Systemic Anti-Cancer Treatment Protocol

Lenvatinib (LENVIMA®)

PROTOCOL REF: MPHALENVHN
(Version No: 1.0)

Approved for use in:

Differentiated thyroid cancer after radioactive iodine when the following conditions are met:

- Confirmed histological diagnosis of differentiated thyroid carcinoma (papillary or follicular or Hürthle cell type)
- Metastatic or inoperable locally advanced disease
- Disease is refractory to radioactive iodine
- Disease is progressive and is either symptomatic or imminently likely to become symptomatic.
- Patient is treatment naïve to both lenvatinib and sorafenib unless either:
    a) Previously enrolled in the company's lenvatinib compassionate access scheme and all other NHS England treatment criteria are fulfilled i.e. if treated previously with sorafenib, lenvatinib will only be accepted for NHS funding if the patient was intolerant of sorafenib according to the conditions set out in b) below or
    b) The patient has had to discontinue sorafenib within 3 months of starting sorafenib because of toxicity (i.e. there is sorafenib toxicity which cannot be managed by dose delay or dose modification) and there has been no disease progression whilst on sorafenib

Note sequential use of lenvatinib and then sorafenib is only funded if the patient has to discontinue lenvatinib because of intolerance within 3 months of its start and if the disease has not progressed whilst the

patient is on lenvatinib. The use of lenvatinib after disease progression on or after sorafenib is not funded and vice versa.

- ECOG performance status of 0 or 1 or 2
- Formal medical review as to whether treatment with lenvatinib should continue or not will be scheduled to occur at least before the end of the first 8 weeks of treatment.
- No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity to current therapy to settle or intercurrent comorbidities to improve)

Blueteq registration is required for all patients

Dosage:

Drug	Daily dosage	Route	Schedule
Lenvatinib	24mg	Oral	ONCE a day continuously (supplied every 28 days)

Treatment with lenvatinib should continue as long as clinical benefit is observed or until there is unacceptable toxicity or patient choice to stop treatment.

Supportive Treatments:

Loperamide 2mg when required

Administration/directions:

The recommended daily dose is 24mg (two 10mg capsules and one 4mg capsule).

The capsules should be taken at about the same time each day, with or without food. The capsules should be swallowed whole with water.

Missed doses

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.

Interactions:

No data is available that can be used to exclude the risk that lenvatinib could be an inducer of CYP3A4 or Pgp in the gastrointestinal tract. This could potentially lead to decreased exposure to oral CYP3A4/Pgp substrates. This should be considered if co-administering oral CYP3A4/Pgp substrates for which retained efficacy is very important. CYP3A4 substrates known to have a narrow therapeutic index (e.g. astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine)) should therefore be administered with caution in patients receiving lenvatinib.

Oral contraceptives

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

Main Toxicities:

Lenvatinib	
Hypertension	Hypertension can occur early in the course of treatment Blood pressure (BP) should be well controlled prior to treatment. For known hypertension, patients should be on a stable dose of antihypertensive therapy for at least 1 week prior to treatment. 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. The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice – use NICE Clinical Guideline CG 127 – Hypertension in adults diagnosis and management Accessible here: https://www.nice.org.uk/guidance/CG127Hypertension in adults: diagnosis and management | Guidance and guidelines | NICE
Perforations, fistulas, intra-abdominal abscesses.	Gastrointestinal perforation or fistulae have been reported. In most cases, gastrointestinal perforation and fistulae occurred in patients with risk factors such as prior surgery or radiotherapy Lenvatinib should not be started in patients with fistula to avoid worsening and lenvatinib should be permanently discontinued in patients with oesophageal or tracheobronchial tract involvement and any Grade 4 fistula
Haemorrhage	Serious tumour related bleeds; including fatal haemorrhagic events have occurred in clinical trials and have been reported in post-marketing experience. The degree of tumour invasion/infiltration of major blood vessels (e.g. carotid artery) should be considered because of the potential risk of severe haemorrhage associated with tumour shrinkage/necrosis following lenvatinib therapy. In the case of bleeding, dose interruptions, adjustments, or discontinuation may be required.
Thromboembolic events	Arterial thromboembolisms (cerebrovascular accident, transient ischaemic attack, and myocardial infarction) have been reported. Lenvatinib has not been studied in patients who have had an arterial thromboembolism within the previous 6 months, and therefore should be used with caution in such patients. Lenvatinib should be discontinued following an arterial thrombotic

