DRUG NAME: Nivolumab

SYNONYM(S):

COMMON TRADE NAME(S): OPDIVO®

CLASSIFICATION: monoclonal antibody

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

MECHANISM OF ACTION:

Nivolumab is a fully human monoclonal antibody known as an immune-checkpoint inhibitor. Nivolumab enhances antitumour immunity by selectively blocking the interaction of the programmed death 1 (PD-1) receptor with its known ligands, PDL-1 and PDL-2, causing the disruption of the negative signalling that regulates T-cell activation and proliferation.[1]

USES:

Primary uses:
*Melanoma

Other uses:
Renal cell cancer[2,3]
Hodgkin's lymphoma[4]
Lung cancer, non-small cell[5-7]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- product contains 2.3 mg (0.1 mmol) ***sodium*** per mL of solution; consider sodium content when treating patients on a controlled sodium diet[8]

Pregnancy: In animal reproduction studies, nivolumab administration resulted in increased abortion and premature infant death. There is no available human data, however a central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Therefore, based on its mechanism of action, nivolumab may cause fetal harm if administered to a pregnant woman. Also, human IgG4 is known to cross the placental barrier. As nivolumab is an immunoglobulin G4, it has the potential to be transmitted from the mother to the developing fetus where it may increase the risk of immune-mediated disorders. Females of reproductive potential are advised to use effective contraception during treatment and for five months following the last dose of nivolumab.[5]

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.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
gastrointestinal	*emetogenic potential:* low[9]
	abdominal pain (16%, severe 2%)
	constipation (24%)
	nausea (29%, severe 2%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	vomiting (19%, severe 1%)
general disorders and administration site conditions	*extravasation hazard:* none[10]
	asthenia (19%, severe 2%)
	chest discomfort, non-cardiac chest pain (13%)
	edema (17%, severe 2%)
	fatigue (50%, severe 7%)
	peripheral edema (10%)
	pyrexia (17%)
immune system (see paragraph following **Side Effects** table)	***colitis*** (1-2%)
	diarrhea (18-21%, severe 1-3%)
	hepatitis (1%)
	hyperthyroidism (2-3%)
	hypothyroidism (4-8%)
	nephritis, renal dysfunction (1%)
	pneumonitis (1-6%)
infections and infestations	upper respiratory tract infection (11%)
investigations	alkaline phosphatase increase (14-22%)
	ALT increase (12-16%)
	AST increase (16-28%)
	total bilirubin increase (3-19%)
	creatinine increase (13-22%)
	weight decrease (13%, severe 1%)
metabolism and nutrition	decreased appetite (35%, severe 3%)
musculoskeletal and connective tissue	arthralgia (13%)
	musculoskeletal pain (36%, severe 6%)
respiratory, thoracic and mediastinal	cough (17%)
skin and subcutaneous tissue	pruritus (19%)
	rash (21%, severe <1%)

Adapted from standard reference[5] unless specified otherwise.

Clinically significant ***immune-mediated adverse reactions*** can occur, including pneumonitis, colitis, hepatitis, nephritis, hypothyroidism and hyperthyroidism, as well as other reactions. Immune reactions may be delayed and may also occur after nivolumab has been discontinued. Based on the type and severity of the reaction, management may include withholding or discontinuing nivolumab, administering high-dose corticosteroids, and if appropriate, initiation of hormone replacement therapy. Following resolution of the reaction to grade 1 or less, corticosteroids should be tapered over at least one month. Nivolumab should not be resumed while patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Restarting nivolumab may be

considered following completion of corticosteroid taper. Permanent discontinuation of nivolumab is usually recommended following grade 3 or 4 immune-mediated reactions.[5,6]

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. Store in original packaging to protect from light. Do not freeze or shake. Formulation contains 2.3 mg (0.1 mmol) ***sodium*** per mL of solution.[8]

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

SOLUTION PREPARATION AND COMPATIBILITY:

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

Additional information:

- solution should be clear and colourless to pale-yellow in colour; discard if cloudy or discoloured[5]
- can be infused undiluted (10 mg/mL) or diluted with NS or D5W (to 0.35 mg/mL or greater)[11]
- administer using 0.2-1.2 micron in-line filter[8]
- line should be flushed with NS or D5W after each dose[8]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	do NOT use[6]
Intermittent infusion	***over 60 minutes***[8]
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. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

Cycle Length:

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	2 weeks[1,4-7]:	3 mg/kg IV for one dose on day 1 (total dose per cycle 3 mg/kg)
	3 weeks[3,12,13]:	3 mg/kg (range 0.3-10 mg/kg) IV for one dose on day 1 (total dose per cycle 3mg/kg [range 0.3-10 mg/kg])

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