BCCA Protocol Summary for Treatment of Metastatic or Advanced Renal Cell Carcinoma Using Nivolumab

Protocol Code: UGUAVNIV

Tumour Group: Genitourinary

Contact Physician: Dr. C. Kollmannsberger

ELIGIBILITY:

- Metastatic or advanced renal cell carcinoma after failure of first-line tyrosine kinase inhibitor (TKI) therapy (SUNITinib, SORAfenib, or pazopanib).
- Third-line therapy after failure of first-line (SUNITinib, SORAfenib, or pazopanib) and second-line TKI (axitinib).
- Patients are eligible to receive nivolumab or everolimus, but not sequential use of these agents.
- Good performance status
- Adequate hepatic and renal function
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of nivolumab
- BC Cancer Agency Compassionate Access Program (CAP) approval must be obtained

EXCLUSIONS:

- ECOG performance status > 2
- Active central nervous system metastases (should be asymptomatic and/or stable)
- 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, AST, ALT, total bilirubin, LDH, electrolytes, TSH, morning serum cortisol, chest x-ray (or CT chest)
- **Before each treatment:** CBC & differential, platelets, creatinine, alkaline phosphatase, AST, ALT, total bilirubin, LDH, electrolytes, TSH
- **If clinically indicated:** chest x-ray, morning serum cortisol, lipase, glucose, serum or urine HCG (required for women 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 treatment (Optional).
PREMEDICATIONS:
- Antiemetics are not usually required
- Antiemetic protocol for low emetogenic chemotherapy protocols (see SCNAUSEA)
- If prior infusion reactions to nivolumab: diphenhydramine 50 mg PO, acetaminophen 325 to 1000 mg PO and hydrocortisone 25 mg IV 30 minutes prior to treatment.

TREATMENT:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BCCA Administration Guideline</th>
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</thead>
<tbody>
<tr>
<td>nivolumab</td>
<td>3 mg/kg (maximum 240 mg)</td>
<td>IV in 100 mL* NS over 1 hour using a 0.2 to 1.2 micron in-line filter</td>
</tr>
</tbody>
</table>

* Keep final concentration to 1-10 mg/mL

- 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 scan shows an additional 10% tumour burden volume and/or development of new lesions.

DOSE MODIFICATIONS:
No specific dose modifications. Toxicity managed by treatment delay and other measures (see Appendix for Immune-mediated Adverse Reaction Management Guide).

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 Appendix for Immune-mediated Adverse Reaction Management Guide).
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.

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

Date activated: March 1, 2017
Date revised: 1 Apr 2017 (Tests clarified, minor typo corrected)
References:
2. Bristol-Myers Squibb Canada. OPDVIO® product monograph. Montreal, Canada; 26 October 2016
### Appendix. Immune-mediated adverse reaction management guide

#### Pneumonitis

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Radiographic changes only</th>
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<tbody>
<tr>
<td>• Physician notified of assessment</td>
<td></td>
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<tr>
<td>• Consider withholding nivolumab</td>
<td></td>
</tr>
<tr>
<td>• Monitor every 2 to 3 days</td>
<td></td>
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<tr>
<td>• Consider pulmonary and infectious disease consultation</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 2</th>
<th>Mild to moderate symptoms, worsens from baseline</th>
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<tbody>
<tr>
<td>• Physician notified and collaborative symptom management initiated</td>
<td></td>
</tr>
<tr>
<td>• Withhold nivolumab</td>
<td></td>
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<tr>
<td>• Consider high resolution CT scan</td>
<td></td>
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<tr>
<td>• Monitor daily</td>
<td></td>
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<tr>
<td>• predniSONE 1 mg/kg/day PO</td>
<td></td>
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<tr>
<td>• Patient education of steroid use</td>
<td></td>
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<tr>
<td>• Pulmonary and infectious disease consultation</td>
<td></td>
</tr>
<tr>
<td>• Consider bronchoscopy, lung biopsy</td>
<td></td>
</tr>
<tr>
<td>• Book nursing follow up call as needed</td>
<td></td>
</tr>
</tbody>
</table>

| Reassess at least every 3 weeks |
| If improved |
| • Resume nivolumab (if withheld) when stable |
| If worsens |
| • Treat as Grade 2 or Grades 3 or 4 |

