BC Cancer Protocol Summary for First-Line Treatment of dMMR/MSI-H Metastatic Colorectal Cancer using Pembrolizumab

***Protocol Code*:** *GIAVPEM*

***Tumour Group*:** *Gastrointestinal*

***Contact Physician*:** *GI Systemic Therapy*

ELIGIBILITY:

Patients must have:

- Measurable metastatic colorectal adenocarcinoma, de novo or relapsed,
- dMMR/MSI-H (tested on primary or metastatic tumour),
- No prior treatment for metastatic disease

Patients should have:

- ECOG performance status 0 to 2
- Life expectancy 3 months or more
- Adequate hepatic and renal function
- Access to a treatment center with expertise to manage immune-mediated adverse reactions of pembrolizumab

Notes:

- At time of subsequent disease progression, retreatment is allowed for an additional 1 year of treatment:
  - Retreatment without CAP approval is allowed for an additional 18 cycles for 3-weekly dosing or 9 cycles for 6-weekly dosing (or a combination of both) if patient has completed the initial pembrolizumab treatment without disease progression.
- Patients are eligible to receive pembrolizumab or combination ipilimumab with nivolumab, but not sequential use of these agents. Switching for intolerance is permitted.
- BC Cancer Compassionate Access Program (CAP) approval is not required to switch between 3-weekly and 6-weekly dosing of pembrolizumab.

EXCLUSIONS:

Patients must not have:

- Prior immunotherapy for metastatic colorectal cancer

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)

TESTS:

- Baseline: CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, albumin,sodium, potassium, TSH, morning serum cortisol, 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
- 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
- Weekly telephone nursing assessment for signs and symptoms of side effects while on treatment (optional)

PREMEDICATIONS:

- Antiemetics are not usually required.
- If required, antiemetic protocol for low emetogenicity (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:

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

* Select dose per Dose Banding Table (appendix).

- Initial pembrolizumab treatment: Repeat **every 3 weeks** until disease progression, unacceptable toxicity or a maximum of 35 cycles for 3-weekly dosing or 18 cycles for 6-weekly dosing (or a combination of both) or 2 years of treatment. Patients may have treatment breaks for reasons other than progression (e.g., toxicities, treatment holiday, vacation).
- Retreatment may be allowed (refer to Eligibility).

DOSE MODIFICATIONS:

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)**

PRECAUTIONS:

- **Serious immune-mediated reactions**: these can be severe to fatal and usually occur during the treatment course. They may include enterocolitis, intestinal perforation or hemorrhage, hepatitis, dermatitis, neuropathy, endocrinopathy, 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**).
- **Infusion-related reactions:** isolated cases of severe reaction have been reported. In case of a severe reaction, pembrolizumab infusion should be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive pembrolizumab with close monitoring. Premedications with acetaminophen and anti-histamine may be considered if there is a history of reaction.

Contact the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair with any problems or questions regarding this treatment program.

References:

1. Andre T, Shui KK, Kim TW, Jensen BV, et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. N Engl J Med. 2020;383(23):2207-2218.
2. Andre T, Amonkar MA, Norquist JM, Shui KK, et al. Health-related quality of life in patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer treated with first-line pembrolizumab versus chemotherapy (KEYNOTE-177): an open-label, randomised, phase 3 trial. The Lancet Oncology 2021;22(5), 665-677.

Appendix. Dose Bands

PEMBROLIZUMAB DOSE BANDING TABLE (2 mg/kg capped 200 mg)

Ordered Dose (mg)		Rounded dose (mg)
From:	To:	
Less than 70		**Pharmacy prepares specific dose**
70	80.49	**75**
80.5	92.49	**85**
92.5	110.49	**100**
110.5	137.49	**125**
137.5	162.49	**150**
162.5	187.49	**175**
187.5	200	**200**