

# BC Cancer Protocol Summary for First-Line Treatment of Locally Advanced or Metastatic Gastroesophageal Cancer using Oxaliplatin, Capecitabine and Pembrolizumab

**Protocol Code:**

*GIGAVCOXP*

**Tumour Group:**

*Gastrointestinal*

**Contact Physician:**

*GI Systemic Therapy*

## ELIGIBILITY:

Patients must have:

- Locally advanced or metastatic esophageal carcinoma (adenocarcinoma or squamous cell carcinoma) or gastroesophageal junction adenocarcinoma,
- No prior palliative chemotherapy, and
- PD-L1 expression with combined positive score (CPS) greater than or equal to 1, or [dMMR/MSI-H](#)

Patients should have:

- ECOG performance status 0 to 2
- Adequate marrow reserve, hepatic and renal function
- Access to a treatment center with expertise to manage immune-mediated adverse reactions of pembrolizumab

Notes:

- Patients started on GIGAVCOXP prior to 1 Feb 2025 with CPS unknown or less than 1 may continue per provider discretion
- Patients who were started on, or had completed first-line chemotherapy prior to 1 July 2022, and have not progressed, may switch to GIGAVCOXP if all other eligibility criteria are met
- Patients who received prior adjuvant immunotherapy are eligible if there was a disease-free interval of 6 months or greater
- At time of subsequent disease progression, pembrolizumab retreatment (with or without chemotherapy) is allowed for an additional 1 year of therapy (17 cycles) if:
  - Patients have completed 2 years of therapy without progression
  - Patients have stopped pembrolizumab for reasons other than progression (e.g. toxicity or complete response)
  - CAP approval not required for retreatment

## EXCLUSIONS:

Patients must not have:

- HER-2 positive disease
- Severe renal impairment (creatinine clearance less than 30 mL/min)
- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months), unstable angina, uncontrolled high blood pressure

- Uncontrolled CNS metastases
- Congenital long QT syndrome – avoid oxaliplatin
- Severe pre-existing peripheral neuropathy

### CAUTIONS:

- Active, known or suspected autoimmune disease
- Patients with long term immunosuppressive therapy or systemic corticosteroids (requiring more than 10 mg prednisONE/day or equivalent)
- Patients with baseline greater than 3 loose BMs per day

### TESTS:

- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, albumin, sodium, potassium, DPYD test (not required if previously tested, or tolerated fluorouracil or capecitabine), TSH, morning serum cortisol, chest x-ray or CT chest
- Baseline if clinically indicated: ECG, CEA, CA 19-9, creatine kinase, troponin, free T3 and free T4, GGT, lipase, random glucose, serum or urine HCG (required for women of childbearing potential if pregnancy suspected), serum ACTH levels, testosterone, estradiol, FSH, LH
- Prior to each cycle: CBC & Diff, creatinine, ALT, total bilirubin, sodium, potassium, TSH
- If clinically indicated: CEA, CA 19-9, morning serum cortisol, lipase, random glucose, alkaline phosphatase, albumin, GGT serum or urine HCG (required for women of childbearing potential if pregnancy suspected), free T3 and free T4, creatine kinase, troponin, serum ACTH levels, testosterone, estradiol, FSH, LH, ECG, chest x-ray
- For patients on warfarin, weekly INR during fluorouracil therapy until stable warfarin dose established, then INR prior to each cycle
- Weekly telephone nursing assessment for signs and symptoms of side effects while on treatment (Optional)

### PREMEDICATIONS:

- Antiemetic protocol for moderately emetogenic chemotherapy (see SCNAUSEA)
- If prior infusion reactions to pembrolizumab: diphenhydramine 50 mg PO, acetaminophen 325 to 975 mg PO, and hydrocortisone 25 mg IV 30 minutes prior to pembrolizumab
- If Grade 1 or 2 oxaliplatin hypersensitivity reactions:
  - 45 minutes prior to oxaliplatin:
    - dexamethasone 20 mg IV in 50 mL NS over 15 minutes
  - 30 minutes prior to oxaliplatin:
    - diphenhydramine 50 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)
- **Counsel patients to avoid cold drinks and exposure to cold air, especially for 3-5 days following oxaliplatin administration.**
- **Cryotherapy (ice chips) should NOT be used as may exacerbate oxaliplatin-induced pharyngo-laryngeal dysesthesias.**

