Regimen Monograph

A - Regimen Name

CRBPGEMC+BEVA Regimen

Gemcitabine-CARBOplatin-Bevacizumab

Disease Site

Gynecologic - Ovary
epithelial ovarian, fallopian tube or primary peritoneal

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 first recurrence platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior VEGF-targeted therapy.

Approval was based on an improvement in progression-free survival in patients with first recurrence after 6 months of platinum-based chemotherapy; no overall survival benefit was demonstrated.

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B - Drug Regimen

bevacizumab	15 mg /kg	IV	Day 1

(This drug is not currently publicly funded for this regimen and intent)

(given prior to carboplatin/gemcitabine on day 1)

gemcitabine	1000 mg /m²	IV	Day 1 and 8
CARBOplatin	AUC 4	IV	Day 1

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

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

For a usual total of 6 cycles (10 permissible if continued response) of carboplatin/gemcitabine/bevacizumab, followed by bevacizumab alone until disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate (Carboplatin AUC < 5) (D1)
Low (D8)

Other Supportive Care:

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. The following recommendations have been adapted from clinical trials or product monographs. Bevacizumab should not be initiated in patients with recurrent hemoptysis, uncontrolled hypertension

or wounds that require healing. Prior to treatment, a dental evaluation should be performed and major dental procedures completed. May consider hypersensitivity prophylaxis for patients who have had prior mild hypersensitivity reactions and are continuing on treatment.

Dosage with toxicity

Ensure ANC ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L prior to starting treatment. The following tables include suggested dose modifications for gemcitabine and carboplatin.

Dose on Day 1 of cycle

Worst Toxicity in Previous Cycle			**Gemcitabine**	**Carboplatin**
Non-Hematologic (related organ)		**Hematologic (counts x 10^9/L)**	**% Full Dose***	**% Full Dose***
Grade 3	or	Febrile neutropenia, thrombocytopenic bleeding, ANC < 0.5 for > 5 days or < 0.1 for > 3 days, or platelets < 25	75%**	75%#
Grade 4			Consider discontinuing, or ↓ to 75%	Consider discontinuing, or ↓ to 75%
Day 8 holds in > 1 cycle			75%	100%
Pneumonitis, Hemolytic Uremic Syndrome (HUS), Capillary Leak Syndrome (CLS)			Discontinue	Discontinue
Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN)			Discontinue	Discontinue

* do not retreat until ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and toxicity ≤ grade 2.
**if toxicity recurs after gemcitabine dose reduction, omit day 8 gemcitabine
use Egorin formula if isolated thrombocytopenia

Dose on Day 8 of cycle

Toxicity on Day 8 of cycle					Day 8 dose
Non-hematologic (related organ)		**Hematologic**			**Gemcitabine (% Full Dose)**
		ANC (x 10^9/L)		**Platelets (x 10^9/L)**	
≤ grade 2	and	≥ 1.5	and	≥ 100	100%
≤ grade 2	and	1.0-1.49	and/or	75-99	↓ to 50%
grade 3 or 4	and/or	< 1.0	and/or	< 75	Omit
Pneumonitis HUS SJS TEN CLS		-		-	Discontinue

Dose reductions are not recommended for bevacizumab; the drug should be held or discontinued based on toxicity as recommended in the table below. If bevacizumab was discontinued due to toxicity prior to completion of chemotherapy, chemotherapy was continued for 6 to 10 cycles in the clinical trial. If bevacizumab was held for more than 6 weeks, the drug was discontinued.
(continued on the next page)

Bevacizumab action	**Toxicity**		
	Any grade	**Grade 3**	**Grade 4**
Hold:	Uncontrolled hypertension		
	Delayed wound healing		
	Proteinuria ≥ 2g/ 24 hours*		
	Surgery**		
Discontinue:		Hypertension not controlled with medical management	Hypertension
	Wound dehiscence, poor healing requiring medical intervention; necrotizing fasciitis		
	Nephrotic syndrome; non- recovery of proteinuria ≥ 2g/24 hours		
	Severe hypersensitivity reaction		
	Tracheo-esophageal fistula, other non-GI fistulae		Any internal fistula
	GI Perforation or fistula		
	PRES, hypertensive encephalopathy		
	Arterial thromboembolism	Pulmonary embolism	Venous thromboembolism (including pulmonary embolism)
	Symptomatic cardiac failure		
	Recurrent hemoptysis > 2.5 mL	Bleeding (any)	Bleeding (any)
	Intracranial bleeding		

* may restart when < 2g/24hrs

** for 28 days PRIOR (if surgery elective) and AFTER major surgery, or until wound healed

Hepatic Impairment

No dosage adjustment recommended for bevacizumab.

Bilirubin		AST/ALT	Gemcitabine (% previous dose)	Carboplatin (% previous dose)
1-2 x ULN	And / or	<2 x ULN	100%	100%
2-4 x ULN		2-5 x ULN	Caution	100%
> 4 x ULN		> 5 x ULN	Caution, consider ↓	Caution, consider ↓

Renal Impairment

No dosage adjustment recommended for bevacizumab, however patients > 65 years old may be increased risk of arterial thrombotic events as well as myelosuppression, fatigue, hypertension, dysphonia, proteinuria and GI effects.

CrCl (mL/min)	Gemcitabine (% previous dose)	Carboplatin (% previous dose)
> 60	100%	Use Calvert formula
40-60	100%	
20-40	Caution	
< 20	Consider discontinuing or ↓	Discontinue

Dosage in the Elderly

Use with caution; patients > 65 years old have an increased risk of arterial thrombotic events as well as myelosuppression, fatigue, proteinuria, hypertension, dizziness, dysphonia, anorexia and GI effects.

