Lenvatinib & pembrolizumab
(endometrial cancer and renal cell carcinoma)

Indication

Lenvatinib in combination with pembrolizumab is indicated for:

- the treatment of adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation. Performance status 0-1
- untreated advanced renal cell carcinoma (RCC)

Regimen details

Pembrolizumab 200mg IV infusion in 100ml 0.9% sodium chloride **or** 395mg subcutaneous injection
Lenvatinib 20mg oral once daily continuously
(if using branded lenvatinib use Lenvima brand for endometrial cancer and Kisplyx brand for RCC)

Cycle frequency

Every 3 weeks

Number of cycles

Maximum 35 cycles of pembrolizumab
Patients may continue lenvatinib until disease progression or unacceptable toxicity

Administration

Lenvatinib

Lenvatinib is for oral use. The capsules should be taken at about the same time each day, with or without food. The capsules should be swallowed whole with water. Caregivers should not open the capsule, to avoid repeated exposure to the contents of the capsule.
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

Intravenous pembrolizumab

Pembrolizumab should be administered in 100mL sodium chloride 0.9% over 30 minutes.

Pembrolizumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 5.0µm).

After the infusion, the line should be flushed with 30mL sodium chloride 0.9%.

Patients should be monitored every 30 minutes during the infusion (blood pressure, pulse and temperature) and for infusion related reactions. For mild to moderate reactions, decrease the infusion rate and closely monitor. Premedication with paracetamol and chlorphenamine should be used for further doses. For severe infusion related reactions discontinue treatment

Pembrolizumab subcutaneous

Inject into the subcutaneous tissue of the thigh or abdomen, avoiding the 5 cm area around the navel. Do not inject

into skin that is damaged, sore, bruised, scarred, scaly, or has red patches. Rotate injection sites for subsequent injections.

- Inject 395mg over 1 minute
- Inject 790mg over 2 minutes

Pre-medication

None

Emetogenicity

Low emetogenic potential

Additional supportive medication

Supply loperamide and emollient with first cycle

Extravasation

Neutral

Investigations – pre first cycle

Blood pressure must be well controlled before starting treatment with lenvatinib

Electrolyte disturbances must be corrected before starting treatment with lenvatinib

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating lenvatinib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm

Temporary interruption of lenvatinib should be considered in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of lenvatinib following a major surgical procedure. Therefore, the decision to resume lenvatinib following a major surgical procedure should be based on clinical judgment of adequate wound healing.

Investigation	**Validity period** (or as per local policy)
FBC	14 days
Coagulation screen	14 days
U+E (including creatinine)	14 days
LFT inc AST	14 days
Calcium, Phosphate, Magnesium, cholesterol	14 days
Thyroid function	14 days
Glucose	14 days
HIV screen, HepB S Antigen, HepB core Antibody , Hep C antibody	14 days
Cortisol	14 days
CK, amylase, proBNP, troponin	14 days
ECG	14 days
BP	14 days
Urinalysis for proteinuria	14 days
Cortisol	14 days
Luteinizing hormone	14 days
Follicle stimulating hormone	14 days
Testosterone	14 days

Investigations –pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	48 hours

Coagulation screen	48 hours
U+E (including creatinine)	48 hours
LFT inc AST	48 hours
Calcium, Phosphate, Magnesium, cholesterol	48 hours
Thyroid function	48 hours
Random Glucose or BM stix	48 hours
Cortisol	Alternate cycles
CK, amylase, proBNP, troponin	Alternate cycles
ECG	Cycles 1-2-3, then Alternate cycles
BP	48 hours
Urinalysis for proteinuria	48 hours

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	**Limit**
Neutrophil count	≥ 1.5 x 109/L
Platelets	≥ 100 x 109/L
Hb	>90
Creatinine Clearance (CrCl)	≥ 30mL/min unless over 10% decline in Creatinine
LFTS	Consult with prescriber if abnormal particularly if over 20% above upper range normal.
Proteinuria	Over 2+
Other tests	Consult prescriber if abnormal

Dose modifications

Do not modify dose of Pembrolizumab. Consider immunotherapy-driven toxicity as a potential reason for all changing laboratory results and discuss with a consultant if any concerns.

Dose modifications from recommended lenvatinib daily dose in EC patients[a]		
Starting Dose in combination with pembrolizumab		20 mg orally once daily (two 10-mg capsules) (median dose in trial was 14mg)
Persistent and Intolerable Grade 2 or Grade 3 Toxicities		
Adverse Reaction	**Modification**	**Adjusted Dose**
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	14 mg orally once daily (one 10-mg capsule + one 4-mg capsule)
Second occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline	10 mg orally once daily (one 10-mg capsule)
Third occurrence (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 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.
	Grade 4	Discontinue	Do not resume.
Proteinuria	≥ 2 g / 24 hours	Interrupt	Resolves to less than 2 g / 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.
Posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (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.
Gastrointestinal perforation or fistula	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume.
Non-gastrointestinal 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).			

Renal impairment: 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.

Renal Toxicity: Renal impairment and renal failure have been reported in patients treated with lenvatinib.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 Impairment: 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.

Hepatic Toxicity: In EC, liver-related adverse reactions most commonly reported in patients treated with lenvatinib and pembrolizumab included increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Hepatic failure and hepatitis (<1%) have been reported in patients with EC treated with lenvatinib and pembrolizumab.

QT interval prolongation

QT/QTc interval prolongation has been reported at a higher incidence in patients treated with lenvatinib than in patients treated with placebo. Electrocardiograms should be monitored at baseline and periodically during treatment in all patients with particular attention to those with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, and those taking medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics. Lenvatinib should be withheld in the event of development of QT interval prolongation >500 ms. Lenvatinib should be resumed at a reduced dose when QTc prolongation is resolved to <480 ms or baseline.

Impairment of thyroid stimulating hormone suppression/ Thyroid dysfunction

Hypothyroidism has been reported in patients treated with lenvatinib. 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.

Wound healing complications

No formal studies of the effect of lenvatinib on wound healing have been conducted. Impaired wound healing has been reported in patients receiving lenvatinib. Temporary interruption of lenvatinib should be considered in patients undergoing major surgical procedures.

Osteonecrosis of the jaw (ONJ)

Cases of ONJ have been reported in patients treated with lenvatinib

Hypocalcaemia:

Hypocalcaemia was reported in 3.9% of lenvatinib plus pembrolizumab-treated patients and Grade ≥3 reactions occurred in 1.0% of patients. The median time to onset was 148.0 days. No lenvatinib dose modifications were reported.

Elderly patients

Patients of age ≥75 years were more likely to experience urinary tract infections and Grade ≥3 hypertension (≥ 10% increase compared to patients of age <65 years

Ethnicity

Asian patients had a higher (≥ 10% difference) incidence than Caucasian patients of anaemia, malaise, neutrophil count decrease, stomatitis, platelet count decreased, proteinuria and PPE while Caucasian patients had a higher incidence of mucosal inflammation, abdominal pain, diarrhoea, urinary tract infection, weight decreased, hypomagnesaemia, dizziness, asthenia and fatigue.

Body weight (thyroid cancer data)

Patients with low body weight (<60 kg) had a higher incidence of PPE, proteinuria, of Grade 3 or 4 hypocalcaemia and hyponatraemia, and a trend towards a higher incidence of Grade 3 or 4 decreased appetite.

Immuntherapy toxicities

Immunotherapy toxicities should be aggressively managed as can cause permanent and life threatening complications.
Refer to UKONS and ESMO guidance for treatment of immune related toxicities.
Available at:
https://www.healthierlsc.co.uk/canceralliance/chemotherapy-protocols/immunotherapy-toxicity-guidelines

Toxicity	Definition	Action
Colitis	Grade 1	Continue and closely monitor
	Grade 2-3	Withhold until symptoms resolve to ≤ grade 1
	Grade 4	Permanently discontinue pembrolizumab
Pneumonitis	Grade 1	Continue and closely monitor
	Grade 2	Withhold until symptoms resolve to ≤ grade 1
	Grade 3-4 or recurrent grade 2	Permanently discontinue pembrolizumab
Nephritis	Grade 2 (creatinine 1.5-3 x ULN)	Withhold until symptoms resolve to ≤ grade 1

	Grade 3 (creatinine > 3 x ULN)	Permanently discontinue pembrolizumab
Endocrine	Symptomatic hypophysitis	Withhold until symptoms resolve to ≤ grade 1
	Type 1 diabetes with grade > 3 hyperglycaemia (glucose > 13.9 mmol/L) or ketoacidosis	Withhold until ≤ grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hyperthyroidism ≥ grade 3	Withhold until ≤ grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hypothyroidism	Continue and manage with replacement therapy
Hepatitis	AST/ALT 3-5 x ULN or Bilirubin > 1.5-3 x ULN	Withhold until resolves to ≤ grade 1
	AST/ALT > 5 x ULN or Bilirubin > 3 x ULN	Permanently discontinue pembrolizumab
	Liver metastasis and baseline AST/ALT 3-5 x ULN or AST/ALT increases ≥ 50% for ≥ 1 week	Permanently discontinue pembrolizumab
Infusion-related reactions	Grade 3-4	Permanently discontinue pembrolizumab

Pembrolizumab should be permanently discontinued if:

- Grade 4 toxicity (except for endocrinopathies that are controlled with replacement hormones)
- Corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks
- Treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose
- Any event occurs a second time at Grade ≥ 3 severity
- Grade 3 or 4 myocarditis
- Grade 3 or 4 encephalitis
- Grade 3 or 4 Guillain-Barré syndrome

Adverse effects –

for full details consult product literature/ reference texts

Hypertension
Hypothyroidism
Diarrhoea
Nausea
Decreased appetite
Vomiting
Weight decrease
Fatigue
Arthralgia
Proteinuria
Anaemia
Constipation
Urinary tract infection
Neutropenia
Alopecia
Immune related toxicity
Infusion reaction

Significant drug interactions

– for full details consult product literature/ reference texts

Corticosteroids: use of systemic corticosteroids at baseline, before starting pembrolizumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions.

Additional comments

Women of child bearing potential should use effective contraception during treatment and for at least 4 months after the last dose.

References

Makker et al. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer N Engl J Med 2022; 386:437-448
Motzer et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma N Engl J Med 2021; 384:1289-1300

THIS PROTOCOL HAS BEEN DIRECTED BY DR HOGG, CONSULTANT ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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