Nivolumab: Drug information

(For additional information see "Nivolumab: Patient drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

Brand Names: US

Opdivo

Brand Names: Canada

Opdivo

Pharmacologic Category

Antineoplastic Agent, Anti-PD-1 Monoclonal Antibody; Antineoplastic Agent, Immune Checkpoint Inhibitor; Antineoplastic Agent, Monoclonal Antibody

Dosing: Adult

Head and neck cancer, squamous cell, recurrent or metastatic: IV: 3 mg/kg once every 2 weeks until disease progression or unacceptable toxicity (Ferris 2016).

Hodgkin lymphoma, classical: IV: 3 **mg/kg** once every 2 weeks until disease progression or unacceptable toxicity (Ansell 2015; Younes 2016).

Melanoma, unresectable or metastatic: IV: 240 **mg** (flat dose) once every 2 weeks (as a single agent) until disease progression or unacceptable toxicity

Off-label dosing: 3 **mg/kg** once every 2 weeks (as a single agent) until disease progression or unacceptable toxicity (Robert 2015; Weber 2015).

Melanoma, unresectable or metastatic, first-line combination therapy: IV: 1 **mg/kg** once every 3 weeks (in combination with ipilimumab) for 4 doses, followed by 240 **mg** (flat dose) once every 2 weeks (nivolumab monotherapy) until disease progression or unacceptable toxicity. **Note:** If nivolumab therapy is withheld, ipilimumab should also be withheld.

Off-label dosing: 1 **mg/kg** once every 3 weeks (in combination with ipilimumab) for 4 doses, followed by 3 **mg/kg** once every 2 weeks (nivolumab monotherapy) until disease progression or unacceptable toxicity (Larkin 2015).

Non-small cell lung cancer, metastatic, progressive: IV: 240 **mg** (flat dose) once every 2 weeks until disease progression or unacceptable toxicity.

Off-label dosing: 3 **mg/kg** once every 2 weeks until disease progression or unacceptable toxicity (Borghaei 2015; Brahmer 2015).

Renal cell cancer, advanced: IV: 240 **mg** (flat dose) once every 2 weeks until disease progression or unacceptable toxicity.

Off-label dosing: 3 **mg/kg** once every 2 weeks until disease progression or unacceptable toxicity

(Motzer 2015).

Urothelial carcinoma (locally advanced or metastatic): IV: 240 **mg** (flat dose) once every 2 weeks until disease progression or unacceptable toxicity.

Off-label dosing: 3 **mg/kg** once every 2 weeks until disease progression or unacceptable toxicity (Sharma 2017).

Small cell lung cancer, progressive (off-label use):

Single agent: IV: 3 **mg/kg** once every 2 weeks until disease progression or unacceptable toxicity (Antonia 2016).

Combination therapy: IV: 1 **mg/kg** once every 3 weeks (in combination with ipilimumab) for 4 doses, followed by 3 **mg/kg** once every 2 weeks (nivolumab monotherapy) until disease progression or unacceptable toxicity (Antonia 2016).

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

*Renal impairment **prior to** treatment initiation:* No dosage adjustment necessary.

*Renal toxicity **during** treatment:*

Creatinine >1.5 to 6 times ULN: Withhold treatment; administer corticosteroids (prednisone 0.5 to 1 mg/kg daily or equivalent) followed by a corticosteroid taper; may resume therapy upon recovery to grade 0 or 1 toxicity. If toxicity worsens or does not improve, increase corticosteroid dose to prednisone 1 to 2 mg/kg daily (or equivalent).

Creatinine >6 times ULN or life-threatening: Permanently discontinue; initiate high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a corticosteroid taper.

Dosing: Hepatic Impairment

*Hepatic impairment **prior to** treatment initiation:*

Mild impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin <1 to 1.5 times ULN and any AST): No dosage adjustment necessary.

Moderate (total bilirubin >1.5 to 3 times ULN and any AST) to severe (total bilirubin >3 times ULN and any AST) impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

*Hepatotoxicity **during** treatment:*

AST or ALT >3 to 5 times ULN or total bilirubin >1.5 to 3 times ULN: Withhold treatment; may resume therapy upon recovery to grade 0 or 1 toxicity.

