Regimen Monograph

A - Regimen Name

CRBPPACL+BEVA Regimen

PACLitaxel-CARBOplatin-Bevacizumab

Disease Site	Lung - Non-Small Cell
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	Treatment of selected patients with unresectable advanced, metastatic, or recurrent non-squamous non-small cell lung cancer who have good performance status (ECOG 0 or 1), with no brain metastases, hemoptysis, history of bleeding diathesis or coagulopathy.

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B - Drug Regimen

PACLitaxel	175 to 200 mg /m²	IV over 3 hours	Day 1
followed by :			
CARBOplatin	AUC 5	IV	Day 1

Adjust Carboplatin dose to AUC target (using Calvert formula) as outlined in "Other Notes" section.

bevacizumab	15 mg /kg	IV over 90 minutes*	Day 1

(This drug is not currently publicly funded for this regimen and intent)
(*if tolerated next infusion can be given over 60 minutes; can thereafter be given over 30 minutes as maintenance dose)

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C - Cycle Frequency

For carboplatin, paclitaxel, for a usual total of 4 to 6 cycles. Bevacizumab monotherapy may be continued therafter (not currently publicly funded).

REPEAT EVERY 21 DAYS

Until disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate + NK1 antagonist (Carboplatin AUC ≥ 5)

Other Supportive Care:

- Paclitaxel: Patients should be pretreated with a corticosteroid as well as an antihistamine and a H2 blocker: For example:
- DEXAMETHASONE 20mg PO 12 & 6 hours or 20mg IV 30 minutes before paclitaxel
- DIPHENHYDRAMINE 50mg IV 30 minutes before paclitaxel
- RANITIDINE 50mg IV 30 minutes before paclitaxel

Also refer to CCO Antiemetic Recommendations.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. Bevacizumab should not be initiated until hypertension is controlled and wound healing has occurred, dental evaluation has been performed and any major dental procedures completed. May consider prophylaxis for patients who have had prior mild hypersensitivity reactions and who are continuing on treatment.

Dosage with toxicity

Hematologic Toxicities

Refer to Appendix 6 for general recommendations.

Hypersensitivity reaction

Reaction	**Paclitaxel**	**Bevacizumab**
Mild (e.g. mild flushing, rash, pruritus)	Possible to complete the infusion under close supervision	May stop the infusion. Give diphenhydramine and corticosteroid if indicated. Resume infusion at slower rate under close supervision.
Moderate (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension)	Stop the infusion and give diphenhydramine 25-50 mg IV and methylprednisolone 125 mg IV. Once symptoms have resolved, resume infusion at a rate of 10% of original rate for 15 minutes, then at 25% of original rate for 15 minutes, and if no further symptoms develop, continue at original rate until infusion is complete.	Stop the infusion and hold for remainder of the day. Give diphenhydramine and corticosteroid, or other supportive measures if indicated. Consider discontinuing bevacizumab. If re-challenge on a different treatment day, use slower infusion rate.
Reaction (continued)	**Paclitaxel**	**Bevacizumab**

Severe (e.g. one or more of: respiratory distress requiring treatment, generalized urticaria, angioedema, hypotension requiring therapy)	Stop the paclitaxel infusion and give diphenhydramine and methylprednisolone as above. Use epinephrine or bronchodilators if indicated. Discontinue. Do not re-challenge.	Stop the infusion and give diphenhydramine and corticosteroid. Use epinephrine or bronchodilators if indicated. Discontinue. Do not re-challenge.

Non-hematologic Toxicities:

Any grade	**Grade 3**	**Grade 4**	**Bevacizumab action**	**Paclitaxel/ carboplatin action**
Uncontrollable hypertension			HOLD	CONSIDER HOLD or DISCONTINUE
Delayed wound healing; Surgery				
Proteinuria ≥2g/24 hours*				
Wound dehiscence			DISCONTINUE	CONSIDER HOLD or DISCONTINUE
Tracheo-esophageal fistula, other non-GI fistulae; GI perforation		Fistula		
Nephrotic syndrome; non recovery of proteinuria ≥2g/24 hours		Hypertension		
Severe Hypersensitivity				
RPLS	Bleeding	Bleeding		
Arterial thromboembolism		Venous thromboembolism		
Symptomatic cardiac failure				
Any grade	**Grade 3**	**Grade 4**	**Bevacizumab**	**Paclitaxel/**

			action	**carboplatin action**
Hemoptysis > 2.5mL; Intracranial bleeding			DISCONTINUE	CONSIDER HOLD or DISCONTINUE
	Neuropathy		No change	Hold until ≤ grade 2, then reduce by 20%
	Neutropenia ≥ 5 days			
	Febrile Neutropenia			
	Paclitaxel/carboplatin related toxicity			