## TREATMENT:

A cycle equals:

Drug	Dose	BC Cancer Administration Guidelines
pembrolizumab	2 mg/kg (maximum 200 mg)	IV in 50 mL NS over 30 minutes on using a 0.2 micron in-line filter
oxaliplatin*	130 mg/m <sup>2</sup>	IV in 250 to 500 mL D5W over 2 hours
capecitabine**	1000 mg/m <sup>2</sup> BID	PO x 14 days

\* Oxaliplatin is not compatible with normal saline. Do not piggyback or flush lines with normal saline. Concurrent use of up to 500 mL D5W hydration at maximum rate of 250 mL/h with peripheral administration of oxaliplatin can be given.

\*\* Capecitabine is available as 150 mg and 500 mg tablets (refer to [Capecitabine Suggested Tablet Combination Table](#) for dose rounding).

*Line should be flushed with D5W pre and post dose as oxaliplatin should not be mixed with normal saline.*

- Each cycle is 21 days (3 weeks).
- Chemotherapy treatment: until disease progression or unacceptable toxicity.
- Pembrolizumab treatment: until disease progression, unacceptable toxicity or a maximum 2 years of treatment
- If patients are intolerant of the chemotherapy after at least 1 cycle, pembrolizumab can be continued as single agent until disease progression, unacceptable toxicity or a maximum of 2 years of treatment.
- Retreatment may be allowed (refer to eligibility).

## DOSE MODIFICATIONS:

### 1. For pembrolizumab:

No specific dose modifications for pembrolizumab. Toxicity managed by treatment delay and other measures (see SCIMMUNE protocol for management of immune-mediated adverse reactions to checkpoint inhibitors immunotherapy, [http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCIMMUNE\\_Protocol.pdf](http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCIMMUNE_Protocol.pdf))

### 2. For oxaliplatin and capecitabine

#### Capecitabine Dosing Based on DPYD Activity Score (DPYD-AS)

Refer to “Fluorouracil and Capecitabine Dosing Based on DPYD Activity Score (DPYD-AS)” on [www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual](http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual).

- A. Dose Modifications for NEUROLOGIC Toxicity
- B. Dose Modifications for HEMATOLOGIC Toxicity
- C. Dose Modifications for NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity

***Neuropathy may be partially or wholly reversible after discontinuation of therapy; patients with good recovery from Grade 3 (not Grade 4) neuropathy may be considered for re-challenge with oxaliplatin, with starting dose one level below that which they were receiving when neuropathy developed.***

**Table 1 - Dose Levels for NEUROLOGIC Toxicity (Section A)**

Agent	Dose Level 0 (Starting Dose)	Neurotoxicity Dose Level –1N	Neurotoxicity Dose Level –2N	Neurotoxicity Dose Level – 3N
oxaliplatin	130 mg/m <sup>2</sup>	100 mg/m <sup>2</sup>	65 mg/m <sup>2</sup>	Discontinue Therapy

*\*If patient has both neurologic and non-neurologic toxicity, the final dose of oxaliplatin is the LOWER of the dose adjustments (ie if hematologic toxicity mandates dose –2 reduction (85mg/m<sup>2</sup>) and neurologic toxicity mandates dose –2N reduction (65 mg/m<sup>2</sup>), then 65 mg/m<sup>2</sup> is given.*

### A. Dose Modifications for NEUROLOGIC Toxicity

Toxicity Grade	Duration of Toxicity		Persistent (present at start of next cycle)
	1 to 7 days	Greater than 7 days	
<b>Grade 1</b>	Maintain dose level	Maintain dose level	Maintain dose level
<b>Grade 2</b>	Maintain dose level	Maintain dose level	Decrease one neurotoxicity dose level
<b>Grade 3</b>	↓1 neurotoxicity dose level	↓1 neurotoxicity dose level	Discontinue therapy
<b>Grade 4</b>	Discontinue therapy	Discontinue therapy	Discontinue therapy
<b>Pharyngo-laryngeal (see precautions)</b>	Increase duration of infusion to 6 hours	N/A	N/A

