ipilimumab increased approximately 22%.

Pharmacokinetics/ Pharmacodynamics

Based on dose/exposure efficacy and safety analyses, no clinically significant differences in safety and efficacy were observed between a nivolumab dose of 240 mg every 2 weeks or 480 mg every 4 weeks or 3 mg/kg every 2 weeks.

Special Populations and Conditions

Population PK analysis suggested the effects of age and race on the nivolumab clearance parameter are not clinically relevant.

Hepatic Insufficiency:

No dedicated clinical studies were conducted to evaluate the effect of hepatic impairment on the PK of nivolumab. OPDIVO has not been studied in patients with moderate (TB >1.5 to 3 times

ULN and any AST) or severe hepatic impairment (TB >3 times ULN and any AST). (see **WARNINGS AND PRECAUTIONS**)

Renal Insufficiency:

No dedicated clinical studies were conducted to evaluate the effect of renal impairment on the PK of nivolumab. Data are not sufficient for drawing a conclusion on patients with severe renal impairment. (see **WARNINGS AND PRECAUTIONS**)

STORAGE AND STABILITY

Store OPDIVO **(**nivolumab) under refrigeration at 2°C to 8°C. Protect OPDIVO from light by storing in the original package until time of use. Do not freeze or shake.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

OPDIVO (nivolumab) Injection is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colourless to pale-yellow liquid for intravenous infusion that may contain light (few) particles. The solution has an approximate pH of 6. OPDIVO is supplied at a nominal concentration of 10 mg/mL nivolumab in either 40-mg or 100-mg single-use vials and contains the following inactive ingredients: sodium citrate dihydrate (5.88 mg/mL), sodium chloride (2.92 mg/mL), mannitol (30 mg/mL), pentetic acid (0.008 mg/mL), polysorbate 80 (0.2 mg/mL), sodium hydroxide and/or hydrochloric acid may have been added to adjust pH, and Water for Injection, USP.

PART II: SCIENTIFIC INFORMATION

Pr OPDIVO® has been issued marketing authorization **with conditions**, pending the results of trials to verify its clinical benefit, for the treatment of adult patients with:

- Previously untreated unresectable or metastatic BRAF V600 mutation-positive melanoma. An improvement in survival has not yet been established.
- Previously untreated unresectable or metastatic melanoma when used in combination with ipilimumab.
  Relative to OPDIVO monotherapy, an increase in progression-free survival (PFS) for the combination of OPDIVO with ipilimumab is established only in patients with low tumour PD-L1 expression (based on the predefined expression level of < 5%)**.**
  An improvement in survival has not yet been established.
- Classical Hodgkin Lymphoma (cHL) that has relapsed or progressed after:
  - autologous stem cell transplantation (ASCT) and brentuximab vedotin, or
  - 3 or more lines of systemic therapy including ASCT.

  An improvement in survival or disease-related symptoms has not yet been established.
- As a monotherapy in patients with advanced (not amenable to curative therapy or local therapeutic measures) or metastatic hepatocellular carcinoma (HCC) who are intolerant to or have progressed on sorafenib therapy.
  The marketing authorization with conditions is primarily based on tumour objective response rate and duration of response. An improvement in survival or disease-related symptoms has not yet been established.
- In combination with ipilimumab, for the treatment of adult patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer after:
  - prior fluoropyrimidine-based therapy in combination with oxaliplatin or irinotecan.

  An improvement in survival has not yet been established.

Patients should be advised of the nature of the authorization. For further information for Pr OPDIVO® please refer to Health Canada's Notice of Compliance with conditions - drug products web site: http://www.hc-sc.gc.ca/dhpmps/prodpharma/notices-avis/conditions/index-eng.php.

Pr OPDIVO® has been issued marketing authorization **without conditions** for the treatment of adult patients with:

- Previously untreated unresectable or metastatic BRAF V600 wild-type melanoma
- Unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.
- Melanoma with regional lymph node involvement, in transit metastases/satellites without metastatic nodes, or distant metastases, as adjuvant therapy after complete resection.
- Locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour

aberrations should have disease progression on a therapy for these aberrations prior to receiving OPDIVO
    - Metastatic NSCLC, expressing PD-L1 ≥ 1% as determined by a validated test with no EGFR or ALK genomic tumour aberrations, and no prior systemic treatment for metastatic NSCLC, when used in combination with ipilimumab.
    - Metastatic NSCLC with no EGFR or ALK genomic tumour aberrations, and no prior systemic therapy for metastatic NSCLC, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy.
- Advanced or metastatic renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy
    - Intermediate/poor-risk advanced or metastatic RCC when used in combination with ipilimumab.
    - Recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) progressing on or after platinum-based therapy.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: nivolumab

Structure: Nivolumab is a fully human monoclonal antibody of the IgG4 class consisting of four polypeptide chains: two identical heavy chains of 440 amino acids and two identical kappa light chains of 214 amino acids, which are linked through inter-chain disulfide bonds.

Molecular formula and molecular mass: The predominant product has a molecular formula of $C_{6462}H_{9990}N_{1714}O_{2074}S_{42}$ (with heavy chain N-terminal pyroglutamate, without C-terminal lysine and with G0F/G0F glycoform) with a calculated molecular weight of 146,221 Da.

Physicochemical properties: The nivolumab drug substance solution is a clear to opalescent, colourless to pale yellow liquid that may contain light (few) particles. The 20mg/mL nivolumab drug substance solution containing 20 mM Sodium Citrate, 50 mM Sodium Chloride, 3.0%w/v Mannitol, 20 uM Pentetic Acid and 0.04% v/v Polysorbate 80, has a pH of approximately 6.0, a pI of approximately 7.8 and an extinction coefficient of 1.68 mL/mg·cm.

Product Characteristics

OPDIVO injection is a clear to opalescent, colourless to pale yellow liquid which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, preservative free, isotonic aqueous solution for intravenous (IV) administration. OPDIVO injection may be administered undiluted at a concentration of 10 mg/mL or further diluted with 0.9% sodium chloride injection (sodium chloride 9 mg/mL (0.9%) solution for injection) or 5% dextrose injection (50 mg/mL (5%) glucose solution for injection) to nivolumab concentrations as low as 1 mg/mL. The drug product is packaged in a 10-cc Type 1 flint glass vial, stoppered with a 20-mm

FluroTec® film-coated butyl rubber stopper, and sealed with a 20-mm aluminum crimp seal with Flip-Off® cap.

NOC/c

CLINICAL TRIALS

Unresectable or Metastatic Melanoma:

In CHECKMATE-066 and CHECKMATE-037 (monotherapy), the safety and efficacy of OPDIVO (nivolumab) as a single agent for the treatment of patients with advanced (unresectable or metastatic) melanoma were evaluated in two randomized, Phase III studies CHECKMATE-066 and CHECKMATE-037. Additional support is provided from an open-label Phase I dose-escalation study, MDX1106-03 (conducted in solid tumour malignancies across several tumour types).

In CHECKMATE-067 (monotherapy and combination therapy) and CHECKMATE-069 (combination therapy), the safety and efficacy of OPDIVO as a single agent or in combination with ipilimumab for the treatment of patients with advanced (unresectable or metastatic) melanoma were evaluated in 2 randomized, multinational, well-controlled, double-blind studies (Studies CHECKMATE-067 and CHECKMATE-069). CHECKMATE-067 is a Phase III study of OPDIVO monotherapy or OPDIVO in combination with ipilimumab versus ipilimumab. CHECKMATE-069 is a Phase II study of OPDIVO in combination with ipilimumab versus ipilimumab.

Controlled Trial in Melanoma Patients Previously Untreated (First-line treatment)

In CHECKMATE-066 , a total of 418 patients were randomized on a 1:1 basis to either OPDIVO administered intravenously over 60 minutes at 3 mg/kg every 2 weeks (n = 210) or dacarbazine 1000 mg/m^2 every 3 weeks (n = 208). Randomization was stratified by PD-L1 status and M stage. Previously untreated patients with BRAF wild-type melanoma were enrolled in the study. Prior adjuvant or neoadjuvant melanoma therapy was permitted if it had been completed at least 6 weeks prior to randomization. Patients with active autoimmune disease, ocular melanoma, or active brain or leptomeningeal metastases were excluded from the study.

The primary efficacy outcome measure was overall survival (OS). Key secondary endpoints included progression-free survival (PFS), and objective response rate (ORR). Exploratory outcome measures included time to response (TTR) and duration of response (DOR). Tumour response was assessed by investigators based on Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1 at 9 weeks after randomization and continued every 6 weeks for the first year and then every 12 weeks thereafter.

Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Treatment after disease progression was permitted for patients who had a clinical benefit and did not have substantial adverse effects with the study drug, as determined by the investigator. Baseline characteristics were balanced between groups. Demographic and baseline disease characteristics are shown in Table 31.

Table 31: Baseline Characteristics in CHECKMATE-066

		OPDIVO 3 mg/kg n=210	Dacarbazine 1000 mg/m^2 n=208
Men		58%	60%
Women		42%	40%
Age (median)		64 years	66 years
Age (range)		(18-86 years)	(25-87 years)
Melanoma Subtypes			
Mucosal		12%	11%
Cutaneous		73%	75%
M-Stage at study entry	(%)		
M0		8%	6%
M1a (soft tissue)		10%	10%
M1b (lung)		21%	23%
M1c (all viscera)		61%	61%
PD-L1 Status			
Positive		35%	36%
Negative/Indeterminate		65%	64%
ECOG			
0	(%)	71%	58%
1	(%)	29%	40%
2	(%)	1%	1%
Not reported	(%)	1%	0%
Baseline LDH			
> ULN		38%	36%
> 2*ULN		10%	11%
History of Brain Metastases			
Yes		3%	4%
No		97%	96%

Based on a formal interim analysis for OS that occurred when 146 deaths were observed, OPDIVO demonstrated clinically meaningful and statistically significant improvement in OS compared with dacarbazine in previously untreated patients with BRAF wild type advanced (unresectable or metastatic) melanoma (HR=0.42 [99.79% CI: 0.25, 0.73]; p<0.0001). Median OS was not reached for OPDIVO and was 10.8 months for dacarbazine (95% CI: 9.33, 12.09). The estimated OS rates at 12 months were 73% (95% CI: 65.5, 78.9) and 42% (95% CI: 33.0, 50.9) , respectively. OS was demonstrated regardless of PD-L1 tumour cell membrane expression levels. Efficacy results are presented in Table 32 and Figure 1.

Table 32: Efficacy of OPDIVO in CHECKMATE-066

Efficacy Parameter	OPDIVO N=210	Dacarbazine N=208
Overall Survival		
Events, n (%)	50/210 (23.8)	96/208 (46.2)
Median (95% CI) (Months)	Not Reached	10.84 (9.33, 12.09)
Hazard ratio[a]	0.42	
99.79% CI [b]	(0.25, 0.73)	
p-value [b]	<0.0001	
Progression-free Survival		
Events, n (%)	108/210 (51.4)	163/208 (78.4)
Median (95% CI) (Months)	5.06 (3.48, 10.81)	2.17 (2.10, 2.40)
Hazard ratio (99.79% CI[c])	0.43 (0.29, 064)	
p-value[c]	<0.0001	
Objective Response Rate[d]		
n (%)	84/210 (40.0)	29/208 (13.9)
95% CI	(33.3, 47.0)	(9.5, 19.4)
Difference of ORR (99.79% CI[c])	26.1 (13.4, 38.7)	
p-value[c,e]	<0.0001	
Complete Response	16 (7.6)	2 (1.0)
Partial Response	68 (32.4)	27 (13.0)
Stable Disease	35 (16.7)	46 (22.1)

Abbreviation: CI = confidence interval

a Based on a Cox proportional hazards model adjusted for PD-L1 status and M-stage.

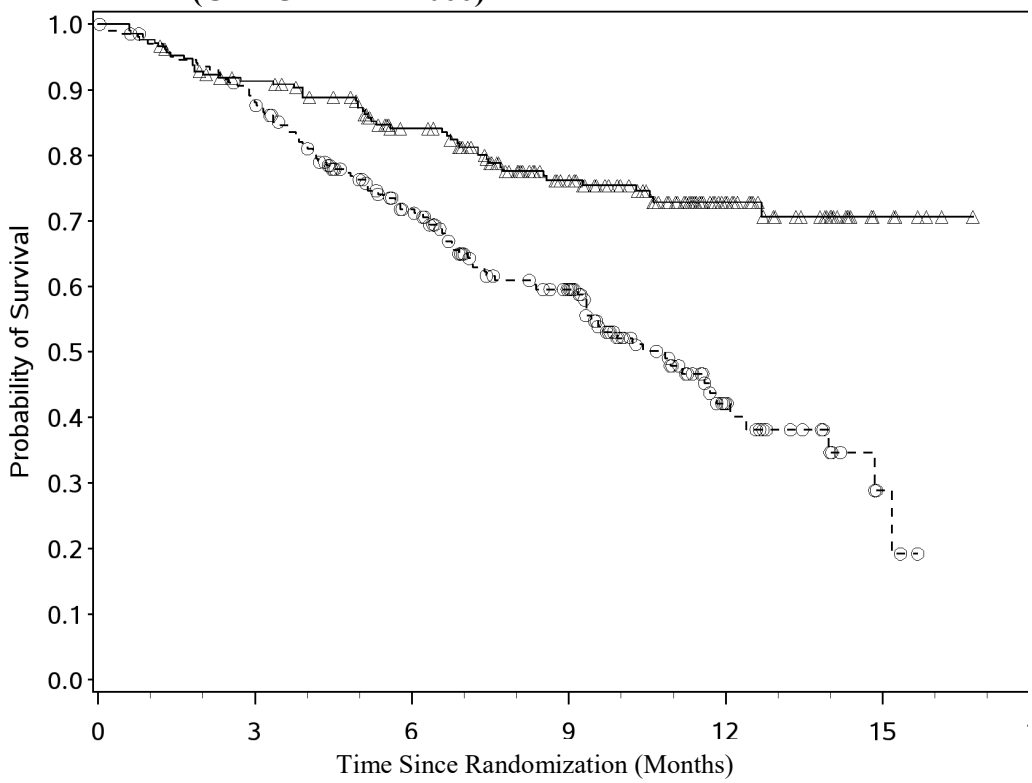
b The 99.79% CI corresponds to a p-value of 0.0021, which is the boundary for statistical significance for this interim analysis.

c A hierarchical testing approach was used to control the Type I error rate of 0.21% for PFS and ORR with corresponding 99.79% CIs

d Responses of CR + PR as per RECIST v1.1 criteria, as assessed by the investigator

e. p-value from CMH test for the comparison of the ORRs.

Figure 1 : Kaplan-Meier Curves of Overall Survival - OPDIVO versus Dacarbazine in BRAF wild-type advanced (unresectable or metastatic) melanoma (CHECKMATE-066)



Symbols represent censored observations.

Median TTR was 2.1 months (range 1.2 to 7.6) in the OPDIVO group and 2.1 months (range 1.8 to 3.6) in the dacarbazine group. Median DOR was not reached in the OPDIVO group (range: 0+ to 12.5+ months) and was 5.98 months (range: 1.1 to 10.0+) in the dacarbazine group. At the time of analysis, 86% (72/84) of OPDIVO-treated patients and 52% (15/29) of dacarbazine-treated patients were still in response. In addition, atypical responses (i.e., tumour shrinkage following initial RECIST progression) have been observed with OPDIVO.

Controlled Trial in Melanoma Patients Previously Untreated First-line treatment as monotherapy or in combination with ipilimumab

CHECKMATE-067 was a multicenter, double-blind trial that randomized (1:1:1) patients with unresectable or metastatic melanoma to receive OPDIVO (nivolumab) in combination with ipilimumab, OPDIVO as a single agent, or ipilimumab alone. Patients in the combination arm received nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks for the first 4 doses, followed

by nivolumab 3 mg/kg as a single agent every 2 weeks. Patients in the OPDIVO single-agent arm received nivolumab 3 mg/kg every 2 weeks. Patients in the comparator arm received ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by placebo every 2 weeks. Patients who had not received prior systemic anticancer therapy for unresectable or metastatic melanoma were enrolled regardless of PD-L1 expression. Prior adjuvant or neoadjuvant therapy was allowed if completed at least 6 weeks prior to randomization and all adverse reactions had returned to baseline or stabilized. Randomization was stratified by PD-L1 expression (≥5% vs. <5% tumour cell membrane expression), BRAF status, and M stage per the American Joint Committee on Cancer (AJCC) staging system. The trial excluded patients with active brain metastasis, ocular/uveal melanoma, autoimmune disease, or medical conditions requiring systemic immunosuppression within 14 days of the start of study therapy. Tumour assessments were conducted 12 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter.

The co-primary outcome measures were to compare progression-free survival (PFS) and overall survival (OS) of OPDIVO monotherapy to ipilimumab monotherapy and that of OPDIVO combined with ipilimumab to ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma Overall response rate (ORR) was a secondary objective. This study evaluated whether PD-L1 expression was a predictive biomarker for the co-primary endpoints as an exploratory objective.

Among the 945 randomized patients, the baseline study population characteristics were generally balanced across the three treatment groups. Demographic and baseline disease characteristics are shown in Table 33. In OPDIVO in combination with ipilimumab group, patients received a median of 4 doses of OPDIVO (range: 1 to 39 doses) and 4 doses of ipilimumab (range: 1 to 4 doses); 56% completed all 4 doses in the initial combination phase. In the single-agent OPDIVO arm, patients received a median of 15 doses (range: 1 to 38 doses). Median duration of follow-up was approximately 12 months.

Table 33: Baseline Characteristics in CHECKMATE-067

	OPDIVO + ipilimumab N=314	**OPDIVO 3 mg/kg n=316**	**ipilimumab n=315**
Men	66%	64%	64%
Women	34%	36%	36%
Age (median)	61 years	60 years	62 years
Age (range)	(18-88 years)	(25-90 years)	(18-89 years)
Race (White)	99%	98%	96%
M-Stage at study entry			
M0/ M1a (soft tissue)/ M1b (lung)	42%	42%	42%
M1c (all viscera)	58%	58%	58%
AJCC Stage IV	95%	92%	93%
PD-L1 Status			
Positive	46%	45%	46%

Table 33: Baseline Characteristics in CHECKMATE-067

	OPDIVO + ipilimumab N=314	OPDIVO 3 mg/kg n=316	ipilimumab n=315
Negative/Indeterminate	54%	55%	54%
BRAF Status			
Mutant	32%	32%	31%
Wildtype	68%	68%	69%
ECOG			
0	73%	75%	71%
1	26%	24%	29%
2	0	0.3%	0
Not reported	0.3%	0	0
Baseline LDH			
> ULN	36%	35%	37%
> 2*ULN	12%	12%	10%
History of Brain Metastases			
Yes	4%	3%	5%
No	97%	98%	95%

OPDIVO in combination with ipilimumab and single-agent OPDIVO demonstrated statistically significant improvement in PFS compared with ipilimumab, with a hazard ratio of 0.42 (99.5% CI: 0.31, 0.57; p<0.0001) and 0.57 (99.5% CI: 0.43, 0.76; p<0.0001), respectively. Statistically significant increases in ORR (p<0.0001) compared with ipilimumab were also demonstrated for both OPDIVO in combination with ipilimumab and OPDIVO as a single agent. Efficacy results are presented in Table 34 and Figure 2.

Table 34: Efficacy Results in CHECKMATE-067 (Intent-to-Treat Analysis)

	OPDIVO + Ipilimumab (n=314)	OPDIVO (n=316)	Ipilimumab (n=315)
Progression-Free Survival			
Events (%)	151 (48%)	174 (55%)	234 (74%)
Median (95% CI)	11.5 months (8.9, 16.7)	6.9 months (4.3, 9.5)	2.9 months (2.8, 3.4)
Hazard Ratio (vs. ipilimumab)[a] (99.5% CI)[b]	0.42 (0.31, 0.57)	0.57 (0.43, 0.76)	
p-value[c]	p<0.0001	p<0.0001	
Objective Response Rate	58%	44%	19%
(95% CI)	(52.0, 63.2)	(38.1, 49.3)	(14.9, 23.8)
p-value[d,e]	p<0.0001	p<0.0001	
Complete Response	11%	9%	2%
Partial Response	46%	35%	17%

Table 34: Efficacy Results in CHECKMATE-067 (Intent-to-Treat Analysis)

	OPDIVO + Ipilimumab (n=314)	OPDIVO (n=316)	Ipilimumab (n=315)
Stable disease (SD)	41 (13%)	34 (11%)	69 (22%)
Progressive disease (PD)	71 (23%)	119 (38%)	154 (49%)
Confirmed Objective Response Rate[f]	50%	40%	14%
(95% CI)	(44, 55)	(34, 46)	(10, 18)
p-value[e]	<0.0001	<0.0001	
Duration of Response			
Proportion ≥6 months in duration	68%	67%	53%
Range (months)	0.0+ to 15.8+	0.0+ to 14.6+	0.0+ to 13.8+

Abbreviation: CI = confidence interval

[a] Based on a Cox proportional hazards model adjusted for PD-L1 status, BRAF status, and M-stage.

