BC Cancer Protocol Summary for First-line Palliative Treatment of Advanced Biliary Tract Cancer using Pembrolizumab, Gemcitabine and Platinum

Protocol Code	*GIAVPEMPG*
Tumour Group	*Gastrointestinal*
Contact Physician	*GI Systemic Therapy*

ELIGIBILITY:

Patients must have:

- Metastatic or unresectable biliary tract (including intra- and extrahepatic biliary tract cancer, including mixed hepatocellular carcinoma-cholangiocarcinoma or gallbladder) cancer, and
- Unresectable or metastatic disease at diagnosis with no prior treatment, or
- Recurrent disease and greater than 6 months since completion of adjuvant therapy or curative surgery

Patients should have:

- Good performance status,
- Adequate hepatic and renal function,
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of pembrolizumab

Notes:

- Patients who are currently on treatment with gemcitabine and platinum per protocol GIAVPG and who have not progressed may switch to GIAVPEMPG if all other eligibility criteria are met
- Patients are eligible to receive chemotherapy with pembrolizumab (GIAVPEMPG) or chemotherapy with durvalumab (GIAVDURPG), but not sequential use of these agents
- At time of subsequent disease progression, pembrolizumab retreatment (with or without chemotherapy) is allowed for an additional 1 year of therapy 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 with ampulla of Vater cancer

CAUTIONS:

- Inadequate renal function (creatinine clearance less than 45 mL/min by GFR measurement or Cockcroft formula) unless treated with CARBOplatin
- Active or previous autoimmune disease
- Patients with long term immunosuppressive therapy or systemic corticosteroids (requiring more than 10 mg predniSONE/day or equivalent)

TESTS:

- Baseline: CBC & Diff, creatinine, sodium, potassium, ALT, alkaline phosphatase, total bilirubin, albumin, TSH, morning serum cortisol, chest x-ray or CT chest
- Baseline if clinically indicated: GGT, lipase, random glucose, serum or urine HCG (required for women of childbearing potential if pregnancy suspected), serum ACTH levels, testosterone, estradiol, FSH, LH, creatine kinase, troponin, free T3 and free T4, ECG, CEA, CA 19-9
- Cycles 1 to 8:
  - Day 1: CBC & Diff, creatinine, ALT, total bilirubin, sodium, potassium, TSH
  - Day 8: CBC & Diff
  - Day 8, if using CISplatin: creatinine
- Cycle 9 onward:
  - Day 1: CBC & Diff, creatinine, ALT, total bilirubin, sodium, potassium, TSH
  - Day 8, if gemcitabine is given: CBC & Diff
- If clinically indicated: alkaline phosphatase, albumin, morning serum cortisol, lipase, random glucose, 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, GGT, CEA, CA 19-9, ECG, chest x-ray
- For patients on warfarin, weekly INR during gemcitabine and platinum 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:

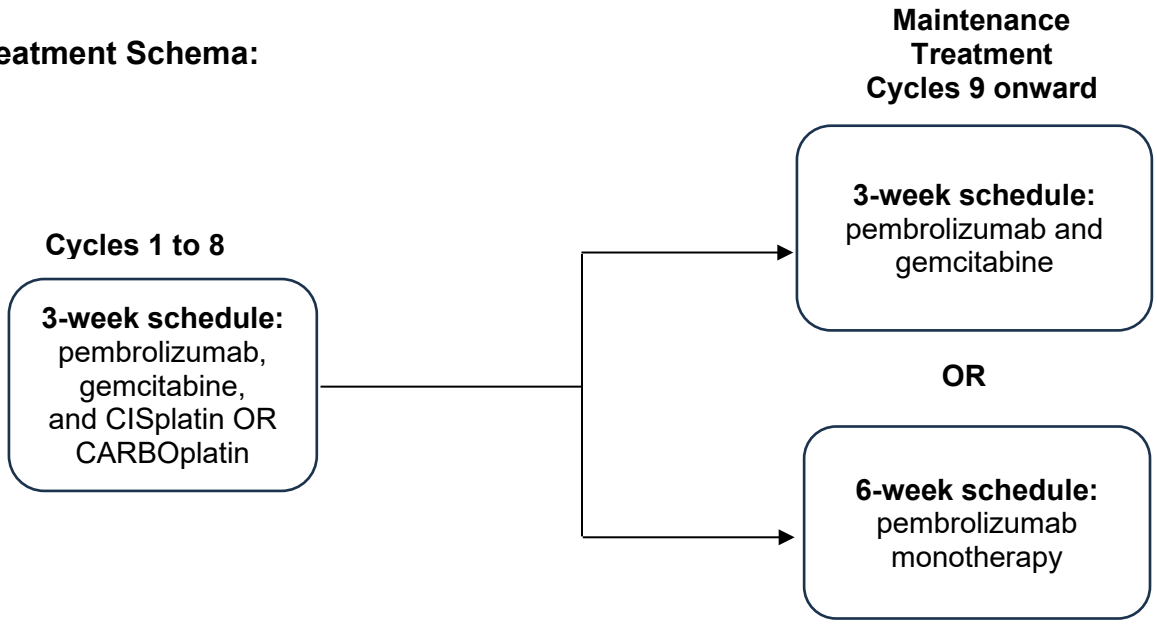
Cycles 1 to 8:

