Chemotherapy Protocol

LUNG CANCER – NON-SMALL CELL (NSCLC)

LORLATINIB

Regimen

- NSCLC - Lorlatinib

Indication

- Anaplastic lymphoma kinase positive advanced non-small-cell lung cancer previously treated with 1st line alectinib or 1st line brigatinib or 1st line ceritinib or 1st line crizotinib followed by a 2nd line ALK tyrosine kinase inhibitor therapy (brigatinib or certitinib).
- Lorlatinib will be used as monotherapy
- The patient has no brain metastases or, if the patient has brain metastases, the patient is symptomatically stable prior to starting lorlatinib.
- The patient will be treated with lorlatinib until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment, whichever is the sooner.
- A formal medical review as to whether treatment with lorlatinib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment.
- WHO ECOG performance status 0, 1 or 2.

Adverse Effects

Drug	Common Side Effects
Lorlatinib	Anaemia, hypercholesterolaemia, hypertriglyceridaemia, mood effects, cognitive effects, peripheral neuropathy, headache, speech effects, vision disorder, pneumonitis, diarrhoea, nausea, constipation, rash, arthralgia, myalgia, oedema, fatigue, weight increase, lipase increase, amylase increase, PR interval prolongation, sleep effects, dyspnoea, cough, vomiting, ALT/AST increase, dizziness, hypertension, hyperglycaemia, Left ventricular ejection fraction decrease

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

Monitoring

- FBC, U&E and LFTs every 2 weeks for 3 cycles, then each cycle
- Lipids, glucose, and amylase/lipase every 1-2 cycles
- ECG at weeks 2, 4 and 6

Dose Modifications and Discontinuation

Lorlatinib Dose Reduction levels

Dose Level	Lorlatinib Dose (mg/day)
0	100
-1	75
-2	50

Lorlatinib should be permanently discontinued if the patient is unable to tolerate the 50mg dose taken orally once daily.

Haematological

Anaemia is a common side effect of lorlatinib this may be managed with blood transfusion, dose interruption, dose reduction or discontinuation as clinically appropriate. No information on dose modifications are available. If neutrophils are less than $1x10^9$/L or platelets less than $100x10^9$ discuss with prescriber.

Hepatic Impairment

Drug	AST/ALT		Total Bilirubin	Dose
Lorlatinib	Less than or equal to 2.5xULN (or less than or equal to 5xULN if due to liver metastases	or	Less than or equal to 1.5xULN	No starting dose adjustments required
	Above 2.5xULN (or 5xULN if due to liver metastases)	or	Above 1.5xULN	Not recommended due to limited information

Renal Impairment

Drug	Creatinine clearance (ml/min)	Dose
Lorlatinib	30 or above	No starting dose adjustments required
	Less than 30	75mg once daily

Central nervous system effects (psychotic effects, changed in cognition, mood, mental state, or speech)

NCI-CTC Grade 2: Moderate OR NCI-CTC 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.

Hypercholesterolaemia or hypertriglyceridaemia

Mild hypercholesterolaemia (cholesterol between ULN and 300 mg/dL or between ULN and 7.75 mmol/L) OR Moderate hypercholesterolaemia (cholesterol between 301 and 400 mg/dL or between 7.76 and 10.34 mmol/L) OR Mild hypertriglyceridaemia (triglycerides between 150 and 300 mg/dL or 1.71 and 3.42 mmol/L) OR Moderate hypertriglyceridaemia (triglycerides between 301 and 500 mg/dL or 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 401 and 500 mg/dL or between 10.35 and 12.92 mmol/L) OR Severe hypertriglyceridaemia (triglycerides between 501 and 1,000 mg/dL or 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 500 mg/dL or over 12.92 mmol/L) OR Life-threatening hypertriglyceridaemia (triglycerides over 1,000 mg/dL or over 11.4 mmol/L)	Introduce the use of lipid-lowering therapy[b] or increase the dose of this therapy[b] in accordance with respective prescribing information or change to a new lipid-lowering therapy[b]. Withhold lorlatinib until recovery of hypercholesterolaemia and/or hypertriglyceridaemia to moderate or mild severity grade. Re-challenge at same lorlatinib dose while maximising 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.

