Selpercatinib (Lung/Thyroid)

Indication

Untreated RET fusion-positive advanced non-small-cell lung cancer (NSCLC)
(NICE TA911)

RET fusion-positive advanced non-small-cell lung cancer (NSCLC) after immunotherapy, platinum-based chemotherapy or both
(NICE TA760)

Advanced RET fusion-positive non-medullary thyroid cancer after sorafenib or lenvatinib

Advanced RET-mutant medullary thyroid cancer after cabozantinib or vandetinib
(NICE TA742)

RET fusion positive non-medullary or RET mutant medullary thyroid cancer previously untreated with any kinase inhibitor therapy
(CDF)

ICD-10 codes

C34, C73

Regimen details

Dosing is based on body weight:

Weight	Drug	Dose	Route
< 50kg	Selpercatinib	120mg BD	PO
≥ 50kg	Selpercatinib	160mg BD	PO

Cycle frequency

Continuous

Number of cycles

Until disease progression or unacceptable toxicity

Administration

Selpercatinib is available as 40mg and 80mg capsules.

Capsules should be swallowed whole and should not be opened, crushed or chewed. Doses may be taken with or without food at approximately the same time each day.

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.

If a patient is also taking a proton pump inhibitor selpercatinib should be taken with a meal. If a patient is taking H2 receptor antagonists, then the selpercatinib should be administered 2 hours before or 10 hours after the H2 receptor antagonist.

Pre-medication

Nil

Emetogenicity
This regimen has low emetic potential – refer to local policy

Additional supportive medication
Loperamide as required

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U&Es (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days
Potassium	14 days
Calcium	14 days
Blood pressure*	14 days
ECG**	14 days

* Blood pressure should be adequately controlled prior to starting treatment
** QTc should be <470ms and serum electrolytes should be in normal range prior to starting treatment. Ensure hypokalaemia, hypomagnesaemia and hypocalcaemia are corrected prior to and during treatment

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Monthly
U&Es (including creatinine)	Every 2 weeks for the first 3 months then monthly
LFTs	Every 2 weeks for the first 3 months then monthly
Magnesium, Potassium, Calcium	Every 2 weeks for the first 3 months then monthly
Blood pressure	Every 2 weeks for the first 3 months then monthly
ECG	Every 2 weeks for the first 3 months then monthly

Standard limits for administration to go ahead
If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	> 1.5 x 10^9/L
Platelets	> 100 x 10^9/L
ALT/AST	< 5 x ULN
Bilirubin	< 1.5 x ULN
CrCl	> 15 ml/min
Magnesium, Potassium, Calcium	Within normal range

Dose modifications

Dose level	Dosing for ≥ 50kg	Dosing for < 50kg
Starting dose	160mg BD	120mg BD
First dose reduction	120mg BD	80mg BD
Second dose reduction	80mg BD	40mg BD
Third dose reduction	40mg BD	Not applicable

- **Haematological toxicity**

If neutrophils < 1.5 x 10^9/L or platelets < 100 x 10^9/L withhold selpercatinib and discuss with consultant.

- **Renal impairment**

Dose adjustment is not necessary in patients with mild, moderate or severe renal impairment. There is no data in patients with end-stage renal disease (<15ml/min) or on dialysis.

- **Hepatic impairment**

No dose adjustment is required for patient 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 dose reduced to 80mg twice daily. All patients with hepatic impairment should be monitored closely.

See toxicity section for management of elevated transaminases after commencing treatment.

