Systemic Anti Cancer Treatment Protocol

Lorlatinib

Protocol Ref: MPHALORLLU
(Version No: 1.0)

Approved for use in:

- Stage IIIB or IV ALK +ve non-small cell lung cancer
- Patient has progressed on
  - 1st line alectinib or
  - 1st line ceritinib
  - 1st line crizotinib followed by either brigatinib or ceritinib
- Performance status 0-2
- Patient has no brain metastases or if the patient has brain metastases, the patient is symptomatically stable prior to starting lorlatinib
- **Blueteq registration required**

Dosage:

Drug	Dosage	Route	Frequency
Lorlatinib	100mg	Oral	Once daily

Medication will be supplied as cycles of 28 days

Treatment is continuous until disease progression or unacceptable toxicity.

Extravasation risk:

Not applicable

Administration:

Lorlatinib may be taken with or without food. Swallow whole, do not chew.

Drug Interactions

- No concomitant use of strong or moderate CYP3A4 inhibitors, strong CYP3A4 inducers or drugs that are CYP3A4 substrates with narrow therapeutic indices. Examples of such drugs include phenobarbital, rifampicin, phenytoin, carbamazepine enzalutamide, mitotane and St John's Wort.
- No concomitant use of CYP2C9 or P-gp substrates with narrow therapeutic indices, sensitive CYP2B6 substrates, or strong CYP2C8 or CYP2C19 inhibitors.
- Grapefruit products may also increase lorlatinib plasma concentrations - avoid
- Please consult SPC available via medicines.org.uk for full list of interactions.

Main Toxicities:

Hyperlipidemia, oedema, peripheral neuropathy, mood effects, cognitive defects, fatigue, anaemia, headache, diarrhoea/constipation, rash, visual disturbances, arthralgia/myalgia and weight increase.

All adverse reactions should be reported to the MHRA via the MHRA yellow card reporting system.

Investigations and Treatment Plan:

	Pre	Cycle 1	Cycle 1 Day 14	Cycle 2	Cycle 3	Ongoing
Medical Assessment	X			X	X	Every three cycles
ECG	X			X	X	ECG to be carried out at medical assessment appointment (Baseline and monthly thereafter). Frequency can be reduced at consultant discretion.
Nursing Assessment	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E & LFT	X	X	X	X	X	Every cycle
Lipid profile		X	X	X	X	Can reduce frequency if lipids stable
LDH		X		X	X	Every cycle-for clinician to review if raised. To be assessed in combination with symptoms and radiological progression
Amylase and/or lipase		X		X	X	As clinically indicated
CT scan	X				X*	*CT scan to be carried out prior to cycle 3 then every three months or as clinically indicated
Blood pressure measurement	X					Repeat if clinically indicated
Informed Consent	X					
PS recorded	X	X	X	X	X	Every cycle
Toxicities documented			X	X	X	Every cycle
Weight recorded	X	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

PR Interval Prolongation:

Degree of PR Interval Prolongation	Lorlatinib Dosing	
	Asymptomatic	Symptomatic
First-degree AV block	Continue lorlatinib at the same dose without interruption. Assess concomitant medications and electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely.	Withhold lorlatinib. Assess concomitant medications and electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely. If symptoms resolve, resume lorlatinib at 1 reduced dose level.
Second-degree AV block	Withhold lorlatinib. Assess concomitant medications and electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely. If subsequent ECG does not show second-degree block, resume lorlatinib at 1 reduced dose level.	Withhold lorlatinib. Assess concomitant medications and electrolyte imbalance that may prolong PR interval. Refer for cardiac observation and monitoring. Consider pacemaker placement if symptomatic AV block persists. If symptoms and the second-degree block resolve or if patients revert to asymptomatic first-degree AV block, resume lorlatinib at 1 reduced dose level.
Complete AV Block	Withhold lorlatinib dose. Assess concomitant medications and electrolyte imbalance that may prolong PR interval. Refer for cardiac observation and monitoring. Temporary pacemaker placement may be indicated for severe symptoms associated with AV block. If AV block does not resolve, placement of a permanent pacemaker may be considered. If pacemaker placed, resume lorlatinib at full dose. If no pacemaker placed, resume lorlatinib at 1 reduced dose level only when symptoms resolve AND PR interval is less than 200 msec.	
PR interval >220 msec or 2nd or 3rd degree AV block (unless paced) prior to initiation of lorlatinib: Lorlatinib was not studied in this population		

