BC Cancer Protocol Summary for First-Line Treatment of Advanced Hepatocellular Carcinoma using Atezolizumab and Bevacizumab

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

ELIGIBILITY:

Patients must have:
- Previously untreated unresectable or metastatic hepatocellular carcinoma,
- Not amenable to curative or locoregional therapies, and
- Child-Pugh A liver function

Patients should have:
- ECOG performance status 0 to 1
- Patient 18 years of age or over
- Adequate hepatic and renal function
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of atezolizumab

Note:
- Patients who were started on first-line lenvatinib (GILEN) or sorafenib (GISORAF) prior to 1 April 2022 may switch to GIATZB if they have not experienced progression and meet other eligibility criteria
- If either atezolizumab or bevacizumab is stopped due to intolerance, patients may continue with the remaining agent in the absence of progression
- 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
- At time of subsequent disease progression, retreatment is allowed if:
  - Patients previously stopped GIATZB due to toxicity (not progression)
  - Progression occurs 6 months or more after stopping treatment with GIATZB
- Only biosimilar bevacizumab will be funded (including patients transitioning from self-pay or from a manufacturer patient assistance program)

EXCLUSIONS:

Patients must not have:
- Active, known or suspected autoimmune disease
- Uncontrolled hepatitis B or hepatitis C infection

- Untreated or incompletely treated esophageal or gastric varices with bleeding or high risk of bleeding
- Known fibrolamellar hepatocellular carcinoma, sarcomatoid hepatocellular carcinoma, or mixed cholangiocarcinoma and hepatocellular carcinoma

CAUTIONS:

- Patients with: 1) uncontrolled hypertension or congestive heart failure; 2) myocardial infarction or stroke within 3 months; 3) bleeding diathesis; 4) recent (less than 6 months) arterial or venous thromboembolism; 5) renal disease including proteinuria; 6) major surgery within 4 weeks; 7) local therapy (including TACE) within 4 weeks
- Patients on therapeutic anticoagulation
- Patients with long term immunosuppressive therapy or systemic corticosteroids (requiring more than 10 mg predniSONE/day or equivalent)

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, INR, albumin, sodium, potassium, TSH, morning serum cortisol, blood pressure measurement, chest x-ray or CT chest
- Baseline if clinically indicated: AFP, GGT, free T3 and free T4, random glucose, lipase, serum or urine HCG (required for women of childbearing potential if pregnancy suspected), serum ACTH levels, testosterone, estradiol, FSH, LH, creatine kinase, troponin, ECG
- Prior to each cycle: CBC & Diff, creatinine, ALT, total bilirubin, INR, albumin, sodium, potassium, TSH, blood pressure measurement
- Prior to each even numbered cycle: dipstick or laboratory urinalysis for protein,
- 24 hour urine for protein if occurrence of proteinuria (dipstick urinalysis shows 2+ or 3+ or laboratory urinalysis for protein is greater than or equal to 1 g/L)
- Blood Pressure measurement to be taken pre and post dose for first 3 cycles only and then pre-therapy with each subsequent visit
- If clinically indicated**:** AFP, alkaline phosphatase, GGT, free T3 and free T4, random glucose, morning serum cortisol, lipase, serum or urine HCG (required for women of childbearing potential if pregnancy suspected), creatine kinase, troponin, serum ACTH levels, testosterone, estradiol, FSH, LH, ECG, chest x-ray
- Weekly telephone nursing assessment for signs and symptoms of side effects while on treatment (Optional)
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR at the beginning of each cycle. See Precautions

PREMEDICATIONS:

- Antiemetics are not usually required.
- If required, antiemetic protocol for low emetogenicity (see SCNAUSEA).
- **If prior infusion reactions to atezolizumab:** diphenhydrAMINE 50 mg PO, acetaminophen 325 to 975 mg PO, and hydrocortisone 25 mg IV 30 minutes prior to treatment

TREATMENT:

A cycle equals -

Drug	Dose	BC Cancer Administration Guideline
atezolizumab	1200 mg	IV in 250 mL NS over 1 hour*
bevacizumab	15 mg/kg**	IV in 100 to 250 mL NS over 30 minutes to 1 hour***

Repeat **every 3 weeks** until disease progression or unacceptable toxicity.

**** Subsequent infusions may be given over 30 minutes if the first infusion is well-tolerated***

***** The bevacizumab dose should be recalculated for patients who experience more than a 10% change in body weight.***

****** First infusion over 60 minutes; subsequent infusions over 30 minutes. Observe for fever, chills, rash, pruritus, urticaria or angioedema and stop infusion and contact the physician if any of these occur. Infusion reactions should be treated according to severity. If the bevacizumab infusion is restarted, then it should be given at an initial rate of 60 minutes or longer.***

If acute hypertension (increase in BP measurement of greater than 20 mm Hg diastolic or greater than 160/100 if previously within normal limits) occurs during bevacizumab infusion – stop treatment. Resume at ½ the original rate of infusion if blood pressure returns to pretreatment range within one hour. If blood pressure does not return to pretreatment range within one hour – hold bevacizumab and subsequent infusions of bevacizumab should be given over 3 hours. Acute hypertension that is symptomatic (e.g. onset of headaches or change in level of consciousness) or BP measurement of greater than 180/110 that does not improve within one hour of stopping bevacizumab is an urgent situation that requires treatment.

