PROTOCOL

Systemic Anti Cancer Therapy Protocol

Sotorasib
KRAS-mutated Advanced or Metastatic NSCLC

PROTOCOL REF: MPHANOEAS
(Version No.: 1.2)

Approved for use:

As monotherapy for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), who have been previously treated with **at least 1 prior systemic therapy for advanced NSCLC**:

- Treatment with the relevant commissioned targeted treatment should have been explored for any actionable mutations (EGFR mutation, ALK gene rearrangement, ROS1 gene rearrangement, BRAF mutation, MET exon 14 skipping alteration, RET gene fusion) prior to initiating treatment with sotorasib.
- Previously treated with platinum doublet chemotherapy and/or PD-1/PD-L1 targeted immunotherapy.

ECOG performance status (PS) score of 0 or 1.

**************Blueteq Form Required**************

Dosage:

Drug	Dosage	Route	Frequency
Sotorasib	960mg	Oral	Once daily continuously

Until unacceptable toxicity or disease progression whichever is first.

Four weeks supply will be issued at each SACT treatment visit.

Administration:

Sotorasib is available as 120mg film-coated tablets. It should be swallowed whole with water and can be taken irrespective of food intake at roughly the same time each day.

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

If vomiting occurs after taking Sotorasib, the patient must not take an additional dose on the same day, and treatment must be continued as prescribed the next day. If nausea occurs advise patient to take tablets at night.

Patients should be advised to use effective contraception throughout the treatment course.

If treatment with an acid-reducing agent is required, sotorasib should be taken 4 hours before or 10 hours after administration of a local antacid.

In case of **swallowing difficulties** the following instructions can be followed:

- Disperse tablets in 120 mL of non-carbonated, room-temperature water (other liquids must not be used) without crushing.
- Stir until tablets are dispersed into small pieces (the tablet will not completely dissolve) and drink immediately. The appearance of the mixture may range from pale to bright yellow.
- The container must be rinsed with an additional 120 mL of water, which should be drunk immediately. If it is not drunk immediately, patients must stir again to

ensure that the tablets are dispersed. The dispersion must be discarded if it is not drunk within 2 hours.

Emetogenic risk:

Mildly emetogenic.

Supportive treatments:

- Metoclopramide 10mg orally three times a day.
- Loperamide 4mg immediately after first episode of loose stool then 2mg to be taken after each subsequent episode (maximum of 8 tablets in 24 hours) as required for management of diarrhoea.

Dosing in renal and hepatic impairment:

Renal	CrCl ≥ 60 ml/min: no dose adjustment CrCL < 60 ml/min: not studied, discuss with clinical team. Haemodialysis: not studied discuss with clinical team Creatinine Clearance (CrCL) calculated using Cockcroft and Gault formula (please use the application available on the Remote Citrix Web Portal).

Hepatic	<u>Mild hepatic impairment</u> AST or ALT < 2.5 × ULN or total bilirubin < 1.5 × ULN - no dose adjustment. <u>Moderate or Severe</u> AST or ALT ≥ 2.5 x ULN or total bilirubin ≥ 1.5 × ULN- not studied, discuss with clinical team.

Interactions:

This list is not exhaustive, for full list of interactions please refer to SmPC or consult with a member of the pharmacy team.

Acid-reducing agents

Co-administration of PPIs (e.g. omeprazole or lansoprazole) and H2 receptor antagonists (e.g. famotidine, cimetidine) with sotorasib is not recommended because the impact on its efficacy is unknown. If treatment with an acid-reducing agent is required, sotorasib should be taken 4 hours before or 10 hours after administration of a local antacid.

Strong CYP3A4 inducers

Co-administration of strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampicin) with sotorasib is not recommended because the impact on sotorasib efficacy is unknown.

CYP3A4 substrates

Sotorasib is a moderate CYP3A4 inducer. Co-administration of sotorasib (e.g. midazolam) with CYP3A4 substrates led to a decrease in their plasma concentrations, which may reduce the efficacy of these substrates.

P-glycoprotein (P-gp) substrates

Co-administration of sotorasib with digoxin (a P-gp substrate) markedly increased Digoxin levels. Therefore co-administration with P-gp substrates, for which minimal concentration changes may lead to serious toxicities should be avoided.

Main toxicities:

The most common (all grades)	Diarrhoea (34%) Musculoskeletal pain (31%) Nausea (25%) Fatigue (21%) Hepatotoxicity (19%) Cough (16%)
The most common severe (grade ≥ 3)	Increased ALT (5%) Increased AST (4%) Diarrhoea (4%).
The most common laboratory abnormalities (≥ 25%)	Decreased lymphocytes Decreased haemoglobin Increased AST Increased ALT Increased alkaline phosphatase, Decreased calcium, Increased urine protein Decreased sodium.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 1 D21	Cycle 2	Cycle 2 D8	Cycle 3	Cycle 3 D15	Cycle 4	Ongoing
Informed Consent	x								
Clinical Assessment	x			x				x	As clinically indicated or every 3 months
SACT Assessment (to include PS and toxicities*)	x	x		x		x		x	Every cycle
On treatment review			x		x		x		To be organized and completed by chemotherapy day unit nursing staff
FBC	x	x		x		x		x	Every cycle
LFTs (ALT, AST and Bilirubin)	x		x		x	x	x	x	Baseline then every 3 weeks for the first 3 months of treatment, then once a month or as clinically indicated.
U&E & Magnesium**	x	x		x		x		x	Every Cycle
CrCl (Cockcroft and Gault)	x	x		x		x		x	Every cycle
CT scan	x							x	Every 3 months or as clinically indicated
ECG									If clinically indicated
Full Observations		x		x		x		x	Every cycle***
Urinalysis									To be checked if Grade 2 or more hypertension. Refer to 'Dose Modifications and Toxicity Management' section
Weight recorded	x	x		x		x		x	Every cycle
Height	x								

* Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g. shortness of breath, cough, and fever), refer to 'Non-haematological Toxicity 'section.

