LAROTRECTINIB (Vitrakvi)

INDICATION (ICD10) solid tumours

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (LAR1a) (LAR1b)

1. Larotrectinib monotherapy for the treatment of malignant solid tumours (including primary cerebral tumours) (ie a carcinoma or a sarcoma or melanoma or a brain or spinal cord tumour) that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion AND disease which is locally advanced or metastatic or for which surgical resection is likely to result in severe morbidity AND who have no satisfactory treatment options, not previously received treatment with any tropomyosin receptor tyrosine kinase (TRK) inhibitor. Has no brain metastases or, if the patient has brain metastases, the patient is symptomatically stable prior to starting larotrectinib. PS 0, 1 or 2.
2. Larotrectinib response assessment and treatment continuation in the treatment of patients who have solid tumours that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion AND disease which is locally advanced or metastatic or for which surgical resection is likely to result in severe morbidity AND who have no satisfactory treatment options and has so far achieved a complete response or a partial response or has stable disease or. A RECIST radiological assessment has been made of the index disease at 10 weeks after the start of Larotrectinib.

REGIMEN

LAROTRECTINIB	100mg	oral	twice daily continuously

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 28 days for up to 12 weeks.
To continue beyond 12 weeks an assessment and separate Blueteq form needs to be completed, treatment may then continue until disease progression or potentially curative surgery takes place. A formal medical review as to whether treatment with larotrectinib should continue or not (on basis of being fit to continue treatment) will be scheduled to occur by the start of the second cycle (month) of treatment.

ADMINISTRATION

Available as 25mg and 100mg capsules, 20mg/ml oral solution.
Grapefruit and grapefruit juice should be avoided while on larotrectinib.

ANTI-EMETICS

Low emetic risk

CONCURRENT MEDICATION REQUIRED

Larotrectinib	None required

EXTRAVASATION AND TYPE OF LINE / FILTERS

Not applicable

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E every cycle
LFTs every cycle for 3 cycles then periodically, more frequently in those with elevated ALT or AST
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Serum creatinine every cycle
Baseline weight and every cycle
PET/CT/MRI baseline, then 10 weeks after starting treatment

MAIN TOXICITES AND ADVERSE REACTIONS

Larotrectinib	Anaemia, neutropenia and leukopenia, dizziness, myalgia, fatigue, ALT or AST increased

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS

(not exhaustive list check SPC/BNF/Stockleys)

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. Larotrectinib is a substrate of cytochrome P450 (CYP) 3A, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Co-administration of Larotrectinib with strong CYP3A inhibitors, P-gp and BCRP inhibitors (e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole or grapefruit) may increase larotrectinib plasma concentrations.

DOSE MODIFICATIONS

Larotrectinib

First dose modification	75mg twice daily
Second dose modification	50mg twice daily
Third dose modification	100mg once daily

Larotrectinib should be permanently discontinued in patients who are unable to tolerate 100mg od.

Non-haematological

Larotrectinib

For all grade 2 adverse reactions, continued dosing may be appropriate, though close monitoring to ensure no worsening of the toxicity is advised.

For grade 3 or 4 adverse reactions:

- Larotrectinib should be withheld until the adverse reaction resolves or improves to baseline or grade 1. Resume at the next dose modification if resolution occurs within 4 weeks.
- Larotrectinib should be permanently discontinued if an adverse reaction does not resolve within 4 weeks.

Hepatic impairment

Larotrectinib

The starting dose of Larotrectinib should be reduced to 50% in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A).

The majority of ALT and AST increases occurred in the first 3 months of treatment.

Grade 2 ALT and/or AST (>3xULN to ≤5xULN)	- Conduct serial laboratory evaluations frequently after the observation of grade 2 toxicity, until resolved, to establish whether a dose interruption or reduction is required.
Grade 3 ALT and/or AST (>5xULN to ≤20xULN) or Grade 4 ALT and/or AST (>20xULN), with bilirubin <2xULN	- Withhold treatment until the adverse reaction resolves or improves to baseline. Monitor liver function frequently until resolution or return to baseline. Permanently discontinue treatment if an adverse reaction does not resolve. - Resume at the next dose modification if adverse reactions resolve. Treatment should only be resumed in patients where the benefit outweighs the risk. - Permanently discontinue treatment if a grade 4 ALT and/or AST elevation occurs after resuming treatment.
ALT and/or AST ≥3xULN with bilirubin ≥2xULN	- Withhold treatment and monitor liver function frequently until resolution or return to baseline. - Consider permanent treatment discontinuation. - Treatment should only be resumed in patients where the benefit outweighs the risk. - If resumed, start at the next lower dose. Monitor liver function frequently upon restart. - Permanently discontinue treatment if adverse reaction recurs after resuming treatment.

Renal impairment

Larotrectinib

No dose adjustment is required for patients with renal impairment.

REFERENCES

1. Hong, D et al; Lancet Oncology 2020; 21 (4): 531-540 NICE TA630
2. Giraud EL, de Lijster B, Krens SD, Desar IME, Boerrigter E, van Erp NP. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Lancet Oncol 2023; 24: e229.

Assessments

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Clinical assessment	X		Pre cycle		Pre cycle	Every cycle
SACT assessment (PS and toxicities)	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E, calcium, magnesium & LFT	X	X	X	X	X	Every cycle
CrCl	X	X	X	X	X	Every cycle
CT scan	X					At cycle 6, Inform consultant team if not booked
Informed consent	X					Verbal each cycle
Height	X					
Weight recorded	X	X	X	X	X	Every cycle