Protocol Contains CHECKPOINT INHIBITOR IMMUNOTHERAPY	
Indication	For patients with endometrial cancer who have progressive disease during or following prior platinum-containing therapy given in any setting (neoadjuvant, adjuvant, chemoradiotherapy or for recurrent or metastatic disease, or for more than one of these settings) and who are not candidates for potentially curative surgery or radiotherapy or chemoradiotherapy.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 21 days. Lenvatinib is to continue until disease progression or unacceptable toxicity or patient choice. Continue pembrolizumab for a maximum of 2 years of treatment (defined as 35 x 3-weekly cycles or its equivalent if 6-weekly dosing is used) or until disease progression or unacceptable toxicity or patient choice (whichever comes soonest). * If one drug is discontinued on account of toxicity, the other drug may continue up to the maximum durations given above. If lenvatinib is permanently discontinued pembrolizumab may be given either 200mg IV every 3 weeks or 400mg IV every 6 weeks. A formal medical review MUST occur by the end of the first 6 weeks of treatment to establish whether treatment should continue.
Monitoring Parameters	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • **Blood parameters** Monitor FBC, U&Es (in particular potassium, calcium and magnesium), LFTs, LDH and glucose baseline, Day **1** and **15** of cycles 1 and 2 and then at each cycle thereafter. Abnormalities in electrolytes should be corrected before starting treatment. • If PLT <75 or neuts <1.0 defer lenvatinib and pembrolizumab by 1-week. • **Blood pressure** (BP) should be well controlled prior to treatment and, if patients are known to be hypertensive, they should be on a stable dose of antihypertensive therapy for at least 1 week prior to starting lenvatinib. Monitor BP prior to treatment and after 1 week of treatment. On cycles 2 and 3 monitor BP prior to and mid cycle. Thereafter monitor prior to each cycle. See Table 3 for the recommended management of hypertension guidance. • **Pre-treatment cardiac assessment:** o ECG baseline, then every 8 weeks or as clinically indicated. o Check BNP, and Troponin T prior to treatment. o Monitor patients for symptoms of cardiac dysfunction throughout treatment. o **ECHO:** at baseline for at risk patients, then every 6/12. • A dental examination and appropriate preventive dentistry should be considered (see cautions below - ONJ). • **Urine protein** should be monitored prior to each cycle If >/=2+ see table 2. Dose interruptions, adjustments, or discontinuation may be necessary. • **Thyroid function** must be assessed at baseline then every 6 weeks or as clinically indicated. • Cortisol monitoring should be undertaken in line with ESMO immunotherapy toxicity guidance available on KMCC website (see link below). Cortisol level should not be taken within 24 hours of the last steroid dose. • Confirm the patient has no symptomatically active brain metastases or leptomeningeal metastases.