** Monitor for hypokalaemia, hyponatraemia and hypocalcaemia and supplement accordingly.

*** Monitor for hypertension. Refer to 'Dose Modifications and Toxicity Management' section. If found to be hypertensive check urinalysis for proteinuria.

Dose Modifications and Toxicity Management:

Dosing should be modified based on sotorasib toxicity.

Table 1. Recommended sotorasib dose reduction levels

Dose reduction level	Dose
First dose reduction	480 mg (four 120 mg tablets) once daily
Second dose reduction	240 mg (two 120 mg tablets) once daily

Table 2. Recommended dose modifications for Sotorasib

Adverse reaction	Severity	Dose modification
Hepatotoxicity	Grade 2 rise in AST or ALT with symptoms or Grade ≥ 3 rise in AST or ALT	• Stop treatment until recovered to ≤ grade 1 or to baseline grade • After recovery, resume treatment at the next dose reduction level
	AST or ALT > 3 × ULN with total bilirubin > 2 × ULN, in the absence of alternative causes	• Permanently discontinue treatment
Interstitial Lung Disease/(ILD)/pneumonitis	Any Grade	• Stop treatment if ILD/pneumonitis is suspected • Permanently discontinue if ILD/pneumonitis is confirmed
Nausea or vomiting despite appropriate supportive care (including anti-emetic therapy)	Grade 3 to 4	• Stop treatment until recovered to ≤ grade 1 or to baseline grade • After recovery, resume treatment at the next dose reduction level
Diarrhoea despite appropriate supportive care (including anti-diarrhoeal therapy)	Grade 3 to 4	• Stop treatment until recovered to ≤ grade 1 or to baseline grade • After recovery, resume treatment at the next dose reduction level
Proteinuria	Grade 3 to 4 4+ proteinuria or Urinary protein ≥ 3.5 g/24 hrs	• Stop treatment until recovered to ≤ grade 1 (1+ proteinuria; urinary protein ≥ULN to less than 1.0 g/24 hrs) or to baseline grade

		• After recovery, resume treatment at the next dose reduction level
Other adverse reactions	Grade 3 to 4	• Stop treatment until recovered to ≤ grade 1 or to baseline grade • After recovery, resume treatment at the next dose reduction level

Haematological toxicity:

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. Monitor for symptomatic anaemia and treat with blood transfusions as required.

Non- Haematological toxicity:

Hepatotoxicity

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, refer to 'Dose Modification' section.

Interstitial Lung Disease (ILD)/Pneumonitis

ILD/pneumonitis occurred in patients treated with sotorasib with prior exposure to immunotherapy or radiotherapy. Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g. shortness of breath, cough, and fever). Immediately withhold in patients with suspected ILD/pneumonitis and contact the clinical

team. **Permanently discontinue if no other potential causes of ILD/pneumonitis are identified.**

Hypertension

Occurs in upto 10% of patients,refer to Table 3.0 below. If patient found to have grade 2 or more hypertension then urinalysis to be done as well, refer to Table 2.0 for grading of proteinuria.

Table 3.0: Recommended dose modifications for Sotorasib for hypertension

Grade	Clinical Presentation	Actions
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 (≥ 24 hrs). • Symptomatic increase by >20 mm Hg (diastolic) or to >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 ≥ 160 mm Hg or DBP ≥ 100 mm Hg. • Medical intervention indicated. • More than one drug or more intensive therapy than previously used indicated.	Stop treatment and inform clinical team. Resume treatment when recovered 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	

References:

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Published: November 27, 2017

Sotorasib 120 mg film-coated tablets, summary of Product Characteristics, Amgen Limited available via https://www.medicines.org.uk/emc (last updated 10th September 2021).

Skoulidis F et al. (2021) Sotorasib for Lung Cancers with KRAS p.G12C Mutation. *N Engl J Med.*384 (25):2371-2381.

SOT1_ver1.0 National Cancer Drugs Fund Application Form – Sotorasib as monotherapy for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) exhibiting a KRAS G12C mutation and who have been previously treated with at least 1 prior systemic therapy for advanced NSCLC_accessed 22nd March 2022.

Circulation/Dissemination

Date added into Q-Pulse	4th August 2022
Date document posted on the Intranet	N/A

Version History

		Author name and designation	Summary of main changes
		Hala Ghoz **Lung SRG Pharmacist**	V1.0 New Regimen Protocol
		Hala Ghoz **Lung SRG Pharmacist**	**V1.1** **Monitoring and dose reduction requirements for hypertension added.** **CDF funding criteria added**
		Hala Ghoz **Lung SRG Pharmacist**	**V1.2** **Orbis Scheme closed- removed** **Funding via CDF- added**