

# BC Cancer Protocol Summary for First-Line Treatment of Advanced Hepatocellular Carcinoma using Ipilimumab and Nivolumab

**Protocol Code**

*GIIPNI*

**Tumour Group**

*Gastrointestinal*

**Contact Physician**

*GI Systemic Therapy*

## **ELIGIBILITY:**

Patients must have:

- Previously untreated unresectable or advanced hepatocellular carcinoma (HCC),
- No amenability to curative or locoregional therapies,
- Child-Pugh A liver function

Patients should have:

- Good performance status,
- Adequate baseline hematological and renal function,
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of immunotherapy checkpoint inhibitors

Notes:

- Patients who had a partial resection or with residual disease that cannot be treated with locoregional therapies are eligible
- Patients are eligible for either ipilimumab and nivolumab (GIIPNI), atezolizumab and bevacizumab (GIATZB) or tremelimumab and durvalumab (GITREMDUR), but not sequential use. Switching for intolerance is permitted, in the absence of disease progression.
- 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. The additional year of treatment should include nivolumab plus ipilimumab for a maximum of 4 cycles, followed by nivolumab monotherapy.

## **EXCLUSIONS:**

Patients must not have:

- Prior systemic therapy for unresectable or advanced hepatocellular carcinoma
- Uncontrolled hepatitis B or hepatitis C infection
- Known fibrolamellar hepatocellular carcinoma, sarcomatoid hepatocellular carcinoma, or mixed cholangiocarcinoma and hepatocellular carcinoma
- Active central nervous system metastases (unless asymptomatic and/or stable)

## **CAUTIONS:**

- Active, uncontrolled 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, INR, TSH, morning serum cortisol, chest x-ray or CT chest
- Baseline if clinically indicated: AFP, troponin, creatine kinase, 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, sodium, potassium, total bilirubin, ALT, albumin, INR, TSH
- If clinically indicated: AFP, alkaline phosphatase, GGT, 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, chest x-ray, ECG
- Weekly telephone nursing assessment for signs and symptoms of side effects during combination phase (Cycles 1 to 4), then optional during 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	1 mg/kg*	IV in 25 to 100 mL NS over 30 minutes using a 0.2 micron in-line filter**
ipilimumab	3 mg/kg*	IV in 50 to 250 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

## 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 a 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.

**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. Yau T, Galle PR, Decaens T et al; CheckMate 9DW investigators. Nivolumab plus ipilimumab versus lenvatinib or sorafenib as first-line treatment for unresectable hepatocellular carcinoma (CheckMate 9DW): an open-label, randomised, phase 3 trial. *Lancet*. 2025 May 24;405(10492):1851-1864.
2. Nivolumab Plus Ipilimumab (Opdivo Plus Yervoy) Canada's Drug Agency (CDA-AMC) Reimbursement Recommendation. *Canadian Journal of Health Technologies*. December 2025; 5(12): 1-15.

## Appendix. Dose Bands

### Induction Phase

#### **NIVOLUMAB DOSE BANDING TABLE (1-3 mg/kg with no capped dose)**

Ordered Dose (mg)		Rounded dose (mg)
From:	To:	
Less than 36		<b>Pharmacy prepares specific dose</b>
36	43.49	<b>40</b>
43.5	51.49	<b>48</b>
51.5	60.49	<b>56</b>
60.5	69.49	<b>66</b>
69.5	77.49	<b>74</b>
77.5	87.49	<b>80</b>
87.5	95.49	<b>90</b>
95.5	109.49	<b>100</b>
109.5	131.49	<b>120</b>
131.5	153.49	<b>140</b>
153.5	175.49	<b>160</b>
175.5	197.49	<b>180</b>
197.5	219.49	<b>200</b>
219.5	239.49	<b>220</b>
239.5	259.49	<b>240</b>
259.5	274.49	<b>260</b>
274.5	329.49	<b>300</b>
329.5	359.49	<b>340</b>
359.5	372.49	<b>360</b>
372.5	439.49	<b>400</b>
439.5	483.49	<b>440</b>
More than 483.49		<b>Pharmacy prepares specific dose</b>

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

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

## **Maintenance Phase**

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

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