[b] The 99.5% confidence level corresponds to the allocated Type I error of 0.01 for the PFS co-primary endpoint, adjusted for two pairwise comparisons versus ipilimumab (0.005 for each comparison).

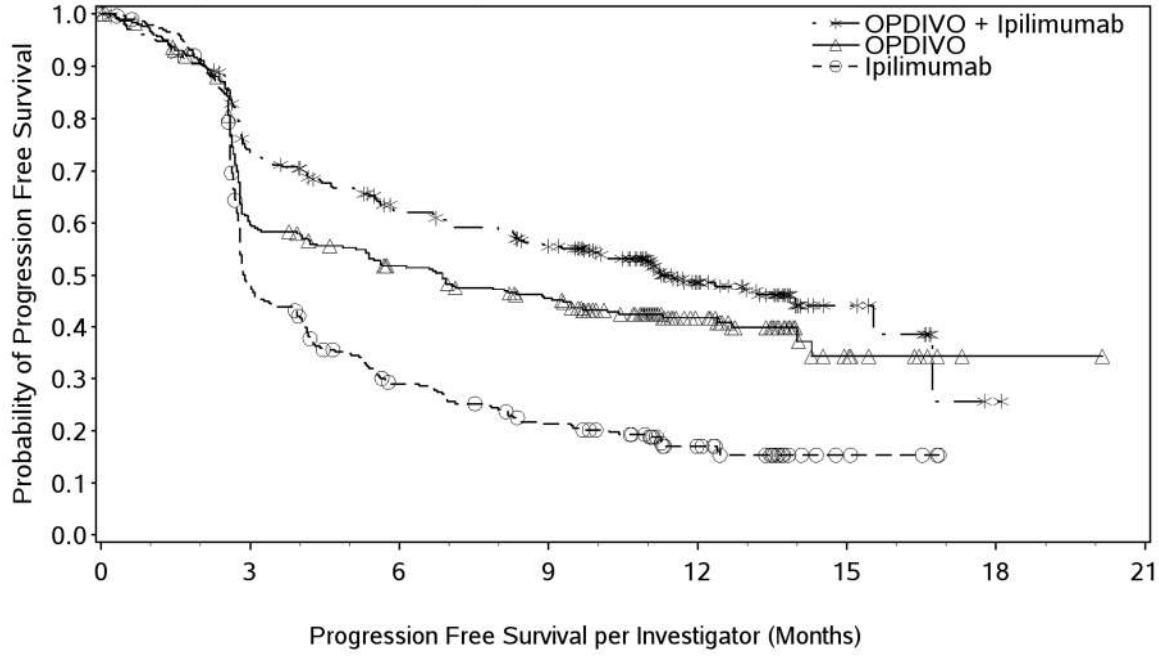
[c] P-value is obtained from a two-sided log-rank test stratified by PD-L1 status, BRAF status, and M-stage and is compared with the allocated Type I error of 0.005 for each comparison versus ipilimumab.

[d] A hierarchical testing approach was used to control the Type I error rate of 0.01

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

f Confirmed CR or PR was determined if the criteria for each where met at a subsequent timepoint (minimum 4 weeks after criteria for an objective response were first met)

Figure 2: Progression-Free Survival: Unresectable or Metastatic Melanoma (CHECKMATE-067)



Number of Subjects at Risk

OPDIVO + Ipilimumab							
314	219	173	151	65	11	1	0
OPDIVO							
316	177	147	124	50	9	1	0
Ipilimumab							
315	137	77	54	24	4	0	0

Efficacy by BRAF status: Progression-free survival results by BRAF mutation status are shown in Table 35 and Table 36.

Table 35: Progression Free Survival by BRAF Status - OPDIVO in Combination with Ipilimumab Compared to Ipilimumab - Exploratory Analysis (CHECKMATE-067)

		OPDIVO + Ipilimumab		Ipilimumab		
	N	N of events/ N of subjects (% subjects)	mPFS (95% CI)	N of events/ N of subjects (% subjects)	mPFS (95% CI)	Unstratified Hazard Ratio (95% CI)
Overall	945	151/314 (48.1)	11.50 (8.90, 16.72)	234/315 (74.3)	2.89 (2.79, 3.42)	0.43 (0.35, 0.53)
BRAF Mutation Status						
Mutant	300	48/102 (47.1)	11.73 (8.02, N.A.)	66/100 (66.0)	4.04 (2.79, 5.52)	0.47 (0.32, 0.68)
Wildtype	645	103/212 (48.6)	11.24 (8.34, N.A.)	168/215 (78.1)	2.83 (2.76, 3.09)	0.41 (0.32, 0.53)

Table 36: Progression Free Survival by BRAF Status - Single Agent OPDIVO Compared to Ipilimumab - Exploratory Analysis (CHECKMATE-067)

		OPDIVO		Ipilimumab		
	N	N of events/ N of subjects (% subjects)	mPFS (95% CI)	N of events/ N of subjects (% subjects)	mPFS (95% CI)	Unstratified Hazard Ratio (95% CI)
Overall	945	174/316 (55.1)	6.87 (4.34, 9.46)	234/315 (74.3)	2.89 (2.79, 3.42)	0.57 (0.47, 0.69)
BRAF Mutation Status						
Mutant	300	57/98 (58.2)	5.62 (2.79, 9.46)	66/100 (66.0)	4.04 (2.79, 5.52)	0.77 (0.54, 1.09)
Wildtype	645	117/218 (53.7)	7.89 (4.86, 12.68)	168/215 (78.1)	2.83 (2.76, 3.09)	0.50 (0.39, 0.63)

Table 37 provides objective response rates by BRAF mutation status.

Table 37: Objective Response by BRAF [V600] Mutation Status - Exploratory Analysis (CHECKMATE-067)

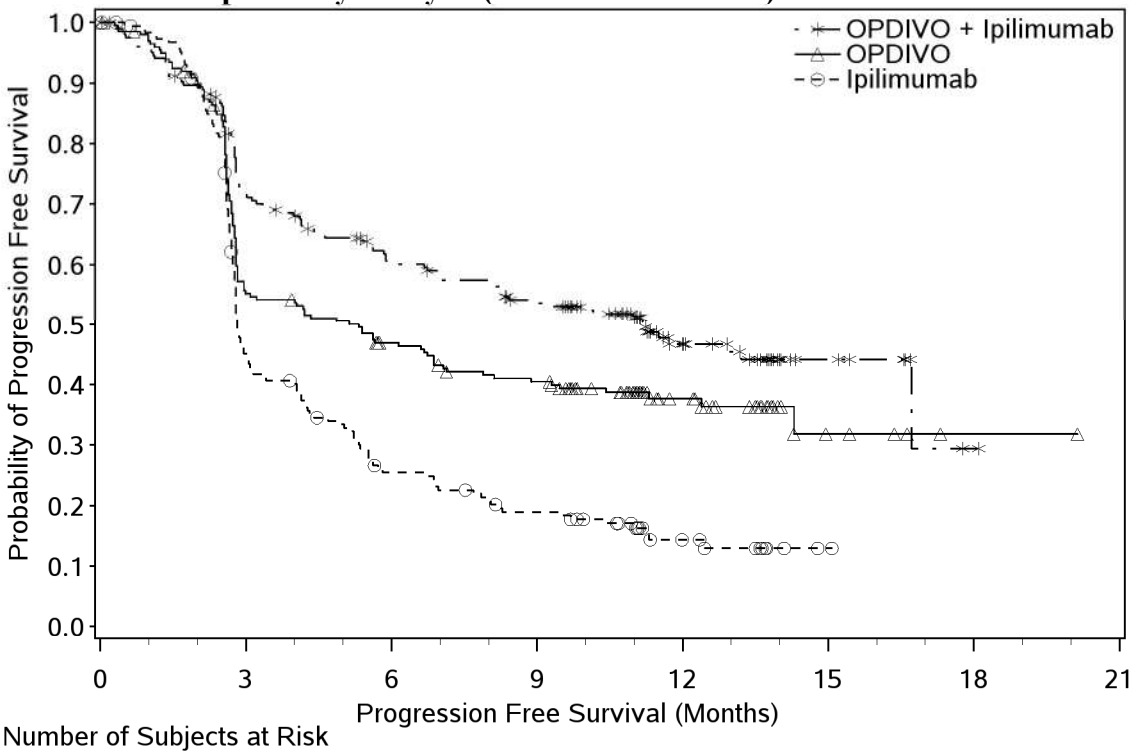
Treatment	BRAF [V600] Mutation-Positive		BRAF Wild-Type	
	Number of Responses/Patients	**ORR% (95% CI)**	**Number of Responses/Patients**	**ORR% (95% CI)[a]**
OPDIVO + Ipilimumab	68/102	66.7 (56.6, 75.7)	113/212	53.3 (46.3, 60.2)
OPDIVO	36/98	36.7 (27.2, 47.1)	102/218	46.8 (40.0, 53.6)
Ipilimumab	22/100	22.0 (14.3, 31.4)	38/215	17.7 (12.8, 23.4)

[a] Descriptive evaluation only, based on Cochran Mantel-Haenszel (CMH) methodology

Efficacy by PD-L1 Expression: Quantifiable PD-L1 expression was retrospectively measured in 89% (278/314) of patients randomized to OPDIVO in combination with ipilimumab, 91% (288/316) of patients randomized to single-agent OPDIVO, and 88% (277/315) of patients randomized to ipilimumab alone. Among patients with quantifiable PD-L1 expression, the distribution of patients across the three treatment groups at each of the predefined PD-L1 expression levels was as follows: ≥1% (56% in the OPDIVO in combination with ipilimumab arm, 59% in the single-agent OPDIVO arm, and 59% in the ipilimumab arm) and ≥5% (24%, 28%, and 27%, respectively). PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Figure 3 and Figure 4 present exploratory efficacy subgroup analyses of PFS based on defined PD-L1 expression levels.

Figure 3: Progression-Free Survival: Patients with <5% PD-L1 Expression - Exploratory Analysis (CHECKMATE-067)



Number of Subjects at Risk

OPDIVO + Ipilimumab							
210	142	112	96	42	9	1	0
OPDIVO							
208	108	88	74	31	5	1	0
Ipilimumab							
202	82	44	31	12	1	0	0

Figure 4: Progression-Free Survival: Patients with ≥5% PD-L1 Expression - Exploratory Analysis (CHECKMATE-067)

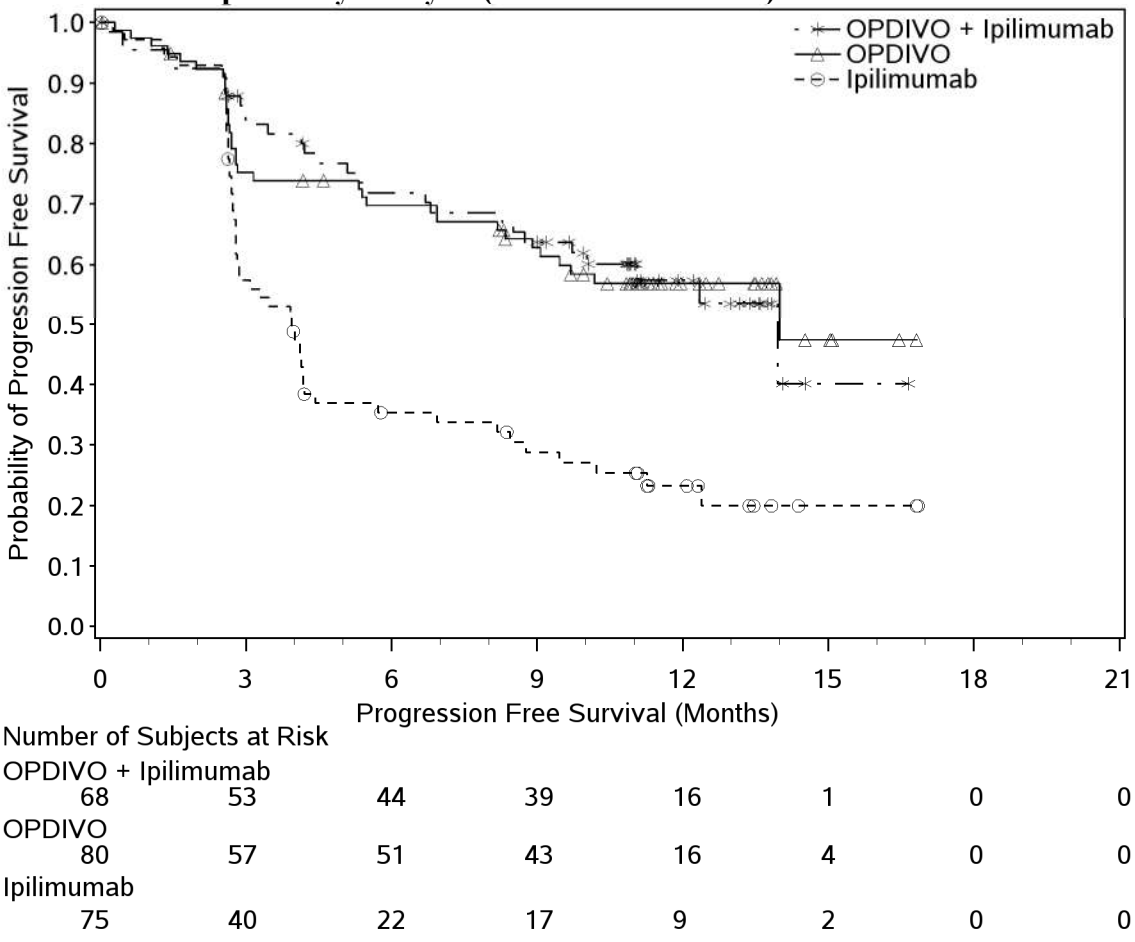


Table 38 shows the objective response rates based on PD-L1 expression level

Table 38: Objective response - Exploratory Analysis (CHECKMATE-067) (Intent to Treat Analysis)

	OPDIVO + **ipilimumab** **(n=314)**	OPDIVO **(n=316)**	**ipilimumab** **(n=315)**
ORR (95% CI) by tumour PD-L1 expression level			
<5%	55% (47.8, 61.6) n=210	41% (34.6, 48.4) n=208	18% (12.8, 23.8) n=202
≥5%	72% (59.9, 82.3) n=68	58% (45.9, 68.5) n=80	21% (12.7, 32.3) n=75
<1%	52% (42.8, 61.1) n=123	33% (24.9, 42.6) n=117	19% (11.9, 27.0) n=113
≥1%	65% (56.4, 72.0) n=155	54% (46.6, 62.0) n=171	19% (13.2, 25.7) n=164

Controlled Trial in Melanoma Patients Previously Untreated (First-line treatment in combination with ipilimumab)

CHECKMATE-069 was a randomized, Phase 2, double-blind study comparing the combination of OPDIVO and ipilimumab with ipilimumab alone in 142 patients with advanced (unresectable or metastatic) melanoma with similar inclusion criteria to CHECKMATE-067 and the primary analysis in patients with BRAF wild-type melanoma (77% of patients). Investigator assessed ORR was 61% (95% CI: 48.9, 72.4) in the combination arm (n=72) versus 11% (95% CI: 3.0, 25.4) for the ipilimumab arm (n=37).

Controlled Trial in Melanoma Patients Previously Treated with Ipilimumab (Second-line treatment)

CHECKMATE-037 was a multicentre, open-label phase III study that randomized patients (2:1) with unresectable or metastatic melanoma to receive either 3 mg/kg of OPDIVO by intravenous (IV) infusion every 3 weeks (Q3W) or Investigator's choice chemotherapy (ICC). Chemotherapy consisted of either dacarbazine (1000 mg/m^2 Q3W) or carboplatin (AUC 6 every Q3W) and paclitaxel (175 mg/m^2 Q3W). Randomization was stratified by BRAF status (wildtype vs. mutation positive) and PD-L1 status by a verified immunohistochemistry (IHC) assay (≥ 5% vs. < 5% cut-off) and best response to prior ipilimumab therapy (prior clinical benefit [complete response, CR; partial response, PR; stable disease, SD] vs. no prior clinical benefit [progressive disease, PD]). Patients were required to have progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor.

The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, ocular melanoma, active brain metastasis, or a history of Grade 4 ipilimumab-related adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event, patients with a condition requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications, a positive test for hepatitis B or C, and a history of HIV. Treatment was continued until disease progression (or discontinuation of study therapy in patients receiving OPDIVO beyond progression), discontinuation due to toxicity, or other reasons. Radiographic assessments of tumour response were performed at 9 weeks following randomization and every 6 weeks for the first 12 months, and then every 12 weeks until disease progression or treatment discontinuation, whichever occurred later. Demographic and baseline disease characteristics are presented in Table 39.

Table 39: Baseline Characteristics in CHECKMATE-037

	OPDIVO 3 mg/kg n=272	ICC n=133
Men	65%	64%
Women	35%	36%
Age (median)	59 years	62 years
Age (range)	(23-88 years)	(29-85 years)
Melanoma Subtypes		
Mucosal	10%	11%
Cutaneous	72%	74%
M-Stage at study entry		
M0	4%	2%
M1a (soft tissue)	6%	8%
M1b (lung)	16%	14%
M1c (all viscera)	75%	77%
Number of Prior Systemic therapies		
1	28%	26%
2	51%	51%
>2	21%	23%
PD-L1 Status		
Positive	49%	50%
Negative/Indeterminate	51%	50%
BRAF Status		
Wild Type	78%	78%
Mutation Positive	22%	22%
No response to prior ipilimumab (BOR of PD)	64%	65%
ECOG		
0	60%	63%
1	40%	36%
2	0	1%
Baseline LDH		
> ULN	52%	38%
> 2*ULN	17%	17%
History of Brain Metastases		
Yes	20%	14%
No	80%	87%

The median duration of exposure was 4.71 months (range: 0.03 to 35.94 months) in the OPDIVO arm and 1.95 months (range: 0.03 to 14.23 months) in the chemotherapy arm.

The co-primary efficacy outcome measures were confirmed overall response rate (ORR) in the first 120 patients treated with OPDIVO, as measured by independent radiology review committee

(IRRC) using RECIST, version 1.1, and comparison of overall survival (OS) of nivolumab to chemotherapy. Additional outcome measures included duration of response.

At the time of the final ORR analysis, results from 120 nivolumab-treated patients and 47 chemotherapy-treated patients who had a minimum of 6 months of follow-up were analysed. The ORR was 31.7 % (95% confidence interval [CI]: 23.5, 40.8), consisting of 4 complete responses and 34 partial responses in OPDIVO-treated patients. There were objective responses in patients with and without BRAF V600 mutation-positive melanoma. The ORR was 10.6% (95% CI: 3.5, 23.1) in the chemotherapy treated patients.

There was no statistically significant difference between OPDIVO and chemotherapy in the final OS analysis. The primary OS analysis was not adjusted to account for subsequent therapies, with 54 (40.6%) patients in the chemotherapy arm subsequently receiving an anti-PD1 treatment and 30 (11.0%) of patients in the OPDIVO arm receiving subsequent therapies.

Efficacy by BRAF status:

The ORRs in the BRAF mutation-positive subgroup were 17% (n = 59; 95% CI: 8.4, 29.0) for OPDIVO and 11% (n= 27; 95% CI: 2.4, 29.2) for chemotherapy, and in the BRAF wild-type subgroup were 30% (n = 213; 95% CI: 24.0, 36.7) and 9% (n =106; 95% CI: 4.6, 16.7), respectively.

The OS HR for OPDIVO (n= 59) versus chemotherapy (n = 27) was 1.32 (95% CI: 0.75, 2.32) for BRAF mutation-positive patients. The OS HR for OPDIVO (n= 213) versus chemotherapy (n = 106) was 0.83 (95% CI: 0.62, 1.11) for BRAF wild-type patients.

