SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

PEMBROLIZUMAB & LENVATINIB

ENDOMETRIAL CANCER

PROTOCOL REF: MPHAPLEC
(Version No. 1.1)

Approved for use in:

- Advanced, recurrent or metastatic endometrial cancer and is not a candidate for any potentially curative treatment with surgery or radiotherapy or chemoradiotherapy.
- Radiographic evidence of disease progression following treatment with at least 1 prior systemic platinum-based regimen in the adjuvant, neoadjuvant (including chemoradiotherapy) or recurrent/metastatic setting.
- ECOG performance status (PS) of 0 or 1.
- Patients who have not received any prior antibody treatment which targets PD-1 or PD-L1 or PD-L2 or CD137 or OX40 or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4)
- Patients who have not received any prior vascular endothelial receptor-targeted agent

Endometrial carcinosarcoma are not eligible

<u>Blueteq registration required</u>

Dosage:

Drug	Dose	Route	Frequency
Pembrolizumab	**200mg**	IV infusion	Day1 every 3 weeks
	Or		
	400mg	IV infusion	Day 1 every 6 weeks
Lenvatinib	**20mg**	Oral	Once daily continuously

Pembrolizumab: For up to a maximum of 2 years or until disease progression/unacceptable toxicity (35 x 3-weekly cycles or its equivalent if 6-weekly pembrolizumab is used).

Where risk factors for toxicity are present the 3 weekly regimen may be favoured.

Lenvatinib: Treatment should continue as long as clinical benefit is observed or until there is unacceptable toxicity or patient choice to stop treatment.

Administration (+/- Counselling Points):

- Lenvatinib capsules should be taken at about the same time each day, with or without food. The capsules should be swallowed whole with water. Alternatively, the lenvatinib capsules may be added without breaking or crushing them to a tablespoon of water or apple juice in a small glass to produce a suspension. The capsules must be left in the liquid for at least 10 minutes and stirred for at least 3 minutes to dissolve the capsule shells. The suspension is to be swallowed. After drinking, the same amount of water or apple juice (one tablespoon) must be added to the glass and swirled a few times. The additional liquid must be swallowed.
- If a patient misses a dose, 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
- Women of childbearing potential should use effective contraception throughout treatment and for at least 4 months following the last dose of Pembrolizumab.

Contact the triage team for the following:

- New or worsening cough, chest pain or shortness of breath
- Diarrhoea or severe abdominal pain (with or without blood/mucous)
- Jaundice, severe nausea or vomiting, or easy bruising or bleeding
- Persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes
- Monitor for signs of infection / sepsis

Emetogenic risk:

Mildly emetogenic

Supportive treatments:

- Metoclopramide 10mg three times daily when required
- Loperamide 2mg when required

Extravasation risk:

Pembrolizumab – non vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

Lenvatinib	
Renal	No adjustment of starting dose is required on the basis of renal function in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended starting dose is 10 mg of lenvatinib taken once daily. Patients with end-stage renal disease have not been studied, therefore the use of lenvatinib in these patients is not recommended.
Hepatic	Limited data are available for the combination of lenvatinib with pembrolizumab in patients with hepatic impairment. No adjustment of starting dose of the combination is required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. In patients with severe (Child-Pugh C) hepatic impairment, the recommended starting dose of lenvatinib is 10 mg taken once daily. Further dose adjustments may be necessary on the basis of individual tolerability.

Pembrolizumab	
Renal	No dose adjustment is needed for patients with mild or moderate renal impairment. Pembrolizumab has not been studied in patients with severe renal impairment
Hepatic	No dose adjustment is needed for patients with mild or moderate hepatic impairment. Pembrolizumab has not been studied in patients with severe hepatic impairment

Interactions:

No data is available that can be used to exclude the risk that lenvatinib could be an inducer of CYP3A4 or Pgp in the gastrointestinal tract. This could potentially lead to decreased exposure to oral CYP3A4/Pgp substrates. This should be considered if co-administering oral CYP3A4/Pgp substrates for which retained efficacy is very important. CYP3A4 substrates known to have a narrow therapeutic index (e.g. astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine)) should therefore be administered with caution in patients receiving lenvatinib.

Oral contraceptives

It is currently unknown whether lenvatinib may reduce the effectiveness of hormonal contraceptives, and therefore women using oral hormonal contraceptives should add a barrier method

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Pembrolizumab**	**400mg (6 weekly) *or 200mg (3 weekly)***	**IV**	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron filter
	Lenvatinib	**20mg**	**PO**	Daily (TTO)

*Where risk factors for toxicity are present e.g. pre-existing autoimmune disease or previous toxicity, the 3 weekly regime may be used.

Routine prophylaxis against infusion related reactions is not required.

However, the patient should be monitored during the infusion, and treatment given if necessary (antihistamines, steroids etc.)

Please refer to the CCC **Hypersensitivity; Management Prevention Policy**

Main toxicities:

For full details on assessment and management of immune-related toxicities refer to CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Pembrolizumab - Immune related toxicities	
Immune-Mediated Pneumonitis Pneumonitis occurred in 3% of melanoma patients (including G3 in 0.2%).	Monitor patients for signs and symptoms and evaluate with radiographic imaging. Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Immune-Mediated Colitis	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Other Immune-Mediated Toxicities: Hepatitis Hypophysitis Nephritis Hyperthyroidism or Hypothyroidism Less frequently: Exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia, Guillain-Barré syndrome	Monitor LFTs, biochemistry, cortisol, regularly. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
Other non-immune adverse events: Fatigue, anaemia Cough, dyspnoea Nausea, decreased appetite Pruritis, rash Constipation, diarrhoea Arthralgia	Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
Laboratory abnormalities: Hyponatraemia, hypocalcaemia, hyperglycaemia, hypertriglyceridaemia	Refer to Immuno-Oncology toxicity specific guidance for adverse event management.

Lenvatinib	
Hypertension	Hypertension can occur early in the course of treatment Blood pressure (BP) should be well controlled prior to treatment. For known hypertension, patients should be on a stable dose of antihypertensive therapy for at least 1 week prior to treatment. Antihypertensive agents should be started as soon as elevated BP is confirmed. BP should be monitored after 1 week of treatment with lenvatinib, then every 2 weeks for the first 2 months and monthly thereafter. The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice – use NICE Clinical Guideline CG 127 – Hypertension in adults diagnosis and management Accessible here: https://www.nice.org.uk/guidance/CG127Hypertension in adults: diagnosis and management | Guidance and guidelines | NICE
Perforations, fistulas, intra-abdominal abscesses.	Gastrointestinal perforation or fistulae have been reported. In most cases, gastrointestinal perforation and fistulae occurred in patients with risk factors such as prior surgery or radiotherapy Lenvatinib should not be started in patients with fistula to avoid worsening and lenvatinib should be permanently discontinued in patients with oesophageal or tracheobronchial tract involvement and any Grade 4 fistula
Haemorrhage	Serious tumour related bleeds; including fatal haemorrhagic events have occurred in clinical trials and have been reported in post-marketing experience. The degree of tumour invasion/infiltration of major blood vessels (e.g. carotid artery) should be considered because of the potential risk of severe haemorrhage associated with tumour shrinkage/necrosis following lenvatinib therapy. In the case of bleeding, dose interruptions, adjustments, or discontinuation may be required. Contact responsible consultant team if concerns.
Thromboembolic events	Arterial thromboembolisms (cerebrovascular accident, transient ischaemic attack, and myocardial infarction) have been reported. Lenvatinib has not been studied in patients who have had an arterial thromboembolism within the previous 6 months, and therefore should be used with caution in such patients. Lenvatinib should be discontinued following an arterial thrombotic event.
Proteinuria	Usually occurs in early in course of treatment. Urine protein should be monitored at each cycle Lenvatinib should be discontinued in the event of nephrotic syndrome.
Cardiovascular	Cardiac failure (<1%) and decreased left ventricular ejection fraction have been reported. Patients should be monitored for clinical symptoms or signs of cardiac decompensation.

Metabolism and nutrition disorders	Hypothyroidism has been reported. Thyroid function should be monitored before initiation of, and periodically throughout, treatment with lenvatinib. Hypothyroidism should be treated according to standard medical practice to maintain euthyroid state. Thyroid stimulating hormone (TSH) levels should be monitored on a regular basis and thyroid hormone administration should be adjusted to reach appropriate TSH levels, according to the patient's therapeutic target.
GI disorders	Diarrhoea has been reported frequently in patients treated with lenvatinib; usually occurring early in the course of treatment. 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.
Renal	Renal impairment and failure have been reported. The primary risk factor identified was dehydration and/or hypovolemia due to gastrointestinal toxicity. Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or renal failure. Dose interruptions, adjustments, or discontinuation may be necessary
Hepatic	Increases in alanine aminotransferase, increases in aspartate aminotransferase, and increases in blood bilirubin can occur. Hepatic failure and acute hepatitis (<1%) have been reported. Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary
Additional side effects	Women of childbearing potential must use highly effective contraception while taking lenvatinib and for one month after stopping treatment. It is currently unknown if lenvatinib increases the risk of thromboembolic events when combined with oral contraceptives Posterior reversible encephalopathy syndrome (PRES) / Reversible posterior leucoencephalopathy syndrome (RPLS) has been reported in patients treated with lenvatinib (<1%) PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control blood pressure. In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary

Investigations and treatment plan:

If suspicion of endocrinopathies: request TSH, T4, T3, ACTH, cortisol, LH, FSH and prolactin (women)

	Pre	Cycle 1	Cycle 2	Prior to cycle 3	Cycle 3	Ongoing
Informed Consent	x					
Clinical Assessment	x			x*		Every 12 weeks thereafter or as clinically indicated
SACT Assessment (to include PS and toxicities)	x	x	x		x	Every cycle
OTR/ Go-ahead	x		x		x	Every cycle
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Calcium, Magnesium, Phosphate, LFTs (AST, ALT, ALP, GGT and bilirubin), TFTs, cortisol, blood glucose, LDH, CRP	x	x	x		x	Every cycle
TFTs, cortisol, blood glucose, HbA1c	x	x	x		x	Every cycle
Lipid profile (cholesterol).	x					At baseline then if clinically indicated
Fatigue profile as per Meditech order set: B12, folate, Iron profile, vitamin D, Zinc, Testosterone (men only), ESR	x					At baseline then if clinically indicated
Full set of observations (*BP, heart rate, temperature, respiratory rate and O_2 sats*)	x	x	x		x	Every cycle
Creatinine Clearance (Cockcroft and Gault)	x					Every cycle only if baseline CrCL <30ml/min or creatinine increases

						above 1.5x upper limit of normal or baseline
CT scan**	x					Every 12 weeks/if clinically indicated
Urine dipstick for protein	x	x	x		x	Every cycle
Trop-T, CK, pro-BNP	x					At baseline and thereafter as clinically indicated (ECG to be reviewed by clinical team)
ECG	x					
Weight recorded	x	x	x		x	Every cycle
Height recorded	x					

*Formal medical review (can be virtual) to assess the tolerability of treatment and whether treatment should continue
Pregnancy test if applicable

Dose Modifications and Toxicity Management:

Dosing delay or discontinuation may be required based on individual safety and tolerability.

Proceed on day 1 of cycle if:-

Platelets	Neutrophils	Serum Creatinine	Bilirubin	AST/ALT	Alkaline Phosphatase	TSH and Free T4
≥ 75 x 10^9/L	≥ 1.0 x 10^9/L	<1.5 x ULN or Baseline	<1.5 x ULN*	<3 x ULN	<3 x ULN	Within range or no change from base line

* ULN = upper limit of normal

The dose should be omitted if appropriate. Inform consultant if there has been an increase in liver function test from previous results.

Lenvatinib

Lenvatinib Dose Reduction Levels	
Starting Dose	20mg
Dose Level -1	14mg
Dose Level -2	10mg
Dose Level -3	8mg

Once a dose reduction has been made, it should not routinely be re-escalated.

Treatment Related Toxicity	Management	Dose Adjustment
Grade 1 or Tolerable grade 2	Continue treatment	No Change
Intolerable grade 2 or grade 3		
First occurrence	Interrupt lenvatinib until resolved to ≤1grade 1 or tolerable	Reduce lenvatinib to dose level -1 (14mg)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to ≤1grade 1 or tolerable	Reduce lenvatinib to dose level -1 (10mg)
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to ≤1grade 1 or tolerable	Reduce lenvatinib to dose level -1 (8mg)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with prescriber
Grade 4: Discontinue Treatment		

Hepatotoxicity

Toxicity Grade	**Bilirubin Level**	**Proteinuria Level**	**Lenvatinib Managment**
Grade 2	>1.5 x ULN	2+ or 3+	See table above for management
Grade 2	>1.5 x ULN	2+ or 3+	
Grade 3	>3 x ULN	4+	
Grade 4	>10 x ULN		

Hypertension

Blood Pressure (BP) level	**Recommended action**
Systolic BP ≥ 140mmHg up to <160mmHg or diastolic BP ≥90mmHg up to ,100mmHg	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
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management.

Proteinuria

Urine Dipstick for protein	Recommendation
First occurrence of ≥ 2+ protein	Undertake 24 hour urine collection immediately (or within max 72 hours). Monitor urine dipstick every 2 weeks until resolved ≤ 1+
Subsequent increase in severity of proteinurea on the same dose level	
Occurrence of ≥ 2+ protein despite reduced dose	

Pembrolizumab:

Detailed guidelines are provided in the CCC clinical network immunotherapy acute oncology guidelines. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.

Toxicity Grade	Action
Grade 1 Mild	No action. Provide symptomatic treatment
Grade 2 Moderate	Withhold Pembrolizumab until resolved to < grade 1. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
Grade 3 and Grade 4 Severe	Withhold Pembrolizumab. Refer to Immuno-Oncology toxicity specific guidance for adverse event management. Pembrolizumab will be permanently discontinued for any unresolving grade 3-4, severe or life-threatening adverse reaction at the treating clinician's discretion.

References:

- Keytruda® SMPC Merck Sharp and Dohme Accessed via https://www.medicines.org.uk/emc/product/2498/smpc [last updated Nov 2022]
- Lenvatinib 10mg capsules SPC. LENVIMA 10 mg hard capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) [last updated Nov 2022]
- Makker, V et al. Lenvatinib plus pembrolizumab for advanced endometrial cancer. February 2022. *N Engl J Med*. 386:437-448

Circulation/Dissemination

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Version History

Date	Version	Author name and designation	Summary of main changes
	1.0	Jennifer Gibson	V1.0 New protocol
May 2023	1.1	Sarah Craig Advanced Pharmacist Teacher Practitioner	V1.1 Minor changes now CDF funded regime