BC Cancer Protocol Summary for the Treatment of Unresectable or Metastatic Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Colorectal Cancer using Ipilimumab and Nivolumab

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

ELIGIBILITY:

Patients must have:

- Histologically confirmed unresectable locally advanced or metastatic colorectal adenocarcinoma,
- Confirmed dMMR/MSI-H tumour status,
- No prior systemic treatment for metastatic disease

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 immunotherapy checkpoint inhibitors

Notes:

- Patients who received prior surgery, radiotherapy, neoadjuvant and/or adjuvant chemotherapy are eligible
- Patients are eligible to receive pembrolizumab or combination ipilimumab with nivolumab, but not sequential use of these agents. Switching for intolerance is permitted.
- At the time of subsequent progression, retreatment with nivolumab (with or without ipilimumab) is allowed for an additional 1 year of treatment if the patient has completed the initial ipilimumab and nivolumab without disease progression and progression occurred more than 6 months following treatment completion.

EXCLUSIONS:

Patients must not have:

- Prior immunotherapy for advanced 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)
- History of interstitial lung disease or pneumonitis

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 during phase (Cycles 1 to 4), then optional in subsequent cycles

PREMEDICATIONS:

- Antiemetics are not usually required
- Antiemetic protocol for low emetogenicity (see SCNAUSEA)
- If prior infusion reactions to ipilimumab or nivolumab: diphenhydrAMINE 50 mg PO, acetaminophen 325 to 975 mg PO, and hydrocortisone 25 mg IV 30 minutes prior to treatment

TREATMENT:

Induction Phase

Drug	Dose	BC Cancer Administration Guideline
nivolumab	3 mg/kg* (maximum 240 mg)	IV in 50 to 100 mL NS over 30 minutes using a 0.2 micron in-line filter**
ipilimumab	1 mg/kg*	IV in 25 to 100 mL NS over 30 minutes using a 0.2 micron in-line filter**

*Select dose per Dose Banding Tables Induction Phase (appendix)
**Use a separate infusion line and filter for each drug

- Repeat every 3 weeks for 4 cycles then proceed to maintenance phase
- If nivolumab is discontinued due to toxicity, ipilimumab should be discontinued.
- If ipilimumab is discontinued due to toxicity, nivolumab may be continued as monotherapy.

Maintenance Phase

Drug	Dose	BC Cancer Administration Guideline
nivolumab	6 mg/kg* (maximum 480 mg)	IV in 50 to 100 mL NS over 30 minutes using a 0.2 micron in-line filter

*Select dose per Dose Banding Tables Maintenance Phase (appendix)

- Start 3 weeks after last induction phase dose and repeat every 4 weeks until clinical disease progression or unacceptable toxicity, up to a maximum of 27 cycles (including doses given during the induction phase) 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 reaction have been reported. In case of severe reaction, ipilimumab and/or nivolumab infusion should be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive ipilimumab and/or nivolumab with close monitoring. Premedications with acetaminophen and antihistamine may be considered.

Call 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 et al. Nivolumab plus ipilimumab versus nivolumab in microsatellite instability-high metastatic colorectal cancer (CheckMate 8HW): a randomized, open-label, phase 3 trial. Lancet 2025; 405:383-395.
2. Nivolumab Plus Ipilimumab (Opdivo Plus Yervoy) Canada's Drug Agency (CDA-AMC) Reimbursement Recommendation. Canadian Journal of Health Technologies. October 2025; 5(10): 1-24.

Appendix. Dose Bands

Induction Phase

NIVOLUMAB DOSE BANDING TABLE (1-3 mg/kg capped at 240 mg)

Ordered Dose (mg)		Rounded dose (mg)
From:	To:	
Less than 36		**Pharmacy prepares specific dose**
36	43.49	**40**
43.5	51.49	**48**
51.5	60.49	**56**
60.5	69.49	**66**
69.5	77.49	**74**
77.5	87.49	**80**
87.5	95.49	**90**
95.5	109.49	**100**
109.5	131.49	**120**
131.5	153.49	**140**
153.5	175.49	**160**
175.5	197.49	**180**
197.5	219.49	**200**
219.5	239.49	**220**
239.5	240	**240**

IPILIMUMAB DOSE BANDING TABLE (1-10 mg/kg with no capped dose)

Ordered Dose (mg)		Rounded dose (mg)
From:	To:	
Less than 41		**Pharmacy prepares specific dose**
41	46.49	**45**
46.5	54.49	**50**
54.5	59.49	**55**
59.5	64.49	**60**
64.5	74.49	**70**
74.5	84.49	**80**
84.5	94.49	**90**
94.5	109.49	**100**
109.5	128.49	**120**
128.5	139.49	**130**
139.5	164.49	**150**
164.5	181.49	**170**
181.5	219.49	**200**
219.5	239.49	**220**
239.5	274.49	**250**
274.5	329.49	**300**
329.5	384.49	**350**
384.5	439.49	**400**
439.5	494.49	**450**
More than 494.49		**Pharmacy prepares specific dose**

Maintenance Phase

NIVOLUMAB DOSE BANDING TABLE (6 mg/kg capped at 480 mg)

Ordered Dose (mg)		Rounded dose (mg)
From:	To:	
Less than 191.5		**Pharmacy prepares specific dose**
191.5	219.49	**200**
219.5	239.49	**220**
239.5	263.49	**240**
263.5	298.49	**280**
298.5	319.49	**300**
319.5	349.49	**320**
349.5	373.49	**360**
373.5	398.49	**380**
398.5	439.49	**400**
439.49	478.49	**440**
478.5	480	**480**