- For CISplatin: antiemetic protocol for moderately emetogenic chemotherapy protocols
- For CARBOplatin: antiemetic protocol for highly 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

Cycle 9 onward:

- Antiemetic protocol for low emetogenic chemotherapy if gemcitabine is given. Antiemetics not usually required for pembrolizumab (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

Treatment Schema:



TREATMENT

Cycles 1 to 8:

Drug	Dose	BC Cancer Administration Guideline
pembrolizumab	2 mg/kg (maximum 200 mg) on Day 1	IV in 50 mL NS over 30 minutes using a 0.2 micron in-line filter
gemcitabine	1000 mg/m^2 on Days 1 and 8	IV in 250 mL NS over 30 min
CISplatin	25 mg/m^2 on Days 1 and 8	IV in 100 to 250 mL NS over 30 min

- Repeat every **3 weeks.**
- Duration of treatment:
  - CISplatin: maximum of 8 cycles
  - gemcitabine: until disease progression or unacceptable toxicity
  - pembrolizumab: until disease progression, unacceptable toxicity, or to a maximum of two years of treatment
- If patients are intolerant of the chemotherapy after at least one cycle, pembrolizumab may be continued as single agent

Cycle 9 onward (maintenance):

- pembrolizumab may be given every 3 weeks with gemcitabine, or every 6 weeks as monotherapy
- Cycle 9 starts 21 days after Cycle 8

Pembrolizumab and gemcitabine option:

Drug	Dose	BC Cancer Administration Guideline
pembrolizumab	2 mg/kg (maximum 200 mg) on Day 1	IV in 50 mL NS over 30 minutes using a 0.2 micron in-line filter
gemcitabine	1000 mg/m^2 on Days 1 and 8	IV in 250 mL NS over 30 min

- Repeat every **3 weeks**

OR

Pembrolizumab only option:

Drug	Dose	BC Cancer Administration Guideline
pembrolizumab	4 mg/kg (maximum 400 mg) on Day 1	IV in 50 mL NS over 30 minutes using a 0.2 micron in-line filter

- Repeat every **6 weeks**

- Duration of treatment:
  - gemcitabine: until disease progression or unacceptable toxicity
  - pembrolizumab: until disease progression, unacceptable toxicity, or to a maximum of two years of treatment
- Retreatment may be allowed (refer to eligibility)

DOSE MODIFICATIONS:

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

1. Hematology

- For gemcitabine and CISplatin:

ANC ($x 10^9$/L)		Platelets ($x 10^9$/L)	Day 1		Day 8	
			gemcitabine	CISplatin	gemcitabine	CISplatin
Greater than or equal to 1.0	and	Greater than or equal to 100	100%	100%	100%	100%
0.5 to less than 1.0	or	75 to less than 100	75%	100%	75%	100%
Less than 0.5	or	Less than 75	Delay	Delay	Omit	Omit

2. Renal Dysfunction:

- For gemcitabine and CISplatin*:

Creatinine Clearance (mL/min)	Day 1		Day 8	
	gemcitabine	CISplatin	gemcitabine	CISplatin
Greater than or equal to 60	100%	100%	100%	100%
45 to less than 60	100%	50%	100%	50%
Less than 45	Delay	Delay	100%	Omit

*** Alternatively, CARBOplatin may be used instead of CISplatin:**

Drug	Dose	BC Cancer Administration Guideline
CARBOplatin	AUC 5 DAY 1 only Dose = AUC x (GFR* +25)	IV in 100 to 250mL NS over 30 minutes.

* *Measured GFR* (e.g., nuclear renogram) is preferred whenever feasible, *particularly* in circumstances of co-morbidity that could affect renal function (third-space fluid accumulations, hypoproteinemia, potentially inadequate fluid intake, etc.). The lab reported GFR (MDRD formula) may be used as an alternative to the Cockcroft-Gault estimate of GFR; the estimated GFR reported by the lab or calculated using the Cockcroft-Gault equation should be capped at 125 mL/min when it is used to calculate the initial carboplatin dose. When a nuclear renogram is available, this clearance would take precedence.

Cockcroft-Gault Formula

$$GFR = \frac{N^* \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

*For males N = 1.23; for females N = 1.04

Note: The *same* method of estimation should be used throughout the treatment course (i.e. if lab reported GFR was used initially, this should be used for dosing in all subsequent cycles and not the Cockcroft-Gault estimate).

PRECAUTIONS:

1. **Serious immune-mediated reactions to pembrolizumab**: 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 to pembrolizumab**: 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. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Irreversible renal failure associated with hemolytic uremic syndrome may occur (rare) with gemcitabine. Use caution with pre-existing renal dysfunction.
5. **Pulmonary Toxicity**: Acute shortness of breath may occur. Discontinue treatment if drug-induced pneumonitis is suspected.
6. **Drug Interaction:** Possible interaction between gemcitabine and warfarin has been reported and may occur at any time. Close monitoring is recommended (monitor INR weekly during gemcitabine therapy and for 1 to 2 months after discontinuing gemcitabine treatment).

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. Kelley RK, Ueno M, Yoo C, et al; KEYNOTE-966 Investigators. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023 Jun 3;401(10391):1853-1865.
2. Pembrolizumab (Keytruda) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies Jul 2024; 4(7): 1-26.