AST or ALT >5 times ULN or total bilirubin >3 times ULN: Permanently discontinue.

Immune-mediated hepatitis:

Grade 2 transaminase elevations (with or without total bilirubin elevations): Withhold treatment

and initiate high-dose systemic corticosteroids (prednisone 0.5 to 1 mg/kg daily or equivalent)

Severe (grade 3) or life-threatening (grade 4) transaminase elevations (with or without bilirubin elevations): Permanently discontinue treatment and initiate high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent)

Dosing: Adjustment for Toxicity

Withhold treatment for any of the following (may resume upon recovery to grade 0 or 1 toxicity):

Note: If receiving combination therapy with ipilimumab, when nivolumab is withheld, ipilimumab should also be withheld.

Adrenal insufficiency (grade 2)

Colitis:

Grade 2 colitis or diarrhea; for grade 2 colitis with a duration >5 days; also administer systemic corticosteroids (prednisone 0.5 to 1 mg/kg daily or equivalent) followed by a corticosteroid taper; may increase to prednisone 1 to 2 mg/kg daily (or equivalent) if colitis worsens or does not improve despite corticosteroid use

Grade 3 colitis or diarrhea (single-agent nivolumab); also administer systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a corticosteroid taper

Diabetes mellitus, type 1 (grade 3 hyperglycemia)

Encephalitis (new onset moderate or severe neurologic toxicity)

Hypophysitis (grade 2 or 3); also administer high-dose systemic corticosteroids (prednisone 1 mg/kg daily or equivalent)

Pneumonitis (grade 2); also administer high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a corticosteroid taper

Rash (grade 3), suspected Stevens-Johnson syndrome or toxic epidermal necrolysis; also administer high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent)

Other immune-mediated toxicities; also administer high-dose systemic corticosteroids followed by a corticosteroid taper (over 1 month)

Other treatment-related toxicity (severe or grade 3, first occurrence)

Permanently discontinue for:

Adrenal insufficiency (grade 3 or 4); also administer high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent)

Colitis or diarrhea (grade 3, if in combination with ipilimumab) or colitis or diarrhea (grade 4); also administer high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a corticosteroid taper

Colitis (recurrent)

Diabetes mellitus, type 1 (grade 4 hyperglycemia)

Encephalitis (immune mediated); also administer high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a corticosteroid taper

Hypophysitis (grade 4); also administer high-dose systemic corticosteroids (prednisone 1 mg/kg daily or equivalent)

Pneumonitis (grade 3 or 4); also administer high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a corticosteroid taper

Rash (grade 4), or confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis; also administer high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent)

Any toxicity requiring corticosteroid dose of prednisone ≥10 mg/day (or equivalent) for longer than 12 weeks.

Other adverse reactions that are life-threatening or grade 4, severe or grade 3 adverse reactions that recur, or persistent grade 2 or 3 treatment-related toxicity lasts beyond 12 weeks.

Infusion-related reaction:

Mild or moderate reaction: Interrupt or slow the infusion rate

Severe or life-threatening reaction: Discontinue

Thyroid disorder (hyperthyroidism or hypothyroidism):

There are no recommended dosage modifications. Initiate antithyroid therapy for hyperthyroidism; administer thyroid hormone replacement therapy for hypothyroidism.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, Intravenous [preservative free]:

Opdivo: 40 mg/4 mL (4 mL); 100 mg/10 mL (10 mL) [contains polysorbate 80]

Generic Equivalent Available (US)

No

Medication Guide and/or Vaccine Information Statement (VIS)

An FDA-approved patient medication guide, which is available with the product information and at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125554s031lbl.pdf#page=60, must be dispensed with this medication.

Administration

Administer as an IV infusion over 60 minutes through a line with a sterile, nonpyrogenic, low protein binding 0.2 to 1.2 micrometer in-line filter. Do not administer other medications through the same IV line. Flush IV line at the end of the infusion.

Combination therapy with ipilimumab: When administered in combination with ipilimumab, infuse

nivolumab first followed by ipilimumab on the same day. Use separate infusion bags and filters for each infusion. If nivolumab therapy is withheld, ipilimumab should also be withheld.