- **Other toxicities**

Toxicity	Definition	Action/Dose adjustment
Increased ALT or AST	Grade 3 or 4 (>5 x ULN)	Suspend selpercatinib until toxicity resolves to baseline. Restart selpercatinib at a dose reduced by 2 dose levels. If after 2 weeks the selpercatinib is tolerated without recurrent increased ALT/AST, increase dosing by 1 dose level. If selpercatinib is tolerated without recurrence for at least 4 weeks, increase back to original dose taken prior to Grade 3 or 4 ALT/AST rise. Permanently discontinue selpercatinib if Grade 3 or 4 ALT/AST increases recur despite dose modifications.
Hypersensitivity *(characterised as a maculopapular rash often preceded by fever with associated arthralgias or myalgias, typically between D7 and 21 of the first cycle of treatment)*	All grades	Suspend dose until toxicity resolves and begin corticosteroids at a dose of 1mg/kg. Resume selpercatinib at 40mg twice daily while continuing steroid treatment. Discontinue selperactinib for recurrent hypersensitivity. If after at least 7 days, selpercatinib is tolerated without recurrent hypersensitivity, incrementally increase the selpercatinib 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	Grade 3 (Average QTc ≥ 501ms or >60 ms change from baseline)	Suspend selpercatinib for QTc intervals >500ms until the QTc returns to <470ms or baseline Resume selpercatinib at 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 2 dose reductions or if the patient has signs/symptoms of serious arrhythmia.
Hypertension	Grade 3 (BP ≥160/100mmHg)	Patient blood pressure should be controlled before starting treatment Selpercatinib should be suspended temporarily for medically significant hypertension until controlled with antihypertensive therapy. Selpercatinib should be resumed at the next lower dose level if clinically indicated

Hypertension	Grade 4 (life-threatening consequences e.g. malignant hypertension, transient or permanent neurological deficit, hypertensive crisis)	Selpercatinib should be discontinued permanently if medically significant hypertension cannot be controlled.
Haemorrhagic events	Grade 3 or 4	Selpercatinib should be suspended until recovery to baseline Discontinue selpercatinib for severe or life-threatening haemorrhagic events
Other adverse reactions	Grade 3 or 4	Selpercatinib should be suspended until recovery to baseline Discontinue selpercatinib for severe or life-threatening events

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

QT interval prolongation/arrhythmias
Hypertension
Haemorrhage

- **Frequently occurring side effects**

Elevated transaminases
Decreased appetite
Headache
Dizziness
Diarrhoea, constipation
Nausea, vomiting
Dry mouth
Rash
Fatigue
Thrombocytopenia
Creatinine increase
Hypomagnesaemia
Abdominal pain
Pyrexia
Oedema

- **Other side effects**

Hypersensitivity

Significant drug interactions – for full details consult product literature/ reference texts

Strong CYP3A4 inhibitors and/or P-gp inhibitors e.g. ketoconazole, itraconazole, voriconazole, ritonavir, saquinavir, telithromycin, Posaconazole, nefazodone, clarithromycin: increased selpercatinib levels, reduce selpercatinib dose by 50%. If the strong CYP3A4 inhibitor is stopped the selpercatinib dose should be increased (after 3-5 half lives of the inhibitor) to the dose used prior to starting the CYP3A4 inhibitor.
Strong CYP3A4 inducers e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, St John's Wort: reduced plasma levels of selpercatinib, avoid combination

CYP2C8 substrates e.g. repaglinide, odiaquine, cerivastatin, enzalutamide, paclitaxel, torasemide, sorafenib, rosiglitazone, buprenorphine, selexipag, dasabuvir, montelukast: increased levels of substrate avoid co-administration with sensitive CYP2C8 substrates.
CYP3A4 substrates e.g. alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, lomitapide, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, tipranavir, triazolam, vardenafil: increased levels of substrate avoid co-administration with sensitive CYP3A4 substrates.
Proton pump inhibitors: selpercatinib should be taken with a meal to optimise absorption
H2 antagonists: selpercatinib should be administered 2 hours before or 10 hours after the H2 receptor antagonist.
P-gp substrates e.g. fexofenadine, dabigatran, digoxin, colchicine, saxagliptin: selpercatinib inhibits P-gp transporters, caution should be used when administered in combination.

Additional comments

Nil

References

- National Institute for Health and Care Excellence (NICE TA742) accessed 21st July 2022 via www.nice.org.uk
- National Institute for Health and Care Excellence (NICE TA760) accessed 21st July 2022 via www.nice.org.uk
- Summary of Product Characteristics – Selpercatinib (Eli Lilly) accessed 21st July 2022 via www.medicines.org.uk
- Drilon, A. *et al*, Efficacy of Selpercatinib in RET Fusion-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2020; 383:813-824
- Wirth, L. *et al*, Efficacy of Selpercatinib in RET-altered Thyroid Cancers. N Engl J Med 2020; 383:825-835

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