### Oxaliplatin Neurotoxicity Definitions

<b>Grade 1</b>	Paresthesias/dysesthesias of short duration that resolve; do not interfere with function
<b>Grade 2</b>	Paresthesias / dysesthesias interfering with function, but not activities of daily living (ADL)
<b>Grade 3</b>	Paresthesias / dysesthesias with pain or with functional impairment which interfere with ADL
<b>Grade 4</b>	Persistent paresthesias / dysesthesias that are disabling or life-threatening
<b>Pharyngo-laryngeal dysesthesias (investigator discretion used for grading):</b> Grade 0 = none; Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe	

**Table 2 Dose Levels for NON-NEUROLOGIC TOXICITY (Sections B & C)**

Agent	Dose Level 0 (Starting dose)	Dose Level -1	Dose Level -2	Dose Level -3
oxaliplatin	130 mg/m <sup>2</sup>	100 mg/m <sup>2</sup>	85 mg/m <sup>2</sup>	Discontinue Therapy
capecitabine	1000 mg/m <sup>2</sup> bid	750 mg/m <sup>2</sup> bid	500 mg/m <sup>2</sup> bid	Discontinue Therapy

## B. Dose Modifications for HEMATOLOGIC Toxicity

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	ANC (x10 <sup>9</sup> /L)	Oxaliplatin	Capecitabine
<ul style="list-style-type: none"> <li>If ANC less than 1.2 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times.</li> <li>If ANC is greater than or equal to 1.2 within 2 weeks, proceed with treatment at the dose level noted across from the <b>lowest ANC</b> result of the delayed week(s).</li> <li>If ANC remains less than 1.2 after 2 weeks, discontinue treatment.</li> </ul>	1	Greater than or equal to 1.2	Maintain dose level	Maintain dose level
	2	1.0 to less than 1.2	Maintain dose level	Maintain dose level
	3	0.5 to less than 1.0	↓ 1 dose level	↓ 1 dose level
	4	Less than 0.5	↓ 2 dose levels	↓ 2 dose levels
	Grade	Platelets (x10 <sup>9</sup> /L)	Oxaliplatin	Capecitabine
<ul style="list-style-type: none"> <li>If platelets less than 75 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times.</li> <li>If platelets greater than or equal to 75 within 2 weeks, proceed with treatment at the dose level noted across from the <b>lowest platelets</b> result of the delayed week(s).</li> <li>If platelets remain less than 75 after 2 weeks, discontinue treatment.</li> </ul>	1	Greater than or equal to 75	Maintain dose level	Maintain dose level
	2	50 to less than 75	Maintain dose level	Maintain dose level
	3	10 to less than 50	↓ 1 dose level	↓ 1 dose level
	4	Less than 10	↓ 2 dose levels	↓ 2 dose levels

### C. Dose Modifications for NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity

If Grade 2, 3 or 4 toxicities occur, daily administration of Capecitabine should be immediately interrupted until these symptoms resolve or decrease in intensity to grade 1.

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	Diarrhea	Oxaliplatin	Capecitabine
<ul style="list-style-type: none"> <li>If diarrhea greater than or equal to Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times.</li> <li>If diarrhea is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the <b>highest</b> Grade experienced.</li> <li>If diarrhea remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.</li> </ul>	1	Increase of 2 to 3 stools/day, or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level
	2	Increase of 4 to 6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level
	3	Increase of 7 to 9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	Maintain dose level	↓ 1 dose level
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	↓ 1 dose level	↓ 2 dose levels*

**\*If treatment with capecitabine is discontinued, then oxaliplatin is also discontinued.**

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	Stomatitis	Oxaliplatin	Capecitabine
<ul style="list-style-type: none"> <li>If stomatitis greater than or equal to Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times.</li> <li>If stomatitis is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the <b>highest</b> Grade experienced.</li> <li>If stomatitis remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.</li> </ul>	1	Painless ulcers, erythema or mild soreness	Maintain dose level	Maintain dose level
	2	Painful erythema, edema, or ulcers but can eat	Maintain dose level	Maintain dose level
	3	Painful erythema, edema, ulcers, and cannot eat	Maintain dose level	↓ 1 dose level
	4	As above but mucosal necrosis and/or requires enteral support, dehydration	↓ 1 dose level	↓ 2 dose levels*