Use

Head and neck cancer, squamous cell (recurrent or metastatic): Treatment of recurrent or metastatic squamous cell carcinoma of the head and neck in patients with disease progression on or after platinum-based therapy.

Hodgkin lymphoma, classical: Treatment of classical Hodgkin lymphoma (cHL) in adult patients that have relapsed or progressed following autologous hematopoietic stem cell transplant (HSCT) and brentuximab vedotin, or 3 or more lines of systemic therapy that includes autologous HSCT.

Melanoma, unresectable or metastatic: Treatment (as a single agent) of BRAF V600 wild-type or BRAF V600 mutation-positive unresectable or metastatic melanoma; treatment of unresectable or metastatic melanoma (in combination with ipilimumab)

Non-small cell lung cancer, metastatic, progressive: Treatment of metastatic non-small cell lung cancer (NSCLC) that has progressed on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression (on approved EGFR- or ALK-directed therapy) prior to receiving nivolumab.

Renal cell cancer, advanced: Treatment of advanced renal cell cancer in patients who have received prior anti-angiogenic therapy.

Urothelial carcinoma, locally advanced or metastatic: Treatment of locally advanced or metastatic urothelial carcinoma in patients with disease progression during or following a platinum-containing therapy or disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing therapy.

Use: Off-Label

Small cell lung cancer (progressive)

Medication Safety Issues

Sound-alike/look-alike issues:

Nivolumab may be confused with atezolizumab, avelumab, durvalumab, necitumumab, pembrolizumab.

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions

>10%:

Cardiovascular: Edema (≤13%), peripheral edema (≤13%)

Central nervous system: Fatigue (≤53%), malaise (≤46%), peripheral neuropathy (new onset and exacerberations: ≤21%), headache (12%)

Dermatologic: Skin rash (1% to 40%; immune-mediated: 9%), pruritus (10% to 25%), vitiligo (≤11%)

Endocrine & metabolic: Hyperglycemia (≤42%), hyponatremia (14% to 41%), increased serum triglycerides (32%), hyperkalemia (19% to 30%), hypocalcemia (11% to 26%), increased serum cholesterol (21%), hypercalcemia (2% to 19%), hypothyroidism (≤17%; including immune-mediated events), thyroiditis (≤17%; including immune-mediated events), hypomagnesemia (10% to 16%), hypokalemia (11% to 14%)

Gastrointestinal: Diarrhea (2% to 31%), increased serum lipase (16% to 29%), decreased appetite (22% to 28%), nausea (17% to 28%), constipation (9% to 23%), increased serum amylase (10% to 18%), vomiting (12% to 17%), abdominal pain (11% to 13%)

Genitourinary: Urinary tract infection (17%)

Hematologic & oncologic: Lymphocytopenia (24% to 42%; grade 3/4: 4% to 9%), anemia (22% to 40%; grade 3/4: 2% to 8%), neutropenia (29% to 37%; grade 3/4: 4% to 6%), thrombocytopenia (15% to 33%; grade 3/4: 2% to 3%), leukopenia (11%)

Hepatic: Increased serum AST (23% to 33%), increased serum alkaline phosphatase (10% to 33%), increased serum ALT (18% to 25%), increased serum bilirubin (9% to 13%)

Immunologic: Graft versus host disease (>10%; within 14 days of stem cell infusion: 20%), antibody development (11%; neutralizing: <1%; no evidence of altered pharmacokinetic profile)

Neuromuscular & skeletal: Weakness (≤56**%**), musculoskeletal pain (19% to 33%), back pain (21%), arthralgia (10% to 21%)

Renal: Increased serum creatinine (10% to 42%)

Respiratory: Upper respiratory tract infection (17% to 48%), cough (10% to 35%; includes productive cough), dyspnea (2% to 27%; includes exertional dyspnea), bronchopneumonia (≤19%), pneumonia (≤19%)

Miscellaneous: Febrile reaction (35%; events without an infectious cause that required steroids), fever (1% to 35%; may include tumor-associated fever), infusion related reaction (≤18%)

1% to 10%:

Cardiovascular: Pulmonary embolism (2% to 3%)

