DRUG NAME: Nivolumab

SYNONYM(S):

COMMON TRADE NAME(S): OPDIVO®

CLASSIFICATION: immunotherapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Nivolumab is a fully human IgG4 monoclonal antibody known as a programmed cell death 1 (PD-1) immune checkpoint inhibitor. The PD-1 pathway is an immune system checkpoint that may be exploited by tumour cells to escape active T-cell surveillance. By blocking the binding of the PD-1 receptor to the PD-1 and PD- 2 ligands, nivolumab reactivates tumour-specific cytotoxic T-lymphocytes in the tumour microenvironment and restimulates anti-tumour immunity.[1,2]

PHARMACOKINETICS:

Distribution	tissue penetration or distribution is not known	
	cross blood brain barrier?	no information found
	volume of distribution[3]	8L
	plasma protein binding	no information found
Metabolism	not defined; expected to be degraded into small peptides and amino acids via catabolic pathways similar to endogenous IgG	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	linear pharmacokinetics in the dose range of 0.1-20 mg/kg	
	urine	no information found
	feces	no information found
	terminal half life	26.7 days
	clearance	8.66 mL/h

Adapted from standard reference[1] unless specified otherwise.

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USES:

Primary uses:

*Colorectal cancer
*Esophageal cancer
*Gastric cancer
*Head and neck cancer
*Liver cancer
*Lung cancer, non-small cell
*Lymphoma, Hodgkin's
*Melanoma
*Mesothelioma
*Renal cell cancer
*Urothelial cancer

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- product contains 2.3 mg/mL ***sodium*** (0.1 mmol/mL); consider sodium content as needed for patients on a controlled sodium diet[1]
- avoid systemic ***corticosteroids*** or ***immunosuppressants*** prior to starting nivolumab due to potential interference with the efficacy of nivolumab; corticosteroids or immunosuppressants may be used during treatment with nivolumab in the management of immune-mediated adverse reactions[1]
- the safety and efficacy of ***vaccination*** in patients receiving immunotherapy is currently being investigated[4-7]

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: In animal studies, no histopathologic changes were detected during routine examination of male and female reproductive organs; however most tested animals were not sexually mature.[1]

Pregnancy: Nivolumab has not been studied in pregnant women. Endogenous IgG4 is known to cross the placental barrier, particularly during the third trimester; therefore, as a human IgG4 antibody, nivolumab is expected to be transmitted from mother to fetus. 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. In animal reproductive studies, maternal nivolumab administration was associated with increases in third trimester fetal loss and increased neonatal mortality. Women of reproductive potential should use effective contraception while on nivolumab and for at least 5 months after treatment has been discontinued.[1,3,8]

Breastfeeding is not recommended due to potential secretion of nivolumab into breast milk. Human IgG is known to be secreted into breast milk; therefore as a human IgG4 antibody, nivolumab is expected to do likewise.[1,3]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[9]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (28-37%, severe 2-3%)[1,3]
	leukopenia (11%, severe 1%)
	lymphopenia (29-48%, severe 6-16%)[1,3]
	neutropenia (15%, severe 1%)
	thrombocytopenia (11-14%, severe 1%)[1,3]
endocrine (see paragraph following **Side Effects** table)	***hyperthyroidism*** (1-3%, severe 1%)[1,3]
	hypophysitis (<1%)
	hypopituitarism (2%)
	hypothyroidism (4-6%)
eye	uveitis (<1%)
gastrointestinal (see paragraph following **Side Effects** table)	*emetogenic potential*: low[10]
	abdominal pain (4-16%, severe 2%)[1,3]
	colitis (17-21%, severe 2%)[1,3]
	constipation (4-24%)[1,3]
	diarrhea (8-21%, severe 1-3%)[1,3]
	nausea (11-29%, severe 2%)[1,3]
	stomatitis (3%)
	vomiting (5-19%, severe 1%)[1,3]
general disorders and administration site conditions	*extravasation hazard:* none[11]
	non-cardiac chest pain (13%)[3]
	edema (3-17%, severe 1-2%)[1,3]
	fatigue (26-50%, severe 7%)[1,3]
	pyrexia (3-17%) [1,3]
immune system (see paragraph following **Side Effects** table)	***dermatologic*** (1%)
	endocrinopathy (1-8%)[1,12]
	gastrointestinal (18-21%)[12]
	hepatitis (1%)[8,12]
	infusion related reaction (2-4%); see paragraph following **Side Effects** table
	nephritis, ***renal failure*** (1-2%)[1,12]
	pulmonary (1-4%)[1,12]
infections and infestations	bronchitis (9%)[3]
	pneumonia (10%, severe 5%)[3]
	upper respiratory tract infection (2-11%)[1,3,13]
investigations (see paragraph following **Side Effects** table)	alkaline phosphatase increase (14-26%, severe 1-3%)[1,3]
	ALT increase (12-25%, severe 2-3%)[1,3]
	AST increase (16-27%, severe 1-4%)[1,3]
	total bilirubin increase (3-13%, severe 3%)[1,3]
	creatinine increase (10-22%, severe 1%)[1,3]
	weight loss(13%)
metabolism and nutrition	appetite, decreased (5-35%, severe 3%)[1,3]
	hypercalcemia (12%, severe 1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hyperglycemia (2%, severe 1%); see paragraph following **Side Effects** table
	hyperkalemia (23%, severe 2 %)
	hypocalcemia (20%)
	hypokalemia (15%, severe 1%)
	hypomagnesmia (21%, severe 1%)
	hyponatremia (35%, 7%)
musculoskeletal and connective tissue	arthralgia (6-13%)
	musculoskeletal pain (6-36%, severe 1-6%)[1,3]
	weakness (19%, severe 2%)
nervous system	headache (1-4%)
	peripheral neuropathy (3-9%)
renal and urinary	***renal failure*** (2%, severe 1%); see paragraph following **Side Effects** table
respiratory, thoracic and mediastinal	cough (3-32%, severe 2%)[1,3]
	dyspnea (2-38%, severe 9%)[1,3]
	pneumonitis, or ***interstitial lung disease*** (2-6%)[1,3]; sometimes fatal[8]; see paragraph following **Side Effects** table
skin and subcutaneous tissue	alopecia (3%)
	dry skin (4%)
	erythema (6%)
	pruritus (7-17%, severe <1%)
	rash (11-21%, severe 1%)[1,3]
	urticaria (1%)
	vitiligo (11%)