<table>
<thead>
<tr>
<th>Grade 3 or 4</th>
<th>Severe symptoms, new or worsening hypoxia, life-threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hospitalize</td>
<td></td>
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<tr>
<td>• Discontinue nivolumab</td>
<td></td>
</tr>
<tr>
<td>• Monitor daily</td>
<td></td>
</tr>
<tr>
<td>• predniSONE 2 to 4 mg/kg/day PO</td>
<td></td>
</tr>
<tr>
<td>• Patient education of steroid use</td>
<td></td>
</tr>
<tr>
<td>• Prophylactic antibiotics for opportunistic infections</td>
<td></td>
</tr>
<tr>
<td>• Pulmonary and infectious disease consultation</td>
<td></td>
</tr>
<tr>
<td>• Consider bronchoscopy, lung biopsy</td>
<td></td>
</tr>
<tr>
<td>• Upon discharge, book nursing follow up call as needed</td>
<td></td>
</tr>
</tbody>
</table>

| Reassess every 1 to 3 days |
| If improved to baseline |
| • Taper steroid over at least 1 month BEFORE resuming nivolumab |
| • Consider prophylactic antibiotics for opportunistic infections |
| If persists or worsens after 2 weeks |
| • Treat as Grades 3 or 4 |

| If improved to baseline |
| If persists or worsens after 2 days |
| • Consider non-steroid immunosuppressive agents (e.g., inFLIXimab, cyclophosphamide, mycophenolate) |

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**Warning:** The information contained in these documents is a statement of consensus of BC Cancer Agency professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is at your own risk and is subject to BC Cancer Agency's terms of use available at [www.bccancer.bc.ca/legal.htm](http://www.bccancer.bc.ca/legal.htm)
Enterocolitis

Grade 1
Diarrhea of less than 4 stools per day over baseline; asymptomatic colitis

- Physician notified of assessment
- Nursing management per BCCA Symptom Management Guidelines: Cancer-Related Diarrhea
- Antidiarrheal treatment
- Book nursing follow up call for next business day and/or create care plan if BCCA nurse unable to follow up

Grade 2
Diarrhea of 4 to 6 stools per day over baseline, IV fluids less than 24 h, normal daily activities, abdominal pain, mucus or blood in stool,

- Physician notified and collaborative symptom management initiated
- Withhold nivolumab
- Antidiarrheal treatment
- If persists beyond 3-5 days or recur, start predniSONE 0.5 to 1 mg/kg/day PO
- Patient education of steroid use
- Nursing management per BCCA Symptom Management Guidelines: Cancer-Related Diarrhea
- Book nursing follow up call as needed

Monitoring
Diarrhea, abdominal pain, mucus or blood in stools-with or without fever, ileus, peritoneal signs

Grade 3 or 4
Grade 3: diarrhea of 7 or more stools per day over baseline, incontinence, IV fluids for 24 h or more, impaired daily activities; colitis with severe abdominal pain, requiring medical interventions, peritoneal signs of bowel perforation
Grade 4: life-threatening colitis, perforation

- Physician notified and collaborative symptom management initiated
- Withhold (if Grade 3) or discontinue (if Grade 4 or persistent Grade 3) nivolumab
- Gastroenterology consultation
- Rule out bowel perforation; if bowel perforation is present, DO NOT administer corticosteroids
- Consider endoscopic evaluation
- predniSONE 1 to 2 mg/kg/day PO
- Prophylactic antibiotics for opportunistic infections
- Patient education of steroid use
- Nursing management per BCCA Symptom Management Guidelines: Cancer-Related Diarrhea
- Book nursing follow up call as needed

Improvement to Grade 1 or less
- Resume nivolumab
- If steroid used, taper over at least 1 month BEFORE resuming nivolumab
- Consider prophylactic antibiotics for opportunistic infections
- Patient education of steroid tapering per physician order

Improvement to Grade 1 or less
- Taper predniSONE over at least 1 month before resuming nivolumab
- Patient education of steroid tapering per physician order