Central nervous system: Neuritis (<10%), peripheral nerve palsy (peroneal: <10%)

Dermatologic: Erythema (10%)

Endocrine & metabolic: Hyperthyroidism (3%; including immune-mediated events), adrenocortical insufficiency (1%; including immune-mediated events), increased gamma-glutamyl transferase

Gastrointestinal: Intestinal perforation (<10%), stomatitis (<10%), colitis (including immune-mediated events: 2% to 3%)

Hepatic: Hepatitis (immune-mediated: 2%)

Immunologic: Sjogren syndrome (<10%)

Neuromuscular & skeletal: Myopathy (<10%), rheumatic disease (spondyloarthropathy: <10%)

Renal: Renal disease (7%), acute renal failure (≥2%), nephritis (≤1%; immune-mediated), renal insufficiency (≤1%; immune-mediated)

Respiratory: Interstitial pulmonary disease (5%), pleural effusion (1% to 5%), pneumonitis (1% to 3%; including immune-mediated events), respiratory failure (≥2%)

Frequency not defined:

Central nervous system: Migraine

Dermatologic: Palmar-plantar erythrodysesthesia

Endocrine & metabolic: Weight loss

Gastrointestinal: Abdominal distress

Neuromuscular & skeletal: Limb pain

<1%, postmarketing, and/or case reports: Demyelinating disease (immune-mediated), diabetic ketoacidosis, duodenitis (immune-mediated), encephalitis (limbic/lymphocytic/viral; may be immune-mediated), facial paralysis (immune-mediated), gastritis (immune-mediated), Guillain-Barré syndrome (immune-mediated), hepatic veno-occlusive disease, hypophysitis (including immune-mediated events), iritis (immune-mediated), lymphadenitis (immune-mediated; histiocytic necrotizing lymphadenitis [Kikuchi lymphadenitis]), motor dysfunction (immune-mediated), myasthenia (myasthenic syndrome; immune-mediated), myocarditis (immune-mediated), myositis (immune-mediated), neuropathy (autoimmune; immune-mediated), pancreatitis (immune-mediated), pituitary insufficiency (immune-mediated), pneumonia due to *Pneumocystis carinii*, polymyalgia rheumatica (immune-mediated), rhabdomyolysis (immune-mediated), sarcoidosis (immune-mediated), sepsis (systemic inflammatory response), sixth nerve palsy (abducens nerve palsy; immune-mediated), type I diabetes mellitus (immune-mediated event), uveitis (immune-mediated), vasculitis

Contraindications

There are no contraindications listed in the manufacturer's US labeling.

Canadian labeling: Hypersensitivity to nivolumab or any component of the formulation.

Warnings/Precautions

Concerns related to adverse effects:

• Adrenal insufficiency: Adrenal insufficiency may occur; may require hormone replacement therapy and/or corticosteroid therapy. The median time to onset across several clinical trials was 3 to 4.3 months (range: 15 days to 21 months). In studies, the median duration of high-dose systemic corticosteroid therapy was 9 to 11 days (range: 1 day to 2.7 months). Monitor for signs/symptoms of adrenal insufficiency both during and after treatment. Administer corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent followed by a taper) for severe (grade 3) or life-threatening (grade 4) adrenal insufficiency. Withhold nivolumab for moderate (grade 2) and permanently discontinue for

severe (grade 3) or life-threatening (grade 4) toxicity.

• Dermatologic toxicity: Immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been observed in patients receiving nivolumab; some cases have been fatal. The median time to onset of immune-mediated rash ranged was 18 days to 2.8 months (range: 1 day to 25.8 months) after nivolumab initiation. Withhold treatment for signs or symptoms of SJS or TEN and refer to specialist for assessment and treatment; discontinue permanently if confirmed. Withhold treatment for grade 3 rash and permanently discontinue for life-threatening (grade 4) rash and administer corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent followed by a taper) for severe (grade 3) or life-threatening (grade 4) immune-mediated rash. High-dose systemic corticosteroids (followed by a corticosteroid taper) were administered to some patients for a median duration of 12 to 14 days (range: 1 day to 9 months); topical corticosteroids were also used to manage dermatologic toxicity. Complete resolution occurred in nearly half of patients; some patient experienced recurrence with rechallenge.

