

Larotrectinib (Vitrakvi)

Indication

Solid tumour that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion

Regimen details

Larotrectinib 100mg twice daily until disease progression or unacceptable toxicity occurs

Cycle frequency

Treatment is given continuously, dispense at monthly cycles

Administration

Oral capsules or solution taken with or without food but not with grapefruit or grapefruit juice

Do not mix with feeding formulas if administered via NG route

Emetogenicity

Mild emetogenic potential

Additional supportive medication

Prescribe metoclopramide 10mg TDS prn with first cycle

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST)

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophil count	$\geq 1.0 \times 10^9/\text{L}$
Platelet count	$\geq 100 \times 10^9/\text{L}$
Bilirubin	$\leq 1.5 \times \text{ULN}$ (see under Dose Modifications below)
AST	$< 1.5 \times \text{ULN}$ (see under Dose Modifications below)

Dose modifications

Reduce starting dose by 50% in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment

No dose reduction necessary in renal impairment

If co-administration with a strong CYP3A4 inhibitor is necessary, reduce larotrectinib dose by 50%

Laboratory parameters	Recommended measures
Grade 2 ALT and/or AST ($>3\times$ ULN and $\leq 5\times$ ULN)	- 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 ($>5\times$ ULN and $\leq 20\times$ ULN) or Grade 4 ALT and/or AST ($>20\times$ ULN), with bilirubin $<2\times$ ULN	- 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 $\geq 3\times$ ULN with bilirubin $\geq 2\times$ ULN	- 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.

For Grade 3 or 4 reactions:

Withhold treatment until reaction improves to baseline or Grade 1. Resume at the next dose modification if resolution occurs within 4 weeks

Permanently discontinue treatment if no resolution within 4 weeks

Dose Modification	Dose
First	75mg twice daily
Second	50mg twice daily
Third	100mg once daily

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

• Serious side effects

Neurologic reactions (dizziness, paraesthesia)

Raised liver enzymes

• Frequently occurring side effects

Vomiting

Nausea

Anaemia

Diarrhoea

Constipation

Cough

Weight gain

Dyspnoea

Headache
Pyrexia
Arthralgia
Back pain
Reduced neutrophil count

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

Adjust dose if given with strong inhibitors of CYP3A4 (see under “Dose modifications”)

Co-administration with strong inducers of CYP3A4 should be avoided

Larotrectinib is an inducer of CYP2B6, CYP2C8, CYP2C9 and CYP2C19

Larotrectinib inhibits OATP1B1 and may increase exposure to statins

The effect on hormonal contraceptives is unknown and women using hormonal contraceptives should add a barrier method

Additional comments

Women of childbearing potential should be advised to use highly effective contraception during treatment and for at least one month after the final dose.

Men of reproductive potential with a non-pregnant partner of child-bearing potential should be advised to use highly effective contraception during treatment and for at least one month after the final dose

References

Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med 2018; 378:731-739

Larotrectinib SPC <https://www.medicines.org.uk/emc/product/10766> Accessed 17/6/2020

THIS PROTOCOL HAS BEEN DIRECTED BY DR LAM, CONSULTANT ONCOLOGIST

Whilst every effort is made to ensure the accuracy of the information in a given protocol it cannot be guaranteed that the protocol is fully up to date. Cancer treatment can be dynamic in nature. Decisions on SACT must therefore be based on the independent judgement of the clinician with reference to changing information on the medicine (eg, available literature and SmPC) and evolving medical practices

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