*may restart when < 2g/24hrs

Hepatic Impairment

Bilirubin		**AST/ALT**	**Paclitaxel**
2-4 x ULN	or	2-4 x ULN	↓ to **135mg/m^2**
> 4 ULN	or	> 4 x ULN	**OMIT** or give maximum dose of **50mg/m^2**

- No adjustment appears necessary for carboplatin or bevacizumab.

Renal Impairment

Creatinine clearance (mL/min)	**Paclitaxel**	**Carboplatin**	**Bevacizumab**
20-50	No adjustment appears necessary	Use Calvert or Chatelut formula (refer to other notes section)	No information found; no adjustment appears necessary
<20		Discontinue	

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F - Adverse Effects

Refer to PACLitaxel, CARBOplatin, bevacizumab drug monograph(s) for additional details of adverse effects

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Hypersensitivity (may be severe) • Alopecia • Musculoskeletal pain • Fatigue • Headache • Peripheral neuropathy and ototoxicity • Myelosuppression +/- infection, bleeding (may be severe) • Nausea and vomiting, constipation, anorexia • Diarrhea • Mucositis • Eye disorders • Hypertension, proteinuria (may be severe) • Dyspnea • Increased LFTs (may be severe) • Electrolyte abnormalities • Renal impairment (may be severe) • Skin/rash (may be severe) • Venous thromboembolism (may be severe) • Fluid retention (may be severe) • Insomnia, dysgeusia, dysphonia	• Arterial thromboembolism • Cardiotoxicity, arrhythmia • Secondary malignancies • GI obstruction, perforation, fistula • PRES, encephalopathy • Pneumonitis • Wound dehiscence • Osteonecrosis of jaw • Pancreatitis • Thrombotic microangiopathy • Rhabdomyolysis • Cholecystitis • Addisons • Hemolyitc uremic syndrome

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G - Interactions

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

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H - Drug Administration and Special Precautions

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

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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.

Recommended Clinical Monitoring

- Baseline and regular liver and renal function tests
- CBC; baseline and before each cycle
- Dental evaluation before starting treatment
- Monitor blood pressure during paclitaxel infusion and every 2-3 weeks during bevacizumab therapy and more frequently in patients who develop hypertension.
- Baseline and regular dipstick urinalysis; 24 hour urine collection is recommended for patients with a 2+ or greater urine dipstick
- Clinical toxicity assessment (including hypersensitivity, musculoskeletal, perforation, fistula, GI symptoms, hemorrhage, infection, ONJ, thromboembolism, wound healing, hypertension, neurologic and cardiac effects); at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Cardiac function tests (Echo, RNA and/or MUGA scans) especially in patients who are close to the lifetime cumulative dose of anthracyclines/anthracenediones; baseline and as clinically indicated

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J - Administrative Information

Approximate Patient Visit	First cycle: 7.5 hours; Second cycle: 7 hours, Subsequent cycles: 6.5 hours
Pharmacy Workload (average time per visit)	36.896 minutes
Nursing Workload (average time per visit)	69.833 minutes

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K - References

Carboplatin, paclitaxel and bevacizumab drug monographs, Cancer Care Ontario.

Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non–small-cell lung cancer. JCO 2004; 22: 2184-2191.

Sandler A, Gray R, Perry MC, et al. Paclitaxel–carboplatin alone or with bevacizumab for non–small-cell lung cancer. NEJM 2006; 355(24): 2542.

PEBC Advice Documents or Guidelines

- Systemic Treatment for Patients with Advanced Non-Small Cell Lung Cancer

May 2019 Updated emetic risk category

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L - Other Notes

Calvert Formula

DOSE (mg) = target AUC X (GFR + 25)

- AUC = product of serum concentration (mg/mL) and time (min)
- GFR (glomerular filtration rate) expressed as measured Creatinine Clearance or estimated from Serum Creatinine (by Cockcroft and Gault method or Jelliffe method)

(Calvert AH, Newell DR, Gumbrell LA, et al, Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol, 1989; 7: 1748-1756)

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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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