# BC Cancer Protocol Summary for Treatment of Endometrial Cancer With Microsatellite Stability or Mismatch Repair Proficiency using Pembrolizumab and Lenvatinib

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| ***Protocol Code*:** | *GOENDAVPL* |
| ***Tumour Group*:** | *Gynecology* |
| ***Contact Physician*:** | *Dr. Alannah Smrke* |

## ELIGIBILITY:

Patients must have:

- Advanced, recurrent, or metastatic endometrial carcinoma,
- Microsatellite stable (MSS) or proficient mismatch repair (pMMR) tumour,
- Disease progression after platinum-based chemotherapy, and
- No option for curative surgery or radiation

Patients should have:

- ECOG 0 to 2,
- Adequate hematologic, hepatic and renal function,
- Adequately controlled blood pressure,
- Access to a treatment center with expertise to manage immune-mediated adverse reactions of pembrolizumab

Notes:

- Treatment of endometrial carcinosarcoma with GOENDAVPL or GOENDAVPL6 requires BC Cancer "Compassionate Access Program" request approval prior to treatment
- At time of subsequent disease progression, retreatment with pembrolizumab is allowed, with or without lenvatinib, 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.

## EXCLUSIONS:

Patients must not have:

- Microsatellite instability high (MSI-H) or deficient mismatch repair (dMMR) disease,
- Endometrial leiomyosarcoma or stromal sarcoma,
- Active central nervous system (CNS) metastases. Treated or stable CNS metastases are eligible,
- History of significant thrombosis,
- Pre-existing significant QTc prolongation or be unable to discontinue medications that can prolong QTc

## CAUTIONS:

- Active, known or suspected autoimmune disease
- Patients with long term immunosuppressive therapy or systemic corticosteroids (requiring more than 10 mg predniSONE/day or equivalent)
- Significant cardiovascular or gastrointestinal dysfunction
- Proteinuria greater than or equal to 1 g/24h

## TESTS:

- Baseline: CBC & Diff, platelets, creatinine, ALT, alkaline phosphatase, total bilirubin, GGT, sodium, potassium, magnesium, calcium, albumin, TSH, random glucose, urinalysis, blood pressure measurement, ECG, morning serum cortisol, chest x-ray or CT chest if not previously done.
- Every two weeks for first 2 months: blood pressure, ALT, alkaline phosphatase, total bilirubin, albumin
- Blood pressure monitoring at home: See Precautions
- Prior to each treatment (combination pembrolizumab and lenvatinib treatment, or during lenvatinib monotherapy): CBC & Diff, platelets, creatinine, ALT, alkaline phosphatase, total bilirubin, sodium, potassium, magnesium, calcium, albumin, TSH, urine protein, blood pressure
- 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
- If clinically indicated: morning serum cortisol, lipase, random glucose, creatine kinase, 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, GGT, total protein, phosphorus, C-reactive protein (CRP), troponin, ECG, chest x-ray, MUGA scan or echocardiogram if clinically indicated or if history of cardiac problem
- For patients at risk of developing QT prolongation: Routine ECG (at the discretion of ordering physician). See Precautions
- For patients on warfarin: regular INR monitoring
- Cycle 1 and 2: weekly nursing assessment for signs and symptoms of side effects while on treatment
- Cycle 3 onward: weekly nursing assessment for lenvatinib (optional)

**PREMEDICATIONS:**

- For lenvatinib: antiemetic protocol for moderate emetogenicity (see SCNAUSEA). No antiemetics required prior to pembrolizumab infusion
- 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 | 2 mg/kg (maximum 200 mg) | IV in 50 mL NS over 30 minutes using a 0.2 micron in-line filter |
| lenvatinib | 20 mg once daily continuously | PO |

