Regimen Monograph

Regimen Name | Drug Regimen | Cycle Frequency | Premedication and Supportive Measures | Dose Modifications | Adverse Effects | Interactions | Drug Administration and Special Precautions | Recommended Clinical Monitoring | Administrative Information | References | Other Notes | Disclaimer

A - Regimen Name

CAPE+BEVA Regimen

Capecitabine-Bevacizumab

Disease Site

Gastrointestinal
- Colorectal
- Small bowel and appendix

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

Bevacizumab is funded in combination with fluoropyrimidine (i.e. capecitabine) for first line treatment of patients with metastatic colorectal, small bowel or appendiceal cancer for whom combination chemotherapy with oxaliplatin or irinotecan is unsuitable. Patients should have ECOG performance status ≤ 2. See NDFP eligibility form for detailed funding criteria.

Supplementary Public Funding

capecitabine
ODB - General Benefit (capecitabine) (ODB Formulary)

bevacizumab
New Drug Funding Program (Bevacizumab (Biosimilar) - Metastatic Colorectal, Small Bowel, or Appendiceal Cancer) (NDFP Website)

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B - Drug Regimen

Different bevacizumab products are **not interchangeable**.

capecitabine	1000 mg /m²	PO	BID* on Days 1 to 14

*Total daily dose: 2000 mg/m^2 (Outpatient prescription in 150 mg and 500 mg tablets)

bevacizumab	7.5 mg /kg	IV	Day 1

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

Capecitabine

Topical emollients (e.g. hand creams, udder balm) may ameliorate the manifestations of hand-foot syndrome.

Supportive care should be provided, including loperamide for diarrhea.

Bevacizumab

Consider hypersensitivity prophylaxis for patients who have had prior mild hypersensitivity reactions and are continuing on treatment.

Hypertension should be controlled prior to starting treatment.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Patients should be tested for DPD deficiency before starting treatment with capecitabine. Refer to the DPD Deficiency Guidance for Clinicians for more information.

In patients with unrecognized DPD deficiency, acute, life-threatening toxicity may occur; if acute grade 2-4 toxicity develops, treatment should be stopped immediately and permanent discontinuation considered based on clinical assessment of the toxicities.

Dosage with toxicity

Dose modifications of capecitabine, but not bevacizumab were allowed after occurrence and resolution of grade 3-4 hematologic and grade 2-4 non-hematologic toxicities. If temporary hold or discontinuation of one drug was required, patients may continue on the other drug if clinically appropriate.

Capecitabine

Do not start treatment with capecitabine unless baseline neutrophil counts are ≥ 1.5 x 10^9/L and/or platelet counts of ≥ 100 x 10^9/L. Doses should not be re-escalated if reduced for toxicity. Missed or omitted doses of capecitabine should not be replaced. Dose modifications are mandatory for gastrointestinal, dermatological toxicity and hyperbilirubinemia. Practitioner may elect not to reduce dose for other toxicities unlikely to become serious or life-threatening.

Toxicity	Action During a Course of Therapy	Dose Adjustment for Next Cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2 non-heme toxicity 1st appearance 2nd appearance 3rd appearance 4th appearance	 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Discontinue treatment permanently	 100% 75% 50% --

Grade 3 heme or non-heme toxicity 1st appearance 2nd appearance 3rd appearance, OR any evidence of Stevens-Johnson syndrome or Toxic epidermal necrolysis	 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Discontinue treatment permanently	 75% 50% --
Grade 4 heme or non-heme toxicity 1st appearance, including SJS or TEN, OR cardiotoxicity OR acute renal failure 2nd appearance OR any occurrence of confirmed leukoencephalopathy	 Discontinue permanently OR If physician deems it to be in the patient's best interest to continue and no evidence of Stevens-Johnson syndrome or toxic epidermal necrolysis, interrupt until resolved to grade 0-1. Discontinue permanently	 Discontinue OR 50% --

Bevacizumab

Dose reductions are not recommended. Bevacizumab should be held or discontinued based on toxicity.

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

Capecitabine

In patients with mild to moderate hepatic impairment, exposure is increased but no dose adjustment is necessary, although caution should be exercised. Use dose modification table above for increases in bilirubin. The use of capecitabine in patients with severe hepatic impairment has not been studied

Bevacizumab

No information found. Not a major route of metabolism or excretion.

Renal Impairment

Creatinine Clearance (mL/min)	Capecitabine (% dose)	Bevacizumab*
51 - 80	100 % with close monitoring	No data
30 - 50	75 % (use with caution)	No data
<30	CONTRAINDICATED	No data

*Not a major route of metabolism, excretion

Dosage in the Elderly

Capecitabine

No dose adjustment for the starting dose is required, but patients should be closely monitored and dose modification should be performed as described above. Older patients are more susceptible to the effects of fluoropyrimidine-based therapies with increased grade 3 / 4 adverse effects, especially when used in combination.