If no response within 5 days or recur
- Consider treatment with inFLIXimab; if refractory to inFLIXimab, consider mycophenolate
- Continually evaluate for evidence of gastrointestinal perforation or peritonitis
- Consider repeat endoscopy

Grade 1
Diarrhea of less than 4 stools per day over baseline; asymptomatic colitis

- Physician notified of assessment

BC Cancer Agency Protocol Summary UGUAVNIV
Activate1 Mar 2017    Revised: 1 Apr 2017
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Liver

Monitoring
Abnormal liver function test, jaundice, tiredness

Grade 2
AST/ALT 3 to less than 5 X ULN
or
Total bilirubin 1.5 to 3 X ULN

- Physician notified and collaborative symptom management initiated
- Withhold nivolumab
- Rule out infectious or malignant causes or obstruction
- Increase LFTs monitoring to every 3 days until resolution
- Book future nursing follow up call as needed

If AST/ALT 3 × ULN or lower and bilirubin 1.5 × ULN or lower, or return to baseline
- Resume nivolumab

If elevation persists more than 5-7 days or worsen
- predniSONe 0.5 to 1 mg/kg/day PO
- consider prophylactic antibiotics for opportunistic infections
- taper predniSONe over at least 1 month before resuming nivolumab
- Patient education of steroid tapering per physician order

Grades 3 or 4
AST/ALT more than 5 X ULN
or
Total bilirubin more than 3 X ULN
or
AST/ALT increases ≥50% baseline and lasts ≥1 week in patients with liver metastasis who begin treatment with Grade 2 elevation of AST/ALT

- Physician notified and collaborative symptom management initiated
- Discontinue nivolumab
- Rule out infectious or malignant causes or obstruction
- Increase LFTs monitoring to every 1 to 2 days until resolution
- Gastroenterology consultation
- predniSONe 1 to 2 mg/kg/day PO
- Prophylactic antibiotics for opportunistic infections
- Patient education on steroid use
- Book future nursing follow up call as needed

If LFTs return to Grade 2 or less
- Taper predniSONe over at least 1 month

For persistent Grades 3 or 4 for more than 3 to 5 days, worsens, or recurs:
- Consider non-steroid immunosuppressive agents (e.g., mycophenolate)
Renal

Monitoring
Increase in serum creatinine, decreased urine output, hematuria, edema

- **Grade 1**
  - Creatinine >1 - 1.5 x ULN
    - Creatinine weekly
    - When return to baseline
      - Resume routine creatinine

- **Grade 2**
  - Creatinine >1.5 - 3.0 x ULN
    - Physician notified and collaborative symptom management initiated
    - Withhold nivolumab
    - Nephrology consultation
    - Creatinine every 2 to 3 days
    - Prednisone 0.5 to 1 mg/kg/day PO
    - Patient education on steroid use
    - Consider renal biopsy
    - Book future nursing follow up call as needed
    - If improved to Grade 1
      - Taper steroid over at least 1 month
      - **Before** resuming nivolumab and routine creatinine
    - If persists for more than 7 days or worsens
      - Treat as Grade 4

- **Grade 3**
  - Creatinine >3.0 - 6.0 x ULN
    - Physician notified and collaborative symptom management initiated
    - Discontinue nivolumab
    - Nephrology consultation
    - Creatinine daily
    - Prednisone 1 to 2 mg/kg/day PO
    - Patient education on steroid use
    - Consider renal biopsy
    - Book future nursing follow up call as needed
    - If improved to Grade 1
      - Taper steroid over at least 1 month

- **Grade 4**
  - >6.0 x ULN
    - Physician notified and collaborative symptom management initiated
    - Discontinue nivolumab
    - Nephrology consultation
    - Creatinine daily
    - Prednisone 1 to 2 mg/kg/day PO
    - Patient education on steroid use
    - Consider renal biopsy
    - Book future nursing follow up call as needed
    - If improved to Grade 1
      - Taper steroid over at least 1 month
Endocrine