Efficacy by tumour PD-L1 expression:

In patients with tumour PD-L1 expression ≥1%, ORR was 33.5% for OPDIVO (n=179; 95% CI: 26.7, 40.9) and 13.5% for chemotherapy (n=74; 95% CI: 6.7, 23.5). In patients with tumour PD-L1 expression <1%, ORR per IRRC was 13.0% (n=69; 95% CI: 6.1, 23.3) and 12.0% (n=25; 95% CI: 2.5, 31.2), respectively.

The OS HR for OPDIVO (n= 179) versus chemotherapy (n = 74) was 0.69 (95% CI: 0.49, 0.96) in patients with tumour PD-L1 expression ≥1%. The OS HR for OPDIVO (n= 69) versus chemotherapy (n = 25) was 1.52 (95% CI: 0.89, 2.57) in patients with tumour PD-L1 expression <1%.

Adjuvant Treatment of Melanoma

Randomized phase III study of OPDIVO versus ipilimumab (CHECKMATE-238)

CHECKMATE-238 was a phase III randomized, double-blind trial enrolling patients with completely resected (rendered free of disease with negative margins on resected specimens) Stage IIIB/C or Stage IV melanoma. Patients were randomized (1:1) to receive OPDIVO (n=453) administered as an intravenous infusion over 60 minutes at 3 mg/kg every 2 weeks or ipilimumab (n=453) administered as an intravenous infusion at 10 mg/kg every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to 1 year. Randomization was stratified by PD-L1 status (positive [based on 5% level] vs negative/indeterminate) and American Joint Committee on

Cancer (AJCC) stage (Stage IIIB/C vs Stage IV M1a-M1b vs Stage IV M1c, 7th edition). The trial excluded patients with a history of ocular/uveal melanoma, autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥6 months prior to randomization.

The primary efficacy outcome measure was recurrence-free survival (RFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death, whatever the cause, whichever occurs first and assessed by the investigator. Disease was assessed at baseline and every 12 weeks (± 7 days) for the first year, then every 12 weeks (± 14 days) for the second year, then every 6 months until 5 years or until local, regional, or distant recurrence (whichever comes first) for Stage IV subjects and until distant recurrence for Stage III subjects. Overall survival (OS) was evaluated as secondary objective; however, OS data was considered immature at the time of interim analysis for RFS and hence OS results are not presented.

A total of 906 patients were randomized (453 to OPDIVO and 453 to ipilimumab). The median age was 55 years (range: 18 to 86), 58% were male, 95% were white, and 90% had ECOG performance status of 0. Forty-two percent (42%) of patients were BRAF V600 mutation positive, 45% were BRAF wild type, and 13% were BRAF status unknown. With regard to disease stage, 34% had Stage IIIB, 47% had Stage IIIC, and 19% had Stage IV. The majority of patients (85.3%) were randomized within 12 weeks of surgery. The median duration of follow-up was 19.5 months (range: 0.0 to 25.0 months).

CHECKMATE-238 demonstrated a statistically significant improvement in RFS for patients randomized to the OPDIVO arm compared with the ipilimumab 10 mg/kg arm.

Efficacy results for the primary endpoint are presented in Table 40 and Figure 5.

Table 40: Efficacy Results in CHECKMATE-238

Recurrence-free Survival	**OPDIVO N=453**	**Ipilimumab 10 mg/kg N=453**
Number of Events, n (%)	154 (34.0%)	206 (45.5%)
Type of Event		
Disease at Baseline	1 (0.2%)	2 (0.4%)
Local Recurrence	30 (6.6%)	44 (9.7%)
Regional Recurrence	31 (6.8%)	34 (7.5%)
Distant Metastasis	85 (18.8%)	117 (25.8%)
New Primary Melanoma	7 (1.5%)	4 (0.9%)
Hazard Ratio[a] (97.56% CI) p-value[b]	0.65 (0.51, 0.83) p<0.0001	
Median (months) (95% CI)	Not Reached	Not Reached (16.56, NR)

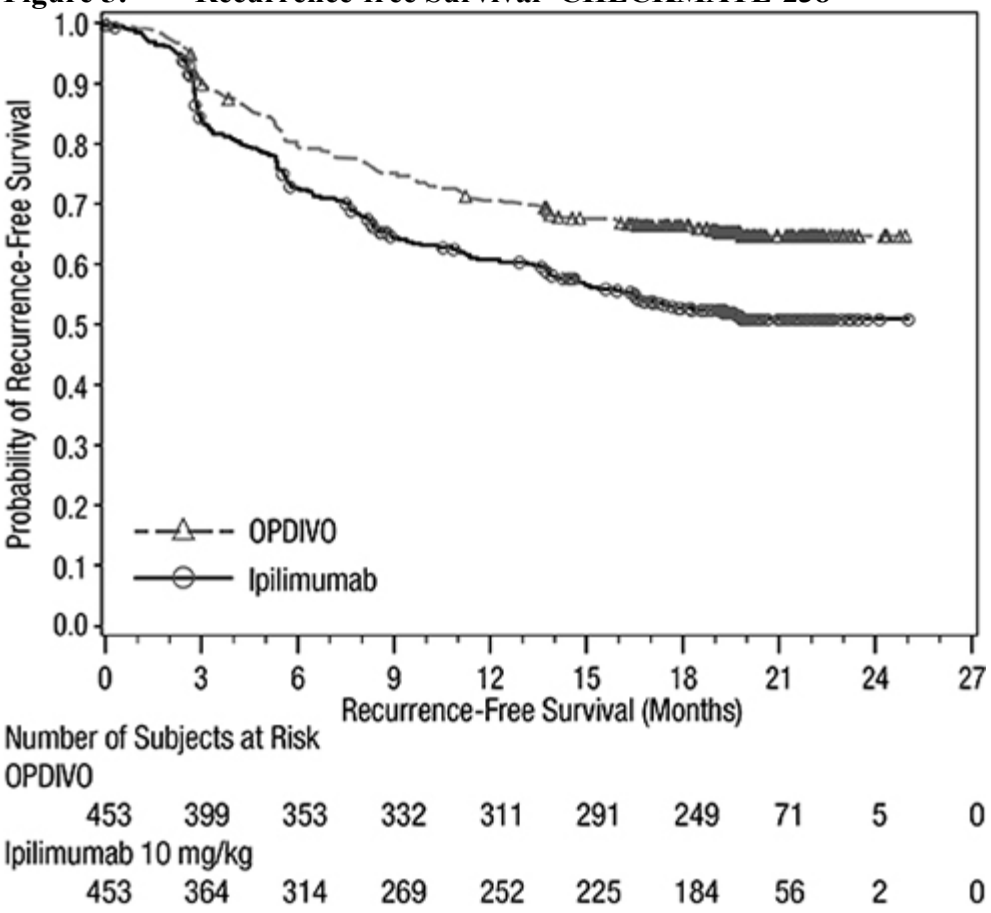
Table 40: Efficacy Results in CHECKMATE-238

Recurrence-free Survival	OPDIVO N=453	Ipilimumab 10 mg/kg N=453
Rate (95% CI) at 12 months	70.5 (66.1, 74.5)	60.8 (56.0, 65.2)
Rate (95% CI) at 18 months	66.4 (61.8, 70.6)	52.7 (47.8, 57.4)

[a] Based on a stratified proportional hazards model stratified by tumour PD-L1 expression and stage of disease.

[b] p-value is derived from a log-rank test stratified by tumour PD-L1 expression and stage of disease; the corresponding O'Brien-Fleming efficacy boundary significance level at the interim analysis is 0.0244.

Figure 5: Recurrence-free Survival -CHECKMATE-238



Metastatic NSCLC:

Second-line Treatment of Metastatic NSCLC:

Controlled Trial in Squamous NSCLC Patients Previously Treated with Chemotherapy (Second-line treatment)

CHECKMATE-017 was a randomized (1:1), open-label study enrolling 272 patients with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Patients were randomized to receive OPDIVO

(n=135) administered intravenously at 3 mg/kg every 2 weeks or docetaxel (n=137) administered intravenously at 75 mg/m^2 every 3 weeks. This study included patients regardless of their PD-L1 status. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrollment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents. The first tumour assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter.

The major efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures were investigator-assessed objective response rate (ORR) and progression-free survival (PFS). In addition, this trial evaluated whether PD-L1 expression was a predictive biomarker for efficacy.

In CHECKMATE-017, the median age was 63 years (range: 39 to 85) with 44% ≥65 years of age and 11% ≥75 years of age. The majority of patients were white (93%) and male (76%). Baseline disease characteristics of the population were Stage IIIb (19%), Stage IV (80%) and brain metastases (6%). Baseline ECOG performance status was 0 (24%) or 1 (76%).

The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the pre-specified interim analysis when 199 events were observed (86% of the planned number of events for final analysis) (Table 41 and Figure 6).

Table 41: Efficacy Results in CHECKMATE-017 (Intent-to-Treat Analysis)

	OPDIVO (n=135)		**Docetaxel (n=137)**
Overall Survival			
Events (%)	86 (64%)		113 (82%)
Median survival in months (95% CI)	9.2 (7.3, 13.3)		6.0 (5.1, 7.3)
p-value[a]		0.00025	
Hazard ratio (96.85% CI)[b]		0.59 (0.43, 0.81)	
Objective Response Rate[c]			
n (%)	27 (20%)		12 (8.8%)
(95% CI)	(13.6, 27.7)		(4.6, 14.8)
Difference in ORR (95% CI)		11.3% (2.9, 19.6)	
p-value[d]		0.0083	
Complete Response	1 (0.7%)		0
Partial Response	26 (19.3%)		12 (8.8%)
Progression-free Survival			
Events (%)	105 (78%)		122 (89%)
Median survival in months (95% CI)	3.5 (2.1, 4.9)		2.8 (2.1, 3.5)

Table 41: Efficacy Results in CHECKMATE-017 (Intent-to-Treat Analysis)

	OPDIVO (n=135)	Docetaxel (n=137)
p-value[a]	0.0004	
Hazard ratio (95% CI)[b]	0.62 (0.47, 0.81)	

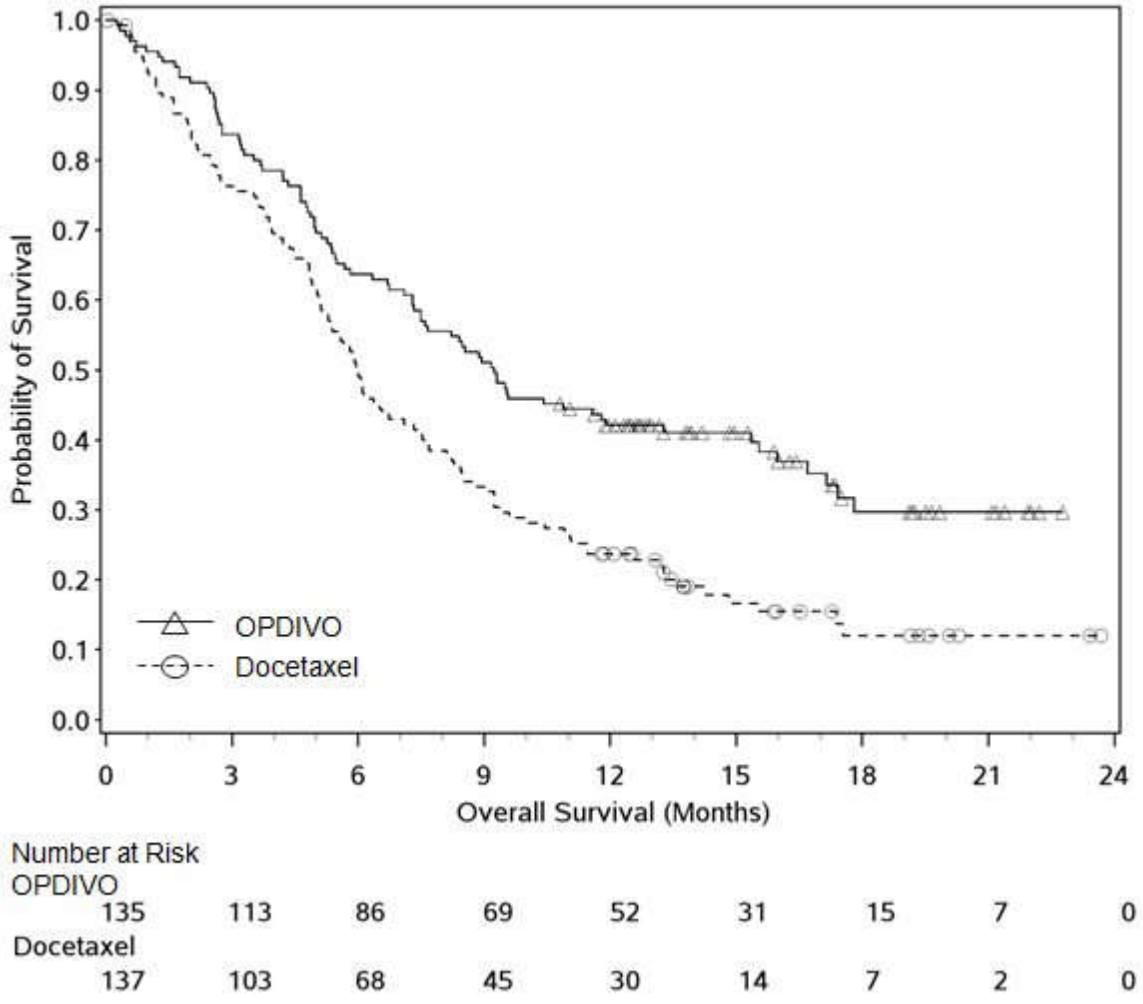
[a] P-value is derived from a log-rank test stratified by region and prior paclitaxel use; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0315.

[b] Derived from a stratified proportional hazards model.

[c] Responses of CR+PR as per RECIST v1.1 criteria, as assessed by investigator; confidence interval based on the Clopper and Pearson method.

[d] Based on the stratified Cochran-Mantel-Haenzel test.

Figure 6: Overall Survival - CHECKMATE-017



The estimated OS rates at 12 months were 42% (95% CI: 33.7, 50.3) for OPDIVO and 24% (95% CI: 16.9, 31.1) for docetaxel. The median time to onset of response was 2.2 months (range: 1.6 to 11.8 months) for patients randomized to OPDIVO and 2.1 months (range 1.8 to 9.5 months) for

patients randomized to docetaxel. At the time of this analysis, 17/27 (63%) of OPDIVO patients and 4/12 (33%) of docetaxel patients with a confirmed response had ongoing responses. The median duration of response was not reached (range from 2.9 to 20.5+ months) for OPDIVO patients and 8.4 months (range 1.4 to 15.2+ months) for docetaxel patients.

Pre-study tumour tissue specimens were systematically collected prior to randomization in order to conduct pre-planned analyses of efficacy according to predefined PD-L1 expression status. Quantifiable PD-L1 expression was measured in 87% of patients in the OPDIVO group and 79% of patients in the docetaxel group. PD-L1 expression levels for the two treatment groups (OPDIVO vs docetaxel) at each of the predefined PD-L1 expression levels were ≥1% (54% vs 52%), ≥5% (36% vs 36%), or ≥10% (31% vs 31%). PD-L1 testing was conducted using the PD-L1 IHC 28-8 pharmDx assay. Survival benefit was observed regardless of PD-L1 expression or non-expression status by all pre-defined expression levels (1%, 5% and 10%). However, the role of the PD-L1 expression status has not been fully elucidated.

Squamous NSCLC Single-Arm Trial

CHECKMATE-063 was a single-arm, open-label study conducted in 117 patients with locally advanced or metastatic squamous-NSCLC after two or more lines of therapy; otherwise similar inclusion criteria as CHECKMATE-017 were applied. The major efficacy outcome measure was confirmed objective response rate (ORR) as measured by independent review committee (IRC) using Response Evaluation Criteria in Solid Tumours (RECIST 1.1). Based on IRC review and with a minimum follow-up of at least 10 months on all patients, confirmed ORR was 15% (17/117) (95% CI: 9, 22), of which all were partial responses. In the 17 responders, the median duration of response was not reached at a follow-up of approximately 11 months, with a range of 1.9+ to 11.5+ months.

Controlled Trial in Non-Squamous NSCLC Patients Previously Treated with Chemotherapy (Second-line treatment)

CHECKMATE-057 was a randomized (1:1), open-label study of 582 patients with metastatic non-squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen which may have included maintenance therapy. An additional line of TKI therapy was allowed for patients with known EGFR mutation or ALK translocation. Patients were randomized to receive OPDIVO (n=292) administered intravenously at 3 mg/kg every 2 weeks or docetaxel (n=290) administered intravenously at 75 mg/m^2 every 3 weeks. This study included patients regardless of their PD-L1 status. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrollment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents. The first tumour assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures were investigator-assessed objective response

rate (ORR) and progression-free survival (PFS). In addition, this trial evaluated whether PD-L1 expression was a predictive biomarker for efficacy.

In CHECKMATE-057, the mean age was 62 years (range: 21 to 85) with 42% ≥65 years of age and 7% ≥75 years of age. The majority of patients were white (92%) and male (55%); baseline ECOG performance status was 0 (31%) or 1 (69%). Seventy-nine percent of patients were former/current smokers.

The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis) (Table 42 and Figure 7).

Table 42: Efficacy Results in CHECKMATE-057 (Intent-to-Treat Analysis)

	OPDIVO (n=292)		**Docetaxel (n=290)**
Overall Survival			
Events (%)	190 (65%)		223 (77%)
Median survival in months (95% CI)	12.2 (9.7, 15.0)		9.4 (8.0, 10.7)
p-value[a]		0.0015	
Hazard ratio (95.92% CI)[b]		0.73 (0.59, 0.89)	
Objective Response Rate[c]			
n (%)	56 (19%)		36 (12%)
(95% CI)	(14.8, 24.2)		(8.8, 16.8)
Difference in ORR (95% CI)		6.8% (0.9, 12.7)	
p-value [d]		0.0235	
Complete Response	4 (1.4%)		1 (0.3)
Partial Response	52 (17.8%)		35 (12.1%)
Progression-free Survival			
Events (%)	234 (80%)		245 (85%)
Median survival in months (95% CI)	2.3 (2.8, 3.3)		4.2 (3.5, 4.9)
p-value		0.3932	
Hazard ratio (95% CI)[b]		0.92 (0.77, 1.11)	

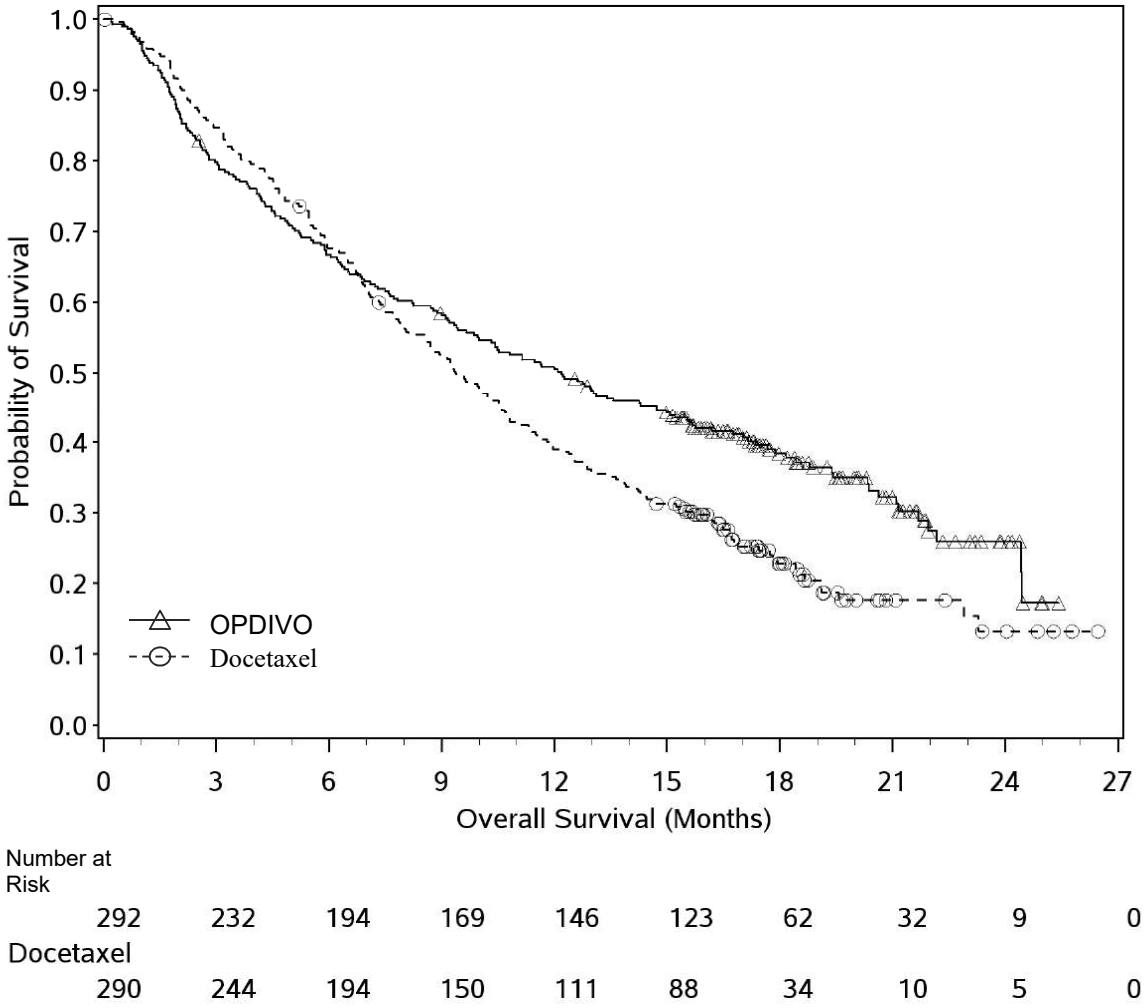
[a] P-value is derived from a log-rank test stratified by prior maintenance therapy and line of therapy; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0408.

