BC Cancer Protocol Summary for the Treatment of Metastatic or Advanced Renal Cell Carcinoma Using Ipilimumab and Nivolumab

Protocol Code	*GUAVIPNI*
Tumour Group	*Genitourinary*
Contact Physician	*Dr. C. Kollmannsberger*

ELIGIBILITY:

- First line treatment for intermediate or poor-risk advanced renal-cell carcinoma
- Any histology
- Good performance status
- Adequate hepatic and renal function
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of checkpoint inhibitors

EXCLUSIONS:

- Prior systemic therapy for metastatic disease
- Uncontrolled central nervous system metastases (if CNS mets present they should be asymptomatic and/or stable)
- Concurrent active autoimmune disease
- Use with cautions in patients with long term immunosuppressive therapy or systemic corticosteroids (Requiring more than 10 mg prednisone/day or equivalent)

TESTS:

- Baseline: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, glucose, TSH, morning serum cortisol, chest x-ray
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): HBsAg, HBcoreAb
- Note: tuberculin skin test strongly recommended
- Before each treatment: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, creatinine kinase, glucose
- If clinically indicated: chest x-ray, morning serum cortisol, lipase, serum or urine HCG (required for woman of child bearing potential if pregnancy suspected), Free T3 and Free T4, serum ACTH levels, testosterone, estradiol, FSH, LH, ECG
- Weekly telephone nursing assessment for signs and symptoms of side effects while on induction phase with ipilimumab and nivolumab. Optional when patients are on nivolumab

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	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 50 mL NS over 30 minutes using a 0.2 micron in-line filter*

*Use a separate infusion line and filter for each drug

- Repeat **every 3 weeks** for 4 cycles

Maintenance Phase

Drug	2-Weekly 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

- Start 3 weeks after last induction phase dose and repeat **every 2 weeks** until disease progression or unacceptable toxicity
- If pseudo progression on imaging is suspected, may continue treatment for another 6 weeks. Discontinue treatment if confirmatory progression on subsequent scan (6-10 weeks)

OR

Drug	4-Weekly 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

- Start 6 weeks after last induction phase dose and repeat **every 4 weeks** until disease progression or unacceptable toxicity
- If pseudo progression on imaging is suspected, may continue treatment for another 8 weeks. Discontinue treatment if confirmatory progression on subsequent scan (8-12 weeks)

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,
http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCIMMUNE_Protocol.pdf**).**

PRECAUTIONS:

- **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,** http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCIMMUNE_Protocol.pdf).
- **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 anti-histamine may be considered.

Call Dr. C. Kollmannsberger or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Bristol-Myers Squibb: OPDIVO (nivolumab) product monograph. Montreal, Quebec: 15 November 2018.
2. Bristol-Myers Squibb: Yervoy (ipilimumab) product monograph. Montreal, Quebec: 3 March 2022**.**
3. Momtaz P, Park V, Panageas KS, et al. Safety of infusing ipilimumab over 30 minutes. J Clin Oncol 2015; 33(30): 3454-3458
4. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018; 378(14):1277-90
5. Waterhouse D, Horn L, Reynolds C, et al. Safety profile of nivolumab administered as 30-min infusion: analysis of data from CheckMate 153. Cancer Chemother Pharmacol 2018; 81: 679-86.
6. Weber JS, et al. Management of adverse events following treatment with anti-programmed death-1 agents. Oncologist 2016; 21(30):1-11.