Regimen Monograph

A - Regimen Name

PACL(W)+RAMU Regimen

Paclitaxel (weekly)-Ramucirumab

Disease Site

Gastrointestinal
- Esophagus
- Gastric / Stomach

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

For the treatment of patients with advanced or metastatic gastric cancer or gastro-esophageal junction adenocarcinoma, with an ECOG performance status of 0 or 1 and with disease progression following first-line chemotherapy (see NDFP eligibility form for detailed funding criteria).

Supplementary Public Funding

ramucirumab

New Drug Funding Program (Ramucirumab - Advanced or Metastatic Gastric Cancer or Gastroesophageal Junction Adenocarcinoma) (NDFP Website)

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B - Drug Regimen

ramucirumab	8 mg /kg	IV	Days 1 and 15 ONLY
THEN			
PACLitaxel	80 mg /m²	IV	Days 1, 8 and 15

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity occurs

If paclitaxel is later discontinued due to toxicity or intolerance, may continue with single agent ramucirumab until disease progression

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low

- Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Premedications (prophylaxis for infusion reactions):

On days 1 and 15:*

- diphenhydramine 25-50mg IV (or equivalent)
- ranitidine 50 mg IV OR Famotidine 20 mg IV ^
- dexamethasone 10 mg IV ^

* MUST give diphenhydramine prior to each ramucirumab dose. Also give acetaminophen and/or dexamethasone IV with prior grade 1 or 2 IR to ramucirumab.

^ Consider discontinuing ranitidine and/or dexamethasone if there was no IR in the first 2 paclitaxel doses.

On day 8 (paclitaxel only):**

To be given 30-60 minutes prior to paclitaxel infusion.

- Dexamethasone 10 mg IV
- Diphenhydramine 25-50 mg IV/PO
- Ranitidine 50 mg IV OR Famotidine 20 mg IV

**Consider discontinuing pre-medications if there was no IR in the first 2 paclitaxel doses.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs.

Do not treat until the following have been met (see table below). If paclitaxel cannot be given on day 1, delay for up to 28 days and then restart; if it cannot be given on day 8 or 15, the dose should be skipped. If ramucirumab cannot be given, the dose should be skipped.

Table 1: Parameters to be Met Before Treatment

	Ramucirumab		Paclitaxel	
	Day 1	Day 15	Day 1	Day 8 or 15
Neutrophils			≥ 1.5 x 10^9/L	≥ 1 x 10^9/L
Platelets			≥ 100 x 10^9/L	≥ 75 x 10^9/L
Bilirubin & Creatinine			≤ 1.5 x ULN	≤ 1.5 x ULN
AST/ALT*			≤ 3 x ULN	≤ 3 x ULN
Drug related toxicity	≤ grade 1 or baseline (except hypertension, VTE and other toxicity in this table and below)			
Proteinuria	< 2 + or < 2g/24 hours			
* ≤ 5 x ULN with known liver metastases				

<u>Dosage with toxicity</u>

Table 2: Dose Levels

Dose level	Paclitaxel (mg/m^2)	Ramucirumab (mg/kg)
0	80	8
-1	70	6
-2	60	5

Table 3: Dose Modifications for Toxicity

Toxicity	Severity	Ramucirumab dose	Paclitaxel dose*** (reductions for Day 1 ONLY)
Febrile neutropenia (Grade 3 or Grade 4) or Neutropenia ≥ 5-7 days or Thrombocytopenia	Grade 4	Consider hold* until recovery. Restart at the same dose.	Hold* until recovery. Restart at 1 dose level ↓.
Neurotoxicity or other paclitaxel-related non-hematologic toxicity (except alopecia)	Grade 3	Continue	Hold* until recovery. Restart at 1 dose level ↓.
Neurotoxicity	Grade 4	Discontinue	Discontinue
Hypertension	Grade 3 or 4	Hold until controlled with antihypertensive therapy. Discontinue if cannot be controlled.	Continue
Proteinuria	1st occurrence urine protein ≥ 2 g/24 hours	Hold** and restart at 1 dose level ↓ once urine protein < 2 g/24 hours	Continue
	2nd occurrence urine protein ≥ 2 g/24 hours		Continue
	3rd occurrence OR urine protein > 3 g/24 hours OR nephrotic syndrome	Discontinue	Continue
Delayed wound healing	n/a	Hold for at least 4 weeks prior to scheduled surgery until the wound is fully healed. Discontinue if wound healing complications arise.	Continue
Cardiac failure	Any	Consider hold. Discontinue if severe or as clinically indicated.	

