BC Cancer Protocol Summary for Second-Line Therapy for Metastatic or Locally Advanced Gastric or Gastroesophageal Junction Cancer Using Weekly PACLitaxel and Ramucirumab

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

ELIGIBILITY:

- Metastatic or locally advanced (unresectable) gastric or gastro-esophageal junction adenocarcinoma.
- Disease progression after first-line chemotherapy
- ECOG performance status 0-1
- Adequate hematologic, liver, and cardiac function

EXCLUSIONS:

- Peripheral neuropathy Grade 2 or higher
- Prior severe arthromyalgia unresponsive to treatment
- Gastrointestinal perforation, fistulae, or any arterial thromboembolic event within 6 months.
- Caution with patients with known coronary artery disease
- Significant gastrointestinal or non-GI bleeding or any significant venous thromboembolism within 3 months.
- Bowel obstruction, inflammatory bowel disease or chronic diarrhea.
- Uncontrolled or poorly-controlled hypertension despite standard medical management.
- Major surgery within 28 days of administration.
- CNS metastases

TESTS:

- Baseline: CBC & diff, platelets, bilirubin, ALT, TSH, urine dipstick for protein, blood pressure measurement and appropriate imaging study. Optional: CEA, CA 19-9
- Prior to Days 1, 8 and 15: CBC & diff, platelets
- Prior to Days 1 and 15: urine dipstick or laboratory urinalysis for protein, blood pressure measurement
- 24 hour urine for protein if proteinuria dipstick urinalysis shows 2+ or higher or laboratory urinalysis for protein is greater than or equal to 1 g/L.
- If clinically indicated: bilirubin, ALT, TSH, CEA, CA 19-9

PREMEDICATIONS:

- **Chemotherapy must not be started unless the following drugs have been given**:

  45 minutes prior to **Treatment**:
  - dexamethasone 10 mg IV in 50 mL NS over 15 minutes

  30 minutes prior to **Treatment**:
  - diphenhydrAMINE 25 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)

- **NOTE:** If no PACLitaxel hypersensitivity reactions occur, premedications may be omitted for subsequent Day 8 and 15 PACLitaxel doses and may be omitted at physician's discretion. **However, prior to each dose of ramucirumab, diphenhydramine 25 mg IV should be administered.**
- If hypersensitivity reactions occur with PACLitaxel, premedications for re-challenge include dexamethasone 20 mg PO given 12 hours and 6 hours prior to treatment, plus IV premedications given 30 minutes prior to PACLitaxel: dexamethasone 10 mg, diphenhydrAMINE 25 mg, and H_2-antagonist (e.g., famotidine 20 mg). If no hypersensitivity reactions occur, standard premedications (see above) will be used for subsequent PACLitaxel doses.
- If Grade 1 or 2 hypersensitivity reactions occur with ramucirumab:
  - Reduce ramucirumab infusion rate by 50% for the duration of the infusion and all subsequent infusions.
  - Standard premedications (see above) will be used for subsequent ramucirumab doses along with **acetaminophen** 650 mg PO.

- Antiemetics not usually required.

TREATMENT:

Drug	**Dose**	BC Cancer **Administration Guideline**
ramucirumab	8 mg/kg on Days 1 and 15	IV in 250 to 500 mL NS over 1 hour to 1 hour 30 min** using a 0.2 micron in-line filter*
Administer ramucirumab prior to PACLitaxel infusion		
PACLitaxel	80 mg/m^2 on Days 1, 8 and 15	IV in 100 to 250 mL NS over 1 hour (use non-DEHP bag and non-DEHP tubing with 0.2 micron in-line filter*)

*Use a different filter for each drug
**Maximum rate for ramucirumab: 25 mg/min

- Cycle length = 4 weeks. Repeat every 28 days until disease progression

DOSE MODIFICATIONS:

1. **Hematological**

ANC (x 10^9/L)		Platelets (x 10^9/L)	PACLitaxel Dose	PACLitaxel Dose after Neutropenic Sepsis
Greater than or equal to 1.5	and	Greater than or equal to 100	80 mg/m^2	65 mg/m^2
1.0 to less than 1.5	or	75 to less than 100	65 mg/m^2	50 mg/m^2
Less than 1.0	or	Less than 75	Day 1: Delay and reduce next dose to 65 mg/m^2 Day 8 and 15: Omit and reduce next dose to 65 mg/m^2	Day 1: Delay and reduce next dose to 50 mg/m^2 Day 8 or 15: Omit and reduce next dose to 50 mg/m^2

Ramucirumab is not dose reduced or delayed for hematology unless ramucirumab is the possible cause.

2. **Hepatic dysfunction**:

PACLitaxel

ALT		Total bilirubin	PACLitaxel Dose (mg/m^2)
less than 10 x ULN	and	less than or equal to 1.25 x ULN	80
less than 10 x ULN	and	1.26 to 2 x ULN	60
less than 10 x ULN	and	2.01 to 5 x ULN	40
greater than or equal to 10 x ULN	and/ or	greater than 5 x ULN	not recommended

ULN = upper limit of normal

Ramucirumab

No dosage adjustment necessary for total bilirubin < 3 x ULN and any AST or ALT. Use in patients with Child-Pugh class B or C cirrhosis only if the potential benefits outweigh the potential risks.

3. **Proteinuria**:

If ramucirumab is held on day 15 for proteinuria, proceed with PACLitaxel dose.