- Each cycle is 21 days (3 weeks).
- Duration of treatment:
  - Lenvatinib: until progression or unacceptable toxicity.
  - Initial pembrolizumab therapy: maximum 36 cycles for 3-weekly dosing or 18 cycles for 6-weekly dosing (or a combination of both), including doses given as GOENDAVPL and GOENDAVPL6, to a maximum of 2 years of treatment.
  - Retreatment may be permitted (see eligibility)

**Lenvatinib Dose Adjustment at Initiation:**

Renal:

| Pre-Existing Renal Impairment (CrCl in mL/min) | Daily Lenvatinib Dose |
|---|---|
| 30 or greater | 20 mg |
| Less than 30 | 10 mg |

Hepatic:

| Pre-Existing Hepatic Impairment (Child-Pugh Class) | Daily Lenvatinib Dose |
|---|---|
| A or B | 20 mg |
| C | 10 mg |

## DOSE MODIFICATIONS:

- Toxicity profiles of pembrolizumab and lenvatinib may overlap. Interruption of lenvatinib can be considered in an effort to determine causative agent when appropriate

### Pembrolizumab:

- 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).

### Lenvatinib:

**Table 1** - Persistent or intolerable Grade 2 or 3 adverse reactions or Grade 4 lab abnormalities*

| Adverse Reaction | Modification | Daily Lenvatinib Dose*** |
|---|---|---|
| First occurrence | Hold dose until resolved to Grade 1 or baseline | 14 mg |
| Second occurrence** | | 10 mg |
| Third occurrence** | | 8 mg |
| Fourth occurrence** or per physician discretion | | 4 mg |

* excluding laboratory abnormalities judged to be non-life-threatening, which could be managed as Grade 3
** refers to the same or a different adverse reaction that requires dose modification
*** reduce dose in succession based on prior dose level (14 mg, 10 mg, 8 mg, or 4 mg daily). Dose reductions should be maintained and not re-escalated

1. **Hematologic:**

| ANC ($x10^9$/L) | | Platelets ($x10^9$/L) | Lenvatinib Dose |
|---|---|---|---|
| Greater than or equal to 1.0 | and | Greater than or equal to 75 | 100% |
| Less than 1.0 | or | Less than 75 | Delay |

2. **Hypertension:**
   - Expect decrease in blood pressure if lenvatinib is held or discontinued

| Blood Pressure (mmHg) | Lenvatinib Dose |
|---|---|
| Systolic 160 or higher<br>or<br>Diastolic 100 or higher | ▪ Hold until systolic less than 160 and diastolic less than 100<br>▪ Optimize anti-hypertensive therapy<br>▪ Restart per Table 1 |
| Life-threatening hypertension | Discontinue |

3. **Proteinuria:**

| Proteinuria | Lenvatinib 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 2 g/24 h<br>▪ Repeat 24 hour urine prior to next treatment<br>▪ When proteinuria less than 2 g/24h; resume at reduced dose per Table 1 |
| 24 hour urine protein: greater than or equal to 3.5 g/24h | Discontinue |

4. **Diarrhea:**

- Treat lenvatinib-associated Grade 1 or higher diarrhea with standard anti-diarrheal therapy
- Diarrhea that continues despite holding lenvatinib should raise clinical suspicion of immunotherapy-induced enterocolitis

| Grade | Diarrhea | Lenvatinib Dose |
|---|---|---|
| **1** | Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline | ▪ Hold for Grade 3 diarrhea or persistent Grade 2 until resolves to less than Grade 2<br>▪ Initiate/escalate diarrhea management. Monitor for dehydration<br>▪ See Table 1 for dose adjustment<br>▪ Discontinue for Grade 4 diarrhea |
| **2** | Increase of 4 to 6 stools per day over baseline; moderate increase in output compared to baseline | |
| **3** | Increase of greater than or equal to 7 stools per day over baseline; incontinence; hospitalization indicated | |
| **4** | Life-threatening | |

