DRUG NAME: Tremelimumab

SYNONYM(S): CP-675[1], tremelimumab-actl[2]

COMMON TRADE NAME(S): IMJUDO®

CLASSIFICATION: immunotherapy

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

MECHANISM OF ACTION:

Tremelimumab is a humanized IgG2 monoclonal antibody immune checkpoint inhibitor that binds to cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and blocks the interaction with its ligands (CD80 and CD86). CTLA-4 is expressed on T-cells and is a negative regulator of T-cell activation. By blocking the inhibitory signals mediated by the CTLA-4 pathway, tremelimumab increases T-cell activation and proliferation which may result in enhanced antitumour immune activity.[3]

PHARMACOKINETICS:

Distribution	limited extravascular distribution[4]	
	cross blood brain barrier?	not expected to cross the blood brain barrier[4]
	volume of distribution	central: 3.5 L; peripheral: 2.6 L
	plasma protein binding	no information found
Metabolism	expected to undergo catabolism to small peptides or amino acids; not subject to hepatic metabolism pathway[4]	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	expected to be cleared as small peptides or amino acids OR incorporated in the endogenous amino acid pool[4]	
	urine	not expected due to the large molecular size
	feces	no information found
	terminal half life	17-18 days
	clearance	0.26-0.29 L/day
Sex	no clinically meaningful difference	
Elderly	no clinically meaningful difference	
Ethnicity	no clinically meaningful difference	

Adapted from standard reference[1,3,5] unless specified otherwise.

USES:

Primary uses:
*Liver cancer

Other uses:
Lung cancer, non-small cell[2]

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- tremelimumab can cause severe and fatal ***immune-mediated*** adverse reactions, including enterocolitis, intestinal perforation, hepatitis, dermatitis, neuropathy, endocrinopathy, etc.; reactions may manifest any time during treatment as well as after treatment has been discontinued[6]
- avoid systemic ***corticosteroids*** or ***immunosuppressants*** prior to starting tremelimumab due to potential interference with the efficacy of tremelimumab; corticosteroids or immunosuppressants may be used during treatment for the management of immune-mediated adverse reactions[7]
- the safety and efficacy of ***vaccination*** in patients receiving immunotherapy is currently being investigated[8-11]

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: No human or animal fertility studies have been conducted. In repeat-dose toxicity animal studies, minimal/mild mononuclear cell inflammation/infiltration was observed in the seminal vesicles, testes, and epididymides of male test subjects. The prostate was more affected in incidence and severity (moderate inflammation) than other male reproductive organs. In female test subjects, mononuclear cell inflammation/infiltration was observed in the uterus (minimal/mild), vagina (moderate to high), and mammary gland (mild to moderate). Clinical relevance of these findings with respect to human fertility is unknown.[4]

Pregnancy: Based on its mechanism of action, tremelimumab may cause fetal harm if administered to a pregnant woman. Human IgG2 is known to cross the placenta; therefore, tremelimumab may also be transmitted from mother to fetus. CTLA-4 plays a role both in maintaining maternal immune tolerance to the fetus (needed to preserve pregnancy) and in the immune regulation of the newborn. Therefore, CTLA-4 inhibition may increase the risk of pregnancy loss and/or the development of immune-mediated disorders or an altered immune response in the newborn. In animal studies, CTLA-4 blockade in some species resulted in increased resorptions and reduced numbers of live fetuses. Some offspring, that appeared healthy at birth, developed lymphoproliferative disorders and died with multiorgan tissue destruction. However, in other species, administration of tremelimumab during organogenesis was not associated with maternal toxicity nor produced effects on embryo-fetal development at exposure levels 4-31 times the recommended dose range.[2,3] Due to the potential for fetal harm, contraception is recommended for female patients of reproductive potential, during treatment with tremelimumab and for 3 months after treatment has ended.[2,3]

Breastfeeding is not recommended due to the potential secretion into breast milk. There is no data on the presence of tremelimumab in human milk or its effects on the breastfed child or milk production. However, human IgG2 is known to be excreted in human breast milk. Due to the potential for serious adverse reactions in the breastfed child, women are advised not to breastfeed during treatment and for 3 months after the last dose of tremelimumab.[2,3]

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. When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.
Side effect data reported from combination therapy (e.g., with durvalumab) is indicated with an asterisk (*).

