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

Protocol Code	*GUAVNIVC*
Tumour Group	*Genitourinary*
Contact Physician	*Dr. Krista Noonan*

ELIGIBILITY:

Patients must have:

- Advanced or metastatic or renal cell carcinoma (RCC),
- No prior treatment in the metastatic setting,
- Any histology and IMDC risk group,
- No option for curative surgery or radiation, and
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of nivolumab

Patients should have:

- Good performance status,
- Adequately controlled blood pressure, and
- Adequate hepatic and renal function

Notes:

- Patients with stable CNS metastases are eligible
- PD-L1 status and CPS score not required
- Patients may receive GUAVNIVC if relapse occurs more than 6 months following completion of GUAJPEM or GUAJPEM6, if all other eligibility criteria are met
- Patients are eligible to receive one of the following, but not sequential use of these agents except for intolerance:
  - Nivolumab with cabozantinib (GUAVNIVC or GUAVNIC4),
  - Nivolumab with ipilimumab (GUAVIPNI),
  - Pembrolizumab with lenvatinib (GUAVPEML or GUAVPEML6), or
  - Pembrolizumab with aXitinib (GUAVPEMAX)
- At time of subsequent disease progression, retreatment with nivolumab is allowed with or without cabozantinib for an additional one year of therapy (26 cycles of nivolumab at 2-weekly dosing or 13 cycles at 4-weekly dosing, or a combination of both) if:
  - Patients have completed 2 years of therapy without progression
  - Disease progression occurred during a treatment break
- BC Cancer Compassionate Access Program (CAP) approval is not required to switch between 2-weekly and 4-weekly dosing of nivolumab

EXCLUSIONS:

Patients must not have:

- Prior tyrosine kinase inhibitor therapy,
- Recurrence within 6 months of adjuvant pembrolizumab,
- Uncontrolled hypertension, and
- Pre-existing significant QTc prolongation or unable to discontinue medications that can prolong QTc

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, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, morning serum cortisol, total protein, albumin, dipstick or laboratory urinalysis for protein, uric acid, calcium, magnesium, blood pressure, heart rate, chest x-ray or CT chest if not previously done, ECG
- Baseline if clinically indicated: 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, MUGA scan or echocardiogram
- Cycles with nivolumab and cabozantinib:
  - Prior to each cycle: CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, dipstick or laboratory urinalysis for protein, uric acid, blood pressure, heart rate
  - If clinically indicated: chest x-ray, 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, total protein, albumin, GGT, calcium, magnesium, phosphate, troponin, INR, ECG, MUGA scan or echocardiogram
- Cycles with cabozantinib monotherapy:
  - Prior to each cycle: CBC & Diff, creatinine, ALT, total bilirubin, uric acid, dipstick or laboratory urinalysis for protein, blood pressure, heart rate
  - If clinically indicated: total protein, albumin, GGT, alkaline phosphatase, LDH, sodium, potassium, calcium, magnesium, phosphate, TSH, ECG, 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
- For patients on warfarin: regular INR monitoring
- Blood pressure monitoring at home: See Precautions
- Weekly telephone nursing assessment for signs and symptoms of side effects while on nivolumab and cabozantinib combination treatment (Optional)

PREMEDICATIONS:

- For nivolumab: Antiemetics are not usually required
- For cabozantinib: Antiemetic protocol for moderate emetogenic chemotherapy protocols (see SCNAUSEA)
- If prior infusion reactions to nivolumab: 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
nivolumab	3 mg/kg on Day 1 (maximum 240 mg)	IV in 50 to 100 mL NS over 30 minutes using a 0.2 micron in-line filter
cabozantinib	40 mg once daily continuously	PO

- **Duration of treatment:**
  - cabozantinib: Continuous treatment, until disease progression or unacceptable toxicity (may continue nivolumab if cabozantinib omitted due to toxicity).
  - nivolumab: Repeat every 2 weeks until disease progression or unacceptable toxicity (may continue cabozantinib if nivolumab omitted due to toxicity) to a maximum of 52 cycles or 2 years of treatment (including doses given 4-weekly)
  - Retreatment may be permitted (see eligibility)