Monitoring
Persistent or unusual headaches, extreme tiredness, weight gain or loss, mood or behaviour changes (e.g., decreased libido, irritability, forgetfulness) dizziness or fainting, hair loss, feeling cold, constipation, voice gets deeper

Asymptomatic TSH elevation
- Physician notified and collaborative symptom management initiated
- Continue nivolumab
  - If TSH less than 0.5 x LLN, or TSH greater than 2 x ULN, or consistently out of range in 2 subsequent measurements: include free T4 at subsequent cycles as clinically indicated
  - Consider endocrinology consultation

Symptomatic endocrinopathy
- Physician notified and collaborative symptom management initiated
- Evaluate endocrine function
- Consider pituitary scan
- Withhold nivolumab if abnormal lab or pituitary scan
- Endocrinology consultation
- prednisONE 1 to 2 mg/kg/day PO
- Repeat labs in 1 to 3 weeks; MRI in 1 month if symptoms persist but normal lab or pituitary scan
- Appropriate hormone replacement if symptomatic with

If improved with or without hormone replacement:
- Taper steroid over at least 1 month BEFORE resuming nivolumab
- Consider prophylactic antibiotics for opportunistic infections

Continue standard monitoring
- Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component

Suspicion of adrenal crisis (e.g., severe dehydration, hypotension, shock out of proportion to current illness)
- Physician notified and collaborative symptom management initiated
- Rule out sepsis
- Withhold nivolumab
- Evaluate endocrine function
- Endocrinology consultation
- Consider pituitary scan
- Repeat labs in 1 to 3 weeks; MRI in 1 month if symptoms persist but normal lab or pituitary scan
- Endocrinology consult
- Stress dose of IV steroids with mineralocorticoid activity
- IV fluids

When adrenal crisis ruled out:
- Treat as symptomatic endocrinopathy
**Skin**

**Monitoring**
Rash, pruritus (unless an alternate etiology has been identified)

- **Grade 1 to 2**
  30% of skin surface or less
  - Physician notified of assessment
  - Nursing management per ASCO Skin Reactions to Targeted Therapies
    - Sun safety (see Your Medication Sun Sensitivity and Sunscreens)
    - Skin care; moisturizers, soaps
    - Topical corticosteroids
    - diphenhydrAMINE PO
  - Book nursing follow up call for next business day and/or create care plan if BCCA nurse unable to follow up

- If persists more than 1-2 weeks or recurs
  - Consider skin biopsy
  - **Withhold nivolumab**
  - predniSONE 0.5 to 1 mg/kg/day PO
  - Patient education on steroid use
  - Once improving, taper predniSONE over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume nivolumab

- If improves to Grade 1
  - taper predniSONE over at least 1 month, add prophylactic antibiotics for opportunistic infections, and resume nivolumab

- **Grade 3-4**
  More than 30% of skin surface, life-threatening
  - Physician notified and collaborative symptom management initiated
  - **Withhold or discontinue nivolumab**
  - Consider skin biopsy
  - Dermatology consult
  - predniSONE 1 to 2 mg/kg/day PO (or methylIPREDNISolone 1 to 2 mg/kg/day IV)
  - Patient education on steroid use
  - Book nursing follow up call for next business day and/or create care plan if BCCA nurse unable to follow up
Other immune-mediated adverse reactions

If severe or clinically significant:
- Discontinue nivolumab
- prednison 1 to 2 mg/kg/day PO
- Corticosteroid eye drops for uveitis, iritis or episcleritis
- Consider referring to a specialist

1. **Blood and lymphatic:** hemolytic anemia
2. **Cardiovascular:** angiopathy, myocarditis, pericarditis, temporal arteritis, vasculitis
3. **Endocrine:** autoimmune thyroiditis
4. **Eye:** blepharitis, conjunctivitis, episcleritis, iritis, scleritis, uveitis
5. **Gastrointestinal:** pancreatitis
6. **Infectious:** meningitis
7. **Musculoskeletal:** arthritis, polymyalgia rheumatica
8. **Renal and urinary:** nephritis
9. **Respiratory:** pneumonitis
10. **Skin:** psoriasis, leukocytoclastic vasculitis