5. **Nausea/vomiting:**

- Treat lenvatinib-associated Grade 1 or higher nausea or vomiting with anti-emetics and oral hydration

| Grade | Nausea and/or Vomiting | Lenvatinib Dose |
|---|---|---|
| **1** | Nausea with loss of appetite without alteration in eating habits or vomiting with no intervention indicated | ▪ Hold for Grade 3 or persistent Grade 2 nausea or vomiting until resolves to less than Grade 2<br>▪ Initiate/escalate symptomatic management.<br>▪ See Table 1 for dose adjustment<br>▪ Discontinue if Grade 4 |
| **2** | Nausea with oral intake decreased without significant weight loss, dehydration or malnutrition, or vomiting with outpatient IV hydration; medical intervention indicated | |
| **3** | Nausea with inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated or vomiting with tube feeding, TPN, or hospitalization indicated | |
| **4** | Life threatening consequences | |

6. **QT prolongation:**

| Severity | QT Prolongation | Lenvatinib Dose |
|---|---|---|
| **Grade 1** | QTc 450 to 480 ms | Maintain dose |
| **Grade 2** | QTc 481 to 500 ms | Maintain dose or reduce dose per Table 1. Assess risk for developing torsades de pointes |
| **Grade 3** | QTc greater than or equal to 501 ms on 2 separate ECGs | Hold until Grade 1 or baseline; resume at reduced dose per Table 1 |
| **Grade 4** | QTc greater than or equal to 501 ms or greater than 60 ms from baseline or signs and symptoms of serious arrhythmia | Discontinue |

7. **Hepatotoxicity/hepatic failure during treatment:**

| Severity | Lenvatinib Dose |
|---|---|
| AST, ALT, or alkaline phosphatase greater than 5 to 20 x ULN<br>or<br>Total bilirubin greater than 3 to 10 x ULN | Hold until less than Grade 2 or baseline; consider resuming at reduced dose per Table 1 |
| AST, ALT or alkaline phosphatase greater than 20 x ULN<br>or<br>Total bilirubin greater than 10 x ULN | Discontinue |
| Hepatic failure with asterixis; mild encephalopathy; drug induced liver injury; limiting self care ADL, or with life-threatening consequences; moderate to severe encephalopathy; coma | |

8. **Renal impairment/renal failure during treatment:**

| Severity | Lenvatinib Dose |
|---|---|
| Grade 3 including creatinine increase greater than 3 x baseline, or greater than 3 to 6 x ULN | Hold until less than Grade 2 or baseline; consider resuming at reduced dose per Table 1 |
| Grade 4 including creatinine greater than 6 x ULN | Discontinue |

**PRECAUTIONS:**

1. **Serious immune-mediated reactions to pembrolizumab**: 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 pembrolizumab with severe reactions (Grade 3 or 4). Patients with mild or moderate infusion reactions may receive pembrolizumab with close monitoring and use of premedication.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer information on febrile neutropenia. There are no dose modifications for lenvatinib.
4. **Hypertension:** Patients with hypertension should exercise caution while on lenvatinib. Rigorous treatment of blood pressure is necessary, since lenvatinib can cause a rapid onset of high blood pressure.

   **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 at the next appointment. Blood pressure should be monitored monthly thereafter while on treatment.**

   Temporary suspension of lenvatinib is recommended for patients with severe hypertension (greater than 160 mmHg systolic or greater than 100 mmHg diastolic). Treatment with lenvatinib may be resumed at a reduced dose once hypertension is controlled (see also http://www.hypertension.ca).

