BC Cancer Protocol Summary for Treatment of Advanced Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinoma using Pembrolizumab, Capecitabine, Oxaliplatin, and Trastuzumab

Protocol Code:	*GIGAVPCOXT*
Tumour Group:	*Gastrointestinal*
Contact Physician:	*GI Systemic Therapy*

ELIGIBILITY:

Patients must have:

- Metastatic or inoperable locally advanced gastric, gastroesophageal junction or esophageal adenocarcinoma,
- No prior treatment in the advanced setting,
- HER-2 overexpression defined as either IHC3+, or FISH amplification ratio of greater than or equal to 2 per BC Cancer central laboratory, and
- PD-L1 expression with combined positive score (CPS) greater than or equal to 1

Patients should have:

- Good performance status,
- Access to a treatment centre with expertise in managing immunotherapy mediated toxicities of pembrolizumab,
- No signs or symptoms of cardiac disease. For patients with cardiac risk factors or history of cardiac disease, a MUGA or ECHO should be done to document normal left ventricular ejection fraction (LVEF),
- Adequate marrow reserve, renal and liver function

Notes:

- Patients currently on treatment with GIGAVCOXT without progression may receive GIGAVPCOXT if all other eligibility criteria are met
- At time of subsequent disease progression, pembrolizumab retreatment (with or without trastuzumab and/or chemotherapy) is funded for an additional 1 year of therapy (17 cycles) if:
  - Patients have completed 2 years without progression
  - Patients have stopped pembrolizumab for reasons other than progression (e.g., toxicity or complete response)
  - CAP approval not required for retreatment
- Patients are still eligible for this protocol if they receive less than or equal to 3 cycles of standard chemotherapy while the results of HER-2 and/or PD-L1 testing are pending

EXCLUSIONS:

Patients must not have:

- Uncontrolled CNS metastases,
- Prior immunotherapy for advanced disease. Prior treatment with adjuvant nivolumab permitted if disease-free interval of 6 months or longer,

- 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,
- Baseline LVEF less than 50%,
- Severe renal impairment (creatinine clearance less than 30 mL/min),
- Avoid in patients with congenital long QT syndrome,
- 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 recent myocardial infarction, uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure or other serious medical illness,
- Patients with symptomatic peripheral neuropathy,
- Patients with baseline greater than 3 loose bowel movements per day

TESTS:

- Baseline: CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, albumin, sodium, potassium, TSH, morning serum cortisol, *DPYD* test (not required if previously tested, or tolerated fluorouracil or capecitabine), chest x-ray or CT chest
- Baseline if clinically indicated: CEA, CA19-9, 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, ECG, echocardiogram or MUGA scan
- Prior to each cycle: CBC & Diff, creatinine, ALT, total bilirubin, sodium, potassium, TSH
- If clinically indicated: CEA, CA19-9, morning serum cortisol, lipase, random glucose, 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, alkaline phosphatase, albumin, GGT, creatine kinase, troponin, ECG, chest x-ray, echocardiogram or MUGA scan
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle
- Consider weekly nursing assessment for capecitabine toxicity in first two cycles and when increasing capecitabine dose
- Weekly telephone nursing assessment for signs and symptoms of pembrolizumab 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 to 5 days following oxaliplatin administration**
- **Cryotherapy (ice chips) should NOT be used as may exacerbate oxaliplatin-induced pharyngo-laryngeal dysesthesias**

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
pembrolizumab	2 mg/kg (maximum 200 mg)	IV in 50 mL NS over 30 minutes using a 0.2 micron in-line filter
trastuzumab	8 mg/kg for 1st cycle ONLY	IV in 250 mL NS over 1 hour 30 minutes for 1st cycle (Observe for 1 hour post-infusion)
	then 6 mg/kg with subsequent cycles	IV in 250 mL NS over 1 hour for 2nd cycle and over 30 min for all subsequent cycles. (Observe for 30 minutes post-infusion*)
oxaliplatin**	130 mg/m^2	IV in 250 to 500 mL D5W over 2 hours
capecitabine$^{\text{Ŧ}}$	1000 mg/m^2 BID x 14 days (Days 1 to 14) (Total daily dose = 2000 mg/m^2/day)	PO

* Observation period not required after 3 consecutive treatments with no reaction.

** Concurrent use of up to 500 mL D5W hydration at maximum rate of 250 mL/h with peripheral administration of oxaliplatin can be given

Ŧ Capecitabine is available as 150 mg and 500 mg tablets (refer to Capecitabine Suggested Tablet Combination Table for dose rounding).

- Oxaliplatin line should be flushed with D5W pre and post dose as oxaliplatin should not be mixed with normal saline.
- Repeat every **3 weeks** to a maximum of 36 cycles or 2 years of treatment

- Retreatment may be permitted (see eligibility)
- If patients are intolerant of one or more components of the treatment after at least 1 cycle of pembrolizumab with oxaliplatin, trastuzumab and capecitabine, the other component(s)* can be continued

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

DOSAGE MODIFICATIONS :

Pembrolizumab:

- No specific dose modifications. 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).

Trastuzumab :

- No dose modifications required. Trastuzumab is discontinued if unacceptable toxicity occurs
- Notes:
  - Weight will be measured at each scheduled physician visit. Consider change in trastuzumab dose for weight change greater than 10%
  - If an interruption in treatment of greater than 6 weeks occurs, consider repeating the loading dose of 8 mg/kg, then resume usual dosing

Capecitabine and oxaliplatin (Sections A, B & C) :

- **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.