Arterial thromboembolism Life-threatening VTE Bleeding	Grade 3 or 4	Discontinue	Discontinue
GI perforation Fistula PRES Cystoid macular edema	Any	Discontinue	Discontinue
Other related non-hematologic toxicity	Grade 4	Discontinue	Discontinue

*Do not restart until hematologic toxicity has recovered to levels described to Table 1, and non-hematologic toxicity < grade 2 or baseline.

**If urine protein does not return to < 2 g/24 hours, discontinue. ***If must be held on day 8 or 15, the dose should be skipped.

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Ramucirumab:

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion. • Manage the symptoms. **Restart:** • Slow the rate to 50% of the original rate at which the IR occurred for the remainder of the infusion.	• Consider re-challenge pre-medications (H1-receptor antagonist, dexamethasone and acetaminophen) and reduce administration rate by 50% at which the IR occurred.
3 or 4	• Stop the infusion. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Paclitaxel:

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • After symptom resolution, restart with pre-medications ± reduced infusion rate.	• Consider re-challenge with pre-medications and at a reduced infusion rate. • After 2 subsequent IRs, consider replacing with a different taxane.^ Give intensified pre-medications and reduce the infusion rate. • May consider adding oral montelukast ± oral acetylsalicylic acid.
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Re-challenge is discouraged, especially if vital signs have been affected. • Consider desensitization if therapy is necessary. • There is insufficient evidence to recommend substitution with another taxane at re-challenge. • High cross-reactivity rates have been reported.

^Ramucirumab is only funded if used in combination with paclitaxel based on the results of the RAINBOW study (Wilke et al., 2014).

Hepatic Impairment

For paclitaxel, patients with hepatic impairment may be at risk of myelosuppression (see table for suggested dosage adjustment). For ramucirumab, no dosage adjustment is recommended for patients with hepatic impairment. New onset or worsening ascites, encephalopathy or hepatorenal syndrome can occur in patients with Child-Pugh B or C cirrhosis. Treat only if potential benefit outweighs risk in these patients.

Bilirubin and/or AST/ALT	Paclitaxel dose (mg/m^2)
2-4 x ULN	60
>4 x ULN	40 or omit

Renal Impairment

For paclitaxel, no dosage adjustment required, but consider for patients with HIV-AIDS if creatinine ≥ 2 x ULN. For ramucirumab, no dosage adjustment is recommended in mild to moderate renal impairment. No data is available for CrCl < 30 ml//min.

Dosage in the Elderly

No dose adjustment required. No overall differences in safety or effectiveness were observed between patients ≥65 years compared with younger patients. Elderly patients on paclitaxel may be more at risk of toxicity.

Dosage based on ethnicity

Higher incidences of grade 3 proteinuria and nephrotic syndrome were reported in Asian patients living in East Asia compared to Caucasian patients.

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F - Adverse Effects

Refer to ramucirumab drug monograph(s) for additional details of adverse effects

Very common	Common	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Alopecia • Peripheral neuropathy (may be severe) • Fatigue • Musculoskeletal pain	• Myelosuppression ± infection, bleeding(may be severe) • Nausea/vomiting • Infusion-related reactions • Abdominal pain • Diarrhea • Peripheral edema	• Increased LFTs (may be severe) • Rash • Proteinuria (may be severe) • ECG changes • Hypertension (may be severe) • Mucositis	• Arterial thromboembolism • Venous thromboembolism • Cardiotoxicity • Arrhythmia • Arterial aneurysm • Arterial dissection • Thrombotic microangiopathy • GI obstruction, perforation • Fistula • Pancreatitis • Increased creatinine • Hypothyroidism (not

		• Injection site reaction	usually severe) • PRES • Delayed wound healing • Injection site reactions • Radiation recall • Cystoid macular edema / optic nerve disorder • Typhlitis • Secondary malignancy • Pneumonitis • Seizure • Nephrotic syndrome

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G - Interactions

Refer to ramucirumab, PACLitaxel drug monograph(s) for additional details

- Caution with the use of paclitaxel and CYP2C8/CYP3A4 substrates, inducers, or inhibitors.
- Use of angiogenesis inhibitors and bisphosphates may increase the risk of osteonecrosis of the jaw.