Bevacizumab

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 capecitabine, 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
• Hand-foot syndrome (may be severe)	• Diarrhea (may be severe) • Hypertension (may be severe) • Proteinuria (may be severe) • Nausea, vomiting • Hemorrhage (may be severe)	• Mucositis • ↑ LFTs (may be severe) • Abdominal pain • Constipation • Fatigue • Venous thromboembolism (may be severe) • Rash (may be severe) • Myelosuppression +/- infection, bleeding (may be severe) • Insomnia • Eye disorders (may be severe) • Musculoskeletal pain • Headache • Cough, dyspnea • Dysphonia • Dysgeusia • Anorexia • Neuropathy	• Arterial thromboembolism • Cardiotoxicity • Arrhythmia • Pulmonary hypertension • GI obstruction, perforation, fistula • Idiopathic thrombocytopenic purpura • Thrombotic microangiopathy • Hypersensitivity • Leukoencephalopathy, PRES • Seizure • Osteonecrosis of the jaw • Pneumonitis • Necrotizing fasciitis • Delayed wound healing • Renal failure

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G - Interactions

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

- Use bevacizumab with caution with bisphosphonates and anti-angiogenic drugs given increased risk of ONJ
- Avoid concomitant administration of capecitabine and sorivudine and its analogs (wait at least 4 weeks after sorivudine treatment before starting capecitabine)
- Caution and monitor for effectiveness when capecitabine is given with proton-pump inhibitors; consider switching to an antacid
- 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 capecitabine, bevacizumab drug monograph(s) for additional details.

Different bevacizumab products are **not interchangeable**.

Administration

Capecitabine:

- Clinical studies performed with capecitabine administered 30 minutes after food. Administering capecitabine on an empty stomach may result in slightly higher exposure and thus toxicity.
- If a capecitabine dose is missed, skip this and give the next dose at the usual time. Missed or omitted doses should not be replaced.
- Store tablets at 15ºC to 30ºC in the original package.

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 bevacizumab, Chinese hamster ovary cell product, other recombinant human or humanized antibodies, capecitabine, its excipients, or 5-fluorouracil
- Patients with severe renal impairment (CrCl <30 mL/min)
- Patients with known near or complete absence of DPD (dihydropyrimidine dehydrogenase) deficiency. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Concomitant use with sorivudine or related analogues (i.e. brivudine) (see Drug Interactions)
- Patients with untreated CNS metastases
- Patients with recurrent hemoptysis (>2.5ml), serious hemorrhage, or with squamous NSCLC

Precautions

- Capecitabine contains lactose and should not be used in patients with hereditary galactose/glucose/lactase disorders
- Patients with risk factors for dehydration, pre-existing renal dysfunction or on nephrotoxic agents
- Patients with partial DPD deficiency - use with extreme caution. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Patients with a history of arterial thromboembolism or significant cardiovascular disease or cardiac failure
- Patients with coagulopathies (congenital, acquired or therapeutic)
- 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

Pregnancy & lactation

- These drugs are not recommended for use in pregnancy. Adequate contraception (including at least 2 contraceptive methods) should be used by both sexes during treatment, and for at least **6 months** after the last dose.
- Breastfeeding is not recommended.

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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

- Blood pressure; Baseline and every 2-3 weeks during therapy; more frequently in patients who develop hypertension
- CBC; Baseline and at each visit
- Renal function tests; Baseline and at each visit
- 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 and as clinically indicated
- INR and/or PT; baseline and regular if on anticoagulants
- Clinical assessment of hypersensitivity, perforation, fistula, diarrhea, mucositis, dehydration, rash, hand-foot syndrome, ONJ, hemorrhage, infection, myelosuppression, thromboembolism, delayed 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
- Liver function tests; baseline and regular (if severe organ failure suspected)

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J - Administrative Information

Outpatient prescription for home administration (capecitabine)

Approximate Patient Visit	First dose: 1.5 hours; Second dose: 1 hour; Subsequent: 0.5 hour
Pharmacy Workload (average time per visit)	17.013 minutes
Nursing Workload (average time per visit)	40 minutes

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K - References

Bevacizumab and capecitabine drug monographs, Cancer Care Ontario.

Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. Lancet Oncol 2013;14(11):1077-85.

Giessen C, von Weikersthal LF, Hinke A, et al. A randomized, phase III trial of capecitabine plus bevacizumab (Cape-Bev) versus capecitabine plus irinotecan plus bevacizumab (CAPIRI-Bev) in first-line treatment of metastatic colorectal cancer: the AIO KRK 0110 trial/ML22011 trial. BMC Cancer 2011;11:367.

April 2023 Updated DPD deficiency information in the Dosing and Special Precautions 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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