Systemic Anti Cancer Therapy Protocol

Larotrectinib
NTRK Gene Fusion-positive Solid Tumours

PROTOCOL REF: MPHALAROST
(Version No: 1.0)

Approved for use in:

- In adults and children over 12 years with solid tumours (including primary cerebral tumours) that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion and fulfil the following criteria:
    - Disease is locally advanced or metastatic or for which surgical resection is likely to result in severe morbidity AND no other satisfactory treatment options available.
    - No previous treatment with NTRK inhibitor.
- Performance Status: 0, 1 or 2.

*************Completion of TWO Blueteq forms required************

*__Blueteq registration is required-prior to initiation of treatment__ with Larotrectinib, this **covers the funding of the first TWELVE weeks ONLY** of treatment. PET/CT/MR scans of index assessable/measureable disease and also of the brain must be done prior to commencing treatment and repeated at 10 weeks from the start of treatment (if not indicated before 10 weeks on account of assessing risk of disease progression). A RECIST response on the repeated assessment must be made and **another blueteq form will need to be completed detailing this information for continuation of funding for Larotrectinib BEYOND the initial 12 week period.**

Dosage:

Drug	Dose	Route	Frequency
Larotrectinib	**100mg***	Orally	TWICE daily, continuous

Treatment will be supplied every 28 days

Treatment continues until disease progression or unacceptable toxicity

***Please NOTE: dosing applies for patients over 18 years of age. For those aged ≤ 18 years the dose is 100 mg/m^2 twice daily with a maximum of 100 mg twice a day.**

Administration:

- Available as 100mg and 25mg capsules, and if required there is an oral solution (20mg/mL as 100mL bottle).
- Bioavailability of liquid preparation and capsules is identical – no amendment to dose is required.
- The capsules should be swallowed whole with a glass of water. Due to the bitter taste, the capsule should not be opened, chewed or crushed.
- The oral solution should not be mixed with feeding formulas, if administered via nasogastric feeding tube. Mixing with the feeding formulas could lead to tube blockages.
- The capsules or oral solution can be taken **with or without food but should not be taken with grapefruit or grapefruit juice.**
- Women of childbearing potential and males of reproductive potential must use highly effective contraception (barrier method) during treatment and for at least one month after stopping treatment. It is currently unknown whether larotrectinib may reduce the effectiveness of oral contraceptives.
- Larotrectinib has moderate influence on the ability to drive and use machines.
- Dizziness and fatigue have been reported, therefore patients should monitor for the effect during the first 3 months of treatment and only drive if unaffected.

Emetogenic risk:

Mildly emetogenic.

Supportive treatments:

None routinely required.

Extravasation risk:

Not applicable – oral treatment

Dosing in renal and hepatic impairment:

Renal	No dose adjustments required unless endstage renal failure or on dialysis then refer to clinical team.

Hepatic

Mild hepatic impairment (Child-Pugh Class A)- no dose adjustment is recommended

Moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment - starting dose should be reduced to 50%.

Parameters	1 point	2 points	3 points
Total bilirubin (µmol/L)	< 34	34–50	> 50
Serum albumin (g/L)	> 35	28–35	< 28
Prothrombin time, prolongation (s) *Or* INR	< 4 < 1.7	4–6 1.7-2.3	> 6 >2.3
Ascites	None	Mild to Moderate (diuretic responsive)	Severe (diuretic refractory)
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory to medication)

	INR: International Normalised Ratio. Child-Pugh Class A = 5-6 points Child-Pugh Class B = 7-9 points Child-Pugh Class C = 10 or more points **Please note**: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening. **Refer to 'Dose Modifications and Toxicity Management' section for larotrectinib-induced hepatotoxicity.**

Interactions:

This list is not exhaustive. Refer to SmPC for full details on interactions. For any interaction queries please contact Cytopharmacy.

Effect of CYP3A, P-gp and BCRP inhibitors on larotrectinib

If co-administration with a strong CYP3A4 inhibitor, P-gp and BCRP inhibitors (e.g. **atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole or grapefruit) larotrectinib dose should be reduced by 50%.** After the inhibitor has been discontinued for 3 to 5 elimination half-lives, larotrectinib should be resumed at the dose taken prior to initiating the CYP3A4 inhibitor.