• Diabetes mellitus: Type 1 diabetes mellitus may occur, including cases of diabetic ketoacidosis. The median time to onset was 2.5 to 4.4 months (range: 15 days to 22 months). Monitor for hyperglycemia. Withhold nivolumab for severe (grade 3) hyperglycemia until blood sugar has been appropriately controlled. Permanently discontinue for life-threatening (grade 4) hyperglycemia.

• Encephalitis: Immune-mediated encephalitis (without clear etiology) may occur. Withhold nivolumab for new-onset moderate to severe neurologic signs/symptoms; evaluate to rule out other neurologic causes or infection. Evaluate with neurology consultation, brain MRI, and lumbar puncture. For confirmed immune-mediated encephalitis felt to be caused by nivolumab (if other etiologies are ruled out), administer corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent), followed by a corticosteroid taper. Permanently discontinue nivolumab if immune-mediated encephalitis occurs.

• Gastrointestinal toxicity: Diarrhea or colitis occurred commonly in patients receiving nivolumab (some cases were fatal). Immune-mediated colitis (defined as no other clear etiology and requiring corticosteroid use), including cases of grades 2 and 3 colitis, occurred in some patients. The median time to onset of colitis was 1.6 to 5.3 months (range: 2 days to 21 months) from nivolumab initiation; some cases developed after nivolumab was discontinued for other reasons. In studies, the median duration of high-dose systemic corticosteroid therapy was 23 days to 1.1 months (range: 1 day to 12 months). Most patients with grade 2 or 3 immune-related colitis had complete resolution (improvement to grade 0); after resolution, nivolumab was reinitiated in some patients without recurrence, although was permanently discontinued in other patients. Monitor for signs and symptoms of colitis. May require treatment interruption, corticosteroid therapy, and/or permanent discontinuation. Severe colitis (grade 3) or life-threatening colitis (grade 4) should be managed with corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a corticosteroid taper. Moderate colitis (grade 2) of >5 days duration should be managed with corticosteroids (prednisone 0.5 to 1 mg/kg daily or equivalent) followed by a corticosteroid taper; may increase to prednisone 1 to 2 mg/kg daily (or equivalent) if colitis worsens or does not improve despite corticosteroid therapy. Some cases required the addition of infliximab to corticosteroid therapy. Permanently discontinue nivolumab for grade 4 colitis or diarrhea, or colitis that recurs upon reinitiation (single-agent therapy) or for severe or life-threatening colitis (grade 3 or 4) or for colitis that recurs upon reinitiation (in combination with ipilimumab).

• Hepatotoxicity: ALT, AST, alkaline phosphatase, and total bilirubin elevations have occurred in nivolumab-treated patients. Immune-mediated hepatitis (defined as no other clear etiology and

requiring corticosteroid use) occurred in patients receiving nivolumab; most cases included grade 2 and grade 3 hepatitis, although grade 4 toxicity also occurred. The median time to onset was 2.1 to 3.3 months (range: 6 days to 11 months) after nivolumab initiation. Immune-mediated hepatitis was managed with high-dose systemic corticosteroids; in some cases, mycophenolate was added to corticosteroid therapy. In studies, the median duration of high-dose systemic corticosteroid therapy was 23 days to 1.1 months (range: 1 day to 13.2 months). Immune-mediated hepatitis resolved and did not recur with continued corticosteroid use in some patients, although some patients experienced recurrence and permanently discontinued treatment. When used in combination with ipilimumab, a majority of patients had complete resolution of hepatitis after completion of steroid therapy, and some patients had recurrence or worsening hepatitis when nivolumab and ipilimumab were restarted. Monitor liver function at baseline and periodically for changes. Initiate corticosteroids (prednisone 0.5 to 1 mg/kg daily or equivalent for grade 2 or prednisone 1 to 2 mg/kg daily or equivalent followed by a corticosteroid taper for grade 3 or 4) transaminase elevations (with or without total bilirubin elevations). Withhold treatment for moderate (grade 2) immune-mediated hepatitis; permanently discontinue for severe (grade 3) or life-threatening (grade 4) immune-mediated hepatitis.

