BC Cancer Protocol Summary for Palliative Therapy for Recurrent Malignant Gliomas Using Bevacizumab With or Without Concurrent Etoposide or Lomustine

Protocol Code	*CNBEV*
Tumour Group	*Neuro-Oncology*
Contact Physician	*Dr. Brian Thiessen*

ELIGIBILITY:

- Malignant gliomas (grade III and IV) with contrast enhancing progression or recurrence on imaging
- After prior surgery and chemoradiation with standard dose temozolomide (CNAJTZRT):
  - Second relapse after metronomic dosing (CNTEMOZMD), or
  - First relapse if not eligible for CNTEMOZMD (e.g., due to hematological toxicities) or with symptoms related to marked cerebral edema that require high doses of corticosteroids
- May be used with concurrent CNETO or CNCCNU treatments
- ECOG 0-2
- 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:

- Recent intracranial hemorrhage
- Recent stroke or MI (less than 1 year)
- Major surgery within 4 weeks
- Uncontrolled hypertension
- Pregnant or breast-feeding women
- Imaging showing no or minimal contrast enhancement or evidence of gliomatosis cerebri

TESTS:

- **Baseline**: CBC and diff, platelets, serum creatinine, dipstick or laboratory urinalysis for protein, blood pressure measurement and appropriate imaging study
- **Prior to each cycle (i.e. prior to Day 1)**: dipstick or laboratory urinalysis for protein, blood pressure measurement
- 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 every dose for first 3 cycles only (i.e. Day 1 and 15 or Day 1 and 22) and then pre-therapy with each subsequent visit
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR at the beginning of each cycle
- Gadolinium-enhanced MRI of brain every 8-12 weeks (at 8 weeks for q4week cycle, at 12 weeks for q6week cycle and at completion of bevacizumab
- CT or MRI every second cycle
- Weight: at baseline and every scheduled physician's visit

If using concurrent etoposide:
- **Baseline**: CBC and diff, platelets, serum creatinine, ALT, bilirubin
- **Prior to each cycle of etoposide**: CBC and diff, platelets, serum creatinine

If using concurrent lomustine:
- **Baseline**: CBC and diff, platelets, serum creatinine, serum glucose (patients on dexamethasone), ALT, bilirubin.
- **Before each lomustine treatment**: CBC and diff, platelets, ALT, bilirubin, serum creatinine
- **Day 28 of each cycle**: CBC and diff, platelets; perform more frequently for low nadir counts

PREMEDICATIONS:
- Not usually required for bevacizumab

If using concurrent etoposide:
- prochlorperazine 10 mg PO q6h prn or dimenhyDRINATE 25 to 50 mg PO q6h prn

If using concurrent lomustine:
- ondansetron 8 mg PO plus dexamethasone 12 mg PO 30 min before lomustine, then dexamethasone PO 4 mg twice daily x 24 hours

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
bevacizumab*	10 mg/kg on days 1 and 15*** OR 15 mg/kg on days 1 and 22**** (if patient has achieved maximal response on q 4 week regimen)	IV in 100 mL NS over 30 minutes to 1 hour** IV in 100 to 250 mL NS over 30 minutes to 1 hour**

***Repeat every 4 weeks
****Repeat every 6 weeks

Discontinue for clinical or radiographic progression.

For a maximum of 9 cycles. If there is continued evidence of response or stable disease, apply for additional 6 cycles via Compassionate Access Program.

****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 150/100 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; 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.

If using concurrent etoposide:

Drug	Dose	BC Cancer Administration Guideline
etoposide	50 mg once daily on Days 1 to 21	PO

- Repeat every 28 days until progression or intolerance.

If using concurrent lomustine:

Drug	Dose	BC Cancer Administration Guideline
lomustine (CCNU)	90 mg/m² once daily on day 1 every 6 weeks (round dose to closest 10 mg)	PO at bedtime on empty stomach

- Assess after 6 cycles. Further treatment associated with increased risk of pulmonary toxicity. Consider pulmonary function tests if further treatment considered.
- Discontinue lomustine for progressive disease or intolerable side effects.

DOSE MODIFICATIONS:

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)

Urine dipstick analysis or laboratory urinalysis for protein should be performed at baseline and then prior to each cycle (i.e. prior to Day 1):

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+ or 4+ 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 at **5 mg/Kg on days 1 and 15** (4 week cycle**)** OR **10 mg/Kg on days 1 and 22** (6 week cycle**)** 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 150/100	100%
greater than 150/100 asymptomatic	100% Notify physician and start or adjust antihypertensive therapy***
Hypertensive Crisis	Discontinue Therapy

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

3. Hematological:

If using concurrent etoposide:

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	etoposide Dose
greater than or equal to 1.5	and	*greater than or equal to 100*	100%
		less than 100	delay
1.0 to less than 1.5	and	*greater than or equal to 100*	75%
		less than 100	delay
less than 1.0	and	*greater than or equal to 100*	delay
		less than 100	delay

If using concurrent lomustine:

ANC* ($x10^9$/L)		Platelets ($x10^9$/L)	lomustine Dose
greater than or equal to 1.5	and	greater than or equal to 100	100%
1.0 to less than 1.5	and/or	80 to less than 100	80%*
less than 1.0	and/or	less than 80	delay until ANC greater than or equal to 1.5 **AND** platelets greater than or equal to 100. Resume at 60% of original dose (Note: this will be the new 100% dose thereafter)*

If more than 2 delays, CONSULT contact physician.

5. Renal dysfunction:

Creatinine clearance (mL/min)	lomustine dose
greater than or equal to 50	100%
10 to less than 50	75%
less than 10	50%

- If serum creatinine
  - Greater than 150 micromol/L, reconsider the use of lomustine.
  - 1.5 times upper limit normal, reconsider the use of etoposide.

6. **Hepatic dysfunction**:
   Hold lomustine if ALT greater than 5 x ULN or bilirubin greater than 25 micromol/L until liver function returns to normal.

PRECAUTIONS:

1. **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.
2 **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.
3 **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 every 2-3 weeks, while receiving bevacizumab.
4 **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 2 g/24 hr persists for more than 3 months, consider further investigations - possibly a renal biopsy.
5 **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.
6 **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.
7 **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.
8 **Neutropenia**: fever or other evidence of infection must be assessed promptly and treated aggressively if patient is on concurrent etoposide or lomustine.

Call Dr. Brian Thiessen or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Friedman HS, Prados MD, Wen PY et al. Bevacizumab Alone and in Combination with Irinotecan in recurrent Glioblastoma. J Clin Oncol 2009 Oct 1; 27 (28):4733-40.
2. Cohen MH, Shen YL, Keegan P et al. FDA Drug Approval Summary: Bevacizumab (AVASTIN®) as Treatment of Recurrent Glioblastoma Multiforme. Oncologist. 2009 Nov; 14(11):1131-8.
3. Vredenburgh JJ, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 2007;25:4772-28.
4. Wagner S A, Vrendenburgh et al Update on the survival from the original phase II trial of bevacizumab and irinotecan in recurrent malignant Gliomas. J Clin Oncol 2008;26(suppl);abstr 2021.
5. Fulton D; Urtasun R; Forsyth P. Phase II study of prolonged oral therapy with etoposide (VP16) for patients with recurrent malignant glioma. J Neurooncol 1996 Feb;27(2):149-55.