Effect of CYP3A and P-gp inducers on larotrectinib

Co-administration of larotrectinib with strong or moderate CYP3A and P-gp inducers **(e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, or St. John's Wort) may decrease larotrectinib plasma concentrations and should be avoided.**

Effect of larotrectinib on CYP3A substrates

Exercise caution with concomitant use of CYP3A substrates with narrow therapeutic range (e.g. alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, or tacrolimus) in patients taking larotrectinib. If concomitant use of these CYP3A substrates with narrow therapeutic

range is required then **dose reductions** of the CYP3A substrates may be required due to adverse reactions.

Effect of larotrectinib on other transporter substrates

Co-administration of larotrectinib with OATP1B1 substrates (e.g. valsartan, statins) may increase their exposure.

Effect of larotrectinib on substrates of PXR regulated enzymes

Co-administration of larotrectinib with CYP2C8, CYP2C9 or CYP2C19 substrates (e.g. repaglinide, warfarin, tolbutamide or omeprazole) may decrease their exposure.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Larotrectinib**	**100mg**	Orally	Twice daily, continuous

Main toxicities:

Anaemia, neutropenia, increase in AST/ALT, weight gain, fatigue, constipation, nausea, vomiting, dizziness and gait disturbances, myalgia, muscle weakness.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Informed Consent	x					
Clinical Assessment	x			x		As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)*		x	x	x	x	Every cycle
FBC	x	x	x	x	x	Every cycle
U&E, LFTs** (including ALT,AST and Bilirubin) & Magnesium	x	x	x	x	x	Every cycle
CrCl (Cockcroft and Gault) or eGFR	x	x	x	x	x	Every cycle
CT scan	x			x		CT scan to be carried out at baseline and at 10 weeks then every three months or as clinically indicated
LDH	X	X	X	X	X	Every cycle--for clinician to review if raised. To be assessed in combination with symptoms and radiological progression
ECG						If clinically indicated
Full set of observations	x					Repeat if clinically indicated
Weight recorded	x	x	x	x	x	Every cycle

Height	x					

* Monitor for neurologic reactions including dizziness, gait disturbance and paraesthesia. For the majority of neurologic reactions, onset occurred within the first three months of treatment.

**Majority of AST/ALT increases occurred in the first 3 months of treatment during the clinical trials.

Dose Modifications and Toxicity Management:

Dose Modification	Adult and paediatric patients with body surface area of at least 1.0 m^2
1st	75mg twice daily
2nd	50mg twice daily
3rd	100mg once daily

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Refer to 'Main toxicities' section.

Grade 2
Discuss any grade 2 toxicity with clinical team prior to continuing with treatment. If decision made to continue treatment, then close monitoring is advised to ensure no worsening of the toxicity. Patients with Grade 2 ALT and/or AST increases (>3.0 - 5.0 x ULN if baseline was normal or >3.0 - 5.0 x baseline if baseline was abnormal) should be followed with serial laboratory evaluations every one to two weeks after the observation of Grade 2 toxicity until resolved to establish whether a dose interruption or reduction is required.
Grade 3 or 4 adverse reactions
Withold larotrectinib un til the adverse reaction resolves or improves to baseline or Grade 1. Resume at the next dose level if resolution occurs within 4 weeks. **Larotrectinib should be permanently discontinued if an adverse reaction does not resolve within 4 weeks.**

Additional Information

Reporting of all suspected adverse reactions for patients on larotrectinib is particularly important as it is a newly licensed medication. Reporting allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions in accordance with the training provided and the pharmacovigilance protocol.

References:

- BNF available via: https://bnf.nice.org.uk/
- Efficacy of larotrectinib in TRK fusion positive cancers in adults and children. NEJM 2018 378(8): 731-739 Drilon et al
- Larotrectinib, a highly selective TRK inhibitor. Expert review of clinical pharmacology 2019 12:10: 931-939 Federman and McDermott
- NICE TA 630 Larotrectinib for treating NTRK fusion-positive solid tumours
- Published: 27 May 2020.
- SmPC VITRAKVI (Bayer PLC) 100mg hard capsules accessed via https://www.medicines.org.uk/emc (last updated 24 Feb 2021)
- SmPC VITRAKVI (Bayer PLC) 20 mg/mL oral solution accessed via https://www.medicines.org.uk/emc (last updated 18 Sep 2020)