5. **Prolonged QT interval** is a risk associated with lenvatinib use. Use caution in patients with history of QT prolongation or cardiac disease and those receiving concurrent therapy with other QT prolonging medications. Correct electrolyte disturbances prior to treatment. Hold lenvatinib for QTc greater than or equal to 500 ms.
6. **Hemorrhagic events** occur in over one-third of patients, with epistaxis being the most commonly reported hemorrhagic event. Hemorrhage requiring medical intervention may require either a temporary interruption in lenvatinib treatment, dose modification, or permanent discontinuation of lenvatinib, depending on the severity of the hemorrhage. Consider holding lenvatinib before surgery and resume after surgical wounds are fully healed.
7. **Diarrhea:** Both pembrolizumab and lenvatinib 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.
8. **Proteinuria** can occur while on lenvatinib. Dipstick urinalysis is recommended for monitoring throughout treatment. If proteinuria is detected, dose interruption, adjustment, or discontinuation may be necessary. See dose modifications, above. Discontinue lenvantinib for nephrotic syndrome.
9. **Renal toxicity** is associated with lenvatinib use. The primary risk factor is dehydration/hypovolemia secondary to diarrhea and vomiting. To reduce the risk of lenvatinib-induced renal impairment, promptly initiate active management of Grade 1 diarrhea, vomiting, or other gastrointestinal symptoms with standard anti-diarrheal therapy, anti-emetics, and oral hydration.
10. **Hepatotoxicity** including Grade 3 transaminase elevations, acute hepatitis, and hepatic failure has occurred with lenvatinib use. Patients with hepatic impairment may require additional monitoring of adverse reactions. Pembrolizumab with lenvatinib has not been studied in patients with severe hepatic impairment (Child-Pugh C).
11. **Drug interactions with lenvatinib:** Concurrent therapy with drugs that prolong QT/QTc interval or disrupt electrolyte levels should be avoided if possible; periodic monitoring of ECG and electrolytes is suggested. See Cancer Drug Manual.
12. **Posterior Reversible Encephalopathy Syndrome (PRES):** MRI to confirm diagnosis. If patients present with headache, seizure, lethargy, confusion, altered mental function, blindness, or other visual or neurological disturbances, consider dose interruptions, adjustments, or discontinuation.
13. **Nausea** is reported during combination treatment with pembrolizumab and lenvatinib. Offer premedication with antiemetics and escalate treatment as required.
14. **Gastrointestinal perforation and fistula formation:** Upon development, discontinue.
15. **Arterial or venous thromboembolic event:** Assess a patient's risk for myocardial infarction or hemorrhagic stroke prior to initiation of treatment. Discontinue lenvatinib following an arterial thrombotic event.
16. **Weight loss** secondary to decreased appetite and diarrhea can occur with lenvatinib treatment.

17. **Cardiac Dysfunction:** Various cardiac dysfunctions including decreased left or right ventricular function, cardiac failure, and/or pulmonary edema are associated with lenvatinib treatment. Hold lenvatinib for any Grade 3 event until Grade 1 or baseline. Restart at reduced dose or discontinue per physician discretion.
18. **Palmar plantar erythrodysesthesia syndrome (PPES)** is associated with lenvatinib treatment and may require dose interruption and/or adjustment. Patients should be instructed on importance of preventative measures such as moisturizing and sun protection.
19. **Osteonecrosis of the jaw** has been reported in patients treated with lenvatinib. Consider dental exam and preventative dentistry prior to treatment initiation. Avoid invasive dental procedures during lenvatinib treatment if possible.
20. **Stomatitis** can occur during treatment with lenvatinib. Monitor and treat supportively.

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

**References**:


1. Makker V, Colombo N, Casado Herráez Aet al; Study 309–KEYNOTE-775 Investigators. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. N Engl J Med. 2022 Feb 3;386(5):437-448.
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3. Lorusso D, Danesi R, Locati LD, et al. Optimizing the use of lenvatinib in combination with pembrolizumab in patients with advanced endometrial carcinoma. Front Oncol. 2022 Sep 21;12:979519.
4. Makker V, Taylor MH, Oaknin A, et al. Characterization and Management of Adverse Reactions in Patients with Advanced Endometrial Carcinoma Treated with Lenvatinib Plus Pembrolizumab. Oncologist. 2021 Sep;26(9):e1599-e1608.