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H - Drug Administration and Special Precautions

Refer to ramucirumab, PACLitaxel drug monograph(s) for additional details

Administration - Paclitaxel:

- In order to minimize patients' exposure to DEHP leaching from PVC bags or sets, use polyolefin or polypropylene infusion bags and polyethylene-lined administration sets (with a 0.22 micron in-line filter).
- Dilute in Normal Saline or 5% Dextrose to a final concentration of 0.3-1.2 mg/mL.
- For weekly dosing, may be infused over 1 hour - mix in 250mL bag as above (not approved by manufacturer).
- Extended infusion of paclitaxel is not recommended as primary prophylaxis to reduce paclitaxel IRs.
- Excessive shaking, agitation, or vibration may induce precipitation and should be avoided.
- Precipitation may rarely occur with infusions longer than 3 hours.

Administration - Ramucirumab:

- Administer as IV infusion only. DO NOT administer as IV push or bolus.
- Withdraw required volume and transfer to an empty IV container.
- Dilute with normal saline to a total volume of 250 mL. DO NOT use dextrose as a diluent.
- Gently invert container to mix. DO NOT shake.
- Give ramucirumab before administering paclitaxel when used in combination.
- Infuse IV over approximately 60 minutes (maximum rate 25 mg/min) using a separate infusion line, with a protein sparing 0.22 micron filter.
- Flush the line with normal saline at the end of the infusion.
- DO NOT dilute or co-administer with other electrolytes or medications.
- Refrigerate unopened vials in original carton (2-8°C). Protect from light and DO NOT freeze.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Contraindications:

- Patients with a history of severe hypersensitivity reactions to paclitaxel, other drugs formulated in Cremophor EL (polyethoxylated castor oil), or ramucirumab.
- Patients with severe baseline neutropenia (<1.5 x 10^9/L; < 1 x 10^9/L for patients with AIDS-related Kaposi's) (with paclitaxel)

Warnings/Precautions:

- Paclitaxel contains ethanol, and is administered with agents such as antihistamines which cause drowsiness. Patients should be cautioned regarding driving and the use of machinery.
- Treat with ramucirumab only if potential benefit outweighs risk in patients with Child-Pugh Class B or C cirrhosis as clinical deterioration has been reported.
- Use with caution in patients with known or increased risk of coronary artery disease and/or those receiving cardiotoxic chemotherapy.
- Use with caution in patients at risk of bleeding, including those receiving concomitant antiplatelets and/or anticoagulants.
- Ramucirumab has not been evaluated in patients with serious or non-healing wounds and may impair healing. Withhold prior to surgery until the wound has fully healed.
- Use with caution in patients with risk factors for GI perforation, including intra-abdominal metastases, inflammatory bowel disease, diverticulitis, ischemic bowel, peptic ulcers, obstruction and injury from endoscopy and surgery.

Pregnancy/Lactation:

- Paclitaxel and ramucirumab are not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment and at least for **6 months** after the last dose.

- Breastfeeding is not recommended during treatment and for at least **3 months** after the last dose.
- Fertility may be affected.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- Blood pressure; Baseline and every 2 weeks, or more frequently as clinically indicated
- CBC; Baseline and before each dose
- Liver function tests; Baseline and before each dose
- Renal function tests; Baseline and as clinically indicated
- Thyroid function tests; Baseline and every 2 to 3 cycles. Continue after treatment as indicated (thyroid dysfunction may persist)
- Urinalysis (for protein); Baseline and before each cycle; if urine protein level is 2+ or higher, perform 24-hour urine collection (see dose modifications table under proteinuria)
- Continuous cardiac monitoring in patients who developed serious conduction abnormalities with paclitaxel; During subsequent infusions
- Ophthalmology if visual impairment; As clinically indicated
- Clinical toxicity assessment for infusion-related reactions, bleeding, infection, thromboembolism, cardiotoxicity, musculoskeletal, respiratory, GI and neurologic effects, and impaired wound healing; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Approximate Patient Visit	Days 1 and 15: 4 hours; Day 8: 2 hours
Pharmacy Workload (average time per visit)	24.063 minutes
Nursing Workload (average time per visit)	46.5 minutes

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K - References

Paclitaxel and ramucirumab drug monographs, Ontario Health (Cancer Care Ontario).

Wilke H, Muro K, Van Cutsem E, et al; RAINBOW Study Group. 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 Oct;15(11):1224-35.

PEBC Advice Documents or Guidelines

- Systemic Therapy for Advanced Gastric and Gastro-Esophageal Carcinoma

March 2023 Modified Pre-medications, Dosage with Toxicity, Adverse Effects, Interactions, Drug administration/Special Precautions, and Monitoring sections

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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