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

Oxaliplatin Neurotoxicity Definitions

Grade 1	Paresthesias/dysesthesias of short duration that resolve; do not interfere with function
Grade 2	Paresthesias / dysesthesias interfering with function, but not activities of daily living (ADL)
Grade 3	Paresthesias / dysesthesias with pain or with functional impairment which interfere with ADL
Grade 4	Persistent paresthesias / dysesthesias that are disabling or life-threatening
Pharyngo-laryngeal dysesthesias (investigator discretion used for grading): 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

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

Drug	Dose Level 0 (Starting Dose)	Neurotoxicity Dose Level – 1N	Neurotoxicity Dose Level – 2N	Neurotoxicity Dose Level – 3N
oxaliplatin	130 mg/m^2	100 mg/m^2	65 mg/m^2	Discontinue Therapy

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

A. Dose Modifications for NEUROLOGIC Toxicity: oxaliplatin

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

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^2	100 mg/m^2	85 mg/m^2	Discontinue
capecitabine	1000 mg/m^2 bid	750 mg/m^2 bid	500 mg/m^2 bid	Discontinue

B. Dose Modifications for HEMATOLOGIC Toxicity

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	ANC ($x10^9$/L)	oxaliplatin	capecitabine
▪ If ANC less than 1.2 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. ▪ If ANC is greater than or equal to 1.2 within 2 weeks, proceed with treatment at the dose level noted across from the **lowest ANC** result of the delayed week(s). ▪ If ANC remains less than 1.2 after 2 weeks, discontinue treatment.	1	Greater than or equal to 1.2	Maintain dose level	Maintain dose level
	2	1 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

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	Platelets ($x10^9$/L)	oxaliplatin	capecitabine
▪ If platelets less than 75 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. ▪ If platelets greater than or equal to 75 within 2 weeks, proceed with treatment at the dose level noted across from the **lowest platelets** result of the delayed week(s). ▪ If platelets remain less than 75 after 2 weeks, discontinue treatment.	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
▪ If diarrhea greater than or equal to Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If diarrhea is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the **highest** Grade experienced. ▪ If diarrhea remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.	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*

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	Stomatitis	oxaliplatin	capecitabine
▪ If stomatitis greater than or equal to Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If stomatitis is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the **highest** Grade experienced. ▪ If stomatitis remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.	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	
▪ 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. ▪ If hand-foot skin reaction is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the **highest** Grade experienced. ▪ If hand-foot skin reaction remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.	**Grade**	**Palmar-Plantar Erythrodysesthesia (Hand-Foot Skin Reaction)**	**oxaliplatin**	**capecitabine**
	1	Skin changes (e.g., numbness, dysesthesia, paresthesia, tingling, erythema) with discomfort not disrupting normal activities	Maintain dose level	Maintain dose level
	2	Skin changes (e.g., erythema, swelling) with pain affecting activities of daily living	Maintain dose level	Maintain dose level
	3	Severe skin changes (e.g., 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 or equal to 50	100%
30 to less than 50	75%
Less than 30	Discontinue Therapy

Cockcroft-Gault Equation:

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

N = 1.23 male
N = 1.04 female

PRECAUTIONS:

1. **Serious immune-mediated reactions to pembrolizumab**: can be severe to fatal and usually occur during the pembrolizumab 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. **Pembrolizumab 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 SCOXRX: BC Cancer Inpatient Protocol Summary for Oxaliplatin Desensitization for more information.

4. Oxaliplatin-induced **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_2 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
Treatment	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. **Trastuzumab infusion-associated symptoms,** usually chills and fever, can occur in some patients during the first trastuzumab infusion. Symptoms may be treated with acetaminophen, diphenhydrAMINE and meperidine with or without an infusion rate reduction. Rarely, serious infusion-related reactions have been reported. For serious reactions, discontinue the trastuzumab infusion and provide supportive therapy such as oxygen, beta-agonists and corticosteroids
6. **Cardiac toxicity**: Trastuzumab can produce ventricular dysfunction and congestive heart failure in less than 2% of patients. The majority of patients who develop cardiac dysfunction are symptomatic. Regular monitoring of asymptomatic patients is not routinely necessary but can be considered after 6 months of treatment with trastuzumab. If no significant decline in cardiac function, repeated testing is not generally necessary, unless clinically indicated. Discontinue treatment for symptomatic congestive heart failure or serious cardiac arrhythmias. 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.

7. **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.
8. **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.
9. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
10. 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.
11. **Extravasation**: Oxaliplatin causes irritation if extravasated. Refer to BC Cancer Extravasation Guidelines.
12. **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.
13. **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.
14. 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.

15. **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.
16. **Dihydropyrimidine dehydrogenase (DPD) deficiency** may result in severe and unexpected toxicity to capecitabine – stomatitis, diarrhea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population.
17. **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.
18. **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.
19. A **drug interaction** with **trastuzumab and warfarin** has also been reported.

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. Janjigian YY, Kawazoe A, Bai Y, et al.; KEYNOTE-811 Investigators. Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial. Lancet. 2023 Dec 9;402(10418):2197-2208.
2. Pembrolizumab (Keytruda) CADTH [Canada's Drug Agency (CDA-AMC)] Reimbursement Recommendation. Canadian Journal of Health Technologies July 2024; 4(7): 1-32.