DOSE MODIFICATIONS:

- Toxicity profiles of nivolumab and cabozantinib may overlap. Consider interruption of cabozantinib to determine causative agent when appropriate.
- No specific dose modifications for nivolumab. Toxicity managed by treatment delay and other measures (see SCIMMUNE protocol for management of immune-mediated adverse reactions to checkpoint inhibitors immunotherapy.

cabozantinib dose levels:

Starting Dose	Dose Level -1	Dose Level -2
40 mg PO once daily	20 mg PO once daily	20 mg PO every other day

1. Hepatotoxicity during treatment:

<table>
<tr><th>ALT or AST</th><th></th><th>total bilirubin</th><th>cabozantinib</th><th>nivolumab</th></tr>
<tr><td rowspan="3">Less than or equal to 3 x ULN</td><td>and</td><td>Less than or equal to 1.5 x ULN</td><td>100%</td><td>100%</td></tr>
<tr><td>and</td><td>Greater than 1.5 x ULN</td><td>Hold until
• Total bilirubin less than or equal to 1.5 x ULN,
then restart at next lower dose</td><td rowspan="5">*See SCIMMUNE</td></tr>
<tr><td>and</td><td>Greater than 3 x ULN</td><td>Discontinue</td></tr>
<tr><td rowspan="2">Greater than 3 to less than 10 x ULN</td><td>and</td><td>Less than 2 x ULN</td><td>Hold until
• ALT/AST less than or equal to 3 x ULN, and
• Total bilirubin less than or equal to 1.5 x ULN,
then restart at next lower dose</td></tr>
<tr><td>and</td><td>Greater than or equal to 2 x ULN</td><td>Discontinue</td></tr>
<tr><td>Greater than or equal to 10 x ULN</td><td>or</td><td>Greater than 3 x ULN</td><td>Discontinue</td></tr>
</table>

*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.

2. Diarrhea:

Grade	Description	Cabozantinib dose	Nivolumab dose
1	Increase of less than 4 stools per day over baseline	Continue same dose	*See SCIMMUNE
2	Increase of 4 to 6 stools per day over baseline; limiting instrumental ADL	Hold until Grade 1 or less, then restart at next lower dose	
3 despite antidiarrheal treatment	Increase of 7 or more stools per day over baseline; limiting self care ADL; hospitalization indicated		
4 despite antidiarrheal treatment	Life-threatening consequences; urgent intervention indicated		

*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).

3. Palmar-Plantar Erythrodysesthesia (PPE):

Grade	Description	Cabozantinib dose	Nivolumab dose
1	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Continue same dose	100%
2	Skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Hold until Grade 1 or less, then restart at next lower dose	
3	Severe skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self care ADL		

4. **Hypertension:**
   - Initiate antihypertensive therapy if clinically indicated
   - If cabozantinib is discontinued, a drop in blood pressure should be anticipated.
   - Antihypertensive dose adjustment or interruption may be required

Blood Pressure Elevation	Cabozantinib Dose
160 mmHg systolic or greater, or 100 mmHg diastolic or greater	▪ Hold until systolic less than 160 mmHg and diastolic less than 100 mmHg ▪ Once controlled, restart at next lower dose level
Elevated blood pressure with life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Discontinue

5. **Proteinuria:**

Proteinuria	Cabozantinib 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:

1. **Serious immune-mediated reactions to nivolumab**: 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 nivolumab with Grade 3 or 4 reactions. Patients with mild or moderate infusion reactions may receive nivolumab with close monitoring and use of premedication.
3. **Diarrhea:** Both nivolumab and cabozantinib can cause diarrhea. Early diagnosis and appropriate management are essential to minimize life-threatening complications. See Dose Modifications.
4. **Hypertension:** The onset of hypertension usually occurs early in treatment. Blood pressure should be controlled prior to initiation of treatment with cabozantinib. Temporary suspension of cabozantinib is recommended for patients with severe hypertension (greater than 160 mmHg systolic or greater than 100 mmHg diastolic). See Dose Modifications. Discontinue cabozantinib for severe and persistent hypertension despite anti-hypertensive therapy.
   It is recommended that for at least the first 2 months of treatment, patients monitor their blood pressure daily (home measurements, GP's office, etc.) and regularly thereafter. Patients should keep a journal of their blood pressure measurements that can be submitted to the physician at the next appointment.
5. **Cardiac Toxicity:** cabozantinib can cause prolongation of the QTc interval, decreased heart rate and PR interval prolongation. Correct electrolyte disturbances prior to initiation. Use with caution in patients with baseline heart rate less than 60 beats per minute or history of conduction abnormalities, arrhythmia, ischemic heart disease, or congestive heart failure. Discontinue for arterial or venous thromboembolic events that require medical intervention (e.g., myocardial infarction, cerebral infarction). Monitor electrolytes and follow ECGs during treatment as indicated. Caution when combining with medications that cause bradycardia or drugs that can decrease electrolytes. See BC Cancer Drug Manual.
6. **Renal dysfunction:** Use cabozantinib with caution in patients with mild to moderate impairment. Cabozantinib has not been studied in severe renal impairment.
7. **Hemorrhagic events:** Severe and fatal hemorrhagic events have been reported with cabozantinib. Arterial aneurysm and artery dissection, including rupture, have been reported in patients with and without hypertension. Avoid cabozantinib in patients with recent hemorrhage. Discontinue cabozantinib in patients who experience severe hemorrhage.
8. **Hepatotoxicity**: Hepatitis, fatal hepatic failure and hepatic encephalopathy have been reported with cabozantinib treatment. Cabozantinib in combination with nivolumab has not been studied in patients with mild or moderate hepatic impairment. No dosing recommendation can be provided. Avoid in severe hepatic impairment.
9. **Wound healing complications**: cabozantinib may suppress wound healing. Hold treatment at least 4 weeks prior to scheduled surgery, including dental surgery. Treatment resumption is based on clinical judgement. Discontinue treatment in patients with wound dehiscence.
10. **Reversible posterior leukoencephalopathy syndrome (RPLS) (rare)**: Symptoms may include seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is necessary to confirm diagnosis. Discontinue cabozantinib when signs/symptoms or

RPLS are present and provide supportive management of symptoms. The safety of reinitiating treatment is not known.

11. **Drug interactions**: cabozantinib is predominantly metabolized by cytochrome P450 3A4. Potential drug interactions with cytochrome P450 3A4 interacting agents must be considered if combination cannot be avoided and cabozantinib dose modifications may be necessary. Avoid use with concomitant medications known to prolong the QT interval. See BC Cancer Drug Manual.
12. **Venous and arterial thromboembolic events:** Are reported during cabozantinib treatment. Monitor and treat as clinically indicated.
13. **Gastrointestinal (GI) perforation and fistulas:** Have been reported during treatment with cabozantinib. Use caution in patients with a history of inflammatory bowel disease, prior GI surgery and/or metastases to the GI tract.
14. **Palmar-Plantar Erythrodysesthesia (PPE):** Is reported in patients taking cabozantinib. See Dose Modifications, above.

Call Dr. Krista Noonan or tumour group delegate at (604) 930-2098 or 1-800-523-2885 with any problems or questions regarding this treatment program.

References:

1. Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2021 Mar 4;384(9):829-841.
2. Powles T, Burotto M, Escudier B, et al. Nivolumab plus cabozantinib versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended follow-up from the phase III randomised CheckMate 9ER trial. ESMO Open. 2024 May;9(5):102994.
3. Cella D, Motzer RJ, Suarez C, et al. Patient-reported outcomes with first-line nivolumab plus cabozantinib versus sunitinib in patients with advanced renal cell carcinoma treated in CheckMate 9ER: an open-label, randomised, phase 3 trial. Lancet Oncol. 2022 Feb;23(2):292-303.
4. Cabozantinib (Cabometyx) Canada's Drug Agency (CDA-AMC) Reimbursement Recommendation. Canadian Journal of Health Technologies Nov 2023; 3(11): 1-20.
5. Canada's Drug Agency (CDA-AMC) Reimbursement Review. Provisional Funding Algorithm. Renal Cell Carcinoma. Feb 2024.