Chemotherapy Protocol

Lung Cancer

Sotorasib

Regimen

- NSCLC – Sotorasib

Indication

- Sotorasib is indicated as monotherapy for the treatment of adult patients with non-small cell lung cancer (NSCLC);
    - that has been shown to exhibit a KRAS G12C mutation using a validated assay and determined on a tumour tissue biopsy or a plasma specimen (liquid biopsy) or both.
    - the patient's lung cancer has been investigated with respect to other actionable mutations in NSCLC and if these are known to be present and that all commissioned targeted therapies have been fully explored for this mutation.
    - has been treated with platinum doublet chemotherapy and/or PD-1/PD-L1 targeted immunotherapy.
    - has not been previously treated with a drug specifically targeting the KRAS G12C mutation unless the patient has received sotorasib via a company early access scheme
    - has no known brain metastases or if the patient does have brain metastases then the patient is symptomatically stable before starting sotorasib
    - a formal medical review as to how sotorasib is being tolerated will be done before the start of the second month of treatment and the next review to determine whether treatment with sotorasib should continue or not will be scheduled to occur at least by the end of the second month of therapy.
    - where the ECOG performance status is 0, 1 or 2

Toxicity

Drug	Adverse Effect
Sotorasib	Diarrhoea, musculoskeletal pain, nausea, fatigue, hepatotoxicity, cough, electrolyte abnormalities

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

Monitoring

- FBC, U&Es, LFTs at baseline and every two weeks for the first six weeks then prior to day 1 of the cycle thereafter.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and certain drug specific toxicities. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for SACT that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Sotorasib Dose Reductions

Dose reduction level	Dose
First dose reduction	480mg once a day
Second dose reduction	240mg once a day

Haematological

Sotorasib can cause fever and anaemia but does not routinely suppress neutrophils or platelets. In the clinical trial no dose reductions were required for anaemia. Consider blood transfusion or the use of erythropoietin according to NICE TA323 if patient symptomatic of anaemia or has haemoglobin of less than 8g/dL (80g/L)

Prior to prescribing cycle 1 the following criteria must be met;

Criteria	Eligible Level
Neutrophils	Equal to or more than $1x10^9$/L
Platelets	Equal to or more than $100x10^9$/L

Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (AST or ALT less than 2.5×ULN or total bilirubin less than 1.5×ULN). Sotorasib has not been studied in patients with moderate or severe hepatic impairment.

Sotorasib can cause hepatotoxicity, which may lead to drug-induced liver injury and hepatitis. It has been associated with transient elevations of serum transaminases (ALT and AST) which can be asymptomatic. These elevations improved or resolved with dose modification or permanent discontinuation of treatment and did not result in any cases of liver failure or fatal cases in clinical studies.

AST/ALT (units/L) NCI-CTC Grade		Bilirubin (µmol/L)	Sotorasib Dose Adjustment
Grade 3 or above	and	2xULN or more	Discontinue
Grade 2 with symptoms or grade 3 or greater	and		Interrupt treatment until recovered to grade 1 or below then resume treatment at the next dose reduction level

Renal Impairment

Based on population pharmacokinetic analysis, no dose adjustment is recommended for patients with mild renal impairment (creatine clearance, CrCL, greater than or equal to 60mL/min). Sotorasib has not been studied in patients with moderate or severe renal impairment (CrCL less than 60 mL/min).

Diarrhoea

For NCI-CTC grade 3 and above diarrhoea despite appropriate supportive care then stop treatment until the the diarrhoea has resolved grade 1 or below or baseline. After recovery, treatment can be resumed at the next dose level reduction.

Hypertension

Hypertension occurs in up to 10% of patients. If the patient found to have NCI-CTC grade 2 or more hypertension then also undertake an urinalysis for proteinuria. .

