Drug Monograph

A - Drug Name

tremelimumab

COMMON TRADE NAME(S): Imjudo®

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B - Mechanism of Action and Pharmacokinetics

Tremelimumab is a selective, human IgG_2 monoclonal antibody directed against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), a negative regulator of T-cell activity primarily expressed on the surface of T lymphocytes. By binding to CTLA-4, tremelimumab blocks interaction of the receptor with its ligands CD80 and CD86, thereby enhancing T-cell activation and proliferation, resulting in increased T-cell diversity and enhanced antitumour immune activity.

Absorption	Time to reach steady state	12 weeks (in patients with solid tumours who received 1 mg/kg, 3 mg/kg, and 10 mg/kg doses once every 4 weeks x 4 doses)
Distribution	Volume of distribution	central > peripheral
	Cross blood brain barrier?	Unknown
	PPB	Unknown; albumin levels had no clinically significant effect on PK
Metabolism	Not metabolized via hepatic pathways due to its large molecular weight; eliminated through protein catabolism via reticuloendothelial system or target mediated disposition.	

Elimination	Half-life	16.9 days (after single 300mg dose) 18.2 days (at steady state)

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C - Indications and Status

Health Canada Approvals:

- Hepatocellular carcinoma (HCC)

Refer to the product monograph for a full list and details of approved indications

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D - Adverse Effects

Emetogenic Potential: Minimal

The following table lists adverse effects that occurred in ≥ 2% of patients receiving a combination of tremelimumab and durvalumab in a phase III, randomized, open-label study in unresectable HCC. It also includes severe, life-threatening and post-marketing adverse effects from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Myocarditis (<1%)	D L
Dermatological	Rash, pruritus (30%) (including dermatitis, 2% severe)	D L
	Stevens-Johnson syndrome (<1%)	E
Gastrointestinal	Abdominal pain (19%) (2% severe)	E
	Colitis (7%) (4% severe)	E
	Diarrhea (27%) (4% severe)	E
	GI perforation (<1%)	E
General	Edema (9%) (peripheral)	E
	Fever (13%)	I E
Hepatobiliary	↑ Amylase / lipase (9%) (6% severe)	E
	↑ LFTs (15%) (6% severe, including hepatitis)	D

	Pancreatitis (2%)	E
Hypersensitivity	Infusion related reaction (2%)	I
Infection	Infection (8%)	E
Metabolic / Endocrine	Adrenal insufficiency (2%)	D
	Hyperglycemia (<1%)	D
	Hyperthyroidism (10%)	D
	Hypophysitis (1%)	D
	Hypothyroidism (13%)	D
	Thyroiditis (2%)	D
Musculoskeletal	Musculoskeletal pain (3%) (myalgia, immune-mediated arthritis - rare)	E
Nervous System	Guillain-Barre syndrome (<1%)	E
	Other (<1%) Myasthenia gravis, myositis	E
Ophthalmic	Eye disorders (retinal detachment, uveitis) (rare)	E
Renal	Creatinine increased (4%) (may be severe - nephritis rare)	D
Respiratory	Cough (9%)	E
	Pneumonitis (3%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for tremelimumab include rash, pruritus, diarrhea, abdominal pain, ↑ LFTs, fever and hypothyroidism.

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for detailed descriptions of Immune-related toxicities and their management.

Presentation of immune-mediated reactions may be different compared to other anti-cancer agents and early diagnosis and appropriate management is critical.

Immune-related reactions including **rash, pneumonitis, colitis, hepatitis, pancreatitis, nephritis, endocrinopathies and neuropathies** were reported and may be severe or fatal. Onset may vary from days to many months and may occur after treatment has ended.

Other immune-mediated adverse reactions have been reported in patients that received tremelimumab in combination with durvalumab, including encephalitis and immune thrombocytopenia.

Immune-related reactions occurred more often in patients who received tremelimumab in combination with durvalumab compared to durvalumab alone.

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E - Dosing

Refer to protocol by which the patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Avoid the use of corticosteroids or immunosuppressants before starting treatment*.

* doses of ≤ 10 mg/day of prednisone or its equivalent were permitted in the HIMALAYA study

Adults:

Combination therapy for HCC:

Intravenous: 300* mg as a single dose on Day 1 of Cycle 1

*For patients with body weight ≤ 30 kg use weight-based dosing: 4mg/kg

Refer to the DURV+TREM regimen monograph for durvalumab dosing.

Dosage with Toxicity:

- Healthcare professionals should also consult the most recent tremelimumab product monograph for additional information.
- Dose reductions are not recommended for tremelimumab. Doses may be delayed or discontinued based on toxicity.

