SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Lenvatinib (Kisplyx) with Pembrolizumab Advanced Renal Cell Carcinoma

PROTOCOL REF: MPHALPARCC
(Version No: 1.0)

Approved for use in:

- First line treatment of intermediate or poor risk advanced renal cell carcinoma for whom treatment with nivolumab plus ipilimumab would otherwise be suitable
- The patient 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 or
  - Mucinous tubular and spindle cell RCC or
  - Multilocular cystic RCC or
  - XP11 translocation RCC or
  - Unclassified RCC
- The patient's disease is in the intermediate or poor risk category as assessed by the International Metastatic RCC Database Consortium (IMDC) system.
- The patient 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.
- The patient has a Karnofsky performance status of at least 70 (ie PS 0 or 1).

- The patient has no symptomatic brain metastases or leptomeningeal metastases currently requiring steroids for symptom control.
- 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.
- Blueteq registration required.

Dosage:

Drug	Dose	Route	Frequency
Lenvatinib (Kisplyx)	**20 mg**	Oral	Once daily continuously
Pembrolizumab	**200 mg**	IV infusion	3 weekly for 2 years*
	OR		
	400 mg	IV infusion	6 weekly for 2 years*

* To continue until disease progression or unacceptable toxicity or after 2 years of treatment (i.e. maximum of 35 x 3-weekly cycles or its equivalent if 6-weekly dosing is used) whichever occur first.

Administration and Counselling Points:

Lenvatinib

- Lenvatinib is available as 10mg and 4mg hard capsules.
- There are several brands of Lenvatinib. Please ensure that the Kisplyx brand is supplied.
- Lenvatinib should be taken at the same time of day each day consistently with or without food. Capsules should be swallowed whole. If a dose is missed and cannot be taken within twelve hours then it should be missed and the next dose taken at the appropriate time.
- For patients with swallowing difficulty, lenvatinib capsules must not be opened but may be dissolved using the following instructions:
  - Pour a tablespoon of water or apple juice into a small glass and put the capsules into the liquid without breaking or crushing them. Leave for at least 10 minutes then stir for at least 3 minutes to dissolve the capsule shells. Drink the mixture. After drinking, add the same amount of water or apple juice, swirl and swallow.
- Women of childbearing potential should use effective contraception throughout treatment and for at least 1 month following the last dose of Lenvatinib.

Pembrolizumab

- Women of childbearing potential should use effective contraception throughout treatment and for at least 5 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

Interactions:

The interactions listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Lenvatinib

- No significant drug-drug interaction is therefore expected between lenvatinib and other CYP3A4/Pgp substrates.
- Lenvatinib can prolong QT interval therefore caution should be used when using in combination with other QT prolonging drugs such as amiodarone, ciprofloxacin, citalopram, erythromycin, fluoxetine, fluconazole and ondansetron.
- 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.

Pembrolizumab

- The use of systemic corticosteroids, before starting treatment with pembrolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of the agent. However, systemic corticosteroids can be used after starting pembrolizumab to treat immune-related adverse reactions. The use of systemic corticosteroids after starting treatment does not appear to impair the efficacy of pembrolizumab.

Supportive treatments:

- Gastric protection with a proton pump inhibitor or a H2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed

Extravasation risk (if applicable):

Pembrolizumab - neutral

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	Pembrolizumab*	200mg (3 weekly) Or 400mg (6 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	Once daily continuously

* To continue until disease progression or unacceptable toxicity or after 2 years of treatment (i.e. maximum of 35 x 3-weekly cycles or its equivalent if 6-weekly dosing is used) whichever occur first.

Main toxicities:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Blood and lymphatic disorders	Thrombocytopenia, leukopenia, neutropenia, lymphopenia
Cardiac disorders	Myocardial infarction, QT prolongation, cardiac failure, decreased ejection fraction
Endocrine	Hypo- or hyperthyroidism, adrenal insufficiency, thyroiditis, hypophysitis
Gastrointestinal disorders	Diarrhoea, gastrointestinal and abdominal pains, nausea and vomiting, colitis, oral inflammation, oral pain, constipation, dyspepsia, dry mouth, lipase increased, amylase increased, pancreatitis, flatulence, anal fistula
Hepatobiliary disorders	Raised AST, ALT, ALP, bilirubin, GGT, cholecystitis, hypoalbuminaemia, hepatic failure, hepatic encephalopathy
Infections and infestations	Urinary tract infection, perineal abscess
Metabolism and nutrition disorders	Decreased appetite, decreased weight, hypercholesterolaemia, hypocalcaemia, hypokalaemia, dehydration, hypomagnesaemia
Musculoskeletal and connective tissue disorders	Bain pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain
Nervous system disorders	Dizziness, headache, dysgeusia, peripheral neuropathy, cerebral vascular accident, posterior reversible encephalopathy syndrome (PRES)/Reversible posterior leukoencephalopathy syndrome (RPLS), transient ischaemic attack
Psychiatric disorders	Insomnia
Renal and urinary disorders	Proteinuria, raised blood creatinine, raised blood urea, nephrotic syndrome
Respiratory, thoracic and mediastinal disorders	Dysphonia, dyspnea, pneumonitis, pulmonary embolism, pneumothorax
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome (PPE), rash, alopecia, hyperkeratosis, palmar erythema
Vascular disorders	Haemorrhage, hypertension, hypotension, vasculitis, aneurysms and artery dissections
Others	Infusion-related reaction, fatigue, asthenia, oedema peripheral, non-gastrointestinal fistula, impaired healing, dry eye, uveitis

Investigations and treatment plan:

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

	Pre	C1		C2		C3	C4	C5	Ongoing
		Wk1	Wk2	Wk5	Wk7	Wk9	Wk13	Wk17	
Informed Consent	X								
Clinical Assessment	X			X		X		X	For the first three cycles then after each CT scan
SACT assessment (including PS & toxicities)	X	X		X		X	X	X	Every cycle
OTR/Go-ahead	X			X		X	X	X	Every cycle
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs (AST, ALT and bilirubin), TFTs, cortisol, blood glucose, LDH, CRP	X	X		X		X	X	X	Every cycle
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
Creatinine Clearance (Cockcroft and Gault)	X								Every cycle only if baseline CrCL <40ml/min or creatinine increases above

									1.5x upper limit of normal or baseline
Mg &Ca	X			X		X	X	X	Every cycle
Blood Glucose	X			X		X	X	X	Every cycle
Lipid profile (cholesterol)	X						X		Every 12 weeks
CT scan	X						X		Every 12 weeks
Trop-T, CK, pro-BNP	X								At baseline and thereafter as clinically indicated. ECG to be reviewed by clinical team.
ECG	X								
Full set of observations (*BP, heart rate, temperature, respiratory rate and O_2 sats*)	X	X		X		X	X	X	Every cycle
Weight	X	X		X		X	X	X	Every cycle
Height	X								
Urine dipstick for Protein	X			X		X	X	X	Every cycle
Blood Pressure	X		X*	X	X	X	X	X	Monitor after 1 week of treatment,* then every 2 weeks for the first two cycles, then every 4 weeks
Pregnancy test if applicable	X			X		X	X	X	Every cycle if applicable

*Blood pressure check during week 2 can be arranged at GP surgery or for patient to attend chemotherapy clinic.

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Dosing in renal impairment (prior to start of treatment ONLY/Baseline):

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Lenvatinib	≥ 30	No dose adjustment
	< 30	10mg ONCE daily
	Haemodialysis	50% of the original dose
Pembrolizumab	≥ 10	No dose adjustment
	< 10	Use with caution

Further dose reductions may be required based on tolerability. 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. Please refer to Table 1, 2 and 4 for dose adjustment for renal adverse effects.

Dosing in hepatic impairment (prior to start of treatment ONLY/Baseline):

Drug	Grading of hepatic impairment	Dose (% of original dose)
Lenvatinib	Mild (Child-Pugh A)	No dose adjustment
	Moderate (Child-Pugh B)	No dose adjustment
	Severe (Child-Pugh C)	10mg ONCE daily
Pembrolizumab	Mild	No dose adjustment
	Moderate or Severe	Not studied, no need for dose adjustment is needed, use with caution

Further dose reductions may be required based on tolerability. Liver-related adverse reactions most commonly reported in patients treated with Lenvatinib included increases in alanine aminotransferase, increases in aspartate aminotransferase, and increases in blood bilirubin. Hepatic failure and acute hepatitis (less than 1%) have been reported in patients treated with lenvatinib. The hepatic failure cases were generally reported in patients with progressive liver metastases. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary. Please refer to Table 1, 2 and 4 for dose adjustment for hepatic adverse effects.

Non- Haematological toxicity:

Toxicity grades are based on the National Cancer Institute Terminology Criteria (NCI-CTC) for Adverse Events.

Lenvatinib

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Mild to moderate adverse reactions (i.e. NCI-CTC Grade 1 or 2) generally do not warrant interruption of Lenvatinib unless intolerable to the patients despite optimal management. For all other non-haematological NCI-CTC Grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below or baseline.

For toxicities thought to be related to Lenvatinib (see Table 2), upon resolution/improvement of an adverse reaction to Grade 1 or bleow, treatment should be **resumed at a reduced dose of Lenvatinib as suggested in Table 1**.

Table 1: Dose modifications from recommended Lenvatinib daily dose

Dose level	Daily dose
Recommended daily dose	20mg ONCE daily
First dose reduction	14mg ONCE daily
Second dose reduction	10mg ONCE daily
Third dose reduction	8mg ONCE daily

Table 2: Adverse reactions requiring dose modification of Lenvatinib

Adverse reaction	Severity	Action	Dose reduce and resume Lenvatinib
Proteinuria	≥ 2 gm / 24 hours (urine dipstick ≥ 3+)	Interrupt	Resolves to less than 2 gm / 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
PRES/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
GI perforation or fistula	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
Non-GI 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)			

Hypertension

Hypertension is commonly reported in association with Lenvatinib, usually occurring early in the course of treatment. Blood pressure should be well controlled prior to starting treatment and, if patients are known to be hypertensive, they should be on a stable dose of antihypertensive. Early detection and management of hypertension are important during treatment to minimize the need for dose interruptions and reductions. 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. Please see table 3 for management of hypertension.

Table 3: Recommended management of hypertension

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 (see section 4.2)
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue Lenvatinib and institute appropriate medical management.

Pembrolizumab

Pembrolizumab is associated with inflammatory adverse reactions resulting from increased or excessive immune activity, likely to be related to its pharmacology. Immune-related adverse reactions, which can be severe or life-threatening, may involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. Most occur during treatment, however, onset months after the last dose has been reported.

Detailed guidelines for the management of immune-related adverse reactions are provided in the CCC Immno-Oncology toxicity specific guidance for adverse event management.

No dose reductions are recommended. Pembrolizumab should be withheld or discontinued to manage adverse reactions as described in Table 4.

Table 4: Recommended treatment modifications for Pembrolizumab

Immune-related adverse reactions	Severity	Treatment modification
Pneumonitis	Grade 2	Withhold until adverse reactions recover to Grades 0-1*
	Grades 3 or 4, or recurrent Grade 2	Permanently discontinue
Colitis	Grades 2 or 3	Withhold until adverse reactions recover to Grades 0-1*
	Grade 4 or recurrent Grade 3	Permanently discontinue
Nephritis	Grade 2 with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN)	Withhold until adverse reactions recover to Grades 0-1*
	Grade ≥ 3 with creatinine > 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 2 adrenal insufficiency and hypophysitis	Withhold treatment until controlled by hormone replacement
	Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis Type 1 diabetes associated with Grade ≥ 3 hyperglycaemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 3	Withhold until adverse reactions recover to Grades 0-1* For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of Pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued.
	Hypothyroidism	Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hepatitis	Grade 2 with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN	Withhold until adverse reactions recover to Grades 0-1*

	Grade ≥ 3 with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN	Permanently discontinue
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	Permanently discontinue
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold until adverse reactions recover to Grades 0-1*
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Other immune-related adverse reactions	Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold until adverse reactions recover to Grades 0-1*
	Grades 3 or 4 myocarditis Grades 3 or 4 encephalitis Grades 3 or 4 Guillain-Barré syndrome	Permanently discontinue
	Grade 4 or recurrent Grade 3	Permanently discontinue
Infusion-related reactions	Grades 3 or 4	Permanently discontinue
* If treatment-related toxicity does not resolve to Grades 0-1 within 12 weeks after last dose of Pembrolizumab, or if corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks, Pembrolizumab should be permanently discontinued.		

References:

1. NHS England, National Cancer Drugs Fund https://www.england.nhs.uk/cancer/cdf/
2. Electronic medicines compendium. Kisplyx 10mg hard capsules. Available from: https://www.medicines.org.uk/emc/product/7881/smpc#. Last updated 3rd December 2021.
3. Electronic medicines compendium. Keytruda 25mg/ml concertrate for solution for infusion. Available from: https://www.medicines.org.uk/emc/product/2498#. Last updated 28th July 2022.
4. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.
5. Motzer R, Alekseev B, Rha SY, Porta C, Eto M, Powles T, Grünwald V, Hutson TE, Kopyltsov E, Méndez-Vidal MJ, Kozlov V, Alyasova A, Hong SH, Kapoor A, Alonso Gordoa T, Merchan JR, Winquist E, Maroto P, Goh JC, Kim M, Gurney H, Patel V, Peer A, Procopio G, Takagi T, Melichar B, Rolland F, De Giorgi U, Wong S, Bedke J, Schmidinger M, Dutcus CE, Smith AD, Dutta L, Mody K, Perini RF, Xing D, Choueiri TK; CLEAR Trial Investigators. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Engl J Med. 2021 Apr 8;384(14):1289-1300. doi: 10.1056/NEJMoa2035716. Epub 2021 Feb 13. PMID: 33616314.

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