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (16%, severe 3%)
	neutropenia (2%, severe 1%)
	thrombocytopenia (2%, severe <1%)
cardiac	pericardial effusion (3%, severe 2%)
eye	retinal detachment (severe <1%)*
gastrointestinal	*emetogenic potential:* low[12]
	abdominal pain (7-13%, severe 2%)
	constipation (17%, severe <1%)
	diarrhea (20-47%, severe 9-15%)[13,14]
	intestinal perforation (severe <1%)
	nausea (28%, severe 1%)
	vomiting (20%, severe 2%)
general disorders and administration site conditions	*extravasation hazard:* none[15]
	asthenia (14%, severe 3%)
	edema (4-10%, severe <1%)
	fatigue (16-24%, severe 1%)
	pyrexia (16%, severe <1%)
hepatobiliary	ascites (4-8%, severe 1%)[13]
immune system (see paragraph following **Side Effects** table)	adrenal insufficiency (1%, severe <1%)
	colitis (10%, severe 8%)
	dermatitis (44%, severe 2%); includes Stevens-Johnson syndrome* and pemphigoid*
	diabetes mellitus, type I (<1%, severe <1%)*
	encephalitis (<1%)*
	hepatitis (6%, severe 2%)
	hypophysitis/hypopituitarism (1-3%, severe 1%)
	hyperthyroidism (5-10%, severe <1%)*
	hypothyroidism (11-14%, severe <1%)*
	myocarditis (<1%)*
	myositis/polymyositis (<1%)*
	nephritis (6%, severe 1%)
	nervous system disorders (1%, severe <1%); includes neuropathy, myasthenia gravis*, and Guillain-Barre Syndrome*
	pancreatitis (6%, severe 4%)
	pericarditis (<1%)*
	pneumonitis/interstitial lung disease (1%,severe <1%);
	thyroiditis (2%)*
	vasculitis (<1%)*
	influenza (3%)*

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
infections and infestations	oral candidiasis (3%, severe <1%)
	oral soft tissue infection (2%)*
	pneumonia (5%, severe 2%)
	sepsis (3%, severe 2%)
	upper/lower respiratory tract infections (3%)
	urinary tract infection (6%, severe 1%)
injury, poisoning, and procedural complications	***infusion-related reactions*** (2-3%, severe <1%); see paragraph following **Side Effects** table
investigations	albumin decrease (3%, severe <1%)
	ALT increase (10-16%, severe 4%)[13]
	amylase increase (4%)[13]
	AST increase (15-28%, severe 9%)[13]
	bilirubin increase (3-15%)[13]
	creatinine increase (21%, severe <1%)*
	glucose increase (3%, severe 1%)
	lipase increase (5-13%, severe 3-6%)[13,14]
	potassium decrease (1-7%, severe 2%)
	potassium increase (3%, severe 1%)
	sodium decrease (4%, severe 3%)
	weight loss (12%, severe 2%)
metabolism and nutrition	***appetite decrease*** (29%, severe <1%)
	dehydration (8%, severe 3%)
musculoskeletal and connective tissue	arthralgia (5%, severe <1%)
	back pain (6%)
	musculoskeletal chest pain (14%, severe 3%)
	myalgia (3%, severe <1%)
nervous system	dizziness (5%)
	headache (5%)
renal and urinary	acute kidney injury (2%, severe <1%)
respiratory, thoracic and mediastinal	***cough*** (18%)
	dyspnea (32%, severe 9%)
	pleural effusion (3%, severe 1%)
	respiratory failure (severe 1%)
skin and subcutaneous tissue	***pruritus*** (26-28%, severe 1%)
	rash (20-22%, severe 1-3%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
vascular	***pulmonary embolism*** (3%, severe 2%)

Adapted from standard reference[2,3,14] unless specified otherwise.

Immune-mediated adverse reactions are a spectrum of side effects caused by general immunologic enhancement that can occur at any time during tremelimumab treatment or months after discontinuation. The etiology of reported endocrinopathy, diarrhea/colitis, hepatitis, dermatitis, pneumonitis, etc. should be considered immune-mediated until another etiology is confirmed. Early identification and timely intervention are important as symptoms can be severe or fatal if not recognized and treated quickly. Advise patients to promptly report symptoms and to avoid self-treatment without medical advice. Management of symptoms is based on the severity of the reaction and may require treatment interruption, corticosteroids, systemic immunosuppressants, and/or supportive care. Dose reduction is not recommended. Corticosteroids should be appropriately tapered following resolution of symptoms. Referral to appropriate medical specialty may be required to manage immune-mediated complications related to treatment. Most immune-mediated endocrinopathies can be managed by withholding tremelimumab until the patient is clinically stable and/or initiating symptomatic management as indicated (e.g., insulin, thyroid hormone replacement, etc.). Permanently discontinue tremelimumab for a life-threatening reaction, recurrent severe reactions that require systemic immunosuppressive therapy, or if steroid dose cannot be reduced to 10 mg/day or less of prednisone (or equivalent) within 12 weeks of initiating corticosteroids. 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***.

