North West Coast
Strategic Clinical Networks

Chemotherapy Protocol

DRUG REGIMEN
Lorlatinib

Indication for use
Patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on 1 or more ALK tyrosine kinase inhibitors (TKIs)

Regimen
Lorlatinib 100mg orally once daily
Treatment is continued until disease progression or unacceptable toxicity

Investigation prior to initiating treatment
FBC, U&Es, LFTs, Lipid Profile, Coagulation Screen, 12-lead ECG

Contraindications
Concomitant use of strong CYP3A4/5 inducers

Cautions
Concomitant use of strong CYP3A4/5 inhibitors may increase lorlatinib plasma concentrations. If a strong CYP3A4/5 inhibitor must be concomitantly administered, a dose reduction of lorlatinib is recommended.

Grapefruit products may increase lorlatinib plasma concentrations.

Lorlatinib is also an inducer of CYP3A4 and will decrease concentrations of drugs metabolised by CYP3A4

Investigations and consultations prior to each cycle
FBC, U&Es, LFTs, and Lipid Profile: before each cycle
Lipid Profile: day 1 and day 14 in cycle 1; day 1 in cycle 2 and all subsequent cycles; reduce frequency once lipids stabilise
ECG: before each cycle

Acceptable levels for treatment to proceed (if outside these levels contact consultant and see table below)
Lipid profile – cholesterol less than 7.76 mmol/L; triglycerides less than 1.71 mmol/L

Side Effects
Common adverse reactions: oedema, peripheral neuropathy, cognitive effects, dyspnoea, fatigue, weight gain, arthralgia, mood effects, and diarrhoea; the most common (≥20%) laboratory abnormalities were hypercholesterolemia, hypertriglyceridemia, anaemia, hyperglycaemia, increased AST, hypoalbuminemia, increased ALT, increased lipase, and increased alkaline phosphatase.

Serious adverse events reported: pneumonia, dyspnoea, pyrexia, mental state changes, respiratory failure, myocardial infarction, acute pulmonary oedema, embolism, peripheral artery occlusion, and respiratory distress.

Dose Modification Criteria

First dose reduction: Lorlatinib 75 mg taken orally once daily
Second dose reduction: Lorlatinib 50 mg taken orally once daily
Discontinue lorlatinib if unable to tolerate after second dose reduction

Hypercholesterolaemia or Hypertriglyceridaemia	
Grade 1 – 3 hypercholesterolaemia (cholesterol between 7.76 mmol/L and 12.92 mmol/L)	Introduce or increase the dose of lipid-lowering therapy, or change to a new lipid-lowering therapy; continue lorlatinib at the same dose
Grade 1 – 3 hypertriglyceridaemia (triglycerides between 1.71 mmol/L and 11.4 mmol/L)	
Grade 4 hypercholesterolaemia (cholesterol over 12.92 mmol/L)	Introduce or increase the dose of lipid-lowering therapy, or change to a new lipid-lowering therapy; withhold lorlatinib until recovery of hypercholesterolaemia and/or hypertriglyceridaemia to Grade 2 Re-challenge at same lorlatinib dose while maximising lipid-lowering therapy If Grade 4 hypercholesterolaemia and/or hypertriglyceridaemia recurs despite maximal lipid-lowering therapy, reduce lorlatinib by 1 dose level
Grade 4 hypertriglyceridaemia (triglycerides over 11.4 mmol/L)	

Central nervous system effects	
Grade 1	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 – 3	Withhold dose until toxicity is less than or equal to Grade 1. Then resume lorlatinib at 1 reduced dose level
Grade 4	Permanently discontinue lorlatinib

PR interval prolongation Assess concomitant medications and electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely.		
First-degree AV block	Asymptomatic	Continue lorlatinib at the same dose without interruption.
	Symptomatic	Withhold lorlatinib. If symptoms resolve, resume lorlatinib at same dose or at 1 reduced dose level.
Second-degree AV block	Asymptomatic	Withhold lorlatinib. If subsequent ECG does not show second-degree block, resume lorlatinib at same dose or 1 reduced dose level.
	Symptomatic	Withhold lorlatinib. 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. 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, may 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.

Other adverse reactions	
Grade 1 – 2	Consider no dose modification or reduce by 1 dose level
Grade 3 – 4	Withhold lorlatinib until symptoms resolve to less than or equal to Grade 2 or baseline. Then resume lorlatinib at 1 reduced dose level

Specific Information on Administration
Swallow tablets whole. Do not chew, crush or split tablets.
Take at the same time each day. If a dose is missed, then do not make up missed dose.
Do not take an additional dose if vomiting occurs but continue with the next scheduled dose.

THIS PROTOCOL HAS BEEN DIRECTED BY DR YIANNAKIS, CLINICIAN FOR LUNG CANCER RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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