[b] Derived from a stratified proportional hazards model.

[c] Responses of CR+PR as per RECIST v1.1 criteria, as assessed by investigator; confidence interval based on the Clopper and Pearson method

[d] Based on the stratified Cochran-Mantel-Haenzel test.

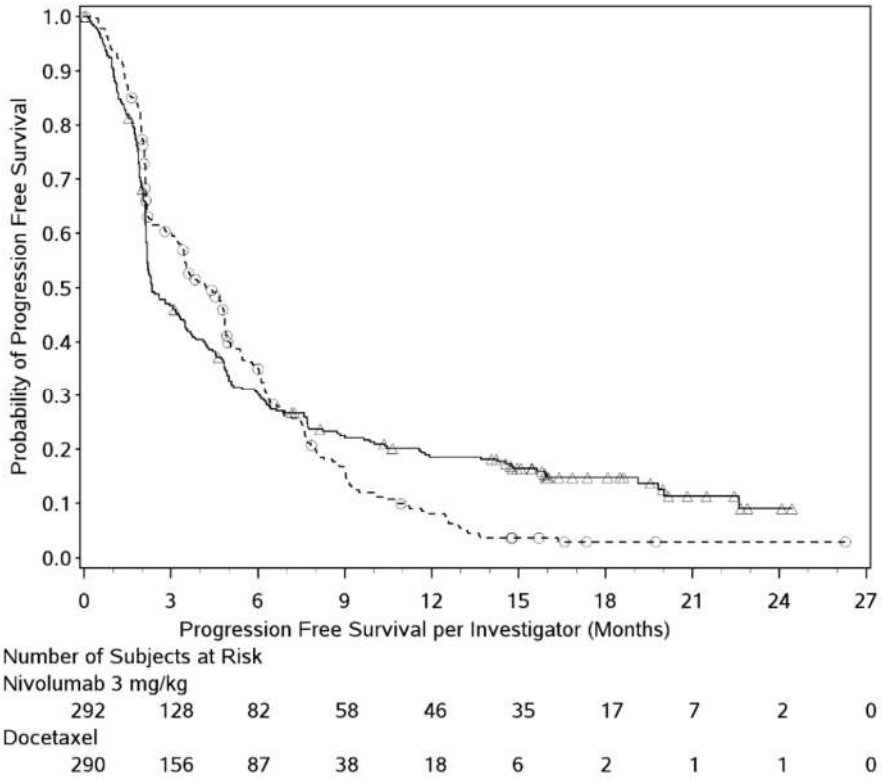
Figure 7: Overall Survival: CHECKMATE-057



The estimated OS rates at 12 months were 50.5% (95% CI: 44.6, 56.1) for OPDIVO and 39.0% (95% CI: 33.3, 44.6) for docetaxel. The median time to onset of response was 2.1 months (range: 1.2 to 8.6 months) for patients randomized to OPDIVO and 2.6 months (range 1.4 to 6.3 months) for patients randomized to docetaxel. At the time of this analysis, 29/56 (52%) of OPDIVO-treated patients and 5/36 (14%) of docetaxel-treated patients with a confirmed response had ongoing responses. The median duration of response of 17.2 months (range from 1.8 to 22.6+ months) for OPDIVO-treated patients and 5.6 months (1.2+ to 15.2+ months) for docetaxel-treated patients.

However, the trial did not demonstrate a statistically significant improvement in PFS for patients randomized to OPDIVO as compared with docetaxel (Table 42 and Figure 8). Immediate benefit of OPDIVO may not become evident in the first months of treatment with OPDIVO as shown by the delayed crossing of the PFS curves followed by sustained separation.

Figure 8: Progression Free Survival: CHECKMATE-057



Archival tumour specimens were evaluated for PD-L1 expression following completion of the trial. Across the study population, 22% (127/582) of patients had non-quantifiable results. Of the remaining 455 patients, the proportion of patients in retrospectively determined subgroups based on PD-L1 testing using the PD-L1 IHC 28-8 pharmDx assay were: 46% (209/455) PD-L1 negative, defined as <1% of tumour cells expressing PD-L1 and 54% (246/455) had PD-L1 expression, defined as ≥ 1% of tumour cells expressing PD-L1. Among the 246 patients with tumours expressing PD-L1, 26% had ≥1%, but <5% tumour cells with positive staining, 7% had ≥ 5% but <10% tumour cells with positive staining, and 67% had greater than or equal to 10% tumour cells with positive staining. PD-L1 testing was conducted using the PD-L1 IHC 28-8 pharmDx assay.

Although the role of PD-L1 expression status has not been fully elucidated, in non-squamous NSCLC, pre-study (baseline) PD-L1 expression status shows an apparent association for benefit from OPDIVO for all efficacy endpoints. Additional analyses of the association between PD-L1 expression status using pre-defined expression levels and efficacy measures suggested a clinically important signal of predictive association. In PD-L1 positive patients, OPDIVO demonstrated improved efficacy vs docetaxel across all efficacy endpoints (OS, ORR, and PFS). In contrast, there were no meaningful differences in efficacy between the treatment groups in the PD-L1 negative subgroups by any expression level. As compared to the overall study population, no meaningful differences in safety were observed based on PD-L1 expression level. In patients with no measurable tumour PD-L1 expression or in those deemed non-quantifiable, close monitoring for unequivocal progression during the first months of treatment with OPDIVO may be clinically prudent.

Figure 9 provides the Kaplan-Meier plots of OS stratified by PD-L1 expression status using the 1% expression level at baseline.

Figure 9: Overall Survival by PD-L1 Expression Level (1%) - CHECKMATE-057

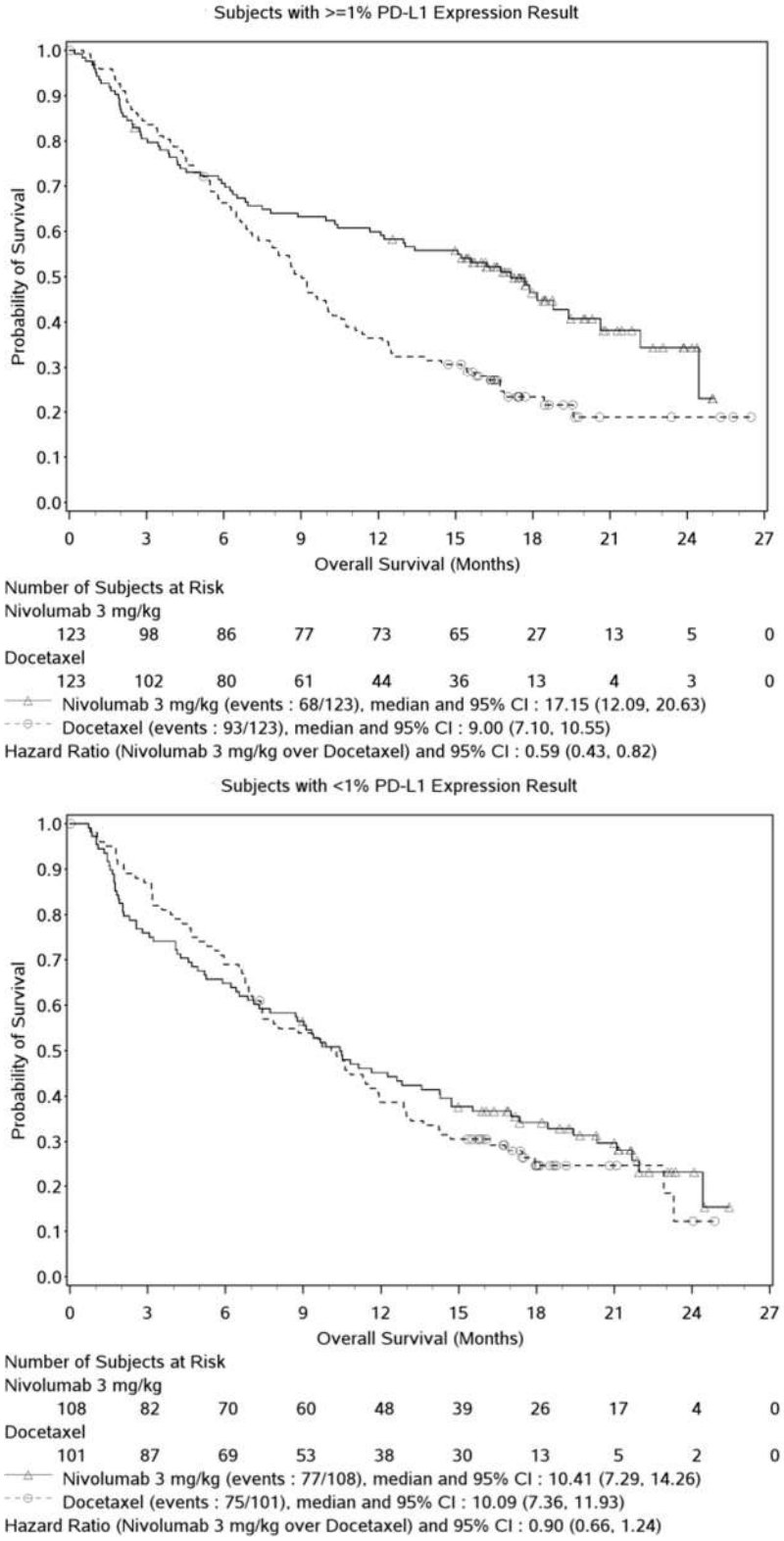
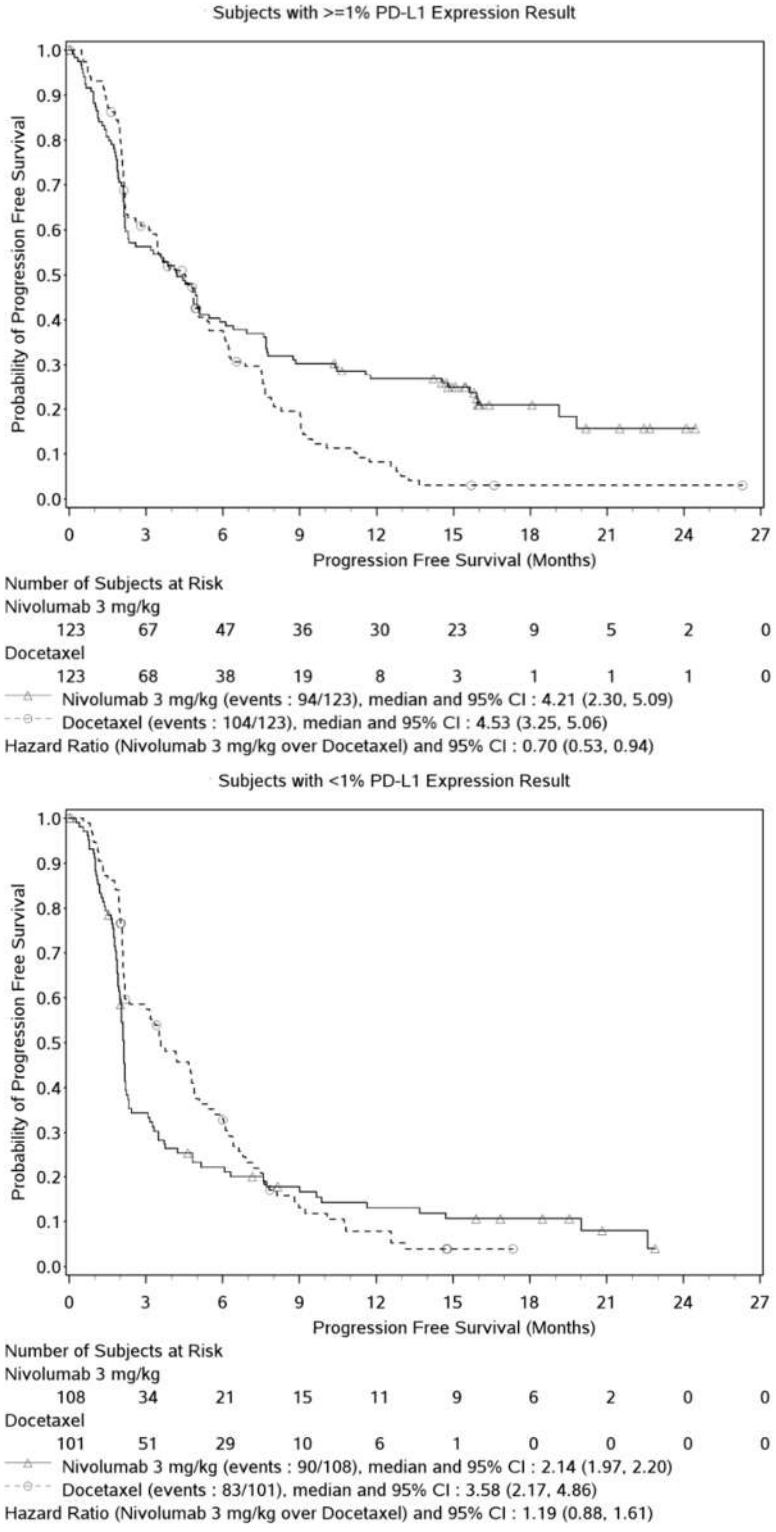


Figure 10 provides the Kaplan-Meier plots of PFS stratified by PD-L1 expression status using the 1% expression level at baseline.

Figure 10: Progression-free Survival by PD-L1 Expression Level (1%) - CHECKMATE-057



Controlled trial of previously untreated metastatic NSCLC, in combination with ipilimumab:

CHECKMATE-227 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 (including EGFR and ALK inhibitors) for metastatic disease. Patients were enrolled regardless of their tumour 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. Randomization was stratified by tumour histology (non-squamous versus squamous).

Primary efficacy results were based on Part 1a of the study which was limited to patients with PD-L1 tumour expression ≥ 1%. Tumour specimens were evaluated prospectively for PD-L1 using the IHC 28-8 pharmDx kit at a central laboratory.

The evaluation of the primary efficacy endpoint relied on the comparison between OPDIVO 3 mg/kg administered intravenously over 30 minutes every 2 weeks in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks and platinum-doublet chemotherapy administered every 3 weeks for up to 4 cycles. Platinum-doublet chemotherapy 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 ipilimumab were permitted to continue OPDIVO monotherapy. Tumour 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 OPDIVO in combination with ipilimumab (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, 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 benefit in OS for patients with PD-L1 tumour expression ≥ 1% randomized to OPDIVO in combination with ipilimumab compared to platinum-doublet chemotherapy alone. Median follow-up for OS was 16.6 months (range: 0.3 to 42.2 months) for OPDIVO in combination with ipilimumab and 14.1 months (range: 0.0 to 42.1 months) for platinum-doublet chemotherapy. Efficacy results for patients whose tumours expressed PD-L1 ≥1% are presented in Table 43 and Figure 11.

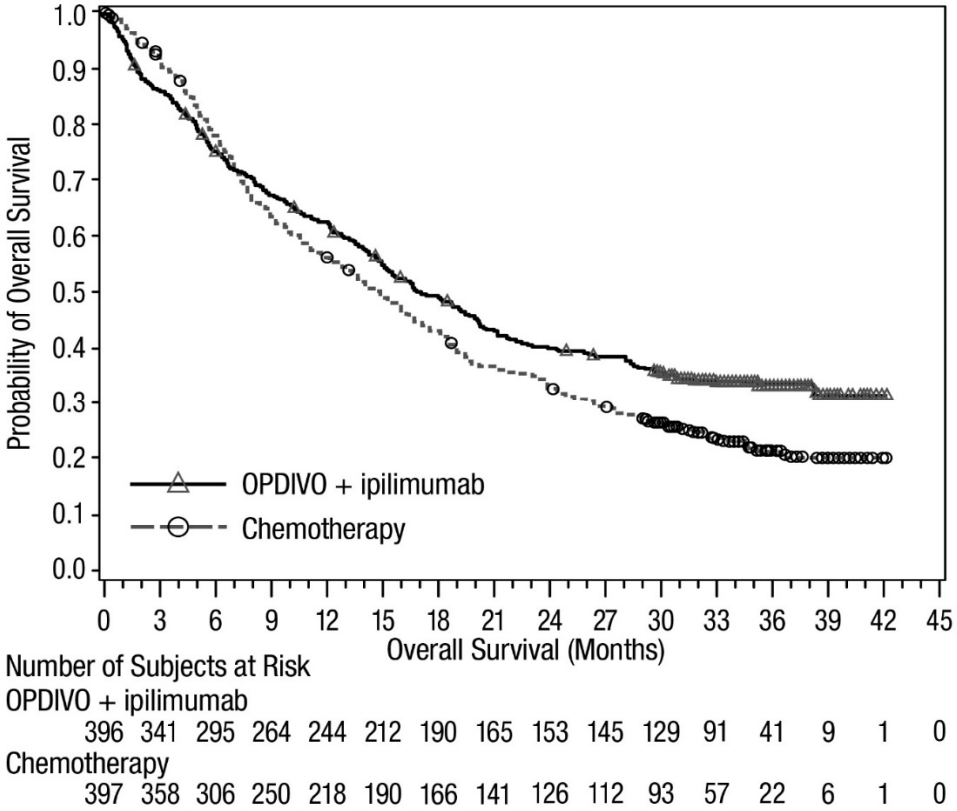
Table 43: Efficacy Results (PD-L1 ≥1%) - CHECKMATE-227

	OPDIVO and Ipilimumab (n=396)	Chemotherapy (n=397)
Overall Survival		
Events (%)	258 (65.2)	298 (75.1)
Median (months)[a]	17.1	14.9
(95% CI)	(15, 20.1)	(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.

Figure 11: 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 OPDIVO plus ipilimumab arm and 5.6 months (95% CI: 4.6, 5.8) in the platinum-based chemotherapy arm. The BICR-assessed confirmed ORR was 36% in the OPDIVO plus ipilimumab arm and 30% in the platinum-based chemotherapy arm. Median duration of response observed in the OPDIVO plus ipilimumab arm was 23.2 months and 6.2 months in the platinum-based chemotherapy arm.

In Part 1a, in an exploratory efficacy subgroup analysis based on histology, an improvement in OS was observed with OPDIVO in combination with ipilimumab relative to platinum-doublet chemotherapy in patients with SQ NSCLC (median OS 14.8 months vs. 9.2 months; HR = 0.69; 95% CI: 0.52, 0.92) and in patients with NSQ NSCLC (median OS 19.5 months vs. 17.2 months; HR = 0.85; 95% CI: 0.69, 1.04).

The findings of an exploratory analysis based on PD-L1 ≥ 50% and PD-L1 1-49% are shown below. See Table 44,

Figure 12 and Figure 13.