**\*If treatment with capecitabine is discontinued, then oxaliplatin is also discontinued.**

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	Palmar-Plantar Erythrodysesthesia (Hand-Foot Skin Reaction)	Oxaliplatin	Capecitabine
<ul style="list-style-type: none"> <li>If hand-foot skin reaction is greater than or equal to Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times.</li> <li>If hand-foot skin reaction is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the <b>highest</b> Grade experienced.</li> </ul>	1	Skin changes (eg, numbness, dysesthesia, paresthesia, tingling, erythema) with discomfort not disrupting normal activities	Maintain dose level	Maintain dose level
	2	Skin changes (eg, erythema, swelling) with pain affecting activities of daily living	Maintain dose level	Maintain dose level



Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	Palmar-Plantar Erythrodysesthesia (Hand-Foot Skin Reaction)	Oxaliplatin	Capecitabine
<ul style="list-style-type: none"> <li>If hand-foot skin reaction remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.</li> </ul>	3	Severe skin changes (eg, moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living	Maintain dose level	↓ 1 dose level

#### Renal dysfunction:

Creatinine Clearance mL/min	Capecitabine Dose only
Greater than 50	100%
30 to 50	75%
Less than 30	Discontinue Therapy

#### Cockcroft-Gault Equation:

$$\text{Estimated creatinine clearance: } = \frac{N (140 - \text{age}) \text{ wt (kg)}}{\text{serum creatinine (micromol/L)}} \text{ (mL/min)}$$

N = 1.23 male

N = 1.04 female

## PRECAUTIONS:

- 1. Serious immune-mediated reactions:** can be severe to fatal and usually occur during the treatment course, but may develop months after discontinuation of therapy. They may include enterocolitis, intestinal perforation or hemorrhage, hepatitis, dermatitis, neuropathy, endocrinopathy, pneumonitis, as well as toxicities in other organ systems. Early diagnosis and appropriate management are essential to minimize life-threatening complications (see SCIMMUNE protocol for management of immune-mediated adverse reactions to checkpoint inhibitors immunotherapy).
- 2. Infusion-related reactions:** isolated cases of severe infusion reactions have been reported. Discontinue pembrolizumab with severe reactions (Grade 3 or 4). Patients with mild or moderate infusion reactions may receive pembrolizumab with close monitoring and use of premedication.
- 3. Platinum hypersensitivity** can cause dyspnea, bronchospasm, itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, epinephrine and bronchodilators. Vasopressors may be required (see table below). For Grade 1 or 2 acute hypersensitivity reactions no dose modification of oxaliplatin is required and the patient can continue treatment with standard hypersensitivity premedication. See Premedications.

Reducing infusion rates (e.g., from the usual 2 hours to 4-6 hours) should also be considered since some patients may develop more severe reactions when rechallenged, despite premedications.

The practice of rechallenging after severe life-threatening reactions is usually discouraged, although desensitization protocols have been successful in some patients. The benefit of continued treatment must be weighed against the risk of severe reactions recurring. The product monograph for oxaliplatin lists rechallenging patients with a history of severe HSR as a contraindication. Various desensitization protocols using different dilutions and premedications have been reported. Refer to SCOXR: BC Cancer Inpatient Protocol Summary for Oxaliplatin Desensitization for more information.

- 4. Pharyngo-laryngeal dysesthesia** is an unusual dysesthesia characterized by an uncomfortable persistent sensation in the area of the laryngopharynx without any objective evidence of respiratory distress (i.e. absence of hypoxia, laryngospasm or bronchospasm). This may be exacerbated by exposure to cold air or foods/fluids. If this occurs during infusion, stop infusion immediately and observe patient. Rapid resolution is typical, within minutes to a few hours. Check oxygen saturation; if normal, an anxiolytic agent may be given. The infusion can then be restarted at a slower rate at the physician's discretion. In subsequent cycles, the duration of infusion should be prolonged (see Dose Modifications above in the Neurological Toxicity table).

