Lenvatinib and Pembrolizumab (Renal)

Indication

Treatment-naïve patients with intermediate or poor risk advanced renal cell carcinoma, for whom treatment with nivolumab plus ipilimumab would otherwise be suitable.
ECOG performance score 0-1.

(TA858)

ICD-10 codes

Codes prefixed with C64.

Regimen details

Day	Drug	Dose	Route
1	Pembrolizumab	200mg every 3 weeks or 400mg every 6 weeks	IV infusion
Continuous	Lenvatinib	20mg OD	PO

Cycle frequency

21 days or 42 days as above.

Number of cycles

Continue until disease progression or unacceptable toxicity (NB. pembrolizumab can continue for a maximum of 2 years but Lenvatinib monotherapy can be continued beyond this, in the absence of disease progression or unacceptable toxicity).

Administration

Lenvatinib
Lenvatinib (Kisplyx®) is available as 4mg and 10mg capsules. The dose is made up of 2 x 10mg capsules
The tablets should be swallowed whole with a glass of water at the same time each day, either with or without food. Alternatively, the 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 should then 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 also be swallowed.
If a dose is missed and it is more than 12 hours from the time the dose was due, the dose should be missed. The patient should take the usual prescribed dose on the following day.

NOTE: The **Kisplyx®** brand is the only product licensed for the treatment of renal cell carcinoma.

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.

Pre-medication
Nil

Emetogenicity
This regimen has mild emetic potential (although nausea is common).

Additional supportive medication
Antiemetics as required.
Loperamide if required.
Emollients as required.

Extravasation
Pembrolizumab is neutral (Group 1)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Thyroid function	14 days
Glucose	14 days
Calcium	14 days
Magnesium	14 days
Cortisol	14 days
Urinalysis for proteinuria	Baseline
Blood pressure*	Baseline
ECG for QTc interval**	Baseline

* Blood pressure should be well controlled (defined as BP ≤ 140/90) prior to commencing treatment with Lenvatinib and if patients are known to be hypertensive, they should be on a stable dose of antihypertensive for at least 1 week prior to treatment with lenvatinib.
** Review concomitant medications that may also lead to QTc prolongation. Electrolyte abnormalities, such as hypokalaemia, hypocalcaemia or hypomagnesaemia must be corrected prior to commencing treatment. Consider echocardiogram if concerns about cardiac status.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	7 days
U+E (including creatinine)	7 days
LFTs	Every 2 weeks for the first 2 months then within 7 days of pembrolizumab administration thereafter
Calcium	7 days
Magnesium	7 days
Potassium	7 days
Glucose	As clinically indicated
Thyroid function	6 weekly
Cortisol	At consultant discretion
Blood pressure*	7 days
Urinalysis for proteinuria	7 days
ECG for QTc interval**	If clinically indicated

* Hypertension may develop within a week of commencing lenvatinib. Patients should be encouraged to monitor their blood pressure at home regularly, ideally daily.
Electrolyte abnormalities, such as hypokalaemia, hypocalcaemia or hypomagnesaemia must be corrected prior to commencing treatment.

Standard limits for administration to go ahead

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

Investigation	Limit
Neutrophils	≥ 1.5 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine Clearance (CrCl)	≥ 30mL/min
Bilirubin	≤ 1.5 x ULN
ALT/AST	≤ 1.5 x ULN
Alkaline Phosphatase	<5 x ULN
QTc	<500ms
Blood pressure	<140/90mmHg

Electrolyte abnormalities, such as hypokalaemia, hypocalcaemia or hypomagnesaemia should be corrected as per local guidelines.

Dose modifications

Lenvatinib dose modifications:

Dose level	Dose
Full dose	20mg OD
First dose reduction	14mg OD
Second dose reduction	10mg OD
Third dose reduction	8mg OD

There is limited data of dosing below 8mg OD.

- **Haematological toxicity**

If neutrophils < 1.5 x 10^9 /L or platelets < 100 x 10^9 /L, discuss with consultant.

- **Renal impairment**

No specific dose adjustment for **lenvatinib** is required in patients with mild or moderate renal impairment. In patients with severe renal impairment (CrCl <30ml/min), the recommended starting dose is 10mg OD. Further dose adjustments may be necessary based on individual tolerability. Treatment is not recommended in patients with end-stage renal disease.

The safety and efficacy of **pembrolizumab** has not been studied in patients with renal impairment. No specific dose adjustments are recommended in mild to moderate renal impairment. Discuss with consultant if CrCl <30mL/min.

- **Hepatic impairment**

No specific dose adjustment for **lenvatinib** is required in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment (Child-Pugh C) the recommended starting dose is 10mg OD.

The safety and efficacy of **pembrolizumab** has not been studied in patients with hepatic impairment. No specific dose adjustments are recommended in mild hepatic impairment. See below for management of hepatitis.

- **Other toxicities**

Lenvatinib:

Mild to moderate adverse reactions (eg. Grade 1 or 2) generally do not warrant interruption of lenvatinib, unless intolerable to the patient despite optimal management. Severe (eg. Grade 3) or intolerable adverse reactions require interruption of lenvatinib until improvement of the reaction to Grade 0-1 or baseline. Treatment should be discontinued in case of life-threatening reactions (Grade 4), with the exception of laboratory abnormalities judged to be non-life-threatening, in which case they should be managed as severe reactions (Grade 3).

Hypertension

Blood pressure	**Action**
Systolic ≥140 - <160 mmHg **or** Diastolic ≥90 - <100 mmHg	Initiate or increase antihypertensive medication Continue lenvatinib
Systolic ≥160 mmHg **or** Diastolic ≥100 mmHg	Withhold lenvatinib When systolic ≤150 mmHg and diastolic ≤95 mmHg and patient has been stable on antihypertensive therapy for at least 48 hours, resume lenvatinib at reduced dose.
Malignant hypertension **or** Neurological deficit **or** Hypertensive crisis	Discontinue lenvatinib and commence urgent appropriate medical management.

Hypertension should be managed aggressively and pro-actively to minimise dose interruptions and reductions. Antihypertensives should be started as soon as elevated BP is confirmed. The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice. Examples of appropriate antihypertensives include

- Step 1 ACE inhibitor (eg. Ramipril - start at 2.5mg then increasing to 5mg)
- Step 2 Adding calcium channel blocker (eg. Amlodipine - start at 5mg then increasing to 10mg) and/or diuretics if required.
- Step 3 If BP not controlled on a combination of antihypertensives, refer for cardiology opinion.

Proteinuria

Definition	Dose adjustment
Grade 1 Urinalysis: 1+ protein Urinary protein ≥ ULN - < 1.0g/24h Urine protein/creatinine ratio < 100mg/mmol (or urine albumin/creatinine ratio <70 mg/mmol)	Continue lenvatinib
Grade 2 Urinalysis: 2+ protein Urinary protein 1.0 - < 3.5g/24h Urine protein/creatinine ratio 100 – 300 mg/mmol (or urine albumin/creatinine ratio 70-250 mg/mol)	If >2+ proteinuria is documented a more formal measurement by either 24 hour urine collection or urine protein/creatinine ratio should be undertaken. If ≥ 2g/24h, stop lenvatinib and resume at reduced dose when <2g/24h
Grade 3 Urinalysis: 3+ protein Urinary protein > 3.5g/24h Urine protein/creatinine ratio >300mg/mmol (or urine albumin/creatinine ratio >250mg/mmol)	Withhold lenvatinib. Then as per Grade 2. In case of chronic persistent proteinuria, discontinue and refer to nephrologist
Grade 4 Nephrotic syndrome	Discontinue

Low body weight

There is limited data for lenvatinib patients with body weight <60 kg in renal cell carcinoma. However, in thyroid cancer, 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. Consider closer toxicity monitoring for patients <60kg.

QT interval prolongation

QT interval prolongation has been reported in patients treated with lenvatinib. Electrocardiograms should be monitored in all patients particularly those with congenital long QT syndrome, congestive heart failure, bradyarrhythmics, 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 greater than 500ms. Lenvatinib should be resumed at a reduced dose when QTc prolongation is resolved to < 480ms or baseline.

Electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia increase the risk of QT prolongation. Any electrolyte abnormalities should be corrected before starting treatment. Periodic monitoring of ECG and electrolytes (magnesium, potassium and calcium) should be considered during treatment. Blood calcium levels should be monitored at least monthly and calcium should be replaced as necessary during lenvatinib treatment. Lenvatinib dose should be interrupted or dose adjusted as necessary depending on severity, presence of ECG changes, and persistence of hypocalcaemia.

If any of the following occur interrupt lenvatinib treatment until grade 0-1 or baseline:

- Proteinuria (≥ 2g/24 hours)
- Grade 3 renal impairment
- Grade 3 cardiac dysfunction
- PRES/RPLS
- Grade 3 hepatotoxicity
- Grade 3 haemorrhage
- Grade 3 GI perforation
- Grade 3 diarrhoea

If any of the following occur discontinue lenvatinib treatment:

- Grade 4 hypertension
- Nephrotic syndrome
- Grade 4 renal impairment
- Grade 4 cardiac dysfunction
- Grade 4 hepatotoxicity
- Arterial thromboembolisms
- Grade 4 haemorrhage
- Grade 4 GI perforation
- Grade 4 non GI fistula
- Grade 4 diarrhoea

Pembrolizumab:

Patients must be advised to seek specialist advice if they experience side effects as these can worsen rapidly. Immune reactions may occur during or after completion of treatment.

Toxicity	Definition	Action/Dose adjustment
Colitis	Grade 1	Continue and closely monitor
	Grade 2-3	Withhold until symptoms resolve to ≤ grade 1
	Grade 4 or recurrent grade 3	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
	If liver metastasis with baseline AST/ALT 3-5 x ULN: - If AST/ALT increases ≥ 50% for ≥ 1 week	Permanently discontinue pembrolizumab
Infusion-related reactions	Grade 3-4	Permanently discontinue pembrolizumab
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold until resolves to ≤ grade 1
	Grade 4 or confirmed SJS or TEN	Permanently discontinue

Other immune-related adverse reactions	Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 3 or 4 Guillain-Barre syndrome	Permanently discontinue

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 prednisolone 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

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Lenvatinib:
Myelosuppression
Electrolyte abnormalities (hypocalcaemia, hypomagnesaemia, hypokalaemia)
Proteinuria, nephrotic syndrome
Renal failure and impairment
Hepatic changes
Cardiac failure
GI perforation or fistula
Non GI fistula
Arterial thromboembolism
Haemorrhage
Aneurysm and artery dissections
Thyroid dysfunction
Posterior reversible encephalopathy syndrome (PRES)
QTc interval prolongation
Wound healing complications

Pembrolizumab:
Myelosuppression
Pneumonitis
Colitis
Hepatitis
Nephritis
Endocrinopathies
Pancreatitis

- **Frequently occurring side effects**

Lenvatinib:
Hypertension
Proteinuria
Diarrhoea
Anorexia
Weight loss
Fatigue
Nausea
Vomiting
Stomatitis
Dysphonia
Headache

Palmar Plantar Erythema
Rash
Peripheral oedema
Joint and muscle ache

Pembrolizumab:
Myelosuppression
Reduced appetite
Headache
Dizziness
Dry eyes
Cough
Diarrhoea
Nausea
Rash, pruritus
Fatigue
Hyperglycaemia
Hypocalcaemia
Hyperthyroidism, hypothyroidism

- **Other side effects**

Pembrolizumab:
Arthralgia

Significant drug interactions – for full details consult product literature/ reference texts

Lenvatinib:
As lenvatinib may **prolong the QT interval** avoid concomitant use of other medications which can lead to QT prolongation (including amiodarone, quinidine, sotolol, chloroquine, clarithromycin). Use with caution in patients taking **medications which may cause electrolyte disturbances**.

Oral contraceptives: it is not known if lenvatinib may reduce the effectiveness of hormonal contraceptives and so women should also use a barrier method.

Agents acting on the renin-angiotensin aldosterone system: use with caution due to potentially higher risk for acute renal failure.

Pembrolizumab:
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 childbearing potential should avoid becoming pregnant and use highly effective contraception during treatment and for at least one month after finishing lenvatinib and four months after the last dose of pembrolizumab. 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.

References

- Motzer R et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Engl J Med. 2021 Apr 8;384(14):1289-1300.
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- Summary of Product Characteristics Pembrolizumab - Keytruda® (MSD) accessed 26 October 2022 via www.medicines.org.uk
- National Institute for Health and Care Excellence TA858 accessed 7 February 2023 via www.nice.org.uk

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