Adapted from standard reference[1] unless specified otherwise.

Immune-mediated adverse events are a spectrum of side effects that arise from general immunologic enhancement caused by nivolumab. Adverse events can occur any time during treatment or months after discontinuation of therapy. Early identification of adverse events and prompt intervention is crucial for the safe use of nivolumab. Although symptoms may be nonspecific, if not recognized and treated early, they can be severe or fatal. ***Endocrinopathies, diarrhea/colitis, liver enzyme test elevations, nephritis, pneumonitis,*** and ***rash*** should be considered immune-mediated until another etiology can be confirmed. Strongly advise patients to report any symptoms promptly and to avoid self-treatment without medical advice. Based on the severity of the reaction, symptom management may include temporarily withholding nivolumab and/or administration of corticosteroids, with or without additional immunosuppressive medication. Permanent discontinuation of nivolumab should be considered for life threatening or recurrent serious adverse events. When prolonged corticosteroid treatment is necessary for management of side effects, corticosteroids should be tapered over at least one month following resolution of symptoms to grade 1 or less, as rapid tapering may lead to relapse or worsening of the symptoms. Antibiotic prophylaxis may be necessary to prevent opportunistic infections (e.g., oral trimethoprim/sulfamethoxaxole for the prevention of *Pneumocystis jiroveci* pneumonia). Referral to appropriate medical specialty may be indicated for the management of complications related to treatment. Restarting nivolumab may be considered depending on the grade of the initial immune mediated adverse event, but only following completion of the corticosteroid taper.[1,14] For further information on management of immune-mediated adverse reactions, see BC Cancer Protocol SCIMMUNE ***Management of Immune-Mediated Adverse Reactions to Checkpoint Inhibitors Immunotherapy***.

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Reported immune-mediated ***endocrinopathies*** have included ***hypothyroidism***, ***hyperthyroidism***, ***hypopitutitarism***, ***hypophysitis***, ***diabetes mellitus***, ***diabetic ketoacidosis,*** and ***adrenal insufficiency***. The median time to onset is 12 weeks (range: 5-34 weeks).[1] Patients may present with fatigue, weight change, headache, mood or behavior changes, forgetfulness, decreased sex drive, voice deepening, or constipation. Perform blood glucose levels and thyroid function tests at baseline and periodically during therapy. For symptomatic endocrinopathy, withhold nivolumab, initiate appropriate hormone therapy and if symptoms are severe, appropriate steroid therapy. Upon improvement, nivolumab may be resumed following completion of corticosteroid taper.[1,3,8,12]

Gastrointestinal adverse immune reactions such as ***diarrhea*** and/or ***colitis*** are commonly reported, and in some cases have been fatal. The median time to onset is 1 to 5 months (range: 2 days to 19 months).[3] Rule out other etiologies such as infectious or disease-related etiologies. For grade 2 and 3 diarrhea and/or colitis, withhold nivolumab and initiate appropriate corticosteroid therapy. Nivolumab may be restarted following completion of corticosteroid taper. In the case of grade 4 symptoms, permanently discontinue nivolumab and initiate corticosteroid regimen.[1,3,8,12]