Table 44: Overall Survival Results by PD-L1 Expression - CHECKMATE-227

Endpoint	OPDIVO and Ipilimumab (n=205)	Chemotherapy (n=192)	OPDIVO and Ipilimumab (n=191)	Chemotherapy (n=205)
	PD-L1 ≥50%		PD-L1 1-49%	
Number (%) of patients with event	116 (56.6%)	137 (71.4%)	142 (74.3)	161 (78.5)
Hazard Ratio (95% CI)	0.70 (0.53, 0.93)		0.94 (0.73, 1.22)	
Median in Months (95% CI)	21.19 (15.51, 38.18)	13.96 (10.05, 18.60)	15.08 (12.16, 18.66)	15.08 (13.34, 17.54)

Figure 12: Kaplan-Meier Curve for Overall Survival by PD-L1 Expression (≥50%) - CHECKMATE-227

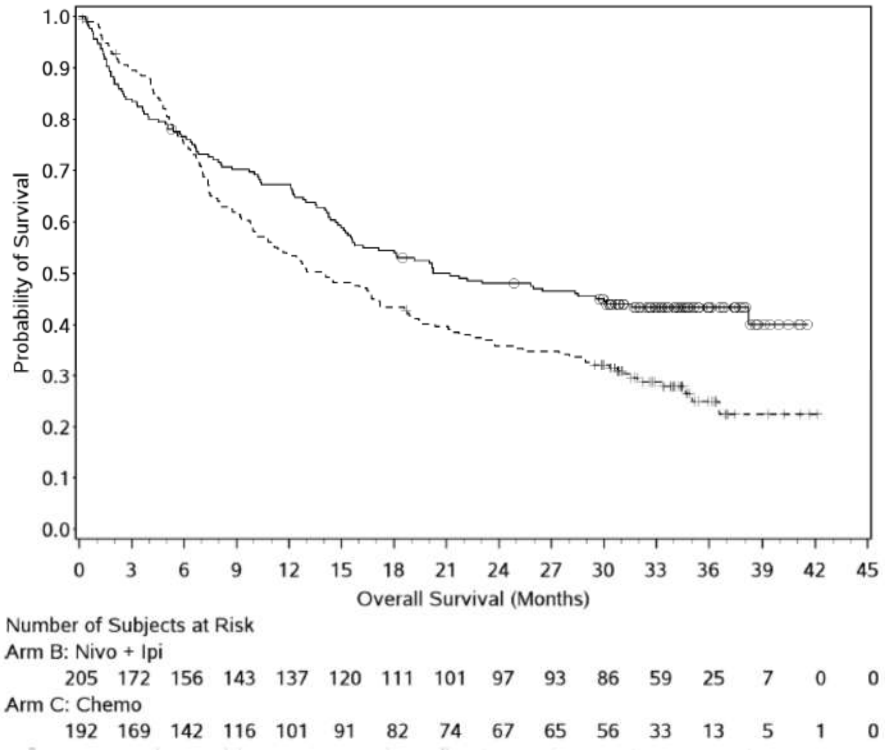
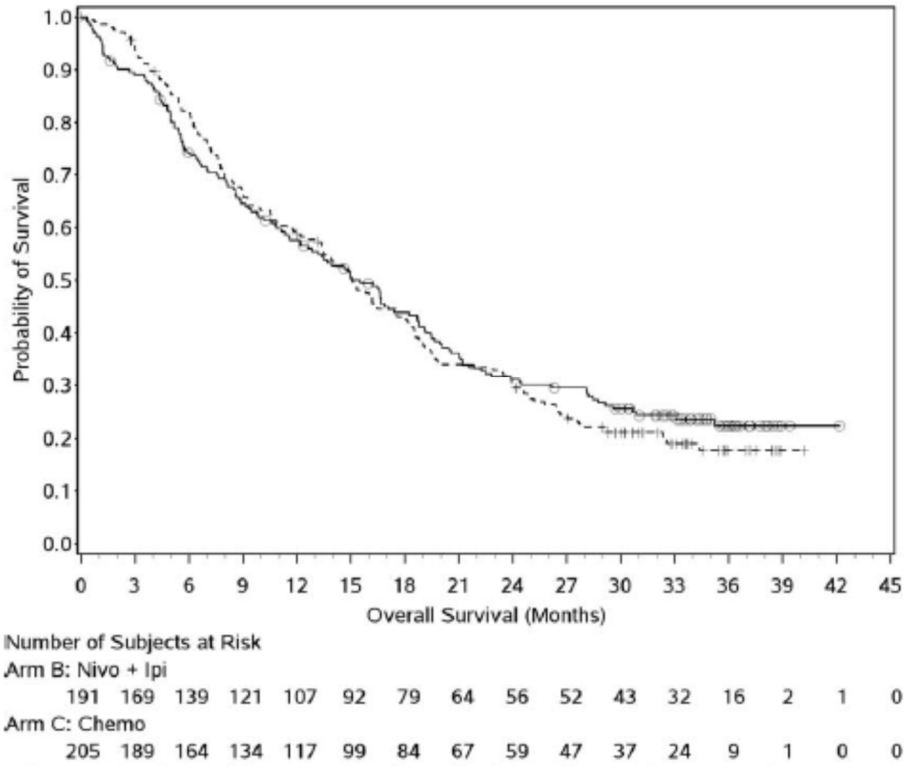


Figure 13: Kaplan-Meier Curve for Overall Survival by PD-L1 Expression (1-49%) - CHECKMATE-227



Controlled Trial in NSCLC Patients Previously Untreated for Metastatic NSCLC

CHECKMATE-9LA 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 anticancer therapy (including EGFR and ALK inhibitors) for metastatic disease. Patients were enrolled regardless of their tumour 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.

Randomization was stratified by tumour PD-L1 expression level (≥1% versus <1%), histology (squamous versus non-squamous), and sex (male versus female). Patients were randomized 1:1 to the following treatment arms:

- OPDIVO 360 mg intravenously every 3 weeks, ipilimumab 1 mg/kg intravenously every 6 weeks and platinum-doublet chemotherapy intravenously every 3 weeks for 2 cycles, followed by OPDIVO 360 mg every 3 weeks and ipilimumab 1 mg/kg every 6 weeks.
- Platinum-doublet chemotherapy intravenously every 3 weeks for 4 cycles. Patients with non-squamous histology could receive optional pemetrexed maintenance therapy.

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. 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 event attributed to ipilimumab were permitted to continue OPDIVO as a single agent. Tumour 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 OPDIVO in combination with ipilimumab 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 tumours with PD-L1 expression ≥1% and 37% had tumours with PD-L1 expression <1%, 31% had tumours with squamous histology and 69% had tumours with non-squamous histology, 17% had brain metastases, and 86% were former/current smokers.

The study demonstrated a statistically significant benefit in OS, PFS, and ORR for patients randomized to OPDIVO in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy compared to 4 cycles of platinum-doublet chemotherapy alone. Median follow-up

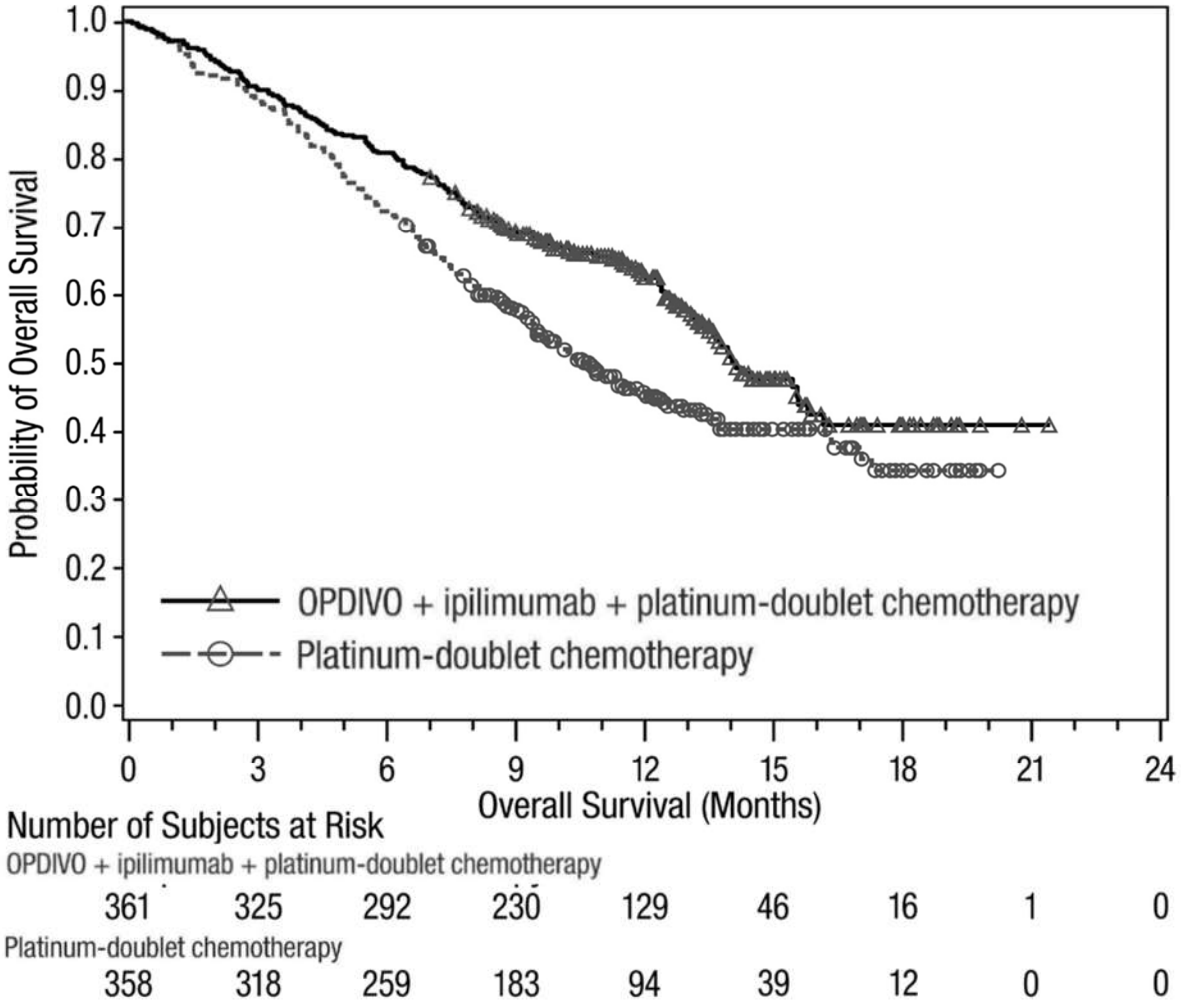
for OS was 10.4 months (range: 0.0 to 21.4 months) for OPDIVO in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy and 9.1 months (range: 0.1 to 20.2 months) for platinum-doublet chemotherapy. Efficacy results from the pre-specified interim analysis when 351 events were observed (87% of the planned number of events for the final analysis) are presented in Table 45 and Figure 14.

Table 45 Efficacy Results - CHECKMATE-9LA

	OPDIVO and Ipilimumab 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 (13.24, 16.16)	10.7 (9.46, 12.45)
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)
Median (months)[d] (95% CI)	6.83 (5.55, 7.66)	4.96 (4.27, 5.55)
Hazard ratio (97.48% CI)[a]	0.70 (0.57, 0.86)	
Stratified log-rank p-value[c]	0.0001	
Overall Response Rate per BICR (%)[e]	136 (37.7)	90 (25.1)
(95% CI)	(32.7, 42.9)	(20.7, 30.0)
Stratified CMH test p-value[f]	0.0003	
Complete response (%)	7 (1.9)	3 (0.8)
Partial response (%)	129 (35.7)	87 (24.3)
Duration of Response per BICR		
Median (months) (95% CI)[d]	10.02 (8.21, 13.01)	5.09 (4.34, 7.00)

[a] Based on a stratified Cox proportional hazard model.
[b] p-value is compared with the allocated alpha of 0.0329 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] Proportion with complete or partial response; 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.

Figure 14: Overall Survival - CHECKMATE-9LA



Based on predefined subgroup analyses of OS, improved OS for OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy compared to platinum-doublet chemotherapy, was observed in patients with squamous or non-squamous histology and irrespective of PD-L1 expression (< 1% versus ≥ 1%).

Metastatic RCC:

Advanced RCC (previously treated):

Controlled Trial in RCC Patients Previously Treated with Anti-angiogenic Therapy (Second-line treatment)

CHECKMATE-025 was a randomized (1:1), open-label study in patients with advanced RCC who had experienced disease progression during or after 1 or 2 prior anti-angiogenic therapy regimens and no more than 3 total prior systemic treatment regimens. Patients had to have a Karnofsky Performance Score (KPS) ≥70%. This study included patients regardless of their PD-L1 status. CHECKMATE-025 excluded patients with any history of or concurrent brain metastases, prior

treatment with an mTOR inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression.

A total of 821 patients were randomized to OPDIVO (n=410) administered intravenously at 3 mg/kg every 2 weeks or everolimus (n=411) administered orally 10 mg daily. The median age was 62 years (range: 18 to 88) with 40% ≥65 years of age and 9% ≥75 years of age. The majority of patients were male (75%) and white (88%) and 34% and 66% of patients had a baseline KPS of 70 to 80% and 90 to100%, respectively. The majority of patients (72%) were treated with one prior anti-angiogenic therapy, and 28% received 2 prior anti-angiogenic therapies. Twenty-four percent of patients had at least 1% PD-L1 expression.

The first tumour assessments were conducted 8 weeks after randomization and continued every 8 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Tumour assessments were continued after treatment discontinuation in patients who discontinued treatment for reasons other than progression. Treatment beyond initial investigator-assessed RECIST 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug as determined by the investigator. OPDIVO was continued beyond progression in 44% of patients.

The primary efficacy outcome measure was overall survival (OS). Secondary efficacy assessments included investigator-assessed objective response rate (ORR) and progression-free survival (PFS). A summary of efficacy outcome measures is presented in Table 46.

Primary Efficacy Outcome Measure:

The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis) (Table 46 and Figure 15). OS benefit was observed regardless of PD-L1 expression level. The estimated OS rates at 12 months were 76% for OPDIVO and 67% for everolimus.

Secondary Efficacy Outcome Measures:

The investigator-assessed ORR using RECIST v1.1 was superior in the OPDIVO group (103/410, 25.1%) compared with the everolimus group (22/411, 5.4%), with a stratified CMH test p-value of < 0.0001. The median time to onset of objective response was 3 months (range: 1.4 to 13 months) after the start of OPDIVO treatment. Forty-three (48.9%) responders had ongoing responses with a duration ranging from 7.4 to 27.6 months. Thirty-three (37.5%) patients had durable responses of 12 months or longer. The ORR with a confirmatory scan was performed after at least 4 weeks. The median duration of response was 23.0 months and 13.7 months in the OPDIVO and everolimus group, respectively. The best overall response (BOR) was CR in 4 subjects (1.0%) in the OPDIVO group and 2 subjects (0.5%) in the everolimus group. BOR was PR in 99 (24.1%) subjects in the OPDIVO group and 20 (4.9%) subjects in the everolimus group.

While not statistically significant, PFS data suggest a benefit with OPDIVO vs everolimus (HR: 0.88 [95%CI: 0.75, 1.03], stratified log-rank test p-value = 0.1135), with separation of the K-M curves after 6 months favoring OPDIVO (Table 46 and Figure 16).

Table 46: Efficacy Results - CHECKMATE-025

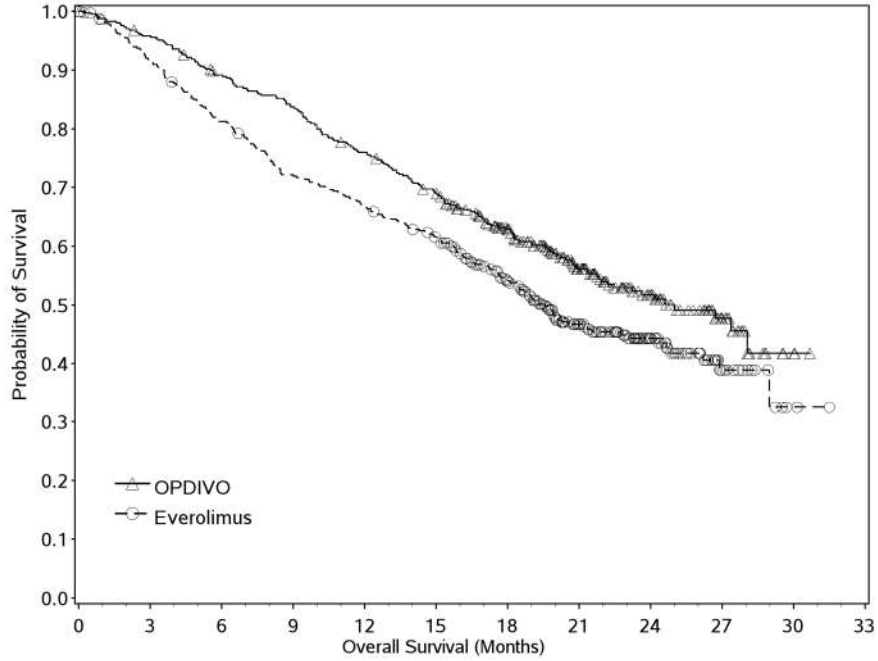
	OPDIVO (n=410)	Everolimus (n=411)
Primary Efficacy Outcome Measure		
Overall Survival[a]		
Events (%)	183/410 (45)	215/411 (52)
Median survival in months (95% CI)	25.0 (21.7, NE)	19.6 (17.6, 23.1)
Hazard ratio (98.52% CI)	0.73[b] (0.57, 0.93)	
p-value	0.0018[c]	
Secondary Efficacy Outcome Measures:		
Progression-free survival		
Events	318/410 (77.6)	322 /411(78.3)
Hazard ratio	0.88	
95% CI	(0.75, 1.03)	
p-value	0.1135	
Median (95% CI)	4.6 (3.71, 5.39)	4.4 (3.71, 5.52)
Objective Response Rate per Investigator (CR+PR)	103/410 (25.1%)	22/411 (5.4%)
(95% CI)	(21.0, 29.6)	(3.4, 8.0)
Odds ratio (95% CI)	5.98 (3.68, 9.72)	
p-value	< 0.0001	
Complete response (CR)	4 (1.0%)	2 (0.5%)
Partial response (PR)	99 (24.1%)	20 (4.9%)
Stable disease (SD)	141 (34.4%)	227 (55.2%)
Median duration of response		
Months (range)	11.99 (0.0-27.6+)	11.99 (0.0+-22.2+)

[a] Based on the 398 observed deaths and O'Brian-Fleming alpha spending function, the boundary for statistical significance requires the p-value to be less than 0.0148 (based on interim analysis)

[b] Hazard ratio is obtained from a Cox proportional-hazards model stratified by MSKCC risk group, number of prior anti-angiogenic therapies, and region with treatment as the sole covariate.

[c] P-value is obtained from a two-sided log-rank test stratified by MSKCC risk group, number of prior anti-angiogenic therapies in the advanced/metastatic setting, and region.

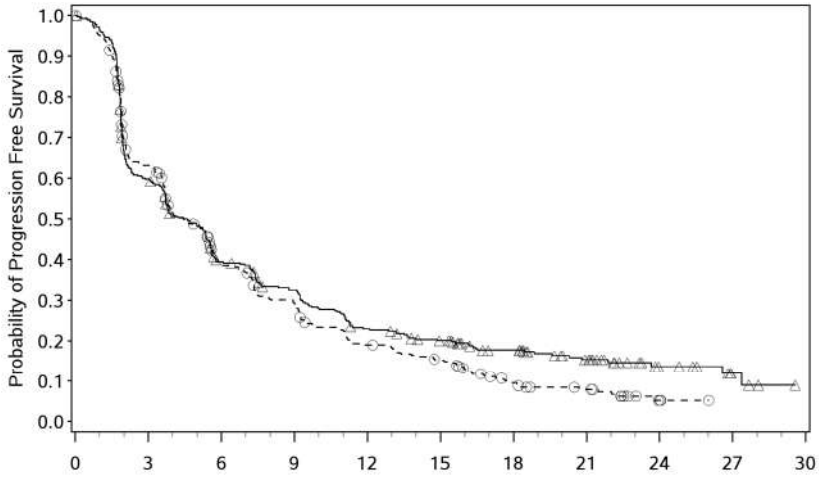
Figure 15: Overall Survival - CHECKMATE-025



Number at Risk

OPDIVO	410	389	359	337	305	275	213	139	73	29	3	0
Everolimus	411	366	324	287	265	241	187	115	61	20	2	0

Figure 16: Progression- Free Survival - CHECKMATE-025



Number of Subjects at Risk

Nivolumab	410	230	145	116	81	66	48	29	11	4	0
Everolimus	411	227	129	97	61	47	25	16	3	0	0

Nivolumab (events: 318/410), median and 95% CI: 4.60 (3.71, 5.39)
Everolimus (events: 322/411), median and 95% CI: 4.44 (3.71, 5.52)
Nivolumab vs Everolimus - hazard ratio and 95% CI: 0.88 (0.75, 1.03); p-value: 0.1135

Advanced RCC (untreated):

CHECKMATE-214 was a randomized (1:1), open-label study in patients with previously untreated advanced RCC. Patients were included regardless of their PD-L1 status. CHECKMATE-214 excluded patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score (0 vs 1-2 vs 3-6) and region (US vs Canada/Western Europe/Northern Europe vs Rest of World).

