BC Cancer Protocol Summary for the Treatment of Solid Tumours with Neurotrophic Tyrosine Receptor Kinase (NTRK) Fusion using Larotrectinib

***Protocol Code**:*	*UTAAVLAR*
***Tumour Group**:*	*Tumour-Agnostic*
***Contact Physician**:*	*Dr. Cheryl Ho*

ELIGIBILITY:

Patients must have:

- Locally advanced or metastatic solid tumours with neurotrophic tyrosine receptor kinase gene fusion (NTRK1, NTRK2, or NTRK3), and no known acquired resistance mutation,
- Relapsed or progressed following standard systemic therapy,
- Advanced disease with no other satisfactory treatment options, and
- BC Cancer “Compassionate Access Program” request approval prior to treatment

Notes:

- Larotrectinib to be used as monotherapy only. Combination of larotrectinib with other treatments is not funded.
- Patients with primary central nervous system (CNS) tumours are eligible if all other criteria are met
- Patients are eligible for one line of NTRK