- **Hepatic impairment:**
  - **Pembrolizumab** - No dose adjustment is needed for patients with mild or moderate hepatic impairment. Pembrolizumab has not been studied in patients with severe hepatic impairment d/w consultant.
  - **Lenvatinib** - In patients with severe (Child-Pugh C) hepatic impairment, the recommended starting dose of lenvatinib is 10 mg taken once daily.
- **Renal impairment:**
  - **Pembrolizumab** - No specific dose adjustment is necessary in patients with mild to moderate renal impairment. Severe renal impairment d/w consultant, pembrolizumab has not been studied in patients with CrCl < 30ml/min.
  - **Lenvatinib** – In severe renal impairment, the recommended starting dose is 10 mg of lenvatinib taken once daily. Not recommended for patients with end-stage renal disease.
- **Dose reductions:**
  - Pembrolizumab - Dose reductions are not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.
  - Lenvatinib - Lenvatinib should be withheld, dose reduced, or discontinued as appropriate. Details for dose adjustment and adverse reactions requiring dose modification are provided in table 1 and 2.
- **Cautions:**
- **Pembrolizumab -**
  - **Immune-related adverse reactions** may appear during or after treatment with pembrolizumab. The most common immune-related reactions are: pneumonitis, colitis, nephritis, hepatitis, symptomatic hypophysitis, hyperthyroidism, hypothyroidism and type 1 diabetes. The following additional, immune related adverse reactions have been reported in patients receiving pembrolizumab: uveitis, arthritis, myositis, pancreatitis, severe skin reactions, myasthenic syndrome, encephalitis, Guillain-Barre syndrome, optic neuritis, rhabdomyolysis, sarcoidosis, myocarditis, haemolytic anaemia and partial seizures arising in a patient with inflammatory foci in brain parenchyma.
    See guidelines for management of immune-related adverse reactions following immunotherapy: https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/
  - Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported. For signs or symptoms of SJS or TEN, pembrolizumab should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, pembrolizumab should be permanently discontinued.
  - **Infusion-related reactions** have been reported in patients receiving pembrolizumab. For severe infusion reactions (grade 3-4), infusion should be stopped and pembrolizumab permanently discontinued.
    Patients with mild or moderate infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.
    *Pembrolizumab may be restarted within 12 weeks beyond the expected cycle length if an adverse reaction remains at Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.
- **Lenvatinib -**
  - Use with caution in patients who have had an arterial thromboembolism within the previous 6 months.
  - Caution in patients with history of aneurysm.
  - Lenvatinib should not be started in patients with fistulae and should be permanently discontinued in patients with oesophageal or tracheobronchial tract involvement and any Grade 4 fistula
  - Lenvatinib may adversely affect the wound healing process.
  - Posterior reversible encephalopathy syndrome (PRES) / Reversible posterior leucoencephalopathy syndrome (RPLS) has been reported in patients. In patients developing PRES / RPLS, treatment of specific symptoms including control of hypertension is recommended along with dose interruption, adjustment or discontinuation.

	○ Diarrhoea: Prompt medical management of diarrhoea should be instituted in order to prevent dehydration. Lenvatinib should be discontinued in the event of persistence of Grade 4 diarrhoea despite medical management. ○ Cases of osteonecrosis of the jaw have been reported in patients treated with lenvatinib, use with caution if using simultaneously or sequentially with antiresorptive therapy and/or other angiogenesis inhibitors. Prior to treatment with lenvatinib, a dental examination and appropriate preventive dentistry should be considered. Reference should be made to the UK chemotherapy board guidance on medication related osteonecrosis of the jaw: https://www.rcplondon.ac.uk/guidelines-policy/medication-related-osteonecrosis-jawguidance-oncology-multidisciplinary • **Common drug interactions (for comprehensive list refer to BNF/SPC):** ○ **Pembrolizumab** ○ The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided. Systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune related adverse reactions. ○ **Lenvatinib** ○ Caution in those taking medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics. • **Missed dose:** ○ **Lenvatinib -** If a patient misses a dose of lenvatinib, and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration. ○ **Pembrolizumab -** If a planned dose is missed, the next dose should be administered as soon as possible. The administration schedule must be adjusted to maintain a 3-week (or 6-week where appropriate) interval between doses. • **Driving:** Lenvatinib may cause fatigue and dizziness, patients who experience these symptoms should use caution when driving or operating machines. Pembrolizumab may have a minor influence on the ability to drive and use machines. Fatigue has been reported following administration of pembrolizumab. • **Pregnancy and Contraception**: ○ Women of childbearing potential should avoid becoming pregnant and must use highly effective contraception while taking lenvatinib and for one month after stopping treatment. ○ Women of childbearing potential should use effective contraception during treatment with pembrolizumab and for at least 4 months after the last dose of pembrolizumab. • Each patient should be given a copy of the Keytruda ® patient alert card at each cycle. • Patients must be advised to contact the oncology team or the 24-hour hot-line immediately if they experience any side effect, as some side effects worsen rapidly. Prompt management of side effects can ensure that the patient continues with treatment. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet.
References	KMCC protocol GYN-048 V1. SPC accesses online 02.01.2026

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1 Dose modifications from recommended lenvatinib daily dose [a]

Adverse reaction	Modification	Lenvatinib dose in combination with pembrolizumab
For persistent and intolerable Grade 2 or 3 toxicities		
First dose reduction	Interrupt until resolved to Grade 0-1 or baseline	14 mg orally once daily (one 10-mg capsule + one 4-mg capsule)
Second dose reduction (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline	10 mg orally once daily (one 10-mg capsule)
Third dose reduction (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline	8 mg orally once daily (two 4 mg capsules)
Life-threatening toxicities (Grade 4): Discontinue[b]		

a Limited data are available for doses below 8 mg
b Treatment should be discontinued in case of life-threatening reactions (e.g., Grade 4) with the exception of laboratory abnormalities judged to be non-life-threatening, in which case they should be managed as severe reactions (e.g., Grade 3).

Table 2 Adverse reactions requiring dose modification of lenvatinib			
Adverse reaction	**Severity**	**Action**	**Dose reduce and resume lenvatinib**
Hypertension	Grade 3 (despite optimal antihypertensive therapy)	Interrupt	Resolves to Grade 0, 1 or 2. See detailed guidance in Table 3.
	Grade 4	Discontinue	Do not resume
Proteinuria	≥ 2 gm / 24 hours	Interrupt	Resolves to less than 2 gm / 24 hours.
Nephrotic syndrome	-------	Discontinue	Do not resume
Renal impairment or failure	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume
Cardiac dysfunction	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
PRES/RPLS	Any grade	Interrupt	Consider resuming at reduced dose if resolves to Grade 0-1.
Hepatotoxicity	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume
Arterial thromboembolisms	Any grade	Discontinue	Do not resume
Haemorrhage	Grade 3	Interrupt	Resolves to Grade 0-1.
	Grade 4	Discontinue	Do not resume
GI perforation or fistula	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
Non-GI fistula	Grade 4	Discontinue	Do not resume
QT interval prolongation	>500 ms	Interrupt	Resolves to <480 ms or baseline
Diarrhoea	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4 (despite medical management)	Discontinue	Do not resume
*Grade 4 laboratory abnormalities judged to be non-life-threatening, may be managed as severe reactions (e.g., Grade 3)			

Table 3 Recommended management of hypertension during treatment with lenvatinib

Blood pressure (BP) level	**Recommended action**
Systolic BP ≥140 mmHg up to <160 mmHg or diastolic BP ≥90 mmHg up to <100 mmHg	Continue lenvatinib and initiate antihypertensive therapy, if not already receiving OR Continue lenvatinib and increase the dose of the current antihypertensive therapy or initiate additional antihypertensive therapy
Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg despite optimal antihypertensive therapy	1. Withhold lenvatinib 2. When systolic BP ≤150 mmHg, diastolic BP ≤95 mmHg, and patient has been on a stable dose of antihypertensive therapy for at least 48 hours, resume lenvatinib at a reduced dose (see section 4.2)
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management.

Repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	Metoclopramide	20mg	PO		
	PEMBROLIZUMAB	**200mg**	IV	30min	In 100ml Sodium Chloride 0.9% via in-line low- protein binding 0.22 microns filter. Flush the line with sodium chloride 0.9% for injection at the end of the infusion.
TTO	Drug	Dose	Route	Directions	
Day 1	**LENVATINIB (Lenvatinib Eisai ®)**	**20mg**	PO	OD continuously. Swallowed whole with water once a day with or without food. Available as 4mg and 10mg capsules.	
	Metoclopramide	10mg	PO	3 times a day when required. (max. 30mg per day including 20mg pre-med dose) Do not take for more than 5 days continuously.	
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Do not take for longer than 3 days without contacting the oncology team. Dispense 30 capsules on cycle 1 then only if required.	

OR ALTERNATIVE DOSING SCHEDULE
Repeat every 42 days

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	Metoclopramide	20mg	PO		
	PEMBROLIZUMAB	**400mg**	IV	30min	In 100ml Sodium Chloride 0.9% via in-line low- protein binding 0.22 microns filter. Flush the line with sodium chloride 0.9% for injection at the end of the infusion.
TTO	Drug	Dose	Route	Directions	
Day 1	**LENVATINIB (Lenvatinib Eisai ®)**	**20mg**	PO	OD continuously. Swallowed whole with water once a day with or without food. Available as 4mg and 10mg capsules.	
	Metoclopramide	10mg	PO	3 times a day when required. (max. 30mg per day including 20mg pre-med dose) Do not take for more than 5 days continuously.	
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Do not take for longer than 3 days without contacting the oncology team. Dispense 30 capsules on cycle 1 then only if required.	