• Hypophysitis: Hypophysitis may occur; some patients developed grades 1, 2, or 3 toxicity. Most patients received corticosteroids; combination therapy was restarted for the majority of the patients without worsening hypophysitis (several patients continued on corticosteroid therapy). The median time to onset was 2.7 to 4.9 months (range: from 27 days to 11 months). Monitor for signs/symptoms of hypophysitis. Administer hormone replacement therapy as clinically indicated and corticosteroids (prednisone 1 mg/kg/day or equivalent followed by a taper) for grade 2 or higher toxicity. In studies, the median duration of high-dose systemic corticosteroid therapy was 14 to 19 days (range: 1 day to 2 months). Withhold nivolumab for moderate (grade 2) or severe (grade 3) and permanently discontinue treatment for life-threatening (grade 4) hypophysitis.

• Infusion-related reactions: Infusion-related reactions have occurred with both single-agent nivolumab and when used in combination with ipilimumab; severe reactions, although rare, were observed when given as a single agent. Monitor closely; discontinue for severe or life-threatening reactions. Mild or moderate reactions may be managed by interrupting or decreasing the infusion rate.

• Nephrotoxicity: Renal dysfunction has occurred with nivolumab therapy. Immune-mediated nephritis (defined as renal dysfunction or ≥ grade 2 creatinine elevations with no other clear etiology and requiring corticosteroid use) or autoimmune nephritis may occur with nivolumab treatment. The median time to onset was 2.7 to 4.6 months (range: 9 days to 12.3 months). For single-agent nivolumab, all patients received high-dose systemic corticosteroids (at least 40 mg prednisone or equivalent per day) for a median duration of 3 weeks (range: 1 day to 15.4 months); complete resolution occurred in about one-half of patients, with no recurrence upon rechallenge. When used in combination with ipilimumab, two-thirds of patients received high-dose systemic corticosteroids (at least 40 mg prednisone or equivalent per day) for a median duration of 2 weeks (range: 1 day to 1.1 months); complete resolution occurred in all patients, some patients resumed combination therapy with no recurrence. Monitor serum creatinine at baseline and periodically during treatment. Initiate corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a corticosteroid taper for life-threatening (grade 4) serum creatinine elevation and permanently discontinue nivolumab. Withhold treatment for moderate (grade 2) and severe (grade 3) creatinine elevations and administer corticosteroids (prednisone 0.5 to 1 mg/kg daily or equivalent) followed by a corticosteroid taper; if toxicity worsens or does not improve, increase to prednisone 1 to 2 mg/kg

daily (or equivalent).

• Pulmonary toxicity: Nivolumab may cause immune-mediated pneumonitis (severe pneumonitis or interstitial lung disease); fatal cases have been reported. Immune-mediated pneumonitis is defined as no other clear etiology and requiring corticosteroid use. The median time to onset was 1.6 to 3.5 months (range: 1 day to 22.3 months) across several clinical trials. Some cases developed after nivolumab was discontinued for other reasons. High-dose systemic corticosteroids (followed by a corticosteroid taper) were administered for a median duration of 26 to 30 days (range: 1 day to 11.8 months). Most patients improved to grade 0 or 1; some patients with grade 2 or 3 pneumonitis had complete resolution (after completing corticosteroid therapy) and nivolumab was reinitiated without recurrence in some patients. Monitor for signs (with radiographic imaging) and symptoms of pneumonitis. May require treatment interruption, corticosteroid therapy, and/or permanent discontinuation. Grades 2, 3, or 4 pneumonitis should be managed with corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a corticosteroid taper. Withhold treatment until resolution for moderate (grade 2) immune-mediated pneumonitis; permanently discontinue for severe (grade 3) or life-threatening (grade 4) immune-mediated pneumonitis.