Immune-mediated ***hepatitis*** manifests as ***elevated transaminases***. The median time to onset is 14 weeks (range: 2 weeks to 8 months).[1,3] Observe patients for signs and symptoms of hepatotoxicity. Monitor liver function tests including AST, ALT, alkaline phosphatase, and total bilirubin at baseline and during therapy. Infectious or disease related etiologies should be ruled out following reports of elevated enzymes. For grade 2 elevations in AST/ALT or total bilirubin, withhold nivolumab until lab values return to grade 1 or baseline and the prescribed corticosteroid regimen, including taper, is complete. Permanently discontinue nivolumab for grade 3 or 4 elevations in AST/ALT or total bilirubin.[1,3]

Significant immune-mediated ***pneumonitis*** or ***interstitial lung disease***, including fatal cases, have occurred during and after nivolumab treatment. The median time to onset is 12 weeks (range: 9-22 weeks).[1] Patients may present with new or worsening cough, chest pain, and/or shortness of breath. For grade 2 pneumonitis, withhold nivolumab, and initiate corticosteroid therapy. Upon improvement, nivolumab may be resumed following corticosteroid taper. Permanently discontinue nivolumab if there is no improvement or a worsening of symptoms following corticosteroid treatment or if the patient presents with a grade 3 or 4 pneumonitis.[1,3,12]

Immune-mediated ***renal*** adverse events include ***increased creatinine***, or ***nephritis***, and ***renal failure***. The median time to onset can range from 1 week to 12 months after starting nivolumab.[3] Monitor patients for edema, hematuria, and decreased urine output and monitor serum creatinine periodically during treatment as indicated. With grade 2 creatinine elevation, withhold nivolumab and initiate corticosteroids, followed by a steroid taper after resolution of symptoms. If toxicity worsens/does not improve or the patient presents with grade 3 or 4 elevations of serum creatinine, permanently discontinue nivolumab.[1,12]

Other less common but clinically significant immune-mediated toxicities have been reported, even after discontinuation of the drug. These toxicities include ***Guillain-Barré syndrome***, ***autoimmune neuropathy***, ***demyelination***, ***encephalitis***, ***pancreatitis, vasculitis***, ***myasthenic syndrome***, and ***uveitis***. For suspected immune-mediated adverse events, confirm etiology and exclude other causes. Based on the severity of the reaction, withhold nivolumab and administer corticosteroids. Nivolumab may be restarted after a corticosteroid taper. Permanently discontinue nivolumab for any severe immune adverse reaction that recurs or is life threatening.[1,3,8]

Severe ***infusion reactions*** have been rarely reported. Patients with mild or moderate infusion reactions may receive nivolumab with close monitoring and premedication in accordance with local infusion reaction prophylaxis guidelines. For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents***. Permanently discontinue nivolumab following a grade 3 or 4 infusion reaction.[1]

INTERACTIONS: none known[1]

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SUPPLY AND STORAGE:

***Injection*:** Bristol-Myers Squibb Canada supplies nivolumab as 40 mg and 100 mg ready-to-use, single use (preservative-free) vials in a concentration of 10 mg/mL. Refrigerate. Protect from light. Do not shake. Product contains 2.3 mg/mL sodium (0.1 mmol/mL).[1]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:
- can be administered undiluted or diluted with NS or D5W[1]
- maximum infusion volumes may apply to some fixed dose regimens and are intended to prevent exceeding compendial endotoxin limits[15-17] of 5.0 EU/kg; however, endotoxin exposure limits will not be exceeded at BC Cancer when preparing nivolumab in infusion bags of 50-100 mL following weight-based dosing for standard BC Cancer protocols (final bag concentration between 1-10 mg/mL)

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous[18]	do NOT use
Intermittent infusion[19-27]	• ***over 30 minutes; administer using a 0.2***-1.2 ***micron in-line filter***[1]
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Intravenous:	Cycle Length: ***2 weeks***[20,22,24,26,28]:	***3 mg/kg IV for one dose on day 1*** (total dose per cycle 3 mg/kg)

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BC Cancer usual dose noted in ***bold, italics***

Cycle Length:	
2 weeks[20,22,24,26,28,29]:	***240 mg IV for one dose on day 1*** (total dose per cycle 240 mg)
3 weeks[30,31]:	1 mg/kg IV for one dose on day 1 (total dose per cycle 1 mg/kg)
3 weeks[32-35]***:***	***4.5 mg/kg IV for one dose on day 1*** (total dose per cycle 4.5 mg/kg)
3 weeks[33-36]:	***360 mg IV for one dose on day 1*** (total dose per cycle 360 mg)
4 weeks[21,23,25,27,28,37]:	***480 mg IV for one dose on day 1*** (total dose per cycle 480 mg)
4 weeks[21,23,25,27,29,37]:	***6 mg/kg IV for one dose on day 1*** (total dose per cycle 6 mg/kg)
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated
Dosage in renal failure:	• mild to moderate impairment: no dose adjustment required[1] • severe renal dysfunction: no information found
Dosage in hepatic failure:	• total bilirubin 1-1.5 X ULN or AST >ULN: no dose adjustment required[1,18] • total bilirubin >1.5 X ULN and any AST: no information found
Dosage in dialysis:	no information found

Children: no information found

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