The primary efficacy population includes those intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the IMDC criteria (less than one year from time of initial renal cell carcinoma diagnosis to randomization, Karnofsky performance status < 80%, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, platelet count greater than the upper limit of normal, and absolute neutrophil count greater than the upper limit of normal).

Patients were randomized to OPDIVO 3 mg/kg plus ipilimumab 1 mg/kg (n=425) administered intravenously every 3 weeks for 4 doses followed by OPDIVO monotherapy 3 mg/kg every two weeks or to sunitinib (n=422) administered orally 50 mg daily for 4 weeks followed by 2 weeks off, every cycle. For intermediate or poor risk patients, 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 31% and 69% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively.

The first tumour assessments were conducted 12 weeks after randomization and continued every 6 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later.

Treatment continued until disease progression or unacceptable toxicity. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator.

The primary efficacy outcome measures were OS, confirmed ORR and PFS as determined by an IRRC, in intermediate/poor risk patients. Among intermediate/poor risk patients, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to OPDIVO plus ipilimumab as compared with sunitinib (Table 47 and Figure 17). The trial did not demonstrate a statistically significant improvement in PFS.

Table 47: Efficacy Results - CHECKMATE-214

	Intermediate/Poor-Risk	
	OPDIVO plus ipilimumab (n=425)	**Sunitinib (n=422)**
Overall Survival		
Deaths (%)	140 (32.9)	188 (44.5)
Median survival (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)
Difference in ORR (99.9% CI)[d]	16.0% (5.6%, 26.4%)	
p-value[d,e]	<0.0001	
Best Overall Response		
Complete Response (CR)	40 (9.4)	5 (1.2)
Partial Response (PR)	137 (32.2)	107 (25.4)
Stable Disease (SD)	133 (31.3%)	188 (44.5%)
Median duration of response in months (95% CI)[f]	NE (21.8, NE)	18.2 (14.8, NE)
Median time to onset of confirmed response in months (min, max)	2.8 (0.9, 11.3)	3.0 (0.6, 15.0)
Progression-free Survival		
Disease progression or death (%)	228 (53.6)	228 (54.0)
Median (months)	11.6	8.4
Hazard ratio (99.1% CI)[a]	0.82 (0.64, 1.05)	
p-value[b,g]	0.0331	

[a] Base on a stratified Cox proportional hazards model stratified by IMDC prognostic score and region.

[b] Based on a stratified log-rank test stratified by IMDC prognostic score and region.

[c] p-value is compared to alpha 0.002 in order to achieve statistical significance.

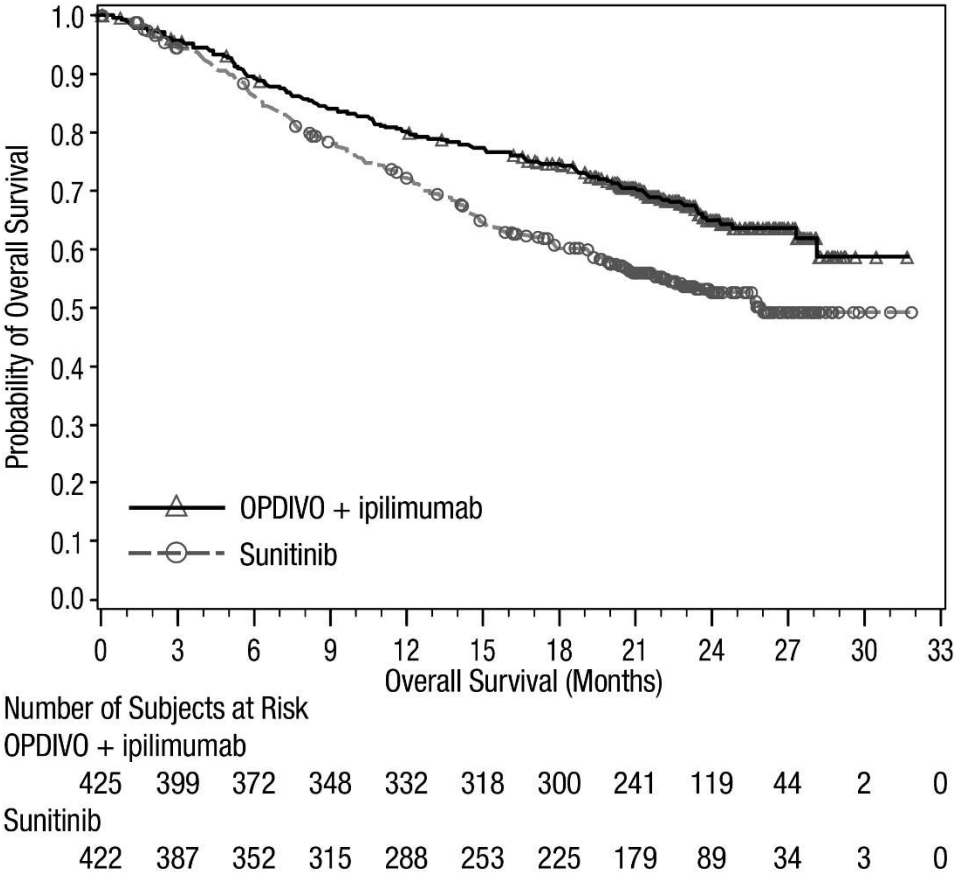
[d] Strata adjusted difference based on the stratified DerSimonian-Laird test.

[e] p-value is compared to alpha 0.001 in order to achieve statistical significance.

[f] Computed using Kaplan-Meier method

[g] Not significant at alpha level of 0.009

Figure 17: Overall Survival (Intermediate/Poor Risk Population) - CHECKMATE-214



The estimated OS rates at 12 months were 80.1% (95% CI: 75.9, 83.6) for OPDIVO and 72.1% (95% CI: 67.4, 76.2) for sunitinib.

OS benefit was observed regardless of PD-L1 expression level, with a hazard ratio of 0.45 (95% CI: 0.29, 0.71) for PD-L1 tumour expression levels ≥ 1%, and a hazard ratio of 0.73 (95% CI: 0.56, 0.96) for PD-L1 tumour expression levels < 1%.

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

Recurrent or Metastatic SCCHN

Controlled Trial in SCCHN Patients Progressing on or after Platinum-Based Therapy

The safety and efficacy of OPDIVO 3 mg/kg as a single agent for the treatment of metastatic or recurrent SCCHN were evaluated in a Phase III, randomised, open-label study (CHECKMATE-141). The study included patients (18 years or older) who experienced disease progression during or within 6 months after prior platinum-based therapy regimen and had an ECOG performance status score of 0 or 1. Prior platinum-based therapy was administered in either the adjuvant, neo-adjuvant, primary, or metastatic setting. Patients were enrolled regardless of their tumour PD-L1 or human papilloma virus (HPV) status. Patients with active autoimmune disease, medical conditions requiring immunosuppression, recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma), or untreated brain metastasis were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrollment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents.

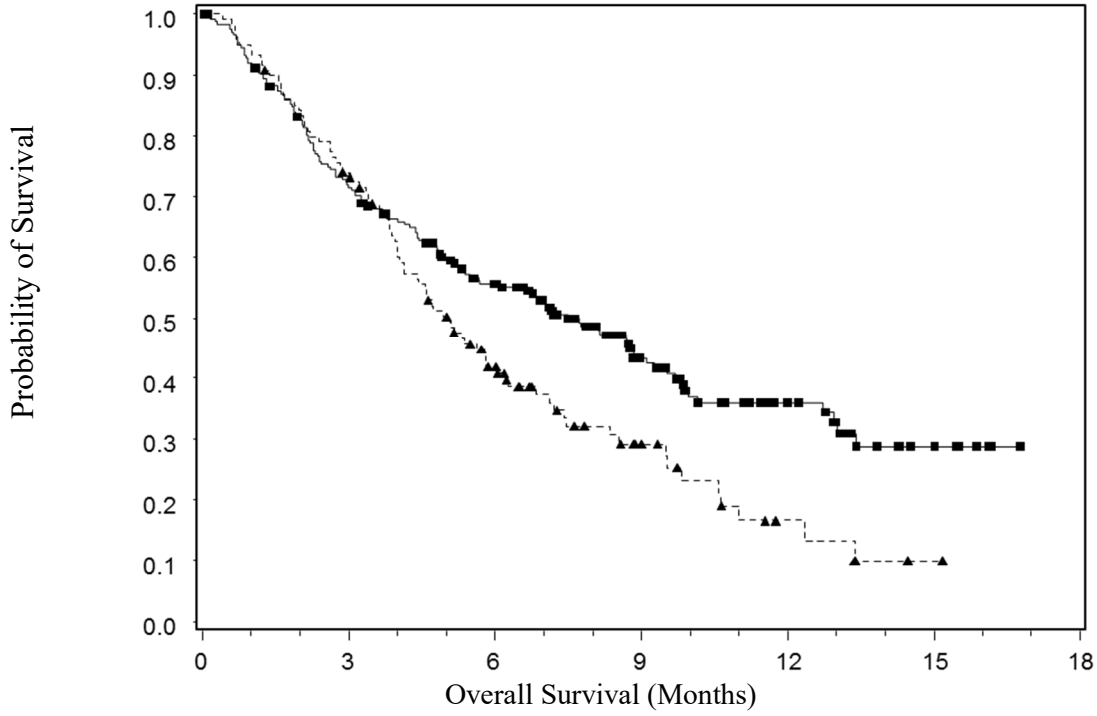
A total of 361 patients were randomised 2:1 to receive either OPDIVO 3 mg/kg (n = 240) administered intravenously over 60 minutes every 2 weeks or investigator's choice (n = 121) of either cetuximab (n = 15), 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly or methotrexate (n = 52) 40 to 60 mg/m^2 weekly, or docetaxel (n = 54) 30 to 40 mg/m^2 weekly. Randomisation was stratified by prior cetuximab treatment. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. Tumour assessments, according to RECIST version 1.1, were conducted 9 weeks after randomisation and continued every 6 weeks thereafter. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted in patients receiving OPDIVO if the patient had a clinical benefit and was tolerating study drug, as determined by the investigator. The primary efficacy outcome measure was OS. Key secondary efficacy outcome measures were investigator-assessed PFS and ORR. Additional prespecified subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression at predefined levels of 1%, 5%, and 10%.

Pre-study tumour tissue specimens were systematically collected prior to randomisation in order to conduct pre-planned analyses of efficacy according to tumour PD-L1 expression. Tumour PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay.

Baseline characteristics were generally balanced between the two groups. The median age was 60 years (range: 28-83) with 31% ≥ 65 years of age and 5% ≥ 75 years of age, 83% were male, and 83% were white. Baseline ECOG performance status score was 0 (20%) or 1 (78%), 76% were former/current smokers, 90% had Stage IV disease, 66% had two or more lesions, 45%, 35% and 20% received 1, 2, or 3 or more prior lines of systemic therapy, respectively, and 25% were HPV-16 status positive.

The Kaplan-Meier curves for OS are shown in Figure 18.

Figure 18: Overall Survival - CHECKMATE-141



Number of Subjects at Risk

OPDIVO						
240	167	109	52	24	7	0
Investigator's choice						
121	87	42	17	5	1	0

OPDIVO (events: 133/240), median and 95% CI: 7.49 (5.49, 9.10)
Investigator's choice (events: 85/121), median and 95% CI: 5.06 (4.04, 6.05)
OPDIVO vs. Investigator's Choice - hazard ratio and 95% CI: 0.70 (0.53 - 0.92); p-value: 0.0101

The trial demonstrated a statistically significant improvement in OS for patients randomised to OPDIVO as compared with investigator's choice at the pre-specified interim analysis when 218 events were observed (78% of the planned number of events for final analysis). OPDIVO did not demonstrate a statistically significant benefit over investigator's choice in the secondary efficacy endpoints of progression-free survival (PFS) and objective response rates (ORR). Efficacy results are shown in Table 48.

Table 48: Efficacy results - CHECKMATE-141

	OPDIVO (n = 240)		investigator's choice (n = 121)
Overall survival			
Events	133 (55.4%)		85 (70.2%)
Hazard ratio[a]		0.70	
(95% CI)		(0.53, 0.92)	
p-value[b]		0.0101	
Median (95% CI) months	7.49 (5.49, 9.10)		5.06 (4.04, 6.05)
Rate (95% CI) at 6 months	55.6 (48.9, 61.8)		41.8 (32.6, 50.7)
Rate (95% CI) at 12 months	36.0 (28.5, 43.4)		16.6 (8.6, 26.8)
Progression-free survival			
Events	190 (79.2%)		103 (85.1%)
Hazard ratio		0.89	
95% CI		(0.70, 1.13)	
p-value		0.3236	
Median (95% CI) (months)	2.04 (1.91, 2.14)		2.33 (1.94, 3.06)
Confirmed objective response[c]	32 (13.3%)		7 (5.8%)
(95% CI)	(9.3, 18.3)		(2.4, 11.6)
Complete response (CR)	6 (2.5%)		1 (0.8%)
Partial response (PR)	26 (10.8%)		6 (5.0%)
Stable disease (SD)	55 (22.9%)		43 (35.5%)

[a] Derived from a stratified proportional hazards model.

[b] P-value is derived from a log-rank test stratified by prior cetuximab; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0227.

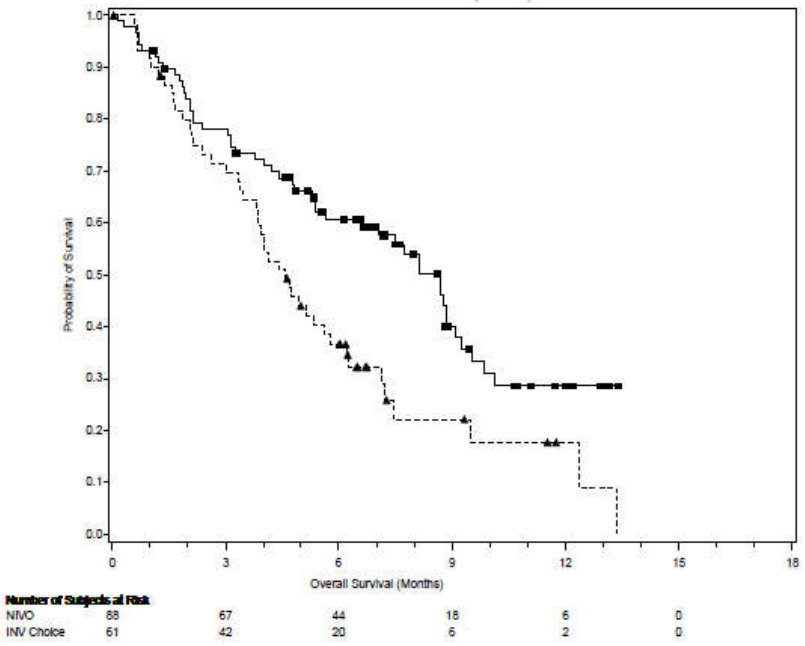
[c] In the OPDIVO group there were two patients with CRs and seven patients with PRs who had tumour PD-L1 expression < 1%.

Tumour PD-L1 expression was quantifiable in 72% of patients - 67% of patients in the OPDIVO group and 82% of patients in the investigator's choice group. Tumour PD-L1 expression levels were balanced between the two treatment groups (OPDIVO vs. investigator's choice) at each of the predefined tumour PD-L1 expression levels of ≥ 1% (55% vs. 62%), ≥ 5% (34% vs. 43%), or ≥ 10% (27% vs. 34%).

Patients with tumour PD-L1 expression by all predefined expression levels in the OPDIVO group demonstrated greater likelihood of improved survival compared to investigator's choice. The magnitude of OS benefit was consistent for ≥ 1%, ≥ 5% or ≥ 10% tumour PD-L1 expression levels, with results shown using a 1% cut-off for PD-L1 expression (Figure 19). In contrast, there were no meaningful differences in OS between OPDIVO and investigator's choice treated patients who were PD-L1 negative (PD-L1 < 1%). In patients with no measurable tumour PD-L1 expression or in those deemed non-quantifiable, close monitoring for unequivocal progression during the first months of treatment with OPDIVO may be clinically prudent.

Figure 19: Overall Survival by PD-L1 Expression Level (1%) - CHECKMATE-141

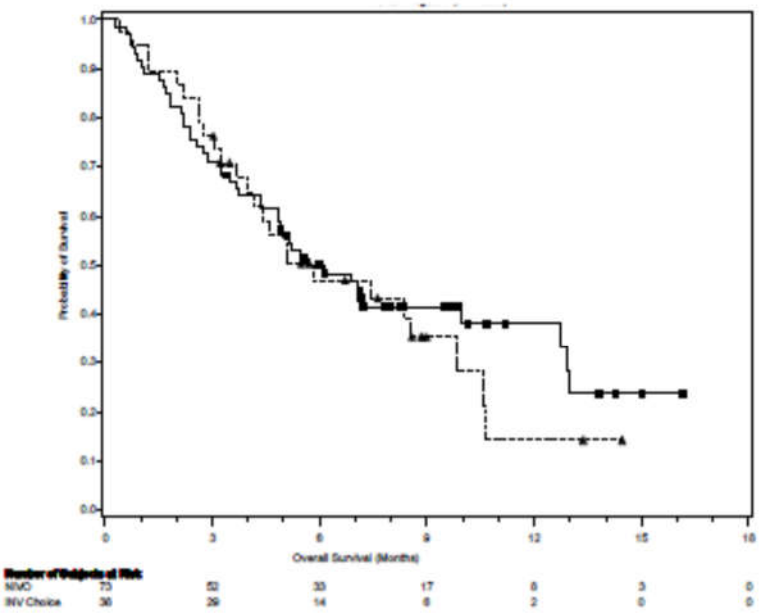
≥ 1% PD-L1 Expression



Nivolumab 3 mg/kg (events : 49/88), median and 95% CI : 8.7 (5.7,9.1)
Investigator's Choice (events : 45/61), median and 95% CI : 4.6 (3.8,5.8)

NIVO vs. INV Choice - hazard ratio (95% CI): 0.55 (0.36, 0.83)

< 1% PD-L1 Expression



Nivolumab 3 mg/kg (events : 45/73), median and 95% CI : 5.7 (4.4,12.7)
Investigator's Choice (events : 25/38), median and 95% CI : 5.8 (4.0,9.8)

NIVO vs. INV Choice - hazard ratio (95% CI): 0.89 (0.54, 1.45)

Classical Hodgkin Lymphoma (cHL):

Open-Label Studies in cHL Patients after Failure of ASCT

Two studies evaluated the efficacy of OPDIVO as a single agent in patients with cHL after failure of ASCT.

CHECKMATE-205 was a Phase 2 single-arm, open-label, multicenter, multicohort study in cHL. Subjects were brentuximab-naïve after failure of ASCT (n=63), may have had brentuximab vedotin following failure of ASCT (n=80), or could have received prior brentuximab vedotin at any time-point relative to ASCT (of which 33 patients who had received brentuximab vedotin only prior to ASCT). CHECKMATE-039 was an open-label, multicenter, dose escalation study that included 23 cHL patients, amongst which, 15 received prior brentuximab vedotin treatment after failure of ASCT. Both studies included patients regardless of their tumour PD-L1 status and excluded patients with ECOG performance status of 2 or greater, autoimmune disease, symptomatic interstitial lung disease, hepatic transaminases more than 3 times ULN, creatinine clearance less than 40 mL/min, prior allogeneic stem cell transplant, or chest irradiation within 24 weeks. In addition, both studies required an adjusted diffusion capacity of the lungs for carbon monoxide (DLCO) of over 60% in patients with prior pulmonary toxicity. In CHECKMATE-205 and CHECKMATE-039, 7 patients were ≥ 65 years of age.

Patients received 3 mg/kg of nivolumab administered intravenously over 60 minutes every 2 weeks until disease progression, maximal clinical benefit, or unacceptable toxicity. A cycle consisted of one dose. Dose reduction was not permitted.

