Lorlatinib

Indication
ALK positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor or disease has progressed after prior treatment with an ALK inhibitor

Regimen details
Lorlatinib 100mg orally once daily

Cycle frequency
Dispense monthly (or less frequently if appropriate)

Number of cycles
Until disease progression or unacceptable toxicity

Administration
Lorlatinib is available as 100mg and 25mg tablets.

The tablets should be taken whole, with or without food, at around the same time each day. If a dose is missed, then it should be taken as soon as the patient remembers unless it is less than 4 hours before the next dose, in which case the patient should omit the missed dose.

Grapefruit and grapefruit juice should be avoided whilst taking lorlatinib

Pre-medication
N/A

Emetogenicity
Minimal (no routine antiemetics required)

Additional supportive medication+
None

Extravasation
N/A

Investigations – pre first cycle
Standard pre-SACT test plus: lipid profile, coagulation ccreen, 12-lead ECG

Investigations –pre subsequent cycles
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 (reduce to 2-monthly after 12 months)

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 30 mL/min
Bilirubin	≤ 1.5 x ULN
AST/ALT	< 2.5 x ULN (<5x ULN if due to malignancy)
Bilirubin	<1.5x ULN
Cholesterol	< 7.76mmol/L (see under dose modifications)
Triglycerides	<1.71mmol/L (see under dose modifications)
Lipase	<2x ULN if signs/symptoms; < 5x ULN if asymptomatic
Amylase	<2x ULN if signs/symptoms; < 5x ULN if asymptomatic

Dose modifications

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

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Pneumonitis
Anaemia
PR interval prolongation/Atrioventricular (AV) block

- **Frequently occurring side effects**

Hyperlipidaemia
Oedema
Peripheral neuropathy
Cognitive effects
Fatigue
Weight increase
Arthralgia/Myalgia
Mood effects
Diarrhoea/Constipation
Nausea
Rash
Visual disturbances

- **Other side effects**

Headache
Speech effects
Lipase increase
Amylase increase

Significant drug interactions – for full details consult product literature/ reference texts

Coumarin anticoagulants, e.g. warfarin: Avoid if possible as may cause elevation and fluctuation in INR. Consider switching to low molecular weight heparin.
Medications which may cause AV block (e.g. beta blockers, calcium channel blockers, digoxin, other antiarrhythmics): use with caution and monitor closely (see above).
Strong CYP3A4/5 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin): avoid coadministration as these may increase lorlatinib plasma concentrations. If a strong CYP3A4/5 inhibitor must be coadministered, the starting lorlatinib dose should be reduced to 75mg once daily.
Grapefruit juice products: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of lorlatinib.
Inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration as these may reduce lorlatinib plasma concentrations.
CYP3A substrates with a narrow therapeutic index (e.g. alfentanil, ciclosporin, fentanyl, hormonal contraceptives, quinidine, sirolimus and tacrolimus): avoid if possible since the concentration of these medicinal products may be reduced by lorlatinib.
P-glycoprotein substrates e.g. digoxin, dabigatran etexilate: use with caution as lorlatinib is a moderate inducer of P-gp so may cause reduced plasma concentrations of these agents.

Additional comments

As lorlatinib can render hormonal contraceptives ineffective, a highly effective non-hormonal method of contraception is required for female patients during treatment and for at least 35 days after completing therapy. Male patients with female partners of childbearing potential must use effective contraception during treatment and for at least 14 weeks after the final dose.

References

Lorviqua SPC:
https://www.medicines.org.uk/emc/product/10701/smpc

THIS PROTOCOL HAS BEEN DIRECTED BY DR YIANNAKIS, CONSULTANT ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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Whilst every effort is made to ensure the accuracy of the information in a given protocol it cannot be guaranteed that the protocol is fully up to date. Cancer treatment can be dynamic in nature. Decisions on SACT must therefore be based on the independent judgement of the clinician with reference to changing information on the medicine (eg, available literature and SmPC) and evolving medical practices.
