

BC Cancer Protocol Summary for Therapy for Advanced Solitary Fibrous Tumours and Hemangiopericytoma using Temozolomide and Bevacizumab

Protocol Code

SATEMBEV

Tumour Group

Sarcoma

Contact Physician

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ELIGIBILITY:

- Locally advanced, recurrent or metastatic solitary fibrous tumours and hemangiopericytoma not amenable to resection (including primary site in the CNS)
- ECOG performance status less than or equal to 2
- Adequate hematologic, renal and hepatic function
- Caution in patients with:
 - Renal disease including proteinuria, bleeding disorders, history of DVT, uncontrolled angina, cardiac arrhythmias, congestive heart failure, prior anthracycline exposure or chest wall radiation or other serious medical illness, patients on anticoagulants
 - Recent (less than 6 months) arterial thromboembolic events

EXCLUSIONS:

- Creatinine greater than 1.5 x normal
- Significant hepatic dysfunction
- Recent stroke or MI (less than 1 year)
- Major surgery within 4 weeks
- Uncontrolled hypertension
- Pregnant or breast-feeding women

TESTS:

- Baseline: CBC and differential, platelets, ALT, Alkaline Phosphatase and bilirubin, creatinine, albumin, sodium, potassium, calcium, glucose and appropriate imaging study.
- Prior to each treatment:
 - Day 1: CBC and differential, platelets, ALT and bilirubin
 - Day 8: Urine dipstick or laboratory urinalysis for protein, Blood Pressure measurement
 - Day 15: CBC and differential, platelets
 - Every ODD cycle: creatinine
 - If clinically indicated: sodium, potassium, magnesium, calcium, glucose
- 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 1g/L)

- Blood pressure measurement to be taken pre and post each bevacizumab dose for first 3 cycles only (Day 8 and 22) and then pre-therapy with each subsequent dose
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR at the beginning of each cycle

PREMEDICATIONS:

- Temozolomide: Antiemetic protocol for high-moderate emetogenic chemotherapy protocols (see [SCNAUSEA](#))
- Bevacizumab: not usually required for bevacizumab

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
temozolomide*	150 mg/m ² once daily on days 1 to 7 and on days 15 to 21 inclusive	PO
<u>bevacizumab</u>	5 mg/kg† on days 8 and 22	IV in 100 mL NS over 15 minutes‡

*refer to [Temozolomide Suggested Capsule Combination Table](#) for dose rounding

- Repeat every 28 days x 6 cycles and assess response. For further treatment, apply to CAP. Re-approval through CAP will be required every 6 cycles.

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

‡ ***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.

Line should be flushed with Normal Saline pre and post dose as Bevacizumab should not be mixed with dextrose solutions.

DOSE MODIFICATIONS:

1. Hematological

Day 1:

ANC (x10 ⁹ /L)		Platelets (x10 ⁹ /L)	Dose (all drugs)
greater than or equal to 1.5	and	greater than or equal to 100	100%
less than 1.5	or	less than 100	Delay*

*Follow CBC weekly and re-institute temozolomide at 100 mg/m² if ANC recovers to greater than 1.5 x 10⁹/L and platelets recover to greater than 100 x 10⁹/L within 3 weeks

Day 15:

ANC (x10 ⁹ /L)		Platelets (x10 ⁹ /L)	Dose (all drugs)
greater than or equal to 1.0	and	greater than or equal to 50	100%
less than 1.0	or	less than 50	Reduce temozolomide to 100 mg/m ² **

** Note: Dose reductions below 100 mg/m² are not permitted. Temozolomide should be discontinued for repeat grade 3 or 4 hematologic toxicity (ANC less than 1 x 10⁹/L, platelets less than 50 x 10⁹/L) at the 100 mg/m² dose.

2. Renal dysfunction:

Serum Creatinine µmol/L	Temozolomide Dose
less than or equal to 2 x upper limit of normal	100%
greater than 2 x upper limit of normal	reduce to 100 mg/m ² ***

***Discontinue treatment if no resolution of renal dysfunction at this dose

3. 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)

Urine dipstick analysis or laboratory urinalysis for protein should be performed prior to day 8 of each cycle of therapy:

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/24hours)	Bevacizumab Dose
less than or equal to 2	100%
greater than 2 – 4	Hold dose and recheck 24 hour urine every 4 weeks, resume therapy when less than or equal to 2 g/24 hour
greater than 4	Discontinue therapy

4. Hypertension:

Blood Pressure (mm Hg)	Bevacizumab Dose
less than or equal to 150/100	100%
greater than 150/100	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.

***Any patients presenting with chest pain, significant leg swelling, shortness of breath, new severe headaches or new neurologic symptoms,**

must be re-assessed by a physician before receiving further bevacizumab infusions.

5. Hepatic dysfunction:

Bilirubin (micromole/L)		ALT	Dose
less than 25	or	less than or equal to 2.5 x ULN	100%
25-85	or	2.6 – 5 x ULN	Reduce Temozolomide to 100 mg/m ²
greater than 85	or	greater than 5 x ULN	Delay**

**Follow LFTs weekly and re-institute temozolomide at 100 mg/m² if bilirubin recovers to less than 85 micromol/L and ALT recover to less than 5 x ULN

- Note: Dose reductions below 100 mg/m² are not permitted. Temozolomide should be discontinued for repeat bilirubin greater than 85 micromol/L and repeat ALT greater than 5 x ULN

PRECAUTIONS:

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Thombocytopenia:** Day 15 platelet counts less than 50 x 10⁹/L should be monitored at least twice weekly until recovering. Platelet counts less than 20 x 10⁹/L and falling should be treated with platelet transfusion.
3. **Hypersensitivity:** serious hypersensitivity reactions, including anaphylactic and anaphylactoid-type reactions, have been reported with bevacizumab. Refer to BC Cancer [Hypersensitivity Guidelines](#).
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.
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. **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 Dr. Christine Simmons or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

Park MS, Patel SR, Ludwig JA et al. Activity of temozolomide and bevacizumab in the treatment of locally advanced, recurrent, and metastatic hemangiopericytoma and malignant solitary fibrous tumor. *Cancer* 2011;117: 4939-47.