• Thyroid disorders: Immune-mediated hyperthyroidism and hypothyroidism/thyroiditis have occurred, mostly grades 1 and 2 hyper-/hypothyroidism (one patient receiving nivolumab in combination with ipilimumab experienced grade 3 autoimmune thyroiditis). The median onset for hyperthyroidism was 23 days to 1.5 months (range: 1 day to 14.2 months); most cases resolved (may require medical management, including corticosteroids and methimazole). Hypothyroidism occurred with a median onset of 2 to 3 months (range: 1 day to 16.6 months). Most patients received subsequent nivolumab (with or without ipilimumab) treatment while continuing thyroid replacement therapy. Monitor thyroid function at baseline and for changes periodically during treatment (in one study, patients were evaluated at baseline, treatment day 1, and every 6 weeks). Isolated hypothyroidism may be managed with hormone replacement therapy; initiate medical management (eg, methimazole) to control hyperthyroidism.

• Other immune-mediated toxicities: Other clinically relevant immune-mediated disorders may occur; may develop after discontinuation of nivolumab. Immune-mediated adverse reactions observed included facial/abducens nerve paresis, autoimmune neuropathy, demyelination, duodenitis, gastritis, Guillain-Barré syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), hypopituitarism, motor dysfunction, myasthenic syndrome, myocarditis, myositis, pancreatitis, polymyalgia rheumatica, rhabdomyolysis, sarcoidosis, systemic inflammatory response syndrome, uveitis, iritis, and vasculitis. If an immune-mediated adverse event is suspected, evaluate to exclude other causes. Based on symptom severity, withhold or permanently discontinue nivolumab, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to grade 0 or 1, begin corticosteroid taper (over at least 1 month). After corticosteroid taper is completed and based on the severity of the reaction, may consider reinitiating nivolumab.

Disease-related concerns:

• Hematopoietic stem cell transplant: Patients who received allogeneic hematopoietic stem cell transplant (HSCT) following discontinuation of nivolumab therapy experienced complications (some fatal) including severe or refractory acute graft versus host disease (some cases occurring within 14 days after stem cell infusion), noninfectious febrile syndrome (requiring corticosteroids), lymphocytic encephalitis, viral encephalitis, and sinusoidal obstructive syndrome (SOS; formerly called veno-occlusive disease). These complications may occur despite intervening therapy between nivolumab

and HSCT. Monitor closely for early signs/symptoms of transplant-related complications and manage promptly.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Metabolism/Transport Effects

None known.

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Belimumab: Monoclonal Antibodies may enhance the adverse/toxic effect of Belimumab. *Risk X: Avoid combination*

Immunosuppressants: May diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

Pregnancy Implications

Adverse events were observed in animal reproduction studies. Nivolumab may be expected to cross the placenta; effects to the fetus may be greater in the second and third trimesters. Based on its mechanism of action, nivolumab is expected to cause fetal harm if used during pregnancy. Women of reproductive potential should use highly effective contraception during therapy and for at least 5 months after the last nivolumab dose.

Breast-Feeding Considerations

It is not known if nivolumab is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, the manufacturer recommends to discontinue breastfeeding during treatment.

Monitoring Parameters

Hepatic and renal function tests (baseline and periodic), thyroid function (baseline and periodically [eg, at treatment day 1 and every 6 weeks]); blood glucose. Monitor for signs/symptoms of adrenal insufficiency, hypophysitis, thyroid disorders, immune-mediated colitis, pneumonitis, rash/dermatologic toxicity, encephalitis (changes in neurologic function); monitor for infusion reactions.

Mechanism of Action

Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that selectively inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor to block the ligands PD-L1 and PD-L2 from binding. The negative PD-1 receptor signaling that regulates T-cell activation and proliferation is therefore disrupted (Robert 2015). This releases PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response.

Combining nivolumab (anti-PD-1) with ipilimumab (anti-CTLA-4) results in enhanced T-cell function that is greater than that of either antibody alone, resulting in improved anti-tumor responses in metastatic melanoma.

Pharmacodynamics/Kinetics

Distribution: V_{dss}: 6.8 L (single-agent); ~8 L (combination therapy with ipilimumab)

Half-life elimination: ~25 days (single-agent and combination therapy with ipilimumab)

Pricing: US

Solution (Opdivo Intravenous)

40 mg/4 mL (4 mL): $1221.67

100 mg/10 mL (10 mL): $3054.18

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names

Opdivo (AT, DK, ES, FR, GB, HK, HU, IL, IS, JP, KR, LT, LU, NL, NO, PL, PT, SA, SG, SK, TH)

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