BC Cancer Protocol Summary for First-Line Treatment of Advanced Hepatocellular Carcinoma using Tremelimumab and Durvalumab

***Protocol Code*:**	*GITREMDUR*
***Tumour Group*:**	*Gastrointestinal*
***Contact Physician*:**	*GI Systemic Therapy*

ELIGIBILITY:

Patients must have:

- Previously untreated unresectable or metastatic hepatocellular carcinoma (HCC), and
- No amenability to curative or locoregional therapies

Patients should have:

- Good performance status,
- Adequate renal function,
- Child-Pugh A or Child-Pugh B7 liver function,
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of tremelimumab and durvalumab

Notes:

- Patients are eligible for either atezolizumab and bevacizumab (GIATZB) or tremelimumab and durvalumab (GITREMDUR), but not both. Switching for intolerance is permitted, in the absence of disease progression
- A one-time retreatment dose of tremelimumab in combination with durvalumab may be offered if patient has progressive disease after a minimum of 4 cycles of durvalumab (eligible if currently being treated with GITREMDUR Cycle 5 or subsequent). A maximum of 2 doses of tremelimumab per patient will be funded.

EXCLUSIONS:

Patients must not have:

- Prior systemic therapy for unresectable HCC,
- Uncontrolled hepatitis B or hepatitis C infection,
- Known fibrolamellar hepatocellular carcinoma, sarcomatoid hepatocellular carcinoma, or mixed cholangiocarcinoma and hepatocellular carcinoma

CAUTIONS:

- Active or previous autoimmune disease
- Patients with long term immunosuppressive therapy or systemic corticosteroids (requiring more than 10 mg predniSONE/day or equivalent)

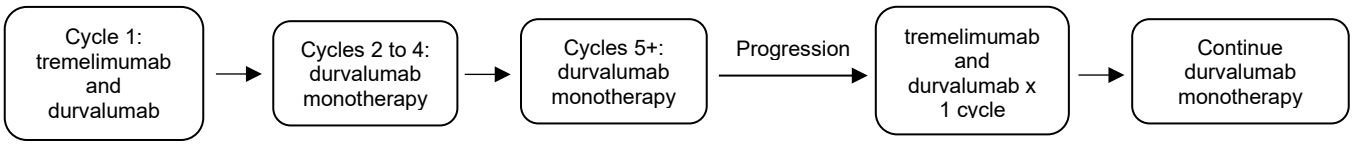
TESTS:

- Baseline: CBC & Diff, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, albumin, sodium, potassium, INR, TSH, morning serum cortisol, chest x-ray or CT chest
- Baseline if clinically indicated: AFP, troponin, creatine kinase, free T3 and free T4, GGT, lipase, random glucose, serum or urine HCG (required for women of childbearing potential if pregnancy suspected), serum ACTH levels, testosterone, estradiol, FSH, LH, ECG
- Prior to each cycle: CBC & Diff, platelets, creatinine, sodium, potassium, total bilirubin, ALT, albumin, INR, TSH
- If clinically indicated: AFP, alkaline phosphatase, GGT, morning serum cortisol, lipase, random glucose, serum or urine HCG (required for women of childbearing potential if pregnancy suspected), free T3 and free T4, creatine kinase, troponin, serum ACTH levels, testosterone, estradiol, FSH, LH, chest x-ray, ECG
- Weekly telephone nursing assessment for signs and symptoms of side effects while on treatment (Optional)

PREMEDICATIONS:

- Antiemetics are not usually required
- Antiemetic protocol for low emetogenicity (see SCNAUSEA)
- If prior infusion reaction to tremelimumab or durvalumab: diphenhydrAMINE 50 mg PO, acetaminophen 325 to 975 mg PO, and hydrocortisone 25 mg IV 30 minutes prior to treatment

Treatment Schema:



TREATMENT:

Cycle 1: (or if one-time tremelimumab with durvalumab retreatment required)

Drug	Dose	BC Cancer Administration Guideline
tremelimumab	300 mg	IV in 50 mL NS over 60 minutes Using a 0.2 micron in-line filter*
durvalumab	20 mg/kg (maximum 1500 mg)	IV in 100 mL NS over 60 minutes Using a 0.2 micron in-line filter*

***** Use a separate infusion line and filter for each drug

Vitals monitoring and observation:
Cycle 1 and for one-time retreatment dose of tremelimumab with durvalumab:
- Vital signs immediately before the start of tremelimumab infusion, at 30 minutes into the infusion (halfway through infusion), at end of infusion, and as clinically indicated
- Patients to be observed for one hour after treatment (i.e., one hour from end of durvalumab infusion) for signs of infusion-related reaction (IRR). Signs may include chills, itching, rash, flushing, shortness of breath, wheezing, dizziness, fever, facial swelling or back/neck pain
- No observation required if no infusion-related reaction with Cycle 1

Cycles 2 onward:
- Cycle 2 to be given 4 weeks after Cycle 1

Drug	Dose	BC Cancer Administration Guideline
durvalumab	20 mg/kg (maximum 1500 mg)	IV in 100 mL NS over 60 minutes Using a 0.2 micron in-line filter

- Repeat **every 4 weeks** unless disease progression or unacceptable toxicity

One-time retreatment dose of tremelimumab with durvalumab (optional):
- A one-time retreatment dose of tremelimumab in combination with durvalumab may be offered in some cases (see eligibility)

DOSE MODIFICATIONS:

No specific dose modifications. Toxicity managed by treatment delay and other measures (see SCIMMUNE for management of immune-mediated adverse reactions to checkpoint inhibitor immunotherapy: http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCIMMUNE_Protocol.pdf).

PRECAUTIONS:

1. **Serious immune-mediated reactions**: can be severe to fatal and usually occur during the treatment course, but may develop months after discontinuation of therapy. They may include enterocolitis, intestinal perforation or hemorrhage, hepatitis, dermatitis, neuropathy, endocrinopathy, pneumonitis, as well as toxicities in other organ systems. Early diagnosis and appropriate management are essential to minimize life-threatening complications (see SCIMMUNE for management of immune-mediated adverse reactions to checkpoint inhibitor immunotherapy: http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCIMMUNE_Protocol.pdf).
2. **Infusion-related reactions to tremelimumab or durvalumab:** isolated cases of severe infusion reactions have been reported. For mild or moderate infusion reactions, decrease the infusion rate to 50% or temporarily interrupt infusion until the reaction has resolved. Consider premedication for subsequent infusions.

Permanently discontinue tremelimumab and/or durvalumab for severe reactions.

3. **Infections:** severe infections such as sepsis, necrotizing fasciitis, and osteomyelitis have been reported during durvalumab treatment. Infections such as influenza, pneumonia and upper respiratory tract infections have been reported in patients treated with tremelimumab. Treat suspected or confirmed infections as indicated. Withhold tremelimumab and durvalumab for severe infections.

Call the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.

References:

1. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. NEJM Evid. 2022 Aug;1(8):EVIDoa2100070.
2. Tremelimumab (Imjudo) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies Nov 2023; 3(11):1-27.
3. CADTH Reimbursement Review. Provisional Funding Algorithm. Unresectable Hepatocellular Carcinoma. Jan 2024.