Lipase/amylase increase

NCI-CTC Grade 3: Severe OR NCI-CTC Grade 4: Life-threatening/Urgent intervention indicated	Withhold lorlatinib until lipase or amylase returns to baseline. Then resume lorlatinib at 1 reduced dose level.

Interstitial lung disease (ILD)/pneumonitis

NCI-CTC Grade 1: Mild OR NCI-CTC Grade 2: Moderate	Withhold lorlatinib until symptoms have returned to baseline and consider initiating corticosteroids. Resume lorlatinib at 1 reduced dose level. Permanently discontinue lorlatinib if ILD/pneumonitis recurs or fails to recover after 6 weeks of lorlatinib hold and steroid treatment.
NCI-CTC Grade 3: Severe OR NCI-CTC Grade 4: Life-threatening/Urgent intervention indicated	Permanently discontinue lorlatinib.

PR interval prolongation/Atrioventricular (AV block)

First degree AV block: Asymptomatic	Continue lorlatinib at the same dose without interruption. Consider effects of concomitant medicinal products and assess and correct electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely.
First degree AV block: Symptomatic	Withhold lorlatinib. Consider effects of concomitant medicinal products and assess and correct 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 Asymptomatic	Withhold lorlatinib. Consider effects of concomitant medicinal products and assess and correct electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely. If subsequent ECG does

	not show second degree AV block, resume lorlatinib at 1 reduced dose level.
Second degree AV block Symptomatic	Withhold lorlatinib. Consider effects of concomitant medicinal products and assess and correct 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 AV block resolve or if patients revert to asymptomatic first-degree AV block, resume lorlatinib at 1 reduced dose level.
Complete AV block	Withhold lorlatinib. Consider effects of concomitant medicinal products and assess and correct electrolyte imbalance that may prolong PR interval. Refer for cardiac observation and monitoring. 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.

Hyperglycaemia

Grade 3 (greater than 250 mg/dL despite optimal anti-hyperglycaemic therapy) OR Grade 4	Withhold lorlatinib until hyperglycaemia is adequately controlled, then resume lorlatinib at the next lower dose. If adequate hyperglycaemic control cannot be achieved with optimal medical management, permanently discontinue lorlatinib.

Other adverse reactions

Grade 1: Mild OR Grade 2: Moderate	Consider no dose modification or reduce by 1 dose level, as clinically indicated.
Greater than or equal to Grade 3: Severe	Withhold lorlatinib until symptoms resolve to less than or equal to Grade 2 or baseline. Then resume lorlatinib at 1 reduced dose level.

Regimen

28 day cycle continued for as long as the patient is deriving benefit from therapy without unacceptable toxicity (12 cycles will be set in Aria).

Drug	Dose	Days	Administration
Lorlatinib	100mg once a day	1-28 (continuous)	Oral

Dose information

- Lorlatinib is avalliable as 100mg and 25mg tablets.

Administration Information

- Lorlatinib can be taken with or without food and should be taken at approximately the same time each day.
- Lorlatinib should be swallowed whole. Tablets should not be ingested if broken, cracked or otherwise not intact.
- If a dose of lorlatinib 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 not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose

Additional information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to Lorlatinib.

References

1. National Institute For Health and Care Excellence (2020). Technology Appraisal 628. Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer NICE:DOH
2. Pfizer (2021). Lorviqua 100mg film coated tablets summary of product characteristics. Available from https://www.medicines.org.uk/emc. Accessed 23/06/2022.

REGIMEN SUMMARY

Lorlatinib

Day One

1. Lorlatinib 100mg tablets once a day continuous oral
   Administration Instructions
   Take at approximately the same time each day.
   Swallow this medicine whole. Do not chew or crush.
   Oral SACT.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	July 2022	N/A	Alexandra Pritchard Pharmacist	Judith Cave Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Trust

Whilst every effort is made to ensure the accuracy of the information given in this protocol it cannot be guaranteed that the protocol is fully up to date. Because of the dynamic nature of cancer treatment, decisions on SACT must be based on the independent judgement of the clinician with reference to changing information on the medicine (e.g. available literature and SmPC) and evolving medical practices.