NCI-CTC Grade	Clinical Presentation	Action
1	Systolic BP (SBP) 120 - 139 mm Hg or diastolic BP (DBP) 80 - 89 mm Hg	Proceed with treatment
2	• SBP 140 - 159 mm Hg or DBP 90 - 99 mm Hg if previously within normal limits. • Change in baseline medical intervention indicated. • Recurrent or persistent (greater than or equal to 24 hrs). • Symptomatic increase by greater than 20 mm Hg (diastolic) or to greater than 140/90 mm Hg. • Monotherapy indicated initiated	Proceed with treatment and inform clinical team. Clinical team to refer patient to GP for monitoring and management of hypertension.
3	• SBP greater than or equal to 160 mm Hg or DBP greater than or equal to 100 mm Hg. • Medical intervention indicated. • More than one drug or more intensive therapy than previously	Stop treatment and inform clinical team. Resume treatment when recovered to less than or equal to grade 1 (Systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg) or to baseline grade. After recovery, resume treatment at the next dose reduction level If Grade 4 hypertension recurs, treatment should be permanently discontinued.
4	• Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis). • Urgent intervention indicated	

For NCI-CTC grade 3 to 4 or above proteinuria or urinary protein greater than or equal to 3.5g/24 hours then stop treatment until it has recovered to grade 1 or baseline.

Interstitial lung disease (ILD)/Pneumonitis

ILD/pneumonitis can occur in patients treated with sotorasib, especially if they have previously received treatment with immunotherapy or radiotherapy. Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis, including but not exclusively, shortness of breath, cough and fever. Immediately withhold in patients with suspected ILD/pneumonitis and contact the clinical lead for the patient. Permanently discontinue sotorasib if no other potential causes of ILD/pneumonitis are identified

Nausea and Vomiting

For NCI-CTC grade 3 or above nausea or vomiting despite appropriate supportive care then stop treatment until recovered to grade 1 or less. Once recovered resume treatment at the next dose level reduction.

Regimen

28 day cycle continued as long as benefit is observed or until unacceptable toxicity occurs (twelve cycles will be set in ARIA)

Cycle 1

Drug	Dose	Days	Route
Sotorasib	960mg	Once a day continuously	Oral

Dose Information

- Sotorasib is available as 120mg tablets

Administration Information

- Sotorasib tablets should be swallowed whole and with water as a single dose at the same time each day. Sotorasib may be taken with or without food.

- If a dose of sotorasib has been missed and less than 6 hours have passed since the scheduled time of dosing then take the dose as normal. If more than 6 hours have passed the dose should be omitted and treatment continued the next day as prescribed. Additional doses should not be taken in place of a missed dose.

- If vomiting occurs after taking sotorasib the patient must not take and additional dose on the same day.

- In case of swallowing difficulties, disperse tablets in 120mL of non-carbonated, room temperature water without crushing. Rather stir the mixture until the tablets are dispersed into small pieces (they will not completely dissolve) and drink immediately. The appearance of the liquid may range from pale to bright yellow. The container must be immediately rinsed with a further 120mL of water stirred and drunk immediately.

Supportive Treatments

As take home medication. This will be supplied on cycle one only. Thereafter it can be added from the favourites tab on ARIA.

- Metoclopramide 10mg oral up to three times a day when required for the relief of nausea and vomiting

- Loperamide 4mg after the first loose stool and 2mg after each subsequent loose stool to a maximum of 16mg in 24 hours.

Additional Information

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

- It must be made clear to all staff, including those in the community, that sotorasib should only be prescribed under the supervision of a consultant oncologist

- Sotorasib interacts with many other agents. Always check for drug interactions particularly with strong CYP3A4 inducers and acid reducing agents. Co-administration of PPIs and H2 antagonists is not recommended. If treatment is required sotorasib four hours before and 10 hours after the administration of the acid reducing agent.

References
1.National Institute for Health and Care Excellence. Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer. TA 781. NICE:DOH

REGIMEN SUMMARY

Sotorasib

Cycle One Day One

1. Sotorasib 960mg once a day for 28 days oral
   Administration Instructions
   Oral SACT.
   Sotorasib tablets should be swallowed whole and with water as a single dose at the same time each day.
   Sotorasib may be taken with or without food

2. Metoclopramide 10mg three times a day when required
   Administration Instructions
   Take 10mg up to three times a day when required for the relief of nausea and vomiting. Please supply 28x10mg tablets or nearest equivalent original pack size.

3. Loperamide as directed
   Administration instructions
   Loperamide 4mg after the first loose stool and 2mg after each subsequent loose stool to a maximum of 16mg in 24 hours

Cycle Two Day One Onwards

4. Sotorasib 960mg once a day for 28 days oral
   Administration Instructions
   Oral SACT.
   Sotorasib tablets should be swallowed whole and with water as a single dose at the same time each day.
   Sotorasib may be taken with or without food

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	July 2022	None	Dr Deborah Wright Pharmacist	Dr L Nolan 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 Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.