DOSE MODIFICATIONS:

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

Bevacizumab:

1. **Proteinuria:**
   There are 3 different measures of proteinuria that may be used to assess the need for modification of bevacizumab therapy – urine dipstick analysis (measured in + values), laboratory urinalysis for protein (measured in g/L) and 24-hour urine collections for protein (measured in g/24 hours).

Degree of Proteinuria	
Neg or 1+ dipstick or less than 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled
2+ or 3+ dipstick or greater than or equal to 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled. Collect 24-hour urine for determination of total protein within 3 days before the next scheduled bevacizumab administration. Adjust bevacizumab treatment based on the table below
If urine dipstick shows 4+ or 3 g/L laboratory urinalysis for protein at baseline or during treatment	Withhold bevacizumab and proceed with 24 hour urine collection.

24-Hour Urine Total Protein (g/24 hours)	**Bevacizumab Dose**
Less than or equal to 2	100%
Greater than 2-4	Hold dose and recheck 24 hour urine every 2 weeks, resume therapy when less than or equal to 2 g/24 hour
Greater than 4	Discontinue Therapy

2. **Hypertension:**

Blood Pressure (mm Hg)	Bevacizumab Dose
less than or equal to 160/100	100%
greater than 160/100 asymptomatic	100% Notify physician and start or adjust antihypertensive therapy*
Hypertensive Crisis	Discontinue Therapy

*** Antihypertensive therapy may include hydroCHLOROthiazide 12.5-25 mg PO once daily, ramipril (ALTACE®) 2.5-5 mg PO once daily, or amlodipine (NORVASC™) 5-10 mg PO once daily.**

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 protocol for management of immune-mediated adverse reactions to checkpoint inhibitors immunotherapy).
2. **Infusion-related reactions:** isolated cases of severe infusion reactions have been reported. Discontinue atezolizumab with severe reactions (Grade 3 or 4). Patients with mild or moderate infusion reactions may receive atezolizumab with close monitoring and use of premedication.
3. **Infections:** Severe infections have been reported. Treat with antibiotics for suspected or confirmed bacterial infections. Hold atezolizumab for Grade 3 or 4 infections. Permanently discontinue for any grade of meningitis or encephalitis.
4. **Gastrointestinal perforations and wound dehiscence:** Can be fatal. Typical presentation is reported as abdominal pain associated with symptoms such as constipation and vomiting. Bevacizumab should be discontinued in patients with gastrointestinal perforation or wound dehiscence requiring medical intervention.
5. **Hemorrhage:** Bevacizumab has been associated with hemorrhage. Cases of CNS hemorrhage, some with fatal outcome, have been observed. Patients should be monitored for signs and symptoms of CNS bleeding. If Grade 3/4 hemorrhage occurs, discontinue bevacizumab. Patients with significant bleeding diatheses should not receive bevacizumab. Platelet inhibitory medications such as NSAIDS (including ASA at doses greater than 325 mg/day) should be discontinued prior to institution of bevacizumab. COX-2 inhibitors are permissible. For patients on warfarin, see Thrombosis.
6. **Thrombosis:** A history of arterial thromboembolic events or age greater than 65 years is associated with an increased risk of arterial thromboembolic events with bevacizumab. If Grade 3 thromboembolic event or incidentally discovered pulmonary

embolus arises, hold bevacizumab for 2 weeks, then consider resumption of bevacizumab if risks of tumour-related hemorrhage are judged low AND the patient is on a stable dose of anticoagulant. If a second Grade 3 thrombosis occurs, or if a Grade 4 thrombosis occurs, discontinue bevacizumab. Patients on warfarin should have INR checked frequently, at least once per cycle, while receiving bevacizumab. In patients on warfarin with an elevated INR, it is recommended to hold the bevacizumab if INR is greater than 3.0.

7. **Proteinuria:** Has been seen in all clinical trials with bevacizumab to date and is likely dose dependent. If proteinuria of greater than or equal to 2g/24 hr persists for more than 3 months, consider further investigations - possibly a renal biopsy.
8. **Hypertension:** Has been seen in all clinical trials with bevacizumab to date and is likely dose dependent. The most commonly used therapies are Calcium Channel Blockers, ACE Inhibitors and Diuretics. Blood pressure should be monitored through routine vital signs evaluations. If hypertension is poorly controlled with adequate medication, discontinue bevacizumab.
9. **Reversible Posterior Leukoencephalopathy Syndrome:** Rarely, patients may develop seizures, headache, altered mental status, visual disturbances, with or without associated hypertension consistent with RPLS. May be reversible if recognized and treated promptly.
10. **Congestive Heart Failure:** Has been reported in up to 3.5% of patients treated with bevacizumab. Most patients showed improvement in symptoms and/or LVEF following appropriate medical therapy.

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. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894–905.
2. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y, et al. IMbrave150: Updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). J Clin Oncol. 2021 Jan 20;39(3_suppl):267–267.
3. Galle PR, Finn RS, Qin S, Ikeda M, Zhu AX, Kim T-Y, et al. Patient-reported outcomes (PROs) from the Phase III IMbrave150 trial of atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (sor) as first-line treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). J Clin Oncol. 2020 Feb 1;38(4_suppl):476–476.
4. Gordan JD, Kennedy EB, Abou-Alfa GK, Beg MS, Brower ST, Gade TP, et al. Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline. J Clin Oncol. 2020 Dec 20;38(36):4317–45.