DRUG NAME: Retifanlimab

SYNONYM(S): retifanlimab-dlwr[1]

COMMON TRADE NAME(S): ZYNYZ® (USA)

CLASSIFICATION: immunotherapy

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

MECHANISM OF ACTION:

Retifanlimab is a humanized IgG4 kappa monoclonal antibody that blocks the binding of programmed death receptor-1 (PD-1) with its ligands PD-L1 and PD-L2. The PD-1 pathway is an immune system checkpoint which may be exploited by tumour cells to prevent active T-cell surveillance of tumours. PD-L1 and PD-L2 are expressed by some tumour cells and other cells in the tumour microenvironment. When these ligands bind to the PD-1 receptor, T-cell function such as T-cell proliferation, cytokine production, and cytotoxic activity is inhibited. However, when retifanlimab binds to the PD-1 receptor on the T cell, this interaction between PD-1 and its ligands is blocked and the activity of the T cells is potentiated.[1]

USES:

Primary uses:	***Other uses:***
Merkel cell carcinoma[1]	

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- the safety and efficacy of ***vaccination*** in patients receiving immunotherapy is currently being investigated [2-5]
- avoid systemic ***corticosteroids or immunosuppressants*** prior to starting retifanlimab due to potential interference with the efficacy of retifanlimab; corticosteroids or immunosuppressants may be used during treatment with retifanlimab for the management of immune-mediated adverse reactions[6]
- patients who may receive or have received ***allogeneic hematopoietic stem cell transplantation*** before or after retifanlimab treatment may be at increased risk of serious complications from their transplant, including graft-versus-host disease and sinusoidal obstruction syndrome[1]
- ***solid organ transplant rejection*** has been reported in patients treated with other PD-1 inhibitors[6]

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. When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

Developed: 14 January 2025
Revised: 1 March 2025

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (5-38%, severe 1%)
	leukocytopenia (12%, severe 1%)
	lymphocytopenia (29%, severe 10%)
	neutropenia (13%, severe 3%)
gastrointestinal	*emetogenic potential:* minimal (rare)[7]
	constipation (12%)
	diarrhea (15-18%)
	nausea (10%)
general disorders and administration site conditions	*extravasation hazard:* none[8]
	fatigue (28-31%, severe 1%)
	pyrexia (10-11%)
immune system (see paragraph following **Side Effects** table)	***immune-mediated adrenal insufficiency*** (1-3%, severe 1%)
	immune-mediated carditis (<1%)
	immune-mediated colitis (2-3%, severe <1%)
	immune-mediated dermatologic reactions (8-18%, severe 1-2%)
	immune-mediated diabetes mellitus (<1%, severe <1%); can present as diabetic ketoacidosis
	immune-mediated hepatitis (1-4%, severe 1-3%)
	immune-mediated hyperthyroidism (6%)
	immune-mediated hypophysitis (1%, severe 1%)
	immune-mediated hypothyroidism (8-10%)
	immune-mediated nephritis (2%, severe 1%)
	immune-mediated pancreatitis, gastritis, duodenitis (1%, severe 1%)
	immune-mediated pneumonitis (3-5%, severe 1-2%)
	immune-mediated thyroiditis (1%)
	immune-mediated uveitis (<1%)
injury, poisoning, and procedural complications	infusion-related reaction (4-6%, severe 2%); see paragraph following **Side Effects** table
investigations	***alkaline phosphatase increase*** (20-21%, severe 1-2%)
	ALT increase (21-25%, severe 3-4%)
	amylase increase (19-22%, severe 1%)
	AST increase (23-26%, severe 2-3%)
	creatinine increase (4%)
	lipase increase (30-36%, severe 3-5%)
	TSH increase (2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
metabolism and nutrition	appetite decrease (5%)
	diabetic ketoacidosis (1%)
	hypercalcemia (8-10%, severe 1%)
	hyperkalemia (20%, severe 1%)
	hypocalcemia (12%, severe 1%)
	hypokalemia (9-15%, severe 1-2%)
	hyponatremia (23-25%, severe 3%)
musculoskeletal and connective tissue	***arthralgias, musculoskeletal pain*** (15-22%, severe 1-3%)
	eosinophilic fasciitis (severe 1%)
	polyarthritis (1%)
nervous system	demyelinating polyneuropathy (severe 1%)
	paresthesias (2%)
renal and urinary	acute kidney injury 2%
	tubulointerstitial nephritis (1%)
skin and subcutaneous tissue	***pruritus*** (18-21%)

Adapted from standard reference[1,6] unless specified otherwise.

Immune-mediated adverse events are a spectrum of side effects that arise from general immunologic enhancement caused by retifanlimab. 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 retifanlimab. Although symptoms may be nonspecific, if not recognized and treated early, they can be severe or fatal. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. ***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 retifanlimab and/or administration of corticosteroids, with or without additional immunosuppressive medication. Referral to appropriate medical specialty may be indicated for the management of complications related to treatment. Permanent discontinuation of retifanlimab 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. Restarting retifanlimab may be considered depending on the grade of the initial immune-mediated adverse event, but only following completion of the corticosteroid taper. Permanently discontinue retifanlimab if there is no resolution of the immune-mediated reaction within 12 weeks of initiating corticosteroids or there is an inability to reduce the corticosteroid to less than 10 mg/day (prednisone equivalent) within 12 weeks of initiating corticosteroids.[1] 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***.

Severe ***infusion-related reactions*** can rarely occur. Depending on the severity of reaction, reactions may be managed by interrupting the infusion, slowing the infusion rate, or permanently discontinuing retifanlimab. Consider premedication with antipyretic and/or antihistamine for patients who have had prior infusion-related reactions. Permanently discontinue retifanlimab following a grade 3 or 4 infusion reaction.[1] For management of infusion-related

Developed: 14 January 2025
Revised: 1 March 2025

reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents***.

INTERACTIONS: none known[1]

SUPPLY AND STORAGE:

Injection: Innomar Strategies Inc. (for Incyte Corporation) supplies retifanlimab as 500 mg ready-to-use, single-dose (preservative free) vials in a concentration of 25 mg/mL. Refrigerate. Store in original carton to protect from light. Do not shake.[6]

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:

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous[1]	do NOT use
Intermittent infusion[6]	***over 30 min;*** administer using ***0.2*** to 5 ***micron in-line*** or add-on filter or 15 micron mesh in-line or add-on filter
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.

Adults:

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

	Cycle Length:	
Intravenous:	***4 weeks***[6]:	***500 mg IV for one dose on day 1*** (total dose per cycle 500 mg) Dose reductions are not recommended.

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Revised: 1 March 2025

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8. BC Cancer Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer; March 1 , 2021.

Developed: 14 January 2025
Revised: 1 March 2025