Indication	Selpercatinib monotherapy treatment: **NSCLC:** o for patients with advanced RET fusion-positive NSCLC following prior treatment with immunotherapy and/or platinum-based chemotherapy. NB Patient must have not previously received selpercatinib (unless via an early access scheme) or any other TKI which targets the RET receptor. o for the 1st line treatment of RET fusion-positive locally advanced or metastatic NSCLC. **Thyroid:** **RET fusion positive non-medullary** o Previously **treated**, following prior treatment with sorafenib and/or lenvatinib or the patient has anaplastic thyroid cancer with no previous TKI therapy o Previously **untreated** with any kinase inhibitor therapy unless the patient has received selpercatinib via a company early access scheme. **RET mutant medullary** o Previously **treated** RET mutant medullary thyroid cancer, following prior treatment with cabozantinib or vandetanib. o Previously **untreated** RET mutant medullary thyroid cancer with no previous kinase inhibitor therapy unless the patient has received selpercatinib via a company early access scheme.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 28 days continuously. Treatment should continue until disease progression, unacceptable toxicity or patient choice. A formal medical review should take place by the start of the 3rd cycle.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • FBC and U&Es baseline, repeat after 1 week of treatment then prior to each cycle for the first 6 cycles and as clinically indicated. Hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiating selpercatinib and during treatment. Selpercatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine. • LFTs, including ALT and AST at baseline, every 2 weeks for the first 3 cycles, monthly for the next 3 cycles of treatment, and as clinically indicated. • ECG at baseline, repeat after 1 week of treatment and then monthly for the first 6 cycles then as clinically indicated. Patients should have a QTcF interval of </=470 ms and serum electrolytes within normal range before starting selpercatinib. Patients may require more frequent ECGs if they are on concurrent medication known to prolong the QT interval. • Monitor blood pressure at each cycle. Pre-existing hypertension should be adequately controlled before starting treatment. Selpercatinib should be discontinued permanently if hypertension cannot be controlled with antihypertensive therapy. • **Tumour lysis syndrome (TLS)** Cases of TLS have been observed in patients treated with selpercatinib. • **Interstitial lung disease (ILD)/Pneumonitis:** Severe, life-threatening, or fatal cases of ILD/pneumonitis have been reported in patients treated with selpercatinib, patients should report any new or worsening respiratory symptoms. Treatment should be withheld pending investigation of

these symptoms and if ILD/pneumonitis is confirmed dose reduction or discontinuation may be required.

- **Hepatic impairment:** Patients with impaired hepatic function should be closely monitored. No dose adjustment is required in mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. In severe (Child-Pugh class C) hepatic impairment patients should be dose reduced to 80mg twice daily.
- **Renal impairment:** No dose adjustment required in mild, moderate or severe renal impairment. No data in patients with end stage renal disease or on dialysis.
- **Management of adverse reactions and dose adjustments:**
  Selpercatinib dose should be reduced by 50% if co-administered with a strong CYP3A inhibitor and/or P-gp inhibitor, see interactions below.
  - Management of some adverse reactions may require dose interruption and/or dose reduction. Dose reductions should be made in 40mg increments, maintaining the twice daily dosing schedule.
    160mg (if applicable) to 120mg to 80mg to 40mg.
  - **Increased ALT/AST grade 3 or 4 (>5.0 x ULN):**
    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 reactions all grades:** Withhold treatment until toxicity resolves and begin corticosteroids at a dose of 1 mg/kg. Resume selpercatinib at 40 mg twice daily while continuing steroid treatment. If after at least 7 days, selpercatinib is tolerated without recurrent hypersensitivity, increase the 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. Discontinue selpercatinib for recurrent hypersensitivity.
  - **QT interval prolongation:**
    Grade 3, suspend dose for QTcF >500ms until QTcF <470 or baseline. Resume at the next lower dose.
    Grade 4, permanently discontinue if QT prolongation remains uncontrolled after 2 dose reductions or if the patient has signs/symptoms of serious arrhythmia.
  - **Hypertension:**
    Grade 3, 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, discontinue permanently if hypertension cannot be controlled.
  - **Haemorrhagic events:**
    Grade 3 or 4**,** selpercatinib should be suspended until recovery to baseline and discontinued for severe life-threatening or recurrent severe events.
  - **Interstitial lung disease (ILD)/Pneumonitis:**
    Grade 2, withhold until resolution, resume at a reduced dose. Discontinue for recurrent ILD/pneumonitis.
    Grade 3 or 4 permanently discontinue.
  - **Other Grade 3 or 4 reactions:**
    Suspend until recovery to baseline or discontinue for severe or life- threatening events.
- **Common drug interactions (for comprehensive list refer to BNF/SPC):**
  - Selpercatinib dose should be reduced by 50% if co-administering with a strong CYP3A inhibitor and/or P-gp inhibitor (e.g. ketoconazole, itraconazole, voriconazole, ritonavir, saquinavir, telithromycin, posaconazole and nefazodone). If the CYP3A 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. ○ Concomitant use of strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampicin, St John's Wort) should be avoided. ○ Sensitive CYP2C8 (e.g. enzalutamide, montelukast, buprenorphine) and CYP3A4 (e.g. alfentanil, simvastatin, midazolam) substrates should be avoided. ○ Selpercatinib should be administered 2 hours before or 10 hours after H2 receptor antagonists. ○ If proton pump inhibitors are co-administered with selpercatinib, both drugs should be taken with food. ○ Selpercatinib is a mild inhibitor of P-gp; caution when used with P-gp substrates (e.g. fexofenadine, dabigatran etexilate, colchicine, saxagliptin) and particularly those with a narrow therapeutic index (e.g. digoxin). ○ Selpercatinib could inhibit D2 deiodinase and thereby decrease the conversion of levothyroxine (T4) to triiodothyronine (T3). Patients could therefore have an insufficient response to levothyroxine and supplementation with liothyronine may be needed. • **Missed dose:** If a patient misses a dose or vomits after the dose they should resume with the next scheduled daily dose, no extra dose should be taken. • **Driving:** Patients should be advised to be cautious when driving or using machines in case they experience fatigue or dizziness during treatment. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet.
References	SPC accessed online 09.09.2024 CDF list V1.322 accessed online KMCC protocol MULTI-023 V2

NB For funding information, refer to CDF and NICE Drugs Funding List

Repeat every 28 days continuously

TTO	Drug	Dose	Route	Directions
Day 1	**SELPERCATINIB**	**< 50 kg 120mg** **>/=50 kg 160mg**	PO	BD Swallow whole, do not open, crush or chew the capsules. Take with or without food, **unless being taken with a PPI then the dose MUST be taken with a meal.** Selpercatinib **must be** administered 2 hours before or 10 hours after H_2 receptor antagonists. Available as 40mg and 80mg capsules. Dispense 30 days supply.
	Metoclopramide	10mg	PO	Up to TDS PRN. Do not take for more than 5 days continuously.
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if required.