SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti-Cancer Therapy Protocol

SELPERCATINIB
RET fusion-positive carcinoma

PROTOCOL REF: MPHASRFC
(Version No. 1.0)

Approved for use in:

- Advanced RET fusion-positive non-small cell lung cancer who require systemic therapy following prior treatment with immunotherapy and/or platinum- based chemotherapy.

Or

- Advanced RET fusion-positive non medullary thyroid cancer who require systemic therapy following prior treatment with sorafenib and /or lenvatinib

Or

- Advanced RET-mutant medullary thyroid cancer who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.

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

Dosage:

Dose is based on body weight

Patients 50kg and over

Drug	Dose	Route	Frequency
Selpercatinib	**160mg**	Oral	TWICE a day continuously

Patients less than 50kg

Drug	Dose	Route	Frequency
Selpercatinib	**120mg**	Oral	TWICE a day continuously

Every 28 days until disease progression or unacceptable toxicity whichever is first.

Administration:

Selpercatinib is available as 80mg and 40mg capsules

Doses should be taken at about the same time every day, preferably in the morning and the evening.

Capsules can be taken with or without food and should be swallowed with a glass of water. Capsules should NOT be chewed, crushed or split before swallowing.

If a patient vomits or misses a dose, the patient should be instructed to take the next dose at its scheduled time; an additional dose SHOULD NOT be taken.

Selpercatinib must be taken with a meal if used concomitantly with a proton pump inhibitor (e.g. omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole)

Selpercatinib should be administered 2 hours before or 10 hours after H_2 receptor antagonists (e.g. ranitidine, cimetidine, famotidine, nizatidine)

Emetogenic risk:

Mildly emetogenic.

Supportive treatments:

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

Dosing in renal and hepatic impairment:

Renal	Dose adjustment is not necessary in patients with mild, moderate or severe renal impairment. There are no data in patients with end stage renal disease, or in patients on dialysis

Hepatic	Close monitoring of patients with impaired hepatic function is important. No dose adjustment is required for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. Patients with severe (Child-Pugh class C) hepatic impairment should be dosed with 80 mg selpercatinib twice daily – See dose modification section for advice regarding changes during treatment.

Interactions:

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

Agents that may affect Selpercatinib plasma concentrations

Acid-reducing agents
Selpercatinib must be taken with a meal if administered concomitantly with proton pump inhibitors e.g. omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole

Selpercatinib must be administered 2 hours before or 10 hours after H_2 receptor antagonists e.g. ranitidine, cimetidine, famotidine, nizatidine

Strong CYP3A4 inhibitors
The dose of selpercatinib should be reduced by **50%** if co-administering with a STRONG CYP3A4 inhibitor including but not limited to ketoconazole itraconazole and voriconazole. If the CYP3A4 inhibitor is discontinued, the selpercatinib dose should be increased (after 3- 5 half lives of the inhibitor) to the dose that was used before starting the inhibitor.

Strong CYP3A4 inducers
Concomitant use of strong CYP3A4 inducers including but not limited to rifampicin, carbamazepine, phenobarbital, phenytoin, rifabutin should be avoided as these may lead to reduced levels of selpercatinib.

Effects of Selpercatinib on other medicinal products

Sensitive CYP2C8 substrates
Co-administration with sensitive CYP2C8 substrates e.g. odiaquine, cerivastatin, enzalutamide, paclitaxel, repaglinide, torasemide, sorafenib, rosiglitazone, buprenorphine,

selexipag, dasabuvir and montelukast should be AVOIDED as selpercatinib can increase levels of these medicinal products.

Sensitive CYP3A4 substrates
Concomitant use with sensitive CYP3A4 substrates e.g. alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, tipranavir, triazolam, vardenafil should be AVOIDED as selpercatinib can increase levels of these medicinal products,.

Co-administration with medicinal products that are substrates of transporters

Selpercatinib inhibits the renal transporter multidrug and toxin extrusion protein 1 (MATE1). *In vivo* interactions of selpercatinib with clinically relevant substrates of MATE1, such as creatinine, may occur

Selpercatinib is an *in vitro* inhibitor of P-gp and BCRP.

Caution should be used when taking a P-gp substrate (e.g., fexofenadine, dabigatran etexilate, digoxin, colchicine, saxagliptin)

Main toxicities:

The most common (all grades)	Dry Mouth (40.3%) Diarrhoea (39%) Oedema (38.7%) Fatigue (38.2%) Hypertension (37.4%) Rash (28.7) Constipation (27.1%) Headache (24%) Nausea (23.5%)
The most common severe (grade ≥ 3)	Hypertension (19.4%) Decreased lymphocytes (16.1%) ALT increased (10.6%) AST increased (9%)
The most common laboratory abnormalities (≥ 25%)	Increased creatinine Decreased magnesium Decreased lymphocyte count Decreased platelet count AST increased ALT increased

Dose Modification	50kg and greater	Less than 50kg
First dose reduction	120mg TWICE a day	80mg TWICE a day
Second dose reduction	80mg TWICE a day	40mg TWICE a day
Third dose reduction	40mg TWICE a day	Not applicable