Infusion-related reactions may occur with tremelimumab. Reactions may include chills, itching, rash, flushing, shortness of breath, wheezing, dizziness, fever, facial swelling or back/neck pain. For a grade 1 or 2 reaction, infusion rate may be slowed or interrupted. Consider premedication for subsequent infusions. Permanently discontinue tremelimumab for a grade 3 or higher reactions. For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents***.

INTERACTIONS: no known interactions

SUPPLY AND STORAGE:

Injection: AstraZeneca Pharmaceuticals LP supplies tremelimumab as 25 mg and 300 mg single-use (preservative free) ready-to-use vials in a concentration of 20 mg/mL. Refrigerate. Protect from light. Do not shake.[3]

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.

Compatibility: consult detailed reference

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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[3,16]	***over 60 min***; administer using 0.2 or 0.22 micron in-line 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. Numerous dosing schedules exist and depend on disease, response and concomitant therapy.

Adults:

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

Intravenous:

Cycle Length: n/a[3,16,17]:

≥30 kg: ***300 mg IV for single dose on day 1*** (total dose 300 mg)

<30 kg: 4 mg/kg IV for single dose on day 1 (total dose 4 mg/kg)

3 weeks[2,18]:

≥30 kg:75 mg IV for one dose on day 1 (total dose per cycle 75 mg)

<30 kg:1 mg/kg IV for one dose on day 1 (total dose per cycle 300 mg)

Dose reduction is not recommended

Concurrent radiation: no information found

Dosage in renal failure:

CrCl ≥30 mL/min: no adjustment required[3]
CrCl <30 mL/min: no information found

$$\text{calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure:

mild to moderate impairment (total bilirubin 1-3xULN): no adjustment required[3]
severe impairment (total bilirubin >3xULN): no information found

Dosage in dialysis: no information found

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Children: safety and efficacy not established

REFERENCES:

1. Lexi-Drugs® - Lexicomp Online (database on the Internet). Tremelimumab. Lexi-Comp Inc., 2023. Available at: http://online.lexi.com. Accessed November 28, 2023
2. AstraZeneca Pharmaceuticals-LP. IMJUDO® full prescribing information. Wilmington, Delaware, USA; November 10, 2022
3. AstraZeneca Canada Inc. IMJUDO® product monograph. Mississauga, Ontario; August 31, 2023
4. European Medicines Agency. Assessment Report - Tremelimumab. Amsterdam, The Netherlands; December 15, 2022
5. AHFS Drug Information® (database on the Internet). Tremelimumab. Lexi-Comp Inc., 2023. Available at: http://online.lexi.com. Accessed November 28, 2023
6. AstraZeneca Canada Inc. IMJUDO® product monograph. Mississauga, Ontario; January 26 2024
7. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Management of Immune Checkpoint Inhibitor-Related Toxicities version 2.2019. National Comprehensive Cancer Network, Inc., 2019. Available at: http://www.nccn.org. Accessed 10 September, 2019
8. 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
9. 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
10. 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
11. 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
12. BC Cancer Supportive Care Tumour Group. (SCNAUSEA) BC Cancer Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; September 1 2022
13. Kelley RK, Sangro B, Harris W, et al. Safety, Efficacy, and Pharmacodynamics of Tremelimumab Plus Durvalumab for Patients With Unresectable Hepatocellular Carcinoma: Randomized Expansion of a Phase I/II Study. Journal of Clinical Oncology 2021;39(27):2991-3001
14. Maio M, Scherpereel A, Calabrò L, et al. Tremelimumab as Second-line or Third-line Treatment in Relapsed Malignant Mesothelioma (DETERMINE): a Multicentre, International, Randomised, Double-blind, Placebo-controlled Phase 2b trial. The Lancet Oncology 2017;18(9):1261-1273
15. 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
16. BC Cancer Gastrointestinal Tumour Group. (GITREMDUR) BC Cancer Protocol Summary for First-Line Treatment of Advanced Hepatocellular Carcinoma using Tremelimumab and Durvalumab. Vancouver, British Columbia: BC Cancer; May 1 2024
17. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma. NEJM Evidence 2022;1(8):1-13;
18. Johnson ML, Cho BC, Luft A, et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: The Phase III POSEIDON Study. Journal of Clinical Oncology 2023;41(6):1213-1227

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