LENVATINIB 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/) (LNV4)

1. Lenvatinib in combination with pembrolizumab for use in treatment-naïve patients with intermediate or poor risk advanced renal cell carcinoma (as assessed by the International Metastatic RCC Database Consortium (IMDC)) for whom treatment with nivolumab plus ipilimumab would otherwise be suitable, has no symptomatic brain metastases or leptomeningeal metastases currently requiring steroids for symptom control. Karnofsky PS of at least 70 (ie ECOG PS 0 or 1). (TA858)

REGIMEN (42 day) (SC) - recommended

Day 1 PEMBROLIZUMAB 790mg subcutaneous* (4.8ml) over 2 minutes
LENVATINIB 20mg orally daily continuously

*Into the thigh or abdomen, avoiding the 5cm area around the navel

REGIMEN (42 day) (IV)

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

REGIMEN (21 day) (IV)

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)
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.

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 IV – neutral

Pembrolizumab IV use low protein binding 0.2 to 5micron in-line or add-on filter
Peripheral line

INVESTIGATIONS

Blood results required before SACT administration
FBC and U&E every cycle
LFTs every 2 weeks for the first 2 months, then monthly
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 (or as specified in Trust guideline)
Random glucose every cycle
Hba1c baseline
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 Wound healing may be delayed, consider temporary treatment disruption for those undergoing major surgery.
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
Blood pressure should be well-controlled prior to initiating lenvatinib, 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 treatment with lenvatinib.	
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.

Pembrolizumab
No dose adjustment is needed.

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.

Pembrolizumab
No dose adjustment is needed.

REFERENCES
1. SPC
2. CDF list