

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

**Protocol Code:** GIGAVFFOXP  
**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 GIGAVFFOXP 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 GIGAVFFOXP 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 (9 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)
  - Additional CAP approval not required for retreatment

## EXCLUSIONS:

Patients must not have:

- HER-2 positive disease
- 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: CEA, CA 19-9, ECG, 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 Day 1 of each cycle: CBC & Diff, creatinine, ALT, total bilirubin, sodium, potassium, TSH
- Prior to Days 15 and 29 of each cycle: CBC & Diff, creatinine, total bilirubin, ALT
- If clinically indicated: CEA, CA 19-9, morning serum cortisol, lipase, random glucose, alkaline phosphatase, albumin, GGT, creatine kinase, troponin, serum or urine HCG (required for women of childbearing potential if pregnancy suspected), free T3 and free T4, 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 treatment
- 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	4 mg/kg on Day 1 (maximum 400 mg)	IV in 50 mL NS over 30 minutes using a 0.2 micron in-line filter
oxaliplatin*	85 mg/m <sup>2</sup> on Days 1, 15 and 29	IV in 250 to 500 mL D5W over 2 hours**
leucovorin†	400 mg/m <sup>2</sup> on Days 1, 15 and 29	IV in 250 mL D5W over 2 hours**
fluorouracil†	400 mg/m <sup>2</sup> on Days 1, 15 and 29	IV push
fluorouracil	2400 mg/m <sup>2</sup> on Days 1, 15 and 29	IV over 46 h in D5W to a total volume of 230 mL by continuous infusion at 5 mL/h via Baxter LV5 INFUSOR ***

- Each cycle is 42 days (6 weeks).
- Chemotherapy treatment: until disease progression or unacceptable toxicity.
- Pembrolizumab treatment: until disease progression, unacceptable toxicity or a maximum of 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).

\* Oxaliplatin is not compatible with normal saline. Do not piggyback or flush lines with normal saline.

\*\* Oxaliplatin and leucovorin may be infused over the same two hour period by using a Y- site connector placed immediately before the injection site. Oxaliplatin and leucovorin should not be combined in the same infusion bag.

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

† fluorouracil IV push is optional in the advanced setting:

fluorouracil IV push	leucovorin administration options
fluorouracil IV push given	<ul style="list-style-type: none"> <li>• leucovorin given as IV infusion OR</li> <li>• leucovorin given as 20 mg/m<sup>2</sup> IV push</li> </ul>
fluorouracil IV push omitted	<ul style="list-style-type: none"> <li>• leucovorin omitted OR</li> <li>• leucovorin given as IV infusion OR</li> <li>• leucovorin given as 20 mg/m<sup>2</sup> IV push</li> </ul>

\*\*\* Alternative administration:

- For 3000 to 5500 mg dose **select INFUSOR per dose range below (doses outside dose banding range are prepared as ordered):**

Dose Banding Range	Dose Band INFUSOR (mg)
Less than 3000 mg	Pharmacy to mix specific dose
3000 to 3400 mg	3200 mg
3401 to 3800 mg	3600 mg
3801 to 4200 mg	4000 mg
4201 to 4600 mg	4400 mg
4601 to 5000 mg	4800 mg
5001 to 5500 mg	5250 mg
Greater than 5500 mg	Pharmacy to mix specific dose

- Inpatients: 1200 mg/m<sup>2</sup>/day in 1000 mL D5W by continuous infusion daily over 23 h for 2 days

Patients with PICC lines should have a weekly assessment of the PICC site for evidence of infection or thrombosis.

## DOSE MODIFICATIONS:

### Fluorouracil 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).

### 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 fluorouracil

- Dose Modifications for NEUROLOGIC Toxicity
- Dose Modifications for HEMATOLOGIC Toxicity
- Dose Modifications for NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity

**Table 1 - Dose Reduction Levels for All Toxicity**

Agent	Starting Dose	Dose Level -1	Dose Level -2*
oxaliplatin	85 mg/m <sup>2</sup>	65 mg/m <sup>2</sup>	50 mg/m <sup>2</sup>
leucovorin	No dose modifications. <ul style="list-style-type: none"> <li>▪ If IV push fluorouracil is omitted, leucovorin may also be omitted or given as 20 mg/m<sup>2</sup> IV push</li> <li>▪ If oxaliplatin is omitted, leucovorin may be given as 20 mg/m<sup>2</sup> IV push</li> </ul>		
fluorouracil push	400 mg/m <sup>2</sup>	320 mg/m <sup>2</sup>	200 mg/m <sup>2</sup>
fluorouracil Infusion	2400 mg/m <sup>2</sup>	2000 mg/m <sup>2</sup>	1600 mg/m <sup>2</sup>

\* For any additional dose reductions, use 20% less than previous level or consider discontinuing this regimen.

\*\* The recommended starting doses are based on the modified FOLFOX6 regimen which is widely accepted but has not been studied in comparison to the original FOLFOX6 regimen. Patients may start with oxaliplatin 100 mg/m<sup>2</sup> as per FOLFOX6 at the discretion of their physician.