Summary of Principles of Management or immune-related adverse effects (iRAEs)

- Immune-related adverse effects (irAEs) are different in their presentation, onset and duration compared to conventional chemotherapy. Patient and provider education is essential.
- Initial irAE presentation can occur months after completion of treatment and affect multiple organs.
- Dose escalation or reduction is not recommended.
- If no other cause can be identified (such as infection), any new symptom should be considered immune-related and prompt treatment initiated.
- Organ-specific system-based toxicity management is recommended.
- **Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for detailed descriptions of Immune-related toxicities and their management.**

Non-immune-related toxicity:

Severity	Action
Grade 2 or 3	Hold until ≤ Grade 1 or baseline
Grade 4*	Discontinue

*Decision to discontinue for lab abnormalities should be based on signs/ symptoms and clinical judgement.

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate • Manage the symptoms.	• May consider pre-medications prior to re-challenge.
3 or 4	• Stop treatment • Aggressively manage the symptoms.	• Permanently discontinue (do not re-challenge)

Dosage with Hepatic Impairment:

Bilirubin		AST	Tremelimumab Dose
≤ ULN	AND	> ULN	No dose adjustment required
>1.0 to 1.5 × ULN	AND	any	
>1.5 to 3 x ULN	AND	any	
>3.0 x ULN	AND	any	Not data available

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Tremelimumab Dose
≥ 30	No dose adjustment required
< 30	Not data available

Dosage in the elderly:

No dose adjustment is required for patients ≥ 65 years of age. No overall differences in efficacy were observed between patients ≥ 65 years of age and younger patients. However, rates of adverse events were higher in patients ≥65 compared to those < 65 years old in clinical trials.

Dosage based on gender:

No dose adjustment is recommended based on gender.

Dosage based on ethnicity:

No dose adjustment is recommended based on race.

Children:

Safety and effectiveness in patients younger than 18 years of age have not been established.

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F - Administration Guidelines

- Dilute in a 0.9% sodium chloride or D5W IV bag to a final concentration between 0.1 mg/mL and 10 mg/mL. Mix by gentle inversion.
- Compatible with polyvinylchloride and polyolefin IV bags.
- Infuse IV over 60 minutes using a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.
- Give tremelimumab prior to durvalumab when administered on the same day.
- Monitor patient for 60 minutes after tremelimumab infusion.
- Do not mix with other drugs or co-administer other drugs through the same infusion line. Flush the line after each dose.

- Store unopened vials under refrigeration (2 to 8^{o}C) and protect from light. Do not freeze or shake.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components.

Other Warnings/Precautions:

- Tremelimumab (in combination with durvalumab) may cause serious immune-mediated reactions affecting multiple organ systems including GI, hepatic, cardiac, respiratory, endocrine and others. Use with caution and monitor closely in patients with pre-existing autoimmune disease and conditions such as colitis, hepatic impairment, respiratory or endocrine disorders, such as hypo or hyperthyroidism or diabetes mellitus.

- Consider the benefit/risk in patients with autoimmune or inflammatory disorders, prior GI bleeds (within 12 months), history of organ transplant, co-infection with hepatitis B and C, hepatic encephalopathy, main portal vein thrombosis, or Child-Pugh Class B or Class C; these patients were excluded from clinical trials.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Crosses placental barrier: Yes
  Human IgG2 is known to cross the placental barrier
- Fetotoxicity: Documented in animals
  In animal studies, CTLA-4 blockade is associated with an increased risk of immune-mediated rejection of the developing fetus and fetal death.

  Tremelimumab is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **3 months** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended during treatment and for at least **3 months** after the last dose.
- Fertility effects: Unknown

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H - Interactions

Tremelimumab is not not expected to have pharmacokinetic drug-drug interactions as it is not metabolized by CYP450 enzymes or other hepatic pathways. No formal drug interaction studies have been conducted.

Use of systemic corticosteroids or immunosuppressants should be avoided prior to starting tremelimumab because of potential interference with efficacy. They can be used to treat immune-mediated reactions after starting the drug.

Acetaminophen may affect the response to immune checkpoint inhibitors. Further clinical studies are needed to determine the exact mechanism and the appropriate clinical management (Bessede et al, 2022).

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests (AST, ALT, bilirubin)	Baseline and as clinically indicated
Renal function tests	Baseline and as clinically indicated
CBC	Baseline and as clinically indicated
Thyroid function tests	Baseline and as clinically indicated
Blood glucose	Baseline and as clinically indicated
Clinical toxicity assessment for infection, fatigue, infusion-related and immune-related reactions, including GI, skin, endocrine, musculoskeletal, respiratory, ocular, cardiac, neurologic toxicity or pancreatitis.	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Durvalumab in combination with Tremelimumab - Previously Untreated Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

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K - References

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Lim K, Abegesah A, Fan C, et al. Population Pharmacokinetics and Exposure-Response Analysis of Tremelimumab 300 mg Single Dose Combined with Durvalumab 1500 mg Q4W (STRIDE) in Patients with Unresectable Hepatocellular Carcinoma. J Clin Pharmacol. 2023 Nov;63(11):1221-1231.

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Schneider BJ, Naidoo J, Santomasso BD, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update. J Clin Oncol. 2021 Dec 20;39(36):4073-4126.

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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