

BC Cancer Protocol Summary for First-Line Treatment of dMMR/MSI-H Metastatic Colorectal Cancer using 6-Weekly Pembrolizumab

Protocol Code:

GIAPVEM6

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, ALT, alkaline phosphatase, 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	4 mg/kg* (maximum 400 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 6 weeks** until disease progression, unacceptable toxicity or a maximum of 18 cycles for 6-weekly dosing or 35 cycles for 3-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:

- 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.

Call 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.
3. CADTH Technology Review: Optimal Use 360 Report. Dosing and timing of immunology drugs. November 2019. Accessed online: <https://www.cadth.ca/> 25 March 2020.
4. Elassaiss-Schaap J, Rossenu S, Lindauer A, et al. Using model-based “learn and confirm” to reveal the pharmacokinetics-pharmacodynamics relationship of pembrolizumab in the KEYNOTE-001 trial. *CPT Pharmacometrics Syst Pharmacol.* 2017 Jan;6(1):21-28. doi: 10.1002/psp4.12132. Epub 2016 Nov 8.
5. Freshwater T, Kondic A, Ahamadi M, et al. Evaluation of dosing strategy for pembrolizumab for oncology indications. *J Immunother Cancer* 2017; 017 May 16;5:43. doi: 10.1186/s40425-017-0242-5. eCollection 2017.
6. Lala M, Li TR, de Alwis DP. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and stimulation. *Eur J Cancer.* 2020;131:68-75.

Appendix. Dose Bands

PEMBROLIZUMAB DOSE BANDING TABLE (4 mg/kg capped 400 mg)

Ordered Dose (mg)		Rounded dose (mg)
From:	To:	
Less than 137.5		Pharmacy prepares specific dose
137.5	162.49	150
162.5	187.49	175
187.5	221.49	200
221.5	242.49	225
242.5	264.49	250
264.5	284.49	275
284.5	332.49	300
332.5	374.49	350
374.5	400	400