**Table 2 - 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	

***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.***

### A. Dose Modifications for oxaliplatin 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	↓ 1 dose level
<b>Grade 3</b>	1 <sup>st</sup> time: ↓ 1 dose level 2 <sup>nd</sup> time: ↓ 1 dose level	1 <sup>st</sup> time: ↓ 1 dose level 2 <sup>nd</sup> time: ↓ 1 dose level	Discontinue
<b>Grade 4</b>	Discontinue therapy	Discontinue therapy	Discontinue therapy
<b>Pharyngo-laryngeal (see precautions)</b>	Maintain dose level	N/A	N/A

## B. Dose Modifications for HEMATOLOGIC Toxicity

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	ANC (x 10 <sup>9</sup> /L)	oxaliplatin	fluorouracil
<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	Maintain dose level
	4	Less than 0.5	↓ 1 dose level	Omit IV push and ↓ 1 infusion dose level
	Grade	Platelets (x 10 <sup>9</sup> /L)	oxaliplatin	fluorouracil
<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	Maintain dose level
	4	Less than 10	↓ 2 dose levels	Maintain dose level

Day 15 or Day 29	Toxicity		Dose Level	
	Grade	ANC (x 10 <sup>9</sup> /L)	oxaliplatin	fluorouracil
<b>Day 15:</b> <ul style="list-style-type: none"> <li>If ANC less than 1.2 on Day 15 of cycle, omit Day 15. Perform CBC in 2 weeks, prior to Day 29.</li> <li>If ANC is greater than or equal to 1.2, proceed with treatment on Day 29 at the dose level noted across from the <b>lowest ANC</b></li> <li>If ANC remains less than 1.2, omit Day 29 and reduce doses for subsequent cycles at the dose level noted across from the <b>lowest ANC</b></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	Maintain dose level
	4	Less than 0.5	↓ 1 dose level	Omit IV push and ↓ 1 infusion dose level
	Grade	Platelets (x 10 <sup>9</sup> /L)	oxaliplatin	fluorouracil
<b>Day 15:</b> <ul style="list-style-type: none"> <li>If platelets less than 75 on Day 15, omit Day 15. Perform CBC in 2 weeks, prior to Day 29.</li> <li>If platelets greater than or equal to 75, proceed with treatment on Day 29 at the dose level noted across from the <b>lowest platelets</b></li> <li>If platelets remain less than 75, omit Day 29 and reduce doses for subsequent cycles at the dose level noted across from the <b>lowest platelets</b></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	Maintain dose level
	4	Less than 10	↓ 2 dose levels	Maintain dose level



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

Prior to Treatment	Toxicity		Dose Level For Subsequent Doses
	Grade	Diarrhea	
<ul style="list-style-type: none"> <li>If diarrhea greater than or equal to Grade 2 on Day 1 of 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
	2	Increase of 4 to 6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level
	3	Increase of 7 to 9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	↓ 1 dose level of IV push and infusional fluorouracil
	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 of oxaliplatin, IV push and infusional fluorouracil
	Grade	Stomatitis	Dose Level For Subsequent Doses
<ul style="list-style-type: none"> <li>If stomatitis greater than or equal to Grade 2 on Day 1 of 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
	2	Painful erythema, edema, or ulcers but can eat	Maintain dose level
	3	Painful erythema, edema, ulcers, and cannot eat	↓ 1 dose level of IV push and infusional fluorouracil
	4	As above but mucosal necrosis and/or requires enteral support, dehydration	↓ 1 dose level of oxaliplatin, IV push and infusional fluorouracil

## 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	Pharyngo-laryngeal 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. 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.
8. **Extravasation:** Oxaliplatin causes irritation if extravasated. Refer to BC Cancer [Extravasation Guidelines](#).
9. **Venous Occlusive Disease** is a rare but serious complications 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.

10. 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.
11. **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.
12. **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). 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.
13. **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. Fluorouracil should be permanently discontinued in patients exhibiting exaggerated or prolonged neutropenia, mucositis, and diarrhea.
14. **Possible drug interaction with fluorouracil and warfarin** has been reported and may occur at any time. For patients on warfarin, weekly INR during fluorouracil 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 fluorouracil, repeat INR weekly for one month.
15. **Possible drug interaction with fluorouracil and phenytoin and fosphenytoin** has been reported and may occur at any time. Close monitoring is recommended. Fluorouracil may increase the serum concentration of these two agents.

**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:

1. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet* 2021; Aug 28; 398 (10302):759-771. doi: 10.1016/S0140-6736(21)01234-4. PMID: 34454674
2. Pembrolizumab (Keytruda) CADTH Reimbursement Recommendation. *Canadian Journal of Health Technologies* 2021; 1(12): 1-19.
3. ter Veer E, Mohammad NH, et al. The efficacy and safety of first-line chemotherapy in advanced esophagogastric cancer: A network meta-analysis. *JNCI* 2016;108(10): djw166. <https://doi.org/10.1093/jnci/djw166>.
4. Cunningham D et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *NEJM* 2008; 358:36-46. January 3, 2008 DOI: 10.1056/NEJMoa073149. (REAL-2 Trial)
5. Peng C, Saffo S, Shusterman M, et al. Analysis of the Impact of Eliminating Bolus 5-fluorouracil in Metastatic Colorectal Cancer. *J Clin Onc*. 2023 Feb 1;41 (4): Suppl.59
6. Peng C, Saffo S, Oberstein PE, et al. Omission of 5-Fluorouracil Bolus From Multidrug Regimens for Advanced Gastrointestinal Cancers: A Multicenter Cohort Study. *J Natl Compr Canc Netw*. 2024 Sep 5;22(8):521-527.
7. Shah MA, Kennedy EB, Alarcon-Rozas AE, et al. Immunotherapy and Targeted Therapy for Advanced Gastroesophageal Cancer: ASCO Guideline. *J Clin Oncol*. 2023 Mar 1;41(7):1470-1491. PMID: 36603169.
8. Snow S, Gabrielson D, Lim H, Tehfe M, Brezden-Masley C. Best Practices for Managing Patients with Unresectable Metastatic Gastric and Gastroesophageal Junction Cancer in Canada. *Curr Oncol*. 2024 Apr 30;31(5):2552-2565.