In the 63 patients in CHECKMATE-205 who received nivolumab after failure of ASCT (brentuximab naive), the median age was 33 years (range: 18 to 65), the majority were male (54%) and white (86%), and patients had received a median of 2 prior systemic regimens (range: 2 to 8). Patients received a median of 25 doses of nivolumab (range 1 to 43), with a median duration of therapy not reached (95% CI 12.5 months, not reached).

In the 95 patients in studies CHECKMATE-205 and CHECKMATE-039 combined who received nivolumab after brentuximab vedotin following failure of ASCT, the median age was 37 years (range: 18 to 72), the majority were male (64%) and white (87%), and patients had received a median of 5 prior systemic regimens (range: 2 to 15). Patients received nivolumab for a median of 28 doses (range 3 to 48), with a median duration of therapy of 16 months (95% CI 9.26, 23.36 months).

In studies CHECKMATE-205 and CHECKMATE-039, efficacy was evaluated by objective response rate (ORR) as determined by an independent radiographic review committee (IRRC). Additional outcome measures included duration of response and PFS.

Efficacy results for patients who received nivolumab after brentuximab vedotin following failure of ASCT is presented in Table 49, and for patients who received nivolumab after failure of ASCT (brentuximab naive) is presented in Table 50.

Table 49: Efficacy results in patients with cHL after brentuximab vedotin following failure of ASCT

	CHECKMATE-205 Cohort B and CHECKMATE-039 n=95	CHECKMATE-205 Cohort B[a,b] n=80	CHECKMATE-039[c] n=15
Objective Response Rate (95% CI)	66% (56, 76)	68% (56, 78)	60% (32, 84)
Complete Remission Rate	6%	8%	0%
Partial Remission Rate	60%	60%	60%
Duration of Response (months)			
Median (95% CI)	13.1 (9.46, NE)	13.1 (8.7, NE)	12.0 (1.8, NE)
Range	0.0+, 23.1+	0.0+, 14.2+	1.8+, 23.1+

[a] Follow-up was ongoing at the time of data submission
b Median duration of follow-up 15.4 months (1.9 to 18.5)
c Median duration of follow-up 21.9 months (11.2 to 27.6)

Updated efficacy results in patients with cHL after brentuximab vedotin following failure of ASCT (median duration of follow-up of 22.7 months) was consistent with interim results initially reported. They had an ORR of 68% (95% CI 56, 78), complete remission rate of 13%, partial remission rate of 55% and median duration of response of 15.9 months (95% CI 7.8, 20.3).

Table 50: Efficacy results in patients with cHL After ASCT (brentuximab vedotin-naive)

	CHECKMATE-205 Cohort A [a,b] n = 63
Objective Response Rate (95% CI)	68% (55, 79)
Complete Remission Rate	22%
Partial Remission Rate	46%
Duration of Response (months)	
Median (95% CI)	NE (NE, NE)
Range	1.4, 16.1+

[a] Follow-up was ongoing at the time of data submission
b Median duration of follow-up 14.0 months (1.0 to 20.3)

Updated efficacy results in patients with cHL after ASCT (brentuximab vedotin-naive) (median duration of follow-up of 19.1 months) was consistent with interim results initially reported. They had an ORR of 65% (95% CI 52, 77), complete remission rate of 29%, partial remission rate of 37% and median duration of response of 20.3 months (95% CI 12.8, 20.3).

Efficacy was also evaluated in 33 patients in Study CHECKMATE-205 who had received brentuximab vedotin only prior to ASCT (Cohort C). The median age was 30 years (range 19 to 53). The majority were male (55%) and white (88%). Patients had received a median of 4 prior systemic regimens (range: 2 to 7). They had an ORR of 70% (95% CI 51, 84), Complete Remission Rate of 18% and Partial Remission Rate of 52%.

Hepatocellular Carcinoma

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of advanced HCC in patients previously treated with sorafenib (patients either progressed on or were intolerant to sorafenib) were evaluated in a Phase 2, open-label, multi-cohort study (CHECKMATE-040). In

the single-arm second-line expansion cohort of this study, 145 patients received nivolumab 3 mg/kg monotherapy administered intravenously every 2 weeks until disease progression or unacceptable toxicity. This cohort included patients with histologic confirmation of HCC and Child-Pugh Class A at screening. Patients were enrolled regardless of PD-L1 status or aetiological subtypes; i.e., uninfected, HCV-infected, or HBV-infected.

Patients with a baseline ECOG performance score > 1, active autoimmune disease, brain metastasis, a history of hepatic encephalopathy, clinically significant ascites on physical exam, infection with HIV, or active coinfection with HBV/HCV or HBV/HDVwere excluded from the study. Tumour assessments were conducted every 6 weeks for 48 weeks and every 12 weeks thereafter. The primary efficacy outcome measure was confirmed ORR, as determined by blinded independent central review (BICR) using RECIST version 1.1. Additional efficacy measures included duration of response and OS.

The median age was 63 years (range: 19 to 81) with 44% (64/145) ≥ 65 years of age and 11% (16/145) ≥ 75 years of age; 77% were men, and 46% were white. 49.7% were uninfected, 20.7% were infected with HCV, and 29.6% were infected with HBV. Baseline ECOG performance status was 0 (64%) or 1 (36%). At baseline, 66.9% of patients were Child-Pugh Class A5, 31.7% were Class A6, and 1.4% were Class B7. Seventy one percent (71%) of patients had extrahepatic spread, 28% vascular invasion, and 38% alfa-fetoprotein (AFP) levels ≥ 400 µg/L. Prior treatment history included surgical resection (66%), radiotherapy (25%), or locoregional treatment (59%). All patients had prior sorafenib with 19% of patients receiving 2 or more prior therapies. Among those patients, 23% were unable to tolerate sorafenib.

The efficacy results after a minimum follow-up of 48 weeks are summarized in Table 51.

Table 51: Efficacy Results as determined by BICR - CHECKMATE-040

	Second-line expansion cohort (n = 145)
Confirmed Objective Response Rate, n (%), RECIST v1.1	21 (14.5)
(95% CI) [a]	(9.2, 21.3)
Complete response (CR), n (%)	2 (1.4)
Partial response (PR), n (%)	19 (13.1)
Confirmed Objective Response Rate, n (%) mRECIST	27 (18.6)
(95% CI):	(12.6, 25.9)
Complete response (CR), n (%)	4 (2.8)
Partial response (PR), n (%)	23 (15.9)
Median Duration of Response, RECIST v1.1	
Months (range)	N.A. (3.2, 13.8+)
(95% CI)	(11.3, NA)
≥ 6 months, n (%)	19 (90.5)
≥ 12 months, n (%)	8 (38.1)
Median Time to Response, RECIST v1.1	
Months (range)	2.8 (1.2, 7.0)

"+" Denotes a censored observation.

[a] Confidence interval is based on the Clopper and Pearson Method.

Efficacy data were updated with a minimum follow-up of 27 months in the second-line expansion cohort (N=145). The BICR-assessed ORR by RECIST v1.1 remained at 14.5% (95% CI: 9.2, 21.3), while the complete response rate was 2.8% and the partial response rate was 11.7%. The

median duration of response was 16.6 months (95% CI: 9.7, NA) with 6 out of the 21 responders (28.6%) with ongoing tumour response at 24 months. These updated efficacy data should be interpreted with caution due to the exploratory nature of these analyses.

There are limited safety and efficacy data available for Child-Pugh Class B patients.

No clinical data are available for Child-Pugh Class C patients.

PD-L1 testing was conducted using the PD-L1 IHC 28-8 pharmDx assay. However, the association between PD-L1 expression status and clinical efficacy measures has not been fully elucidated in the HCC setting.

MSI-H/dMMR mCRC:

The safety and efficacy of nivolumab in combination with ipilimumab were evaluated for the treatment of dMMR or MSI-H mCRC in a Phase 2, multicenter, open-label, single-arm study (CHECKMATE-142).

The study included patients (18 years or older) with locally determined dMMR or MSI-H status, who had disease progression during, after, or were intolerant to, prior therapy with fluoropyrimidine and oxaliplatin or irinotecan, and had an ECOG performance status score of 0 or 1. This study included patients regardless of their tumor PD-L1 status. Patients with active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study.

A total of 119 patients received the combination regimen (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then nivolumab 3 mg/kg every 2 weeks). Treatment continued until unacceptable toxicity or radiographic progression. Tumor assessments were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. Efficacy outcome measures included overall response rate (ORR) as assessed by independent radiographic review committee (IRRC) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and duration of response (DOR).

The median age was 58 years (range: 21 to 88), with 32% ≥ 65 years of age and 9% ≥ 75 years of age; 59% were male and 92% were white.

Baseline ECOG performance status was 0 (57%) and ≥1 (61%), and 29% were reported to have Lynch Syndrome. 25% of patients were BRAF mutation positive, 37% were KRAS mutation positive, and 12% were unknown. 23%, 36%, 24%, and 16% received 1, 2, 3, or ≥4 prior lines of therapy, respectively, and 29% had received an anti-EGFR antibody.

Efficacy results based on a minimum follow-up of approximately 27.5 months for all 119 patients who had prior fluoropyrimidine, oxaliplatin or irinotecan therapy are shown in Table 52.

Table 52: Nivolumab + ipilimumab Combination Therapy Efficacy Results for Patients with MSI-H/dMMR mCRC (CHECKMATE-142)

	nivolumab + ipilimumab[a] All patients (n = 119)
Confirmed objective response[b], n (%)	71 (59.7)
(95% CI)[c]	(50.3, 68.6)
Complete response (CR), n (%)	17 (14.3)
Partial response (PR), n (%)	54 (45.4)

"+" denotes a censored observation
[a] Minimum follow-up 27.5 months, Median follow-up 31.5 months
[b] BICR assessment
[c] Estimated using the Clopper-Pearson method

At the time of this analysis corresponding to the minimum follow-up duration of 27.5 months, the median response duration was not reached (range: 1.9 to 36.9+ months).

TOXICOLOGY

The toxicology studies performed with nivolumab are summarized in Table 53.

Single-Dose toxicity

A single-dose pharmacokinetic and tolerability study of nivolumab was conducted in cynomolgus monkeys. Single IV administration of nivolumab at dose levels of 1 or 10 mg/kg were well tolerated. All animals survived the study, and no effect of nivolumab was observed on clinical observations, body-weight measurements, food consumption, or clinical pathology parameters. Nivolumab was immunogenic in this study; 5 of 6 animals administered 1 mg/kg and 2 of 3 animals administered 10 mg/kg tested positive for anti-nivolumab antibodies (ADA) on Day 28. However, there was no apparent effect of these antibodies on the pharmacokinetics of nivolumab. Immunogenicity in animals is not expected to be predictive of potential immunogenicity in humans.

Repeat-Dose Toxicity

Nivolumab was well tolerated by cynomolgus monkeys when administered as a single agent at ≤ 50 mg/kg, twice weekly (2QW) for up to 3 months with no adverse effects noted. In the 3-month toxicity study, pharmacologically mediated changes in circulating T-cell subpopulations were observed at 10 and/or 50 mg/kg. In addition, there was a reversible 28% decrease in mean plasma triiodothyronine (T3) levels at 50 mg/kg in female monkeys at the end of the dosing phase of the study. However, there were no effects on plasma levels of thyroxine (T4), thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), growth hormone, or alpha-melanocyte-stimulating hormone (α-MSH), or morphologic findings in the thyroid or pituitary glands. No hormone or morphologic changes were observed in males, and there were no effects at the same doses in males or females in a 1-month toxicity study. Therefore, the relevance of the lower T3 levels in females, in the absence of any correlative changes in other hormones or in the thyroid or pituitary gland, is unknown. ADA formation was observed in 13% of the monkeys. In monkeys

without ADA responses, nivolumab exposures (AUC[0-168h]) at 50 mg/kg were 531,000 μg•h/mL (1,062,000 when normalized for 2 weeks of exposure). This dose and exposure are approximately 17 and 35× the recommended human dose and resulting exposure (3 mg/kg administered every 2 weeks [Q2W]; AUC[Tau] 30,640 μg•h/mL), respectively.

Reproduction and Development

Pregnant monkeys were administered nivolumab twice weekly at 10 or 50 mg/kg from the onset of organogenesis (approximately gestation day 20) until parturition. Nivolumab was well tolerated and there were no nivolumab-related effects on viability, clinical signs, food consumption, body weights, immunological endpoints, or clinical/anatomic pathology parameters in these females throughout the study.

However, in the offspring, maternal nivolumab administration was associated with fetal/neonatal mortality characterized by: 1) increases in third trimester fetal losses; and 2) increased neonatal mortality. In a single fetus from a 10-mg/kg dam that aborted on GD 124, moderate interstitial inflammation and follicular-cell hypertrophy/hyperplasia were noted in the thyroid gland. Despite its single occurrence in this study and lack of dose dependency (not observed at 50 mg/kg), the relationship of these thyroid changes to treatment cannot be completely excluded because they were consistent with the pharmacology of nivolumab (ie, immune stimulation).The remaining offspring had no nivolumab-related effects on any of the parameters evaluated throughout the 6-month postnatal period. Based on these results, the no-observed-adverse-effect level (NOAEL) for maternal toxicity was 50 mg/kg (AUC[0-168h] 541,000 μg•h/mL). The lowest-observed-adverse-effect level (LOAEL) for developmental toxicity was 10 mg/kg (AUC[0-168h] 117,000 μg•h/mL), which is approximately 8× the exposure in humans at the recommended dose of 3 mg/kg Q2W. Based on its mechanism of action, fetal exposure to nivolumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice.

Human IgG4 crosses the placental barrier, particularly during the third trimester. Therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. Although it is not known if nivolumab is excreted in human milk, immunoglobulins are known to be excreted in human milk and the potential for infant exposure to nivolumab via breast milk exists. Nivolumab is not recommended during pregnancy, in women of childbearing potential not using effective contraception, or in women breast-feeding unless the clinical benefit outweighs the potential risk.

Impairment of Fertility

No formal studies of effects of nivolumab on fertility have been conducted. Thus, the effect of nivolumab on male and female fertility is unknown. However, as part of the routine histopathological examination of organs collected in toxicity studies, the male and female reproductive organs were evaluated. There were no histopathologic changes in these organs that suggested any adverse effects of nivolumab on male and female fertility; however most animals in these studies were not sexually mature.

Special Toxicology Studies

In animal models, inhibition of PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. M. tuberculosis–infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

Mutagenicity

Mutagenicity studies were not conducted for nivolumab.

Carcinogenicity

Long-term animal studies were not conducted to assess the carcinogenic potential of nivolumab.

Table 53: Summary of Toxicology Studies

Type of Study	Treatment Duration	Species/ Test System	Gender and No. per Group	Doses (mg/kg)[a]	Noteworthy Findings
General Toxicity					
Single-Dose Toxicity IV	1 Dose	Monkey/ Cynomolgus	1 mg/kg: 3 M, 3 F 10 mg/kg: 3 M	1, 10	Nivolumab at ≤ 10 mg/kg was well tolerated. There were no nivolumab-related clinical signs or changes in body weight, food consumption, serum chemistry, or hematology parameters.
Single-Dose Toxicity IV	1 Dose	Monkey/ Cynomolgus (telemetered)	3 M, 3 F	0, 10, 50,	Nivolumab at ≤ 50 mg/kg was well tolerated. There were no nivolumab-related effects on cardiovascular or respiratory parameters.
Repeat -Dose Toxicity IV	1 month (Dosing QW, Necropsy Days 30 and 57)	Monkey/ Cynomolgus	5 M, 5 F	0, 1, 10, 50	Nivolumab at ≤50 mg/kg was well tolerated. There were no nivolumab-related adverse effects.
Repeat-Dose Toxicity IV	3 months (Dosing 2QW, Necropsy Weeks 13 and 17)	Monkey/ Cynomolgus	6 M, 6 F	0, 10, 50	Nivolumab at ≤50 mg/kg was well tolerated. There were no nivolumab-related adverse effects. Clinical chemistry changes were limited to a reversible 28% decrease in T3 levels at Week 13 in females at 50 mg/kg. There were no correlative changes in other hormones, including T4, TSH, α-MSH, or ACTH, or morphologic changes in the thyroid or pituitary glands. At 10 mg/kg and/or 50 mg/kg, there were pharmacologically mediated changes in circulating T-cell subpopulations, including: 1) increases in CD8+ effector memory T cells, and 2) a trend toward increases in CD4+ effector memory T cells and CD8+ central memory T cells.

Table 53: Summary of Toxicology Studies

Type of Study	Treatment Duration	Species/ Test System	Gender and No. per Group	Doses (mg/kg)[a]	Noteworthy Findings
Reproduction and Development					
Pre- and Postnatal Development IV	Approximately 5 months (GD 21 ± 1 to parturition, Dosing 2QW, Necropsy of infants postpartum day 182 ± 1)	Monkey/ Cynomolgus	16 F	0, 10, 50	Nivolumab at 10 or 50 mg/kg was well tolerated by pregnant monkeys and there were no nivolumab-related effects on viability, clinical signs, food consumption, body weights, immunological endpoints, or clinical/anatomic pathology parameters in the females throughout the study. In surviving offspring, no adverse effects on growth indices or on teratogenic, neurobehavioural, immunological, and clinical pathology parameters throughout the 6-month postnatal period, comparable to controls. Nivolumab exposure to infants did not affect the primary response to either hepatitis B surface antigen (HBsAg) or tetanus toxoid, but a trend toward an increased response to HBsAg upon second exposure was observed in the infants, compared to controls. 10 and 50 mg/kg: 1) dose-dependent increases in third trimester fetal losses (12.5% and 33.3% at 10 and 50 mg/kg, respectively, relative to 7.1% in controls), which occurred predominately after GD 120; 2) increased neonatal mortality at 10 mg/kg, which was noted in 3 infants with extreme prematurity during the first 2 postnatal weeks; and 3) moderate interstitial inflammation and follicular-cell hypertrophy/hyperplasia in the thyroid gland (1 fetus from a 10-mg/kg dam that aborted on GD 124). 50 mg/kg: Pregnancy losses in the first trimester were 4* of 16 (compared to 2 of 16 in controls).*One pregancy loss was due to umbilical thrombus and was considered unrelated to nivolumab treatment. The NOAEL for maternal toxicity was 50 mg/kg. An NOAEL for developmental toxicity was not identified.

Table 53: Summary of Toxicology Studies

Type of Study	Treatment Duration	Species/ Test System	Gender and No. per Group	Doses (mg/kg)[a]	Noteworthy Findings
Local Tolerance					
The local tolerance of nivolumab was assessed in the single- and intermittent (QW or 2QW) repeat-dose IV studies in monkeys (described above). Nivolumab was administered at up to 50 mg/kg in a formulation similar to that intended for marketing (Process B,10 mg/mL in 20 mM sodium citrate, 50 mM NaCl, 3% mannitol, 20 μM DTPA, 0.01% polysorbate 80, pH 6.0). No irritation or local tolerance issues were observed in any of the studies.					
Other Studies					
Tissue Crossreactivity *In vitro*	NA	Human	3 donors	1, 10 μg/mL	Nivolumab-FITC specific staining of lymphocytes in a number of tissues, including lymphocytes in the blood. Staining was observed on the membrane, and was consistently present at both concentrations of nivolumab-FITC.
Tissue Crossreactivity *In vitro*	NA	Monkey/ Cynomolgus	2	1, 10 μg/mL	Nivolumab-FITC specific staining of lymphocytes in a number of tissues; staining was observed on the cell membrane and was consistently present at both concentrations of nivolumab-FITC.
Cytokine Release Studies *In vitro*	24 hrs	Human	6 donors	10, 100 μg/mL	Nivolumab alone did not promote cytokine production.
Investigative Ovalbumin challenge study IP/PA	1 month	Mouse/ PD-1 knockout and wild-type C57/BL6	WT: 64 M, 40 F PD-1: 20 M, 16 F	Days 0-7: IP ovalbumin sensitization 10 μg/200 μL Days 14-28: PA ovalbumin challenged 250 μg /50 μL	An increase in sensitivity to pulmonary rechallenge by ovalbumin was observed in PD-1 knockout mice.

Abbreviations: 2QW = Twice weekly; ADA = Anti-drug antibodies; DTPA = Diethylenetriamine pentectic acid; F = Female; FITC = Fluorescein isothiocyanate; GD = Gestation Day; IV = Intravenous; M = Male; NA = Not applicable; QW = Once weekly. PA = Pharyngeal aspiration; IP = Intraperitoneal.