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F - Adverse Effects

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

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Increased LFTs (may be severe) • Nausea, vomiting (may be severe) • Myelosuppression +/- infection, bleeding (may be severe)	• Hypertension (may be severe) • Fatigue, flu-like symptoms • Ovarian failure • Proteinuria (may be severe) • Rash (may be severe) • Nephrotoxicity (may be severe)	• Edema • Insomnia • Musculoskeletal pain, headache • Hearing impaired • Alopecia • Diarrhea (may be severe) • Constipation • Anorexia • Mucositis, dysguesia • Cough, dyspnea (may be severe) • Eye disorders • Neuropathy (may be severe) • Venous thromboembolism (may be severe) • Electrolyte abnormalities	• Cardiotoxicity, arrhythmia • Pulmonary hypertension • Arterial thromboembolism • Hypersensitivity • GI obstruction, perforation • Fistula • Hemolytic uremic syndrome • Capillary leak sydrome • Osteonecrosis of the jaw • PRES, seizure • Thrombotic microangiopathy • Vasculitis • Delayed wound healing • Necrotizing fasciitis • Secondary malignancy

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G - Interactions

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

- Use with caution with bisphosphonates and anti-angiogenic drugs given increased risk of ONJ
- Use with caution with anthracyclines or thoracic radiation; this may increase the risk of cardiotoxicity
- Monitor closely with aminoglycosides and other nephrotoxic drugs including diuretics
- Monitor closely with phenytoin; phenytoin dosage adjustment may be required
- Monitor INR in patients receiving warfarin; warfarin dosage adjustment may be required

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H - Drug Administration and Special Precautions

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

Administration:

Gemcitabine

- May dilute reconstituted drug in normal saline for IV infusion, resulting in a minimum final concentration of at least 0.1 mg/mL.
- Infuse over 30 minutes through free-flowing IV. Infusion time beyond 60 minutes has been shown to increase toxicity.

CARBOplatin

- Mix in 100mL to 250mL bag (5% Dextrose or Normal Saline); infuse IV over 15 to 60 minutes.
- Incompatible with sets, needles or syringes containing aluminum – leads to precipitation and loss of potency.
- Protect from light.

Bevacizumab

- Bevacizumab infusions should not be administered or mixed with Dextrose or Glucose solutions due to potential for drug degradation.
- Mix in 100 mL bag NS. (Dilution should be 1.4 -16.5 mg/mL).
- Do not shake. Should not be mixed or diluted with other drugs.
- Compatible with PVC or polyolefin bags.
- DO NOT ADMINISTER AS AN IV PUSH OR BOLUS
- Infused over 90 minutes as loading dose, if tolerated next infusion can be given over 60 minutes; can thereafter be given over 30 minutes as maintenance dose
- Alternative infusion rates have been described by Mahfoud et al and Reidy et al, but these have not been approved by Health Canada
- Refrigerate unopened vials and protect from light; do not freeze.

Contraindications:

- Patients with known hypersensitivity to Chinese hamster ovary cell product, to other recombinant human or humanized antibodies or platinum-containing compounds
- Patients with untreated CNS metastases
- Patients with recurrent hemoptysis (>2.5ml) or serious hemorrhage

Other Warnings/Precautions:

- Patients who have received extensive prior treatment, have poor performance status and those over 65 years of age
- Patients with a history of arterial thromboembolism or significant cardiovascular disease or cardiac failure
- Patients with coagulopathies (congenital, acquired or therapeutic)
- Hypertension should be controlled prior to starting treatment
- Bevacizumab should not be initiated for at least 28 days following major surgery or until wound healing has occurred; hold for 28 days prior to major elective surgery
- The safety and efficacy of concurrent radiotherapy and bevacizumab has not been established.
- Avoid administration of gemcitabine as a prolonged infusion (more than 60 minutes) or more frequently than weekly since this can increase toxicity
- Use with caution in patients with impaired hepatic function, including concurrent liver metastases or a previous history of hepatitis, alcoholism or liver cirrhosis
- Use with caution in patients with, and those at risk of renal impairment

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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

- CBC; Baseline and at each visit
- Blood pressure; Baseline and every 2-3 weeks during therapy; more frequently in patients who develop hypertension
- Urine dipstick, 24 hour urine collection is recommended for patients with a 2+ or greater urine dipstick; Baseline and at each visit
- Dental evaluation; Baseline
- Liver function tests; Baseline and before each cycle
- Renal function tests, including electrolytes; Baseline and before each cycle
- Clinical assessment of hypersensitivity, GI symptoms, hemorrhage, infection, thromboembolism, myelosuppression, delayed wound healing, 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
- INR for patients receiving warfarin; Baseline and regular

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J - Administrative Information

Approximate Patient Visit	Day 1: 1.5 - 2.5 hours; Day 8: 0.75 hour
Pharmacy Workload (average time per visit)	28.472 minutes
Nursing Workload (average time per visit)	46.667 minutes

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K - References

Bevacizumab, carboplatin and gemcitabine drug monographs, Cancer Care Ontario

Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol. 2012 Jun 10;30(17):2039-45.

PEBC Advice Documents or Guidelines

- Systemic Therapy for Recurrent Epithelial Ovarian Cancer

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L - Other Notes

Calvert Formula: (area under the curve method)

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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