Clinical Symptoms	Pharyngolaryngeal Dysesthesia	Platinum Hypersensitivity
Dyspnea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O <sub>2</sub> saturation	Normal	Decreased
Difficulty swallowing	Present (loss of sensation)	Absent
Pruritus	Absent	Present
Cold induced symptoms	Yes	No
Blood Pressure	Normal or Increased	Normal or Decreased
<b>Treatment</b>	Anxiolytics; observation in a controlled clinical setting until symptoms abate or at physician's discretion	Oxygen, steroids, epinephrine, bronchodilators; Fluids and vasopressors if appropriate

- 5. QT prolongation and torsades de pointes** are reported with oxaliplatin: Use caution in patients with history of QT prolongation or cardiac disease and those receiving concurrent therapy with other QT prolonging medications. Correct electrolyte disturbances prior to treatment and monitor periodically. Baseline and periodic ECG monitoring is suggested in patients with cardiac disease, arrhythmias, concurrent drugs known to cause QT prolongation, and electrolyte abnormalities. In case of QT prolongation, oxaliplatin treatment should be discontinued. QT effect of oxaliplatin with single dose ondansetron 8 mg prechemo has not been formally studied. However, single dose ondansetron 8 mg po would be considered a lower risk for QT prolongation than multiple or higher doses of ondansetron, as long as patient does not have other contributing factors as listed above.
- 6. Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
- 7. Myocardial ischemia and angina occurs rarely in patients receiving fluorouracil or capecitabine.** Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms patients should have urgent cardiac

assessment. Generally re-challenge with either fluorouracil or capecitabine is not recommended as symptoms potentially have a high likelihood of recurrence which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about fluorouracil / capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient's allergy profile.

8. **Diarrhea:** Patients should report mild diarrhea that persists over 24 hours or moderate diarrhea (4 stools or more per day above normal, or a moderate increase in ostomy output). If patient is taking capecitabine, it should be stopped until given direction by the physician. Mild diarrhea can be treated with loperamide (eg. IMODIUM®) following the manufacturer's directions or per the BC Cancer [Guidelines for Management of Chemotherapy-Induced Diarrhea](#). Note that diarrhea may result in increased INR and the risk of bleeding in patients on warfarin.
9. **Dihydropyrimidine dehydrogenase (DPD) deficiency** may result in severe and unexpected toxicity – stomatitis, diarrhea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population.
10. **Possible drug interaction with capecitabine and warfarin** has been reported and may occur at any time. For patients on warfarin, weekly INR during capecitabine therapy is recommended until a stable warfarin dose is established. Thereafter, INR prior to each cycle. Consultation to cardiology/internal medicine should be considered if difficulty in establishing a stable warfarin dose is encountered. Upon discontinuation of capecitabine, repeat INR weekly for one month.
11. **Possible drug interaction with capecitabine and phenytoin and fosphenytoin** has been reported and may occur at any time. Close monitoring is recommended. Capecitabine may increase the serum concentration of these two agents.
12. Oxaliplatin therapy should be interrupted if symptoms indicative of **pulmonary fibrosis** develop – nonproductive cough, dyspnea, crackles, rales, hypoxia, tachypnea or radiological pulmonary infiltrates. If pulmonary fibrosis is confirmed oxaliplatin should be discontinued.
13. **Extravasation:** Oxaliplatin causes irritation if extravasated. Refer to BC Cancer Extravasation Guidelines.
14. **Venous Occlusive Disease** is a rare but serious complication that has been reported in patients (0.02%) receiving oxaliplatin in combination with fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Patients should be instructed to report any jaundice, ascites or hematemesis immediately.
15. Oxaliplatin therapy should be interrupted if **Hemolytic Uremic Syndrome (HUS)** is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.
16. Vascular pain in the affected limb with venous access may be experienced by patients receiving peripheral oxaliplatin. Concurrent hydration in some cases has been shown to decrease associated discomfort.

**Call the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.**

## **REFERENCES:**

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