BC Cancer Protocol Summary for the Treatment of Metastatic Renal Cell Carcinoma using 6-Weekly Pembrolizumab and aXitinib

Protocol Code	*GUAVPEMAX6*
Tumour Group	*Genitourinary*
Contact Physician	*Dr. Christian Kollmannsberger*

ELIGIBILITY:

Patients must have:

- Metastatic renal cell carcinoma,
- No prior treatment in the metastatic setting,
- Any histology and IMDC risk group, and
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of pembrolizumab.

Patients should have:

- ECOG performance status 0 to 2, and
- Adequate hepatic and renal function

Notes:

- Patients are eligible to receive one of the following, but not sequential use of these agents except for intolerance:
  - Nivolumab with cabozantinib (GUAVNIVC or GUAVNIVC4),
  - Nivolumab with ipilimumab (GUAVIPNI),
  - Pembrolizumab with lenvatinib (GUAVPEML or GUAVPEML6), or
  - Pembrolizumab with aXitinib (GUAVPEMAX or GUAVPEMAX6)
- Patients with stable CNS metastases are eligible.
- PD-L1 status and CPS score not required.
- May receive GUAVPEMAX if relapsed greater than 6 months after GUAJPEM or GUAJPEM6, if all other eligibility criteria are met.
- At time of subsequent disease progression, retreatment with pembrolizumab is allowed with or without axitinib for an additional one year of therapy (18 cycles of pembrolizumab at 3-weekly dosing or 9 cycles at 6-weekly dosing, or a combination of both if:
  - Patients have completed 2 years of therapy without progression
  - Patients have stopped pembrolizumab due to toxicity (not progression)
- BC Cancer Compassionate Access Program (CAP) approval is not required to switch between 3-weekly and 6-weekly dosing of pembrolizumab or for retreatment

CAUTIONS:

- Active autoimmune disease, and
- Long term immunosuppressive therapy or systemic corticosteroids (Requiring more than 10 mg predniSONE/day or equivalent)

TESTS:

- Baseline: CBC & Diff, sodium, potassium, creatinine, albumin, ALT, alkaline phosphatase, total bilirubin, LDH, uric acid, TSH, morning serum cortisol, dipstick or laboratory urinalysis for protein, chest x-ray
- Before each treatment:
  - During pembrolizumab and aXitinib combination treatment: CBC & Diff, sodium, potassium, creatinine, ALT, alkaline phosphatase, total bilirubin, LDH, uric acid, TSH, dipstick or laboratory urinalysis for protein
  - During aXitinib treatment: CBC & Diff, creatinine, ALT, total bilirubin, uric acid, dipstick or laboratory urinalysis for protein, TSH every other cycle or if clinically indicated
- If clinically indicated:
  - During pembrolizumab and aXitinib combination treatment: serum or urine HCG (required for woman of child bearing potential if pregnancy suspected), free T3 and free T4, morning serum cortisol, serum ACTH levels, FSH, LH, estradiol, testosterone, albumin, GGT, total protein, lipase, calcium, phosphorus, glucose, C-reactive protein (CRP), creatine kinase (CK), troponin, MUGA scan or echocardiogram, ECG, chest x-ray
  - During aXitinib treatment: sodium, potassium, calcium, phosphorus, albumin, alkaline phosphatase, GGT, LDH, total protein, TSH, MUGA scan or echocardiogram
- 24-hour urine for protein if laboratory urinalysis for protein is greater than or equal to 1 g/L or dipstick urinalysis shows 2+ or 3+ proteinuria
- Weekly telephone nursing assessment for signs and symptoms of side effects while on pembrolizumab and aXitinib combination treatment (Optional).

PREMEDICATIONS:

- 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
aXitinib	5 mg twice daily* continuously	PO

* Dose range 2-10 mg twice daily; adjusted based on side effects.

- pembrolizumab: repeat **every 6 weeks** until disease progression or unacceptable toxicity to a maximum of 18 cycles or 2 years of treatment (including doses given as GUAVPEMAX)
- aXitinib: continue treatment until disease progression or unacceptable toxicity
- Retreatment may be permitted (see eligibility)

DOSE MODIFICATIONS:

- pembrolizumab: No dose modifications. Toxicity managed by treatment delay and other measures (see SCIMMUNE protocol for management of immune-mediated adverse reactions to checkpoint inhibitors immunotherapy.

- aXitinib: Dose adjusted based on side effects. Patients who tolerate aXitinib with starting dose (with no greater than grade 2 adverse reactions) for two consecutive weeks, are normotensive without anti-hypertensive medications, may have dose escalated to a maximum to 10 mg twice daily. Dose may be reduced to as low as 2 mg twice daily. Treatment delay or discontinuation may be needed for toxicity management.

1. Proteinuria:

Proteinuria	aXitinib Dose
Negative or 1+ Dipstick, or less than 1 g/L lab urine protein	Maintain dose
2+ Dipstick or greater, or greater than or equal to 1 g/L lab urine protein	▪ Obtain 24-hour urine, hold treatment for greater than or equal to 1 g/24 h ▪ Repeat 24-hour urine prior to next treatment ▪ When proteinuria less than 1 g/24h; resume at reduced dose level
24-hour urine protein: greater than or equal to 3.5 g/24h	Discontinue

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, reduced rates of administration and use of premedication.
- **Diarrhea:** Both pembrolizumab and aXitinib can cause diarrhea and it is one of the most common adverse reactions with this combination treatment. Early diagnosis and appropriate management are essential to minimize life-threatening complications.
- **Hypertension:** aXitinib can cause a rapid onset of high blood pressure. Temporary suspension of aXitinib is recommended for patients with severe hypertension (greater than 200 mmHg systolic or greater than 110 mmHg diastolic). Treatment with aXitinib may be resumed once hypertension is controlled (see also http://www.hypertension.ca). It is recommended that for at least the first 2 cycles of treatment patients monitor their blood pressure daily (home measurements, GP's office, etc.) and keep a journal of their blood pressure measurements that can be submitted to the physician.
- **Hepatic dysfunction**: No dose adjustment is required with mild hepatic impairment (Child-Pugh class A). Consider a 50% aXitinib dose reduction with moderate hepatic impairment (Child-Pugh class B). The appropriate starting dose for patients with severe hepatic impairment (Child-Pugh class C) is unknown.
- **Drug Interaction:** Screen for potential drug interactions between aXitinib and cytochrome P450 3A4 interacting drugs.

Call Dr. Christian 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. Rini BI, Plimack, ER, Stus R, *et al*. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019;380(12):1116-1127
2. Merck Canada: KEYTRUDA™ pembrolizumab product monograph. Kirkland, Quebec: 6 December 2019.
3. Pfizer Canada: INLYTA™ axitinib product monograph. Kirkland, Quebec: 18 March 2014.