[a] Unless otherwise specified, for repeat-dose toxicity, the highest NOAEL is underlined.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]OPDIVO® is used to treat:

- Adults with skin cancer (advanced melanoma) who have not been treated and who have specific mutations in a gene called BRAF.
- Adults with skin cancer (advanced melanoma) when used together with ipilimumab in patients who have not been treated.
- Adults with a type of blood cancer called classical Hodgkin Lymphoma (a type of lymphatic cancer) when the cancer has come back or spread after a type of stem cell transplant that uses your own cells (autologous), and:
    - you used the drug brentuximab vedotin, or
    - you received at least 3 kinds of treatment including an autologous stem cell transplant.
- Adults with liver cancer (hepatocellular carcinoma) when the cancer has spread or grown after treatment with sorafenib.
- Adults with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer, when used in combination with ipilimumab when your colon or rectal cancer:
    - has come back or spread
    - you have tried treatment with fluoropyrimidine-based therapy in combination with oxaliplatin or irinotecan.

It has been approved for these above uses with conditions (see NOC/c below). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

[Pr]OPDIVO® is used to treat:

- Adults with skin cancer (advanced melanoma) who have not been treated and who do not have a mutation in BRAF (BRAF wild-type).
- Adults with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.
- Adults with skin cancer (melanoma) to help delay or prevent the cancer from coming back after it and its metastases have been completely removed by surgery.
- Adults with lung cancer (advanced non-small cell cancer) that has spread or grown after treatment with a platinum-based chemotherapy. Patients with certain lung cancer mutations (EGFR or ALK) should only be treated with OPDIVO if their cancer grows or spreads during or after treatment with therapies targeting these mutations.
- Adults with lung cancer (advanced non-small cell cancer), if the tumour tests positive for "PD-L1", when used together with ipilimumab in patients who have not been treated.
- Adults with lung cancer (metastatic non-small cell cancer) when used together with ipilimumab and platinum-based chemotherapy in patients who have not been treated.
- Adults with kidney cancer (advanced renal cell carcinoma) that has spread or grown after treatment with medicines that block vessel growth (anti-angiogenic therapies).

- Adults with kidney cancer (advanced renal cell carcinoma) when used together with ipilimumab in patients who have not been treated.
- Adults with cancer of the head and neck (advanced squamous cell carcinoma) when the cancer grows or spreads on or after platinum containing chemotherapy.

It has been approved for these above uses without conditions. This means that it has passed Health Canada's review and can be bought and sold in Canada.

What is a Notice of Compliance with Conditions (NOC/c)?
A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

PrOPDIVO®
(op-DEE-voh)
nivolumab for injection 10 mg/mL

Read this carefully before you start taking **OPDIVO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **OPDIVO.**

Serious Warnings and Precautions

OPDIVO acts on your immune system and may cause inflammation in parts of your body. Inflammation may cause serious damage to your body and some inflammatory conditions may be life-threatening.

OPDIVO given alone or in combination with ipilimumab can cause serious side effects in parts of your body which can lead to death. These serious side effects may include: inflammation of the lungs (pneumonitis or interstitial lung disease), inflammation of the brain (encephalitis), inflammation of the heart muscle (myocarditis), inflammation of the skin (severe skin problems), and decreased number of red blood cells (autoimmune hemolytic anemia).

These side effects are most likely to begin during treatment; however, side effects can show up months after your last infusion. It is important to tell your healthcare professional immediately

if you have, or develop, any of the symptoms listed under the section "What are possible side effects from using OPDIVO and Serious Side Effects and What to do About Them."

If you are given OPDIVO in combination with ipilimumab, it is important that you also read the package leaflet for this medicine.

What is OPDIVO used for?

Skin Cancer:

OPDIVO® is a medicine used in adult patients to treat a type of skin cancer (melanoma) to help delay or prevent the cancer from coming back after it and its metastases have been completely removed by surgery.

OPDIVO may be given to treat a type of skin cancer that has spread or cannot be removed by surgery (advanced melanoma) in adult patients.

OPDIVO may also be given in combination with ipilimumab. It is important that you also read the package leaflet for this medicine. If you have any questions about ipilimumab, please ask your doctor.

Lung Cancer:

OPDIVO is used in adult patients to treat a type of advanced stage lung cancer (called non-small cell lung cancer) that has spread or grown after treatment with platinum containing chemotherapy.

OPDIVO may be given in combination with ipilimumab in adult patients with lung cancer who have not been treated.

OPDIVO may be given in combination with ipilimumab and platinum-based chemotherapy in adult patients with metastatic lung cancer (non-small cell lung cancer) who have not been treated.

Kidney Cancer:

OPDIVO is used in adult patients to treat advanced kidney cancer (called renal cell carcinoma) that has spread or grown after treatment with medicines that block cancer blood vessel growth.

OPDIVO may be given in combination with ipilimumab in adult patients with kidney cancer who have not been treated.

Head and Neck Cancer:

OPDIVO is used in adult patients to treat advanced head and neck cancer (called squamous cell carcinoma of the head and neck) when the cancer grows or spreads on or after platinum containing chemotherapy.

Lymphatic cancer (classical Hodgkin Lymphoma):

OPDIVO is used in adults with a type of blood cancer called classical Hodgkin Lymphoma (a type of lymphatic cancer) when your cancer has come back or spread after a type of stem cell transplant that uses your own stem cells (autologous), and:

- you used the drug brentuximab vedotin, or
- you received at least 3 kinds of treatment including an autologous stem cell transplant.

Liver Cancer:

OPDIVO is used in adult patients to treat liver cancer (called hepatocellular carcinoma) when the cancer has spread or grown after treatment with sorafenib.

Colon or Rectal Cancer:

OPDIVO in combination with ipilimumab is used in adults for the treatment of colon or rectal cancer that is shown by a laboratory test to be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), and:

- you used the drug fluoropyrimidine in combination with oxaliplatin, or irinotecan and the cancer has spread or grown or you no longer tolerating the treatment

It is important that you also read the package leaflet for ipilimumab and if you have any questions, please ask your doctor.

Children:

It is not known if OPDIVO is safe and effective in children less than 18 years of age.

How does OPDIVO work?

OPDIVO contains the active substance nivolumab which helps your immune system to attack and destroy cancer cells.

OPDIVO attaches to a target protein called programmed death-1 receptor (PD-1) that can switch off the activity of T cells (a type of white blood cell that forms part of the immune system, the body's natural defences). By attaching to PD-1, nivolumab blocks its action and prevents it from switching off your T cells. This helps increase their activity against the melanoma, lung, kidney, lymphoid, head and neck, liver, colon or rectal cancer cells.

OPDIVO may be given in combination with ipilimumab.

Ipilimumab contains the active substance ipilimumab, which is a different medicine that also helps your immune system to attack and destroy cancer cells. It is important that you also read the package leaflet for this medicine. If you have any questions about ipilimumab, please ask your healthcare professional.

OPDIVO given with ipilimumab can produce a combined effect on your immune system when taken together.

What are the ingredients in OPDIVO?

The medicinal ingredient in OPDIVO is nivolumab.

The non-medicinal ingredients are hydrochloric acid, mannitol (E421), pentetic acid, polysorbate 80, sodium chloride, sodium citrate, sodium hydroxide, and water for injection.

OPDIVO comes in the following dosage forms:

OPDIVO comes in glass vials containing either 40 mg (in 4 mL) or 100 mg (in 10 mL) of nivolumab.

Do not use OPDIVO if:

you are **allergic** to nivolumab or any of the other ingredients of this medicine. **Talk to your healthcare professional** if you are not sure.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take OPDIVO. Talk about any health conditions or problems you may have, including:

- **Problems with your hormone producing glands** (including the thyroid, parathyroids, pituitary, adrenal glands, and pancreas) that may affect how these glands work. Signs and symptoms that your glands are not working properly may include fatigue (extreme tiredness), weight change, headache or excessive thirst or lots of urine, decreased blood levels of calcium.
- **Diarrhea** (watery, loose or soft stools) or any symptoms of **inflammation of the intestines** (colitis), such as stomach pain and mucus or blood in stool.
- **Abnormal liver function tests.** Signs and symptoms may include eye or skin yellowing (jaundice), pain on the right side of your stomach area, or tiredness.
- **Problems with your lungs** such as breathing difficulties, or cough. These may be signs of inflammation of the lungs (pneumonitis or interstitial lung disease).
- **Abnormal kidney function tests or problems with your kidneys**, such as decreased volume of urine or inflammation of the kidneys (tubulointerstitial nephritis).
- **Had an organ transplant** (such as a kidney transplant).
- **Take other medicines that make your immune system weak.** Examples of these may include steroids, such as prednisone.

Other warnings you should know about:

Tell your healthcare professional immediately if you have any of these signs or symptoms or if they get worse. **Do not try to treat your symptoms with other medicines on your own.** Your healthcare professional may:

- give you other medicines in order to prevent complications and reduce your symptoms,
- withhold the next dose of OPDIVO,
- or, stop your treatment with OPDIVO.

Please note that these signs and symptoms are **sometimes delayed**, and may develop weeks or months after your last dose. Before treatment, your healthcare professional will check your general health.

Check with your healthcare professional before you are given OPDIVO if:

- you have an autoimmune disease (a condition where the body attacks its own cells);
- you have melanoma of the eye;
- have experienced side effects with another drug, such as ipilimumab;
- have been told cancer has spread to your brain;
- or, you are on a low salt diet.

Pregnancy and Breast-feeding:

- you are pregnant or plan to become pregnant. You should not become pregnant while you are getting OPDIVO, OPDIVO can cause harm or death to your unborn baby.
- you must use effective contraception while you are being treated with OPDIVO and for at least 5 months after the last dose of OPDIVO if you are a woman who could become pregnant.
- you are breast-feeding. OPDIVO may pass into your breast milk. You and your doctor should decide if you will take OPDIVO or breast-feed. You should not do both.

Always update your healthcare professional on your medical conditions.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take OPDIVO:

You will receive treatment with OPDIVO in a hospital or clinic, under the supervision of an experienced healthcare professional.

You will get OPDIVO through an infusion (a method of putting the medicine directly into the bloodstream through a vein). It takes about 30 minutes to get a full dose.

OPDIVO is given every 2 weeks, 3 weeks or 4 weeks, depending on the dose you are receiving. Your healthcare professional may change how often you receive OPDIVO or how long the infusion may take.

Usual dose:

When OPDIVO is given on its own, the recommended dose is either 3 mg of nivolumab per kilogram of your body weight every 2 weeks or 240 mg given every 2 weeks or 480 mg given every 4 weeks. Your healthcare professional will discuss with you and help choose the appropriate dose.

When OPDIVO is given in combination with ipilimumab for the treatment of skin cancer, the recommended dose of OPDIVO is 1 mg of nivolumab per kilogram of your body weight every 3

weeks, and ipilimumab is given every 3 weeks on the same day as OPDIVO, for the first 4 doses (combination phase). Thereafter the recommended dose of OPDIVO is either 3 mg of nivolumab per kilogram of your body weight every 2 weeks or 240 mg of nivolumab given every 2 weeks or 480 mg given every 4 weeks (single-agent phase).

When OPDIVO is given in combination with ipilimumab for the treatment of advanced kidney cancer, the recommended dose of OPDIVO is 3 mg of nivolumab per kilogram of your body weight every 3 weeks, and ipilimumab is given every 3 weeks on the same day as OPDIVO, for the first 4 doses (combination phase). Thereafter the recommended dose of OPDIVO is either 3 mg of nivolumab per kilogram of your body weight every 2 weeks or 240 mg of nivolumab given every 2 weeks or 480 mg given every 4 weeks (single-agent phase).

When OPDIVO is given in combination with ipilimumab for the treatment of advanced lung cancer, the recommended dose of OPDIVO is 3 mg of nivolumab per kilogram of your body weight every 2 weeks, and ipilimumab is given every 6 weeks, for up to 2 years.

When OPDIVO is given in combination with ipilimumab and chemotherapy for the treatment of metastatic lung cancer, the recommended dose of OPDIVO is 360 mg of nivolumab every 3 weeks, and ipilimumab is given every 6 weeks, for up to 2 years. Chemotherapy is given every 3 weeks for the first 2 cycles only. OPDIVO, ipilimumab and chemotherapy will be given on the same day.

Depending on your dose, some or all of the content of the OPDIVO vial may be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection before use. More than one vial may be necessary to obtain the required dose.

Overdose:

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

If you stop using OPDIVO:

Stopping your treatment may stop the effect of the medicine. Do not stop treatment with OPDIVO unless you have discussed this with your healthcare professional.

If you have any further questions about your treatment or on the use of this medicine, ask your healthcare professional.

When OPDIVO is given in combination with ipilimumab, you will first be given OPDIVO followed by ipilimumab.

When OPDIVO is given in combination with ipilimumab and chemotherapy, you will first be given OPDIVO followed by ipilimumab and then chemotherapy.

Please refer to the package leaflet of ipilimumab and your prescribed chemotherapy in order to understand the use of these medicines. If you have questions about these medicines, please ask your healthcare professional.

Missed Dose:

It is very important for you to keep all your appointments to receive OPDIVO. If you miss an appointment, ask your healthcare professional when to schedule your next dose.

What are possible side effects from using OPDIVO?

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your healthcare professional will discuss these with you and will explain the risks and benefits of your treatment.

Very common side effects (may affect more than 1 in 10 people):

The most common side effects of OPDIVO when used alone are:

- Nausea
- Diarrhea
- Skin rash, itching
- Feeling tired or weak
- Decreased appetite

The most common side effects of OPDIVO when used in combination with ipilimumab are:

- Underactive thyroid gland (which can cause tiredness or weight gain), overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss)
- Decreased appetite
- Headache
- Shortness of breath (dyspnea)
- Inflammation of the intestines (colitis), diarrhoea (watery, loose or soft stools), vomiting, nausea, stomach pain
- Skin rash sometimes with blisters, itching
- Pain in the joints (arthralgia), pain in the muscles and bones (musculoskeletal pain)
- Feeling tired or weak, fever

The most common side effects of OPDIVO when used in combination with ipilimumab and chemotherapy are:

- Nausea
- Diarrhea
- Vomiting
- Skin rash sometimes with blisters, itching
- Feeling tired or weak
- Underactive thyroid gland (which can cause tiredness or weight gain)

- Decreased appetite
- Decrease in the number of red blood cells (which can make you feel tired or become short of breath)
- Decrease in the number of white blood cells (which can increase your chance for infection)

OPDIVO acts on your immune system and may cause redness, warmth (fever), swelling and pain (inflammation) in parts of your body. This may cause serious damage to your body and some conditions may be life-threatening. You may need treatment to reduce the inflammation and OPDIVO may be stopped.

If you get any serious side effects with OPDIVO when used alone (monotherapy) or in combination with ipilimumab or ipilimumab and chemotherapy (combination) (see table below), talk to your healthcare professional. Side effects may be very common (may affect more than 1 in 10 people), common (may affect less than 1 in 10 but more than 1 in 100 people), uncommon (may affect less than 1 in 100 but more than 1 in 1,000 people), or rare (may affect less than 1 in 1,000 people).

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common *(monotherapy)* **Common to Very Common** *(combination)*	**Inflammation of the intestines (colitis)** *Symptoms may include:* • diarrhea (watery, loose, or soft stools) or more bowel movements than usual. Do not treat the diarrhea yourself • blood or mucous in stools, or dark, tarry, sticky stools • stomach pain (abdominal pain) or tenderness		√	

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common *(monotherapy)* **Very Common** *(combination)*	**Inflammation of the thyroid, adrenal or pituitary glands** *Symptoms may include:* • headaches that will not go away or unusual • unusual tiredness or sleepiness • weight changes (weight gain or weight loss) • changes in mood or behaviour such as less sex drive, being irritable or forgetful, or depression • dizziness or fainting		√	
Uncommon *(monotherapy)* **Common** *(combination)*	**Inflammation of the liver (hepatitis)** *Symptoms may include:* • extreme tiredness • yellowing of your skin (jaundice) or the whites of your eyes • severe nausea or vomiting • pain on the right side of your stomach (abdomen) • bruise easily		√	
Uncommon *(monotherapy, combination)*	**Inflammation of the kidney (nephritis)** *Symptoms may include:* • changes in urine output (increase or decrease) • dark urine (tea-coloured) • swelling of extremities		√	

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common *(monotherapy, combination)*	**Inflammation of the lung (pneumonitis)** *Symptoms may include:* • trouble breathing, shortness of breath • cough (new or worsening) with or without mucus		√	
Uncommon *(monotherapy, combination)*	**Eye problems** *Symptoms may include:* • changes in eyesight • eye pain or redness • blurred or blurry vision, or other vision problems		√	
Uncommon *(monotherapy)* **Uncommon to common** *(combination)*	**Blood sugar problems (diabetes or ketoacidosis)** *Symptoms may include:* • hunger or excessive thirst • need to urinate more often • increased appetite with weight loss, or loss of appetite • muscle weakness • sleepiness or drowsiness • depression • irritability • feeling unwell		√	

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common *(monotherapy, combination)*	**Inflammation of the skin (severe skin problems)** *Symptoms may include:* • severe skin reactions or rash • itching • skin blistering and peeling • ulcers in the mouth or other mucous membranes • raised skin lumps/bumps (skin nodules) • dry skin		√	
Uncommon *(monotherapy, combination)*	**Inflammation of the brain (encephalitis)** *Symptoms may include:* • headache • fever • confusion • memory problems • sleepiness or drowsiness • seeing things that are not really there (hallucinations) • seizures (fits) • stiff neck		√	

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Rare *(monotherapy, combination)*	**Inflammation of the muscles (myositis), inflammation of the heart muscle (myocarditis), or breakdown of skeletal muscle (rhabdomyolysis):** *Symptoms may include:* • muscle or joint pain, stiffness, or weakness • chest pain, irregular heartbeat, or palpitations • confusion or memory problems • severe fatigue • difficulty walking		√	
Rare *(monotherapy, combination)*	**Problems with other organs** *Symptoms may include:* • loss of nerve function or sensation of paralysis • swollen lymph nodes • numbness or tingling in hands or feet • swelling in extremities • abdominal pain, nausea or vomitting (pancreatitis) • indigestion or heartburn		√	

Other serious side effects that have been reported (frequency not known) with OPDIVO alone and/or OPDIVO in combination with ipilimumab include:

- A condition where the immune system makes too many infection fighting cells called histiocytes and lymphocytes that may cause various symptoms (haemophagocytic lymphohistiocytosis).
- A condition where the immune system mistakenly destroys red blood cells (oxygen carrying cells) and results in decreased number of red blood cells (autoimmune hemolytic anemia).

Severe infusion reactions may occur (uncommon: less than 1 in 100 but more than 1 in 1,000). Symptoms may include chills or shaking, itching or rash, flushing, difficulty breathing, dizziness, fever, or feeling like passing out.

Complications of stem cell transplant that uses donor stem cells (allogeneic) after treatment with OPDIVO. These complications can be severe and can lead to death. Your healthcare professional will monitor you for signs of complications if you have an allogeneic stem cell transplant. If you are having a stem cell transplant, tell your transplant doctor that you have received OPDIVO in the past.

Also tell your healthcare professional before you are given OPDIVO if you have received an allogeneic stem cell transplant.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Changes in test results

OPDIVO may cause changes in the results of tests carried out by your healthcare professional. These include:

- Abnormal liver function tests (increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase in your blood, higher blood levels of bilirubin).
- Abnormal kidney function tests (increased amounts of creatinine in your blood).
- A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot).
- An increased level of the enzyme that breaks down fats and of the enzyme that breaks down starch.
- Increased or decreased amount of calcium or potassium.
- Increased or decreased blood levels of magnesium or sodium.

Tell your healthcare professional immediately if you get any of the side effects listed above. Do not try to treat your symptoms with other medicines on your own.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

It is unlikely that you will be asked to store OPDIVO yourself. It will be stored in the hospital or clinic where it is given to you.

Keep out of reach and sight of children.

Do not use OPDIVO after the expiry date which is stated on the label and carton after EXP.

Store in a refrigerator (2°C to 8°C). Do not freeze.

Store in the original package in order to protect from light.

If you want more information about OPDIVO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website at:
- https://www.bms.com/ca/en

  or by contacting the sponsor, Bristol-Myers Squibb Canada Co. at: 1-866-463-6267.

This leaflet was prepared by Bristol-Myers Squibb Canada Co.

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