Regimen Monograph

A - Regimen Name

DURV+TREM Regimen

Durvalumab-Tremelimumab

Disease Site

Gastrointestinal
Hepatobiliary / Liver / Bile Duct

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

First-line treatment of unresectable or metastatic hepatocellular carcinoma in patients who require systemic treatment and have a good performance status and a Child-Pugh score of class A

Supplementary Public Funding

tremelimumab
New Drug Funding Program (Durvalumab in combination with Tremelimumab - Previously Untreated Unresectable or Metastatic Hepatocellular Carcinoma (HCC)) (NDFP Website)

durvalumab
New Drug Funding Program (Durvalumab in combination with Tremelimumab - Previously Untreated Unresectable or Metastatic Hepatocellular Carcinoma (HCC)) (NDFP Website)

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B - Drug Regimen

Administer 1 cycle of DURV+TREM:

tremelimumab	300* mg	IV	Day 1
durvalumab	1500* mg	IV	Day 1

Administer tremelimumab first, followed by durvalumab.

*For patients with body weight ≤ 30 kg, administer durvalumab 20 mg/kg (until weight increases to > 30 kg), and tremelimumab 4 mg/kg.

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C - Cycle Frequency

Administer **DURV+TREM** for **one cycle** only, followed by **DURV(MNT) every 28 days** until loss of clinical benefit or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

- Also refer to CCO Antiemetic Recommendations.

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

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Avoid the use of corticosteroids or immunosuppressants before starting treatment.

Dosage with toxicity

- Healthcare professionals should also consult the most recent tremelimumab and durvalumab product monographs for additional information.
- Dose reductions are not recommended for tremelimumab or durvalumab. 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.**

Tremelimumab and Durvalumab 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 ◦ For durvalumab, stop or slow the rate of infusion by 50%. • Manage the symptoms.	• Consider pre-medications prior to subsequent infusions for durvalumab
3 or 4	• Stop treatment • Aggressively manage the symptoms.	• Permanently discontinue (do not re-challenge)

Hepatic Impairment

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for detailed descriptions for immune-related hepatitis management.

Bilirubin		AST	Tremelimumab Dose	Durvalumab Dose
≤ ULN	AND	> ULN	No dose adjustment required	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	Not data available

Renal Impairment

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for detailed descriptions for immune-related nephritis management.

Creatinine Clearance (mL/min)	Durvalumab Dose	Tremelimumab Dose
≥ 30	No dosage adjustment required	No dose adjustment required
< 30	No data available	No data available

Dosage in the Elderly

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

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F - Adverse Effects

Refer to tremelimumab, durvalumab drug monograph(s) for additional details of adverse effects

The adverse effects listed below are based on the HIMALAYA trial (Abou-Alfa 2022). Severe or life-threatening adverse effects reported from other sources are also listed.

Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Rash, pruritus (may be severe) • Diarrhea (may be severe)	• Abdominal pain • Fatigue • Anorexia • ↑ LFTs • Nausea, vomiting • Fever, infection (may be severe) • Hypo- or hyperthyroidism • Constipation • Insomnia	• Myocarditis • Infusion related reaction • Hepatitis • Nephritis • Pneumonitis • Pancreatitis • Adrenal insufficiency • Diabetes melitus • Thyroiditis • Hypophysitis • Colitis, GI perforation • Guillain-Barre syndrome • Stevens-Johnson syndrome • Toxic epidermal necrolysis • Encephalitis • Meningitis • Immune thrombocytopenic purpura • Myasthenia • Rhabdomyolysis, Myositis • Eye disorders

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G - Interactions

Refer to tremelimumab, durvalumab drug monograph(s) for additional details

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

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H - Drug Administration and Special Precautions

Refer to tremelimumab, durvalumab drug monograph(s) for additional details

Administration

Tremelimumab:

- 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.

Durvalumab:

- Administer by IV infusion over 60 minutes using a sterile, low-protein binding 0.2-0.22 micron in-line filter.
- Durvalumab is supplied as a single-use, preservative-free vial.
- Visually inspect the vial for particulates and discolouration prior to dilution. Undiluted solution should be clear to opalescent and colorless to slightly yellow.
- Using aseptic technique, withdraw the required drug volume and transfer to an IV bag of NS or D5W to a final concentration of 1 to 15 mg/mL.
- Mix by gentle inversion; do not shake.

- Do not co-administer with other drugs; flush line after each dose.
- Store unopened drug vials under refrigeration (2-8^{o}C) in the original package.
- Protect from light and do not freeze.

Contraindications

- Patients who have a hypersensitivity to these drugs or any of their components.

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, history of severe immune-mediated adverse reactions, prior GI bleeds (within 12 months), history of organ transplant, HIV, co-infection with hepatitis B and C, hepatic encephalopathy, main portal vein thrombosis, Child-Pugh Class B or Class C, CNS metastases, or patients who received live attenuated vaccine(s) within 30 days before or after starting durvalumab; these patients were excluded from clinical trials.

Pregnancy and Lactation

- This regimen is **not recommended** for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.

- Breastfeeding is **not recommended** during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).

- Fertility effects: Unknown

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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

- CBC; Baseline and Q3-6 weeks, or as clinically indicated
- Liver function tests; Baseline and Q3-6 weeks, or as clinically indicated
- Renal function tests; Baseline and Q3-6 weeks, or as clinically indicated
- Thyroid function tests; Baseline and as clinically indicated
- Blood glucose; Baseline and as clinically indicated
- Clinical toxicity assessment for infection, fatigue, pancreatitis, infusion-related and immune-related reactions, including GI, skin, endocrine, musculoskeletal, respiratory, ocular, cardiac, and neurologic toxicity; At each visit and as clinically indicated

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

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J - Administrative Information

Approximate Patient Visit	3.5 hours
Pharmacy Workload (average time per visit)	25.133 minutes
Nursing Workload (average time per visit)	53.083 minutes

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K - References

Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evid 2022;1(8):1-12.

CADTH reimbursement recommendation: Tremelimumab in combination with durvalumab (for the first-line treatment of adult patients with unresectable hepatocellular carcinoma who require systemic therapy). November 2023.

Durvalumab drug monograph, Ontario Health (Cancer Care Ontario).

Tremelimumab drug monograph, Ontario Health (Cancer Care Ontario).

August 2024 Expanded to full regimen monograph

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

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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