Degree of Proteinuria	**ramucirumab Dose**
Negative or 1+ dipstick or less than 1 g/L laboratory urinalysis for protein	Administer dose as scheduled
2+ or higher dipstick or greater than or equal to 1 g/L laboratory urinalysis for protein	Withhold and proceed with 24-hour urine protein (see separate table)

24-Hour Urine Total Protein	**ramucirumab Dose**
less than 2 g	100%
2 g to 3 g	Omit until less than 2 g, then resume dose at: - 6 mg/kg if first event - 5 mg/kg if second or further events
greater than 3 g	Discontinue Therapy

4. Hypertension:

If ramucirumab is held on day 15 for hypertension, proceed with PACLitaxel dose.

Blood Pressure (mm Hg)	**ramucirumab dose**
less than or equal to 160/100	100%
greater than 160/100 asymptomatic	100% Notify physician and start or adjust antihypertensive therapy*
uncontrolled hypertension or 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

5. Other non-hematological toxicity of PACLitaxel

Grade	PACLitaxel Dose
Grade 2 motor or sensory neuropathy	Decrease dose by 10 mg/m^2
All other grade 2 non-hematological toxicity	Hold treatment until toxicity resolved to less than or equal grade 1 Decrease subsequent doses by 10 mg/m^2
Greater than or equal to Grade 3	Discontinue treatment

6. Arthralgia and/or myalgia: If arthralgia and/or myalgia of grade 2 (moderate) or higher is not relieved by adequate doses of acetaminophen with codeine (eg, TYLENOL #3®), a limited number of studies report a possible therapeutic benefit using:
   - gabapentin 300 mg PO on day before chemotherapy, 300 mg bid on treatment day, then 300 mg tid x 7 to 10 days

   If symptoms persist, reduce subsequent PACLitaxel doses to 65 mg/m^2.

7. Neuropathy: Dose modification or discontinuation may be required (see BCCA Cancer Drug Manual).

PRECAUTIONS:

1. **Hypersensitivity**: Reactions to PACLitaxel are common. See BC Cancer Hypersensitivity Guidelines.

Mild symptoms (e.g. mild flushing, rash, pruritus)	▪ complete PACLitaxel infusion. Supervise at bedside ▪ no treatment required
Moderate symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension	▪ stop PACLitaxel infusion ▪ give IV diphenhydrAMINE 25 to 50 mg and hydrocortisone IV 100 mg ▪ after recovery of symptoms resume PACLitaxel infusion at 20 mL/h for 5 minutes, 30 mL/h for 5 minutes, 40 mL/h for 5 minutes, then 60 mL/h for 5 minutes. If no reaction, increase to full rate. ▪ if reaction recurs, discontinue PACLitaxel therapy
Severe symptoms (i.e. *one* or more of respiratory distress requiring treatment, generalised urticaria, angioedema, hypotension requiring therapy)	▪ stop PACLitaxel infusion ▪ give IV antihistamine and steroid as above. Add epinephrine or bronchodilators if indicated ▪ discontinue PACLitaxel therapy

2. **Infusion-related reactions:** have been reported with ramucirumab. Reactions usually occur during or following the first or second ramucirumab infusion. Symptoms include rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. Severe symptoms include bronchospasm, supraventricular tachycardia, and hypotension. Infusion reactions should be treated according to severity. For Grade 1 or 2 reactions, if infusion is to be restarted, it should be infused over 2 hours or longer. Immediately and permanently discontinue ramucirumab for Grade 3 or 4 reactions. Refer to BC Cancer Protocol SCDRUGRX: Management of Hypersensitivity Reactions to Chemotherapeutic Drugs.
3. **Extravasation**: PACLitaxel causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
4. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
5. **Gastrointestinal perforations and wound dehiscence**: Can be fatal and may present as abdominal pain associated with symptoms such as constipation and vomiting. Ramucirumab should be discontinued in patients with gastrointestinal perforation or wound dehiscence requiring medical intervention.
6. **Hemorrhage**: has been reported. Cases of gastrointestinal hemorrhage, some with fatal outcome, have been observed. Patients should be monitored for signs and symptoms of bleeding. If Grade 3/4 hemorrhage occurs, discontinue ramucirumab. Patients with significant bleeding diatheses should not receive ramucirumab. Platelet inhibitory medications such as NSAIDS (including ASA at doses greater than 325 mg/day) should be discontinued prior to institution of ramucirumab. COX-2 inhibitors are permissible.
7. **Impaired wound healing:** Ramucirumab should be withheld prior to scheduled surgery and discontinued if there are wound healing complications.
8. **Thrombosis**: serious, sometimes fatal, arterial thromboembolic events (ATEs) including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia have been reported with ramucirumab. Permanently discontinue therapy in patients who experience a severe ATE.
9. **Hypertension**: has been reported with ramucirumab and can usually be managed using standard antihypertensive treatment. Pre-existing hypertension should be controlled before starting ramucirumab treatment. Monitoring of blood pressure is recommended during therapy. If hypertension is poorly controlled with adequate medication, discontinue ramucirumab.
10. **Reversible Posterior Leukoencephalopathy Syndrome**: Rarely, patients may develop seizures, headache, altered mental status, visual disturbances, with or without associated hypertension consistent with RPLS. Discontinue ramucirumab in patients who develop RPLS. RPLS symptoms may be reversible if recognized and treated promptly.
11. **Congestive Heart Failure**: has been reported with ramucirumab. Patients with known or increased risk of coronary artery disease should be treated with caution.
12. **Thyroid dysfunction**: Hypothyroidism has been observed (1.3%). Monitor thyroid function during treatment.

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

REFERENCES

1. Wilke H, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15:1224-35.
2. Fuchs CS, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383:31-9.