Hypercholesterolaemia or Hypertriglyceridaemia:

Mild hypercholesterolaemia (cholesterol between ULN and 7.75 mmol/L) OR Mild hypertriglyceridaemia (triglycerides between 1.71 and 3.42 mmol/L) Moderate hypercholesterolaemia (cholesterol between 7.76 and 10.34 mmol/L) OR Moderate hypertriglyceridaemia (triglycerides between 3.43 and 5.7 mmol/L	Introduce or modify lipid-lowering therapy in accordance with respective prescribing information**; continue lorlatinib at same dose.
Severe hypercholesterolaemia (cholesterol between 10.35 and 12.92 mmol/L) OR Severe hypertriglyceridaemia (triglycerides between 5.71 and 11.4 mmol/L)	Introduce the use of lipid-lowering therapy**; if currently on lipid-lowering therapy, increase the dose of this therapy in accordance with respective prescribing information; or change to a new lipid-lowering therapy. Continue lorlatinib at the same dose without interruption.
Life-threatening hypercholesterolaemia (cholesterol over 12.92 mmol/L) OR Life-threatening hypertriglyceridaemia (triglycerides over 11.4 mmol/L)	Introduce the use of lipid-lowering therapy** or increase the dose of this therapy in accordance with respective prescribing information or change to a new lipid-lowering therapy. Withhold lorlatinib until recovery of hypercholesterolaemia and/or hypertriglyceridaemia to moderate or mild severity grade. Re-challenge at same lorlatinib dose while maximizing lipid-lowering therapy in accordance with respective prescribing information. If severe hypercholesterolaemia and/or hypertriglyceridaemia recur despite maximal lipid-lowering therapy in accordance with respective prescribing information, reduce lorlatinib by 1 dose level.

**The statin with the least interaction with lorlatinib is pravastatin. However, clinical drug-drug interactions have not been formally studied so careful monitoring is advised.

CTCAE grade	**Recommendations**
Central Nervous System Effects (Changes in speech, memory or cognition)	
Grade 1: Mild	Continue at the same dose or withhold dose until recovery to baseline. Then resume lorlatinib at the same dose or reduce by 1 dose level.
Grade 2: Moderate OR Grade 3: Severe	Withhold dose until toxicity is less than or equal to Grade 1. Then resume lorlatinib at 1 reduced dose level.
Grade 4: Life-threatening/Urgent intervention indicated	Permanently discontinue lorlatinib
Lipase/Amylase increase	
Grade 3: Severe OR Grade 4: Life-threatening/urgent intervention indicated	Withhold lorlatinib until lipase or amylase returns to baseline. Then resume lorlatinib at 1 reduced dose level.
Other adverse reactions:	
Grade 1 or Grade 2	Consider no dose modification or reduce by 1 dose level.
Greater than or equal to Grade 3	Withhold lorlatinib until symptoms resolve to less than or equal to Grade 2 or baseline. Then resume lorlatinib at 1 reduced dose level.

Dose Reduction Table:

Level	Dose
Starting Dose	**100mg once daily**
1st Reduction	75mg once daily
2nd Reduction	50mg once daily
Dose reductions below 50mg once daily are not recommended. Lorlatinib should be permanently discontinued if the patient is unable to tolerate 50mg once daily.	

Hepatic Impairment

No dose adjustments are recommended for patients with mild hepatic impairment. No information is available for lorlatinib in patients with moderate or severe hepatic impairment therefore it is not recommended.

Renal Impairment

No dose adjustment is required in patients with a creatinine clearance ≥ 30ml/min. Information for lorlatinib use in patients with severe renal impairment (creatinine clearance < 30ml/min) is very limited and is therefore not recommended.

References:

- NICE BNF
- Lorlatinib SPC available via: https://www.medicines.org.uk/emc/product/10632/smpc
- Solomon et al. Lancet Oncol 2018; 19: 1654-67 Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study.