Investigations and treatment plan:

	Pre	Cycle 1		Cycle 2	Cycle 3	Ongoing
		Day 1	Day 8			
Informed Consent	X					
Clinical Assessment	X				X	As clinically indicated or every 3 months
SACT Assessment (to include PS and toxicities)	X	X		X	X	Every cycle
On treatment review			X			
FBC	X	X		X	X	Every cycle
U&E & LFTs & Magnesium*	X	X		X	X	Every cycle
ECG**	X		X	X	X	Monthly for first 6 months , then as clinically indicated
CrCl (Cockcroft and Gault)	X	X		X	X	Every cycle
CT scan	X					When clinically indicated or every 3 months
Full observations (including BP)	X	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	Every cycle
Height	X					

*Hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiating selpercatinib and during treatment.

** ECGs to monitor QT interval - QT prolongation has been reported in patients receiving selpercatinib

****** 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:

Dose Modification	50kg and greater	Less than 50kg
First dose reduction	120mg TWICE a day	80mg TWICE a day
Second dose reduction	80mg TWICE a day	40mg TWICE a day
Third dose reduction	40mg TWICE a day	Not applicable

Adverse reaction	Severity	Dose modification
Increased ALT or AST	Greater than 5 times the upper limit of normal (grade 3 or 4) if baseline was normal or greater than 5 times baseline if baseline was abnormal	• Suspend dose until toxicity resolves to baseline Resume at a dose reduced by 2 levels. • If after at least 2 weeks selpercatinib is tolerated without recurrent increased ALT or AST, increase dosing by 1 dose level. • If selpercatinib is tolerated without recurrence for at least 4 weeks, increase to dose taken prior to the onset of Grade 3 or 4 increased AST or ALT. • Permanently discontinue selpercatinib if Grade 3 or 4 ALT or AST increases recur despite dose modifications
Hypersensitivity	All grades	• Suspend dose until toxicity resolves and begin corticosteroids at a dose of 1 mg/kg Resume selpercatinib at 40 mg twice daily while continuing steroid treatment. Discontinue selpercatinib for recurrent hypersensitivity. • If after at least 7 days, selpercatinib is tolerated without recurrent hypersensitivity, incrementally

		increase the selpercatinib dose by 1 dose level each week, until the dose taken prior to the onset of hypersensitivity is reached. Taper steroid dose after selpercatinib has been tolerated for at least 7 days at the final dose.
QT interval prolongation Patients should have a QTcF interval of ≤470 ms before starting treatment	Grade 3 - Average QTc >= 501 ms; >60 ms change from baseline	• Suspend dose for QTcF intervals >500 ms until the QTcF returns to <470 ms or baseline • Resume selpercatinib treatment at the next lower dose level.
	Grade 4 - Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	• Permanently discontinue selpercatinib if QT prolongation remains uncontrolled after two dose reductions or if the patient has signs or symptoms of serious arrhythmia.
Hypertension	Grade 1 Systolic 120-139mmHg or diastolic BP 80-89mmHg	Proceed with treatment
	Grade 2 • Systolic 140-159mmHg or diastolic 90-99mmHg if previously within normal limits • Change in baseline and medical intervention indicated, recurrent or persistent (≥24 hours) symptomatic increase by >20mmHG (diastolic) or to >140/90mmHg; monotherapy indicated	Proceed with treatment and inform clinical team. Clinical team to refer patient to GP for monitoring and management of hypertension.

	Grade 3 – Systolic BP ≥ 160mmHg or diastolic BP ≥100mmHg, medical intervention indicated; more than one drug or more intensive therapy than previously indicated	• Patient blood pressure should be controlled before starting treatment. • Selpercatinib should be suspended temporarily for medically significant hypertension until controlled with antihypertensive therapy. Dosing should be resumed at the next lower dose if clinically indicated
	Grade 4 -life threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	• Selpercatinib should be discontinued permanently if medically significant hypertension cannot be controlled.
Haemorrhagic events	Grade 3 (Transfusion indicated, invasive intervention indicated, hospitalization) or grade 4 (life-threatening consequences, urgent intervention indicated)	• Selpercatinib should be suspended until recovery to baseline. • Discontinue Selpercatinib for severe or life-threatening haemorrhagic events.
Other reactions	Grade 3 or 4	• Selpercatinib should be suspended until recovery to baseline. • Discontinue selpercatinib for severe or life-threatening events

References:

1. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Published: November 27, 2017
2. NICE TA742: Selpercatinib for treating advanced thyroid cancer with RET alterations. Published: 03 November 2021

3. NICE TA760: Selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer. Published: 12 January 2022.
4. Retsevmo 80mg Capsules summary of product characteristics Eli Lilly https://www.medicines.org.uk/emc last updated 08 September 2022

Circulation/Dissemination

Date added into Q-Pulse	26th April 2022
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
April 2022	V1.0	**Lisa Dobson** **H&N SRG pharmacist**	New regimen protocol V1.0