DRUG NAME: Pembrolizumab

SYNONYM(S): lambrolizumab[1], MK-3475[2]

COMMON TRADE NAME(S): KEYTRUDA®

CLASSIFICATION: immunotherapy

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

MECHANISM OF ACTION:

Pembrolizumab is a selective humanized IgG4 monoclonal antibody known as a programmed cell death 1 (PD-1) immune checkpoint inhibitor. The PD-1 pathway is an immune control checkpoint that may be exploited by tumour cells to escape active T-cell surveillance. By blocking PD-1 receptors from binding to immune dampening PD-1 and PD- 2 ligands expressed on antigen presenting tumour cells, pembrolizumab reactivates tumour-specific cytotoxic T-lymphocytes in the tumour microenvironment and re-stimulates anti-tumour immunity.[3]

PHARMACOKINETICS:

Distribution	limited extravascular distribution	
	cross blood brain barrier?	no information found
	volume of distribution	7.7 L
	plasma protein binding	0%
Metabolism	catabolized through non-specific pathways; metabolism does not contribute to its clearance[3]	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	linear clearance from the central compartment	
	urine	no information found
	feces	no information found
	terminal half life	26 days
	clearance	0.2 L/day

Adapted from standard reference[3] unless specified otherwise.

Developed: 1 June 2016
Revised: 1 February 2023

USES:

Primary uses:

*Bladder cancer
*Breast cancer
*Cervical cancer
*Colorectal cancer
*Endometrial cancer
*Esophageal cancer
*Head and neck cancer
*Lung cancer, non-small cell
*Lymphoma, B-cell
*Lymphoma, Hodgkin
*Melanoma
*Renal cell cancer
*Urothelial carcinoma

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- avoid systemic ***corticosteroids*** or ***immunosuppressants*** *prior* to starting pembrolizumab due to potential interference with the efficacy of pembrolizumab; corticosteroids or immunosuppressants may be used *during* treatment with pembrolizumab for the management of immune-mediated adverse reactions.[3]
- 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: Developmental toxicity studies have not been conducted. In repeat dose studies in cynomolgus monkeys, no noteworthy effects were detected in male or female reproductive organs; however, the significance of these results is unknown as most of the animals in these studies were sexually immature.[3]

Pregnancy: Pembrolizumab has not been studied in pregnant women. Endogenous IgG4 is known to cross the placental barrier, particularly during the third trimester; therefore, as a humanized IgG4 antibody, pembrolizumab is expected to be transmitted from mother to fetus. In murine models, blocking PD-L1 signaling has disrupted tolerance to the fetus and resulted in increased rates of abortion and stillbirth. Women of reproductive potential should use effective contraception while on pembrolizumab and for four months after treatment has been discontinued.[3]

Breastfeeding is not recommended due to potential secretion of pembrolizumab into breast milk. Human IgG4 is known to be secreted into breast milk; therefore, as a humanized IgG4 antibody, pembrolizumab may also be passed from mother to nursing child. Avoid breastfeeding while on pembrolizumab and for 4 months following the last dose.[3,8]

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.[9,10]

Developed: 1 June 2016
Revised: 1 February 2023

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (12-58%, severe 5-8%)[3,8]
	lymphopenia (25%, severe 4-10%)
	thrombocytopenia (2%)
ear and labyrinth	vertigo (2%)
endocrine (see paragraph following **Side Effects** table)	***hyperthyroidism*** (1-2%)
	hypophysitis (2%, severe 1%)
	hypothyroidism (4-7%)
eye	dry eye (2%)
	uveitis (<1%)
	visual impairment (2%)
gastrointestinal (see paragraph following **Side Effects** table)	*emetogenic potential:* low[11]
	abdominal pain (3-12%)[3,8]
	colitis (1%)
	constipation (5-21%)[3,8]
	diarrhea (11-20%, severe 1%)[3,8]
	dry mouth (2%)
	gastroesophageal reflux disease (3%)
	nausea (8-30%)[3,8]
	pancreatitis (<1%)
	vomiting (3-16%)[3,8]
general disorders and administration site conditions	*extravasation hazard:* none[12]
	asthenia (6-7%)
	chest pain, non-cardiac (2%)
	chills (4-14%)[3,8]
	face edema (2%); peripheral edema (4-17%)[3,8]
	fatigue (33-47%, severe 6%)[3,8]
	influenza like illness (2%)
	pain (2%)
	pyrexia (3-12%)[3,8]
hepatobiliary	***hepatitis*** (1%); see paragraph following **Side Effects** table
immune system (see paragraph following **Side Effects** table)	***colitis***, including microscopic colitis (1%, severe 1%)[3,8]
	hepatitis (1%, severe <1%)
	hyperthyroidism (1-2%, severe <1%)[3,8]
	hypophysitis (1%, severe <1%)[3,8]
	hypothyroidism (7-9%)[3,8]
	infusion related reaction (<1%)
	nephritis (<1%); includes renal failure with evidence of interstitial nephritis
	pneumonitis (1-3%); has been fatal
	rash (<1%)[8]
infections and infestations	upper respiratory tract infection (11%)[8]
	cellulitis (2%)[8]

Developed: 1 June 2016
Revised: 1 February 2023

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pneumonia (2%)[8]
	sepsis (10%)[8]
investigations (see paragraph following **Side Effects** table)	alkaline phosphatase increase (23-26%, severe 1%)[3,8]
	ALT increase (16-21%, severe 1%)
	AST increase (18-28%, severe 2%)
	hypercholesterolemia (11-21%, severe 1%)
	weight loss (2-3%)
metabolism and nutrition	appetite decrease (6-26%)[3,8]
	hyperglycemia (40-52%, severe 3-4%)[3,8]; see paragraph following **Side Effects** table
	hypertriglyceridemia (23-30%)[3,8]
	hypoalbuminemia (32-43%)[3,8]
	hypocalcemia (24-25%, severe 1%)
	hyponatremia (29-40%, severe 9%)[3,8]
musculoskeletal and connective tissue	***arthralgia*** (14-20%)[3,8]
	back pain (2-12%)[3,8]
	muscle spasms (2%)
	muscular weakness (3-5%, severe1%)
	myalgia (5-14%)[3,8]
	myositis (<1%)
	pain in extremity (2-18%, severe 1%)[3,8]
neoplasms	tumour pain (1-2%)
nervous system	dizziness (2-11%)[3,8]
	headache (4-16%)[3,8]
	hypoesthesia (3%)
	lethargy (5%)
	paraesthesia (1%)
	peripheral neuropathy (1-4%)
psychiatric	insomnia (14%)[8]
renal and urinary	***renal failure*** (2%)[8]; see paragraph following **Side Effects** table
respiratory, thoracic and mediastinal	cough (7-30%)[3,8]
	dyspnea (8-23%, severe 1%)
	pleural effusion (2%)[8]
	pneumonitis (1-4%, severe 1%)[3,8]; see paragraph following **Side Effects** table
	wheezing (2%)
skin and subcutaneous tissue	blisters[13] (1%)
	dry skin (2%)
	erythema (2-6%)
	night sweats (1-5%)
	pruritus (12-30%)[3,8]
	rash (1-29%, severe 1%)[3,8]
	Stevens-Johnson syndrome, toxic epidermal necrolysis[13,14] (<1%); sometimes fatal
	vitiligo (9-11%)[3,8]

Developed: 1 June 2016
Revised: 1 February 2023

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
vascular	pulmonary embolism (2%)[8]

Adapted from standard reference[3] unless specified otherwise.

Severe ***infusion reactions*** are rarely reported. Patients with mild or moderate infusion reactions may receive pembrolizumab with close monitoring and premedication in concordance 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 pembrolizumab following a severe or life threatening reaction.[3]

Immune-mediated adverse events are a spectrum of side effects caused by general immunologic enhancement that can occur at any time during pembrolizumab treatment or months after discontinuation. Consider the etiology of reported endocrinopathy, diarrhea/colitis, hepatitis, nephritis, and pneumonitis to be immune-mediated until another etiology is confirmed. Symptoms can be severe or fatal if not recognized and treated quickly; therefore patients should not self-treat without medical advice. Management of symptoms depends on the severity of the reaction and may require treatment interruption and/or administration of corticosteroids. Corticosteroids should be appropriately tapered following resolution of symptoms to grade 1 or less. Pembrolizumab may be restarted following completion of the steroid taper depending on the severity of the initial reaction. Based on limited data, immunosuppressants may be administered if adverse reactions are not controlled by corticosteroids. Referral to appropriate medical specialty may be required to manage other immune-mediated complications related to treatment. Antibiotic prophylaxis should be considered for patients on long term corticosteroid treatment (e.g., oral trimethoprim/sulfamethoxazole for the prevention of *Pneumocystis jiroveci* pneumonia).
Permanently discontinue pembrolizumab for:
- life-threatening reactions (excluding endocrinopathies controlled with hormone replacement therapy),
- corticosteroid dose that cannot be tapered to prednisone 10 mg daily or less within 12 weeks,
- persistent grade 2 or 3 reactions that do not improve to grade 0 or 1 within 12 weeks of last dose, or
- recurrent grade 3 reactions.[3,8,15,16]

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.***

Immune-mediated ***endocrinopathies*** may present as nonspecific symptoms (e.g., extreme weakness, vision changes, dizziness or fainting, or muscle aches).
Commonly reported endocrinopathies are outlined below:
- ***hypophysitis***, including ***hypopituitarism*** (e.g., headache, fatigue) and ***secondary adrenal insufficiency*** (e.g., dehydration, hypotension, electrolyte imbalances);
- autoimmune thyroid disease, including ***hyper-*** and ***hypothyroidism***;
- ***Type 1 diabetes mellitus*** and ***diabetic ketoacidosis.***

Monitor blood glucose and thyroid function at baseline and periodically during therapy. Symptomatic endocrinopathies may require treatment interruption, corticosteroids, and/or hormone replacement therapy as clinically indicated. Isolated ***hypothyroidism*** may be managed solely with thyroid replacement therapy without pembrolizumab interruption or corticosteroid therapy.[1,3,15]

Immune-mediated ***colitis*** may present as severe abdominal pain, diarrhea, black/tarry stools, or stools with blood or mucous. Confirm etiology and treat grade 2/3 colitis by interrupting pembrolizumab and administering systemic corticosteroid therapy until the toxicity resolves to grade 0 or 1. Upon symptom resolution, initiate corticosteroid taper as indicated. Permanently discontinue pembrolizumab for grade 4 immune-mediated colitis and treat with corticosteroids.[1,3,15]

Immune-mediated ***hepatitis*** may occur. Monitor for changes in liver function and symptoms such as jaundice, dark urine, severe nausea and/or vomiting, and easy bruising or bleeding. Withhold pembrolizumab for AST/ALT 3 to 5 times ULN or total bilirubin 1.5 to 3 times ULN and administer corticosteroids. Upon symptom resolution, corticosteroid taper may be initiated as indicated. Permanently discontinue pembrolizumab for AST/ALT greater than

Developed: 1 June 2016
Revised: 1 February 2023

5 times ULN or total bilirubin greater than 3 times ULN. For patients with liver metastasis who begin treatment with grade 2 elevation of AST/ALT, discontinue pembrolizumab if baseline AST/ALT increases 50% or more and lasts 1 week or longer.[1,3,8,15]

Immune-mediated ***nephritis*** has been observed. Monitor for changes in renal function and urine volume or colour. Confirm etiology and treat grade 2 or greater nephritis by interrupting pembrolizumab and administering systemic corticosteroid therapy. Upon symptom resolution, initiate corticosteroid taper as indicated. Permanently discontinue pembrolizumab for grade 3 or 4 nephritis.[3,8,15]

Immune-mediated ***pneumonitis*** is reported and is sometimes fatal. Monitor for shortness of breath, chest pain, and new or worsening cough. If pneumonitis is suspected, evaluate with radiographic imaging and exclude other causes. In patients who develop grade 2 or greater pneumonitis, interrupt pembrolizumab and administer corticosteroids. Upon symptom resolution, initiate corticosteroid taper as indicated. Permanently discontinue pembrolizumab for grade 3/4 reactions and recurrent grade 2 reactions.[1,3,8,15]

Other less common, but clinically significant, immune-mediated toxicities associated with pembrolizumab include: ***arthritis***, ***myositis***, ***Guillain-Barré syndrome***, ***hemolytic anemia***, ***Lambert-Eaton syndrome***, ***myasthenia gravis***, ***uveitis***, ***optic neuritis***, ***rhabdomyolysis***, ***serum sickness***, ***vasculitis, bullous pemphigoid, dermatitis***, and ***partial seizures***. Confirm etiology for any suspected immune-mediated reaction. Permanently discontinue pembrolizumab for any severe immune reaction that is life threatening or recurrent. Management of other reactions is based on the severity of the reaction. Withhold pembrolizumab and administer corticosteroids. Upon symptom resolution to grade 0 or 1, corticosteroid taper may be initiated as indicated. Pembrolizumab may be restarted after the corticosteroid taper based on the severity of the initial reaction.[3,8,15]

INTERACTIONS: none known[3]

SUPPLY AND STORAGE:

***Injection*:** Merck Canada Inc. supplies pembrolizumab as 100 mg single use, ready-to-use vials of solution in a concentration of 25 mg/mL. Vials contain 0.25 mL overfill. Refrigerate. Protect from light. Do not shake.[17]

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[3]:
- prior to reconstitution, vials of pembrolizumab may be at room temperature for up to 24 hours

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion[18]	• ***over 30 minutes;*** administer with a ***0.2***-5 ***micron inline filter***
Continuous infusion	no information found

Developed: 1 June 2016
Revised: 1 February 2023

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

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***

	Cycle Length:	
Intravenous:	***3 weeks***[3,19-22]:	***2 mg/kg IV for one dose on day 1*** (total dose per cycle 2 mg/kg)
	3 weeks[18,23]:	***200 mg IV for one dose on day 1*** (total dose per cycle 200 mg)
	6 weeks[24-28]:	***4 mg/kg IV for one dose on day 1*** (total dose per cycle 4 mg/kg)
	6 weeks[24-29]:	***400 mg IV for one dose on day 1*** (total dose per cycle 400 mg)
Concurrent radiation:	no information found	
Dose in myelosuppression:	modify according to protocol by which patient is being treated	
Dosage in renal failure:[3]	• mild to moderate impairment (CrCl 30-90 mL/min): no dose adjustment required • severe renal impairment (<30 mL/min): no information found	
Dosage in hepatic failure:[1]	• mild impairment (total bilirubin ≤ ULN and AST > ULN OR total bilirubin 1-1.5 X ULN and any AST): no dose adjustment required • moderate or severe impairment (total bilirubin >1.5 X ULN AND any AST): no information found	
Dosage in dialysis:	no information found	

Children:

	Cycle Length:	
Intravenous:	3 weeks[29]	2 mg/kg IV for one dose on day 1 max dose = 200 mg

Developed: 1 June 2016
Revised: 1 February 2023

REFERENCES:

1. AHFS Drug Information® (database on the Internet). Pembrolizumab. Lexi-Comp Inc., 2015. Available at: http://online.lexi.com. Accessed 16 February, 2016
2. Khoja L, Butler MO, Kang SP, et al. Pembrolizumab. J Immunother Cancer 2015;3:36-9. eCollection 2015
3. Merck Canada Inc. KEYTRUDA® product monograph. Kirkland, Quebec; October 1, 2015
4. Brest P, Mograbi B, Hofman P, et al. COVID-19 vaccination and cancer immunotherapy: should they stick together? Br J Cancer 2022;126(1):1-3
5. Chong C, Park VJ, Cohen B, et al. Safety of inactivated influenza vaccine in cancer patients receiving immune checkpoint inhibitors. Clin Infect Dis 2020;70(2):193-199
6. Desage A, Bouleftour W, Rivoirard R, et al. Vaccination and immune checkpoint inhibitors: does vaccination increase the risk of immune-related adverse events? A systematic review of literature. Am J Clin Oncol 2021;44(3):109-113
7. Oosting SF, van der Veldt, A. A. M., GeurtsvanKessel CH, et al. mRNA-1273 COVID-19 vaccination in patients receiving chemotherapy, immunotherapy, or chemoimmunotherapy for solid tumours: a prospective, multicentre, non-inferiority trial. Lancet Oncol 2021;22(12):1681-1691
8. Lexi-Drugs® (database on the Internet). Pembrolizumab. Lexi-Comp Inc., 2016. Available at: http://online.lexi.com. Accessed 16 February, 2016
9. Kerry Savage MD. BC Cancer Agency Melanoma Tumour Group. Personal communication. 19 April2016
10. Robert Tilllmanns. BC Cancer Agency Genitourinary Tumour Group. Personal communication. 19 April2016
11. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 Mar 2012
12. BC Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; 1 November 2014
13. Merck Canada Inc. KEYTRUDA® product monograph. Kirkland, Quebec; 15 March 2017
14. Health Canada. MedEffect® e-Notice - KETRUDA® (pembrolizumab) - Risk of Severe Skin Reactions: Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. 2017. Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/. Accessed March 20, 2017
15. Merck Sharp & Dohme Corp. KEYTRUDA® A Guide to Monitoring Patients During Treatment With Ketruda. Whitehouse Station, New Jersey; October 2015
16. Postow M, Wolchok J. Toxicities associated with checkpoint inhibitor immunotherapy. In: 2015 UpToDate®; Ross,Michael E. (Ed); updated 6Jan2016; accessed 26Jan2016. Waltham, Massachusetts: UpToDate®; Available at www.uptodate.com; 2016
17. Merck Canada Inc. KEYTRUDA® product monograph. Kirkland, Quebec; 21 February 2018
18. Merck Canada Inc. KEYTRUDA® product monograph. Kirkland, Quebec; 9 October 2020
19. Lexi-Drugs® (database on the Internet). Pembrolizumab. Lexi-Comp Inc., 2018. Available at: http://online.lexi.com. Accessed 2 January, 2019
20. BC Cancer Skin and Melanoma Tumour Group. (USMAVPEM) BC Cancer Protocol Summary for the Treatment of Unresectable or Metastatic Melanoma Using Pembrolizumab. Vancouver, British Columbia: BC Cancer; 1 September 2018
21. BC Cancer Lung Tumour Group. (ULUAVPMBF) BC Cancer Protocol Summary for First-Line Treatment of Advanced Non-Small Cell Lung Cancer Using Pembrolizumab. Vancouver, British Columbia: BC Cancer; 1 April 2018
22. BC Cancer Lung Tumour Group. (ULUAVPMB) BC Cancer Protocol Summary for Treatment of Advanced Non-Small Cell Lung Cancer Using Pembrolizumab. Vancouver, British Columbia: BC Cancer; 1 February 2018
23. BC Cancer Genitourinary Tumour Group. (GUAVPEMAX) BC Cancer Protocol Summary for the Treatment of Metastatic Renal Cell Carcinoma Using Pembrolizumab and aXitinib. Vancouver, British Columbia: BC Cancer; 1 March 2021
24. BC Cancer Head and Neck Tumour Group. (HNAVPMBM6) BC Cancer Protocol Summary for Maintenance Treatment of Advanced Squamous Cell Carcinoma of the Head and Neck Using 6-Weekly Pembrolizumab. Vancouver, British Columbia: BC Cancer; December 1, 2021
25. BC Cancer Head and Neck Tumour Group. (UHNAVPMBF6) BC Cancer Protocol Summary for First-Line Treatment of Advanced Squamous Cell Carcinoma of the Head and Neck Using 6-Weekly Pembrolizumab. Vancouver, British Columbia: BC Cancer; December 1, 2021
26. BC Cancer Lung Tumour Group. (ULUAVPMBF6) BC Cancer Protocol Summary for First-Line Treatment of Advanced Non-Small Cell Lung Cancer Using 6-Weekly Pembrolizumab. Vancouver, British Columbia: BC Cancer; 1 April 2020
27. Lala M, Li M, Sinha V, et al. A six-weekly (Q6W) dosing schedule for pembrolizumab based on an exposure-response (E-R) evaluation using modeling and simulation. J Clin Oncol 2018;36(15):3062
28. BC Cancer Lung Tumour Group. (ULUAVPMB6) BC Cancer Protocol Summary for Treatment of Advanced Non-Small Cell Lung Cancer Using 6-Weekly Pembrolizumab. Vancouver, British Columbia: BC Cancer; 1 April 2020
29. Merck Canada Inc. KEYTRUDA® product monograph. Kirkland, Quebec; July 15, 2021

Developed: 1 June 2016
Revised: 1 February 2023