	event.
Proteinuria	Usually occurs in early in course of treatment. Urine protein should be monitored at each cycle Lenvatinib should be discontinued in the event of nephrotic syndrome.
Cardiovascular	Cardiac failure (<1%) and decreased left ventricular ejection fraction have been reported. Patients should be monitored for clinical symptoms or signs of cardiac decompensation.
Metabolism and nutrition disorders	Hypothyroidism has been reported 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. Thyroid stimulating hormone (TSH) levels should be monitored on a regular basis and thyroid hormone administration should be adjusted to reach appropriate TSH levels, according to the patient's therapeutic target.
GI disorders	Diarrhoea has been reported frequently in patients treated with lenvatinib; usually occurring early in the course of treatment Prompt medical management of diarrhoea should be instituted in order to prevent dehydration. Lenvatinib should be discontinued in the event of persistence of Grade 4 diarrhoea despite medical management.
Renal	Renal impairment and failure have been reported. 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	Increases in alanine aminotransferase, increases in aspartate aminotransferase, and increases in blood bilirubin can occur. Hepatic failure and acute hepatitis (<1%) have been reported. Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary
Additional side effects	Women of childbearing potential must use highly effective contraception while taking lenvatinib and for one month after stopping treatment. It is currently unknown if lenvatinib increases the risk of thromboembolic events when combined with oral contraceptives Posterior reversible encephalopathy syndrome (PRES) / Reversible posterior leucoencephalopathy syndrome (RPLS) has been reported in patients treated with lenvatinib (<1%) PRES is a

	neurological disorder which can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control blood pressure. In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary

Investigations:

	Pre	C1 Day 1	C1 Day 8	C1 Day 14	C2 Day 1	C2 Day 14	C3 Day 1	Ongoing
Medical Assessment	X	X			X		X	As clinically indicated (minimum every 3 months)
Nursing Assessment		X			X		X	Every cycle
On treatment review				X		X		
FBC	X	X			X		X	Every cycle
U&E	X	X			X		X	Every cycle
LFTs	X	X		X	X	X	X	Every cycle
Ca and Mg	X	X			X		X	Every cycle
Thyroid function	X	X			X		X	Every cycle
CT scan	X							Every 3 months
Informed Consent	X							
Blood glucose	X							Repeat if clinically indicated
Blood pressure measurement	**X**	**X**	**X**	**X**	**X**	**X**	**X**	Every cycle
Baseline ECG	X							Repeat if clinically indicated
Urine dipstick for protein	X	X			X		X	Every cycle
PS recorded	X	X			X		X	

Toxicities documented	X	X			X		X	
Weight recorded	X	X			X		X	Every cycle

Review thromboembolic risk and consider prophylactic anticoagulants in those at significant risk

Review all other medications for potential drug-drug interactions

Toxicity Management/ Dose Modifications:

Dose interruptions are required for management of CTCAE grade 3

Dose level	New Dose	Number of capsules
Recommended Daily dose	24mg orally once daily	Two 10mg capsules plus one 4mg capsule
First dose reduction	20mg orally once daily	Two 10mg capsules
Second dose reduction	14mg orally once daily	One 10mg capsule plus one 4mg capsule
Third dose reduction	10mg orally once daily	One 10mg capsule

Adverse reaction	Severity	Action	Dose reduce and resume lenvatinib
Hypertension	Grade 3 (despite optimal antihypertensive therapy)	Interrupt	Resolves to Grade 0, 1, 2 ***See detailed table below***
	Grade 4	Discontinue	**Do not resume**
Proteinuria	≥ 2 gm/ 24 hours	Interrupt	Resolves to less than 2 gm/ 24 hours
Nephritic 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 or baseline
	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**

Blood Pressure (BP) level	**Recommended action**
Systolic BP ≥ 140mmHg up to <160mmHg or diastolic BP ≥90mmHg up to ,100mmHg	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.

Hepatic impairment	No adjustment for starting dose is required on basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. In patients with severe impairment (Child Pugh C), the recommended starting dose is 14mg ONCE a day. Further dose adjustments may be required depending on individual tolerability.
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 starting dose is 14mg ONCE a day. Further dose adjustments may be required based on individual tolerability. Treatment is not recommended in patients with end stage renal disease.

References:

- Lenvima 10mg capsules SPC https://www.medicines.org.uk/emc/search?q=lenvima (Date of revision of text 06/2017) accessed 16/03/2018
- Lenvatinib for treating differentiated thyroid cancer after radioactive iodine (LNV2_v1.0) LNV2 National Cancer Drugs Fund Application Form https://www.blueteq-secure.co.uk/trust/default.htm accessed 16/03/2018