LENVATINIB (Kisplyx) PEMBROLIZUMAB (Keytruda)

INDICATION (ICD10) C64

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)

Lenvatinib in combination with pembrolizumab for use in treatment-naïve patients with intermediate or poor risk advanced renal cell carcinoma for whom treatment with nivolumab plus ipilimumab would otherwise be suitable where the following criteria have been met:

2. The prescribing clinician is fully aware of the management of and the treatment modifications that may be required for immune-related adverse reactions due to checkpoint inhibitor treatments including pneumonitis, colitis, nephritis, endocrinopathies, hepatitis, skin toxicity and other immune-related adverse reactions.

3. Has unresectable locally advanced or metastatic renal cell carcinoma (RCC) which has either a clear cell component or is one of the types of RCC as indicated below.

- RCC with a clear cell component or
- Papillary RCC or
- Chromophobe RCC or
- Collecting duct RCC (Bellini collecting duct RCC) or
- Medullary RCC
- Mucinous tubular and spindle cell RCC or
- Multilocular cystic RCC or
- XP11 translocation RCC or
- Unclassified RCC

4. The disease is in the intermediate or poor risk category as assessed by the International Metastatic RCC Database Consortium (IMDC) system which scores 1 point for each of the 6 factors listed below – a score of 0 indicates good risk disease, a score of 1-2 indicates intermediate risk and a score of 3-6 denotes poor risk. The IMDC factors are:

- less than 1 year from time of initial diagnosis of RCC to now
- a Karnofsky performance status of <80%
- the haemoglobin level is less than the lower limit of normal
- the corrected calcium level is >2.5mmol/L
- the platelet count is greater than the upper limit of normal
- the absolute neutrophil count is greater than the upper limit of normal.

Whether the patient is in the intermediate or poor risk prognostic group:

- intermediate risk disease (IMDC score of 1 or 2) or
- poor risk disease (IMDC score of 3-6)

Note: Lenvatinib plus pembrolizumab is not approved for patients with good risk RCC.

5. Is either completely treatment naïve for systemic therapy for RCC or if the patient has received prior systemic therapy in the context of adjuvant/neoadjuvant therapy, then such treatment was completed ≥12 months previously.

Whether previous systemic therapy for RCC has ever/never been received and if it has that this has been received solely in the adjuvant/neoadjuvant disease setting:

- no previous adjuvant/neoadjuvant systemic therapy of any kind and the patient is treatment naïve for the locally advanced/metastatic RCC indication or
- prior adjuvant/neoadjuvant therapy for RCC with agents which target VEGF and the last dose received by the patient was ≥12 months prior to this application and the patient is treatment naïve for the locally advanced/metastatic RCC indication
- prior adjuvant/neoadjuvant therapy for RCC with immune-modulatory therapies [anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, antiCD137 or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibodies] and the last dose received by the patient was ≥12 months prior to this application and the patient is treatment naïve for the locally advanced/metastatic RCC indication.

6. In the absence of lenvatinib plus pembrolizumab, the patient would otherwise be suitable for treatment with nivolumab plus ipilimumab. Note: NICE recommended lenvatinib plus pembrolizumab as an option only in those patients who would otherwise be suitable for nivolumab plus ipilimumab but not in patients suitable for single agent TKI therapy.
7. Has a Karnofsky performance status of at least 70 (ie an ECOG performance score of 0 or 1).
8. Has no symptomatic brain metastases or leptomeningeal metastases currently requiring steroids for symptom control.
9. Is to be treated with lenvatinib until loss of clinical benefit or excessive toxicity or withdrawal of patient consent, whichever is the sooner. Note: there is no stopping rule as to the maximum treatment duration of the lenvatinib part of this indication.
Note: if lenvatinib is permanently discontinued on account of toxicity, treatment with pembrolizumab can be continued as monotherapy as long as there is no evidence of progressive disease and the patient has not already completed 2 years of treatment with pembrolizumab.
10. Is to be treated with pembrolizumab until loss of clinical benefit or excessive toxicity or withdrawal of patient consent or completion of a total treatment duration of 2 years*, whichever occurs first. *2 years treatment is defined as a maximum of 35 x 3-weekly cycles or the equivalent number of 6-weekly cycles. Note: if pembrolizumab is permanently discontinued on account of toxicity, treatment with lenvatinib can be continued as monotherapy as long as there is no evidence of progressive disease.
11. A formal medical review to assess the tolerability of treatment with lenvatinib plus pembrolizumab will be scheduled to occur at least by the start of the 3rd 3-weekly cycle or 2nd 6-weekly cycle of treatment and thereafter on a regular basis.
12. Treatment breaks of up to 12 weeks beyond the expected 3- or 6-weekly cycle length are allowed but solely to allow any toxicities to settle.
13. If the disease progresses on the pembrolizumab and lenvatinib combination and further systemic therapy is appropriate, the next line of treatment will be chosen from those options which are routinely commissioned ie for the next line of systemic therapy, there will be use of one choice of the following (mainly incorporating TKI options which have multiple modes of action):
the currently commissioned 2nd line options of cabozantinib or axitinib or everolimus monotherapy or the currently commissioned 1st line options of sunitinib (still on label as 2nd line treatment) or pazopanib (off label as 2nd line treatment) or tivozanib (off label as 2nd line treatment).
14. Lenvatinib and pembrolizumab will be otherwise prescribed and administered as outlined in their respective Summary of Product Characteristics (SPCs).

REGIMEN (42 day)
Day 1 PEMBROLIZUMAB 400mg in 100ml sodium chloride IV infusion over 30 minutes
LENVATINIB 20mg orally daily continuously

REGIMEN (21 day)
Day 1 PEMBROLIZUMAB 200mg in 100ml sodium chloride IV infusion over 30 minutes
LENVATINIB 20mg orally daily continuously

CYCLE FREQUENCY AND NUMBER OF CYCLES
Lenvatinib continuously until disease progression
Pembrolizumab every 42 days until disease progression up to 17 cycles (maximum 2 years)
Pembrolizumab every 21 days until disease progression up to 35 cycles (maximum 2 years)

ADMINISTRATION
Lenvatinib
Available as 4mg and 10mg capsules
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.

ANTI-EMETICS
Minimal risk all days

CONCURRENT MEDICATION REQUIRED

Lenvatinib	Diarrhoea – Loperamide required Skin – apply moisturizer to hands and feet regularly
Pembrolizumab	None required

EXTRAVASATION AND TYPE OF LINE / FILTERS
Pembrolizumab – neutral
Use low protein binding 0.2 to 5micron in-line or add-on filter
Peripheral line

INVESTIGATIONS
Blood results required before SACT administration
FBC, U&E and LFTs every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Thyroid function* baseline, then every cycle
Random cortisol baseline, then every cycle
Random glucose every cycle
Urine protein
ECG baseline then monitor QT interval
Blood pressure, after 1st week, then every 2 weeks for first 2 months, then monthly
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Lenvatinib	Hypertension, cardiac dysfunction, QT prolongation Proteinurea, diarrhoea Nephrotic syndrome Hepatotoxicity Haemorrhage, arterial thromboembolisms, GI perforation
Pembrolizumab	Immune related toxicities

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Lenvatinib	Check interactions carefully, interacts with a huge number of drugs.
Pembrolizumab	-

DOSE MODIFICATIONS
Lenvatinib

Recommended dose	20mg once daily
First dose reduction	14mg once daily
Second dose reduction	10mg once daily
Third dose reduction	8mg once daily

Non-haematological

Lenvatinib

Arterial thromboembolisms – any grade	Discontinue. Do not resume
Cardiac dysfunction – grade 3	Interrupt. Resolves to grade 0-1 or baseline dose reduce and resume.
Cardiac dysfunction – grade 4	Discontinue. Do not resume
Diarrhoea – grade 3	Interrupt. Resolves to grade 0-1 or baseline dose reduce and resume.
Diarrhoea – grade 4 (despite medical management)	Discontinue. Do not resume
GI perforation or fistula – grade 3	Interrupt. Resolves to grade 0-1 or baseline dose reduce and resume.
GI perforation or fistula – grade 4	Discontinue. Do not resume
Non-GI fistula – grade 4	Discontinue. Do not resume
Hemorrhage – grade 3	Interrupt. Resolves to grade 0-1 dose reduce and resume.
Hemorrhage – grade 4	Discontinue. Do not resume
Hepatotoxicity – grade 3	Interrupt. Resolves to grade 0-1 or baseline dose reduce and resume.
Hepatotoxicity – grade 4	Discontinue. Do not resume
Hypertension - grade 3 (despite optimal antihypertensive therapy)	Interrupt. Resolves to grade 0-1 or 2 dose reduce and resume.
Hypertension - grade 4	Discontinue. Do not resume
Nephrotic syndrome	Discontinue. Do not resume
PRES/RPLS – any grade	Interrupt. Consider resuming at reduced dose if resolves to grade 0-1
Proteinurea ≥2g/24 hours	Interrupt. Resolves to <2g/24 hours dose reduce and resume.
QT prolongation >500ms	Interrupt. Resolves to <480ms or baseline dose reduce and resume.
Renal impairment or failure – grade 3	Interrupt. Resolves to grade 0-1 or baseline dose reduce and resume.
Renal impairment or failure – grade 4	Discontinue. Do not resume

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.
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management.

Pembrolizumab
Immune-related adverse reactions - refer to TV immune-oncology agent immune related adverse event clinical guideline.
If the drug-related toxicity does not resolve to grade 0-1 within 12 weeks after onset of toxicity, discontinuation is recommended.

Hepatic impairment
Lenvatinib
No adjustment of starting dose of the combination is required 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 10mg once daily.

Renal impairment
Lenvatinib
Mild or moderate renal impairment no adjustment of starting dose is required.
Severe renal impairment, the recommended starting dose is 10mg lenvatinib.once daily. Further dose adjustments may be necessary based on individual tolerability.
End-stage renal disease were not studied, therefore the use lenvatinib in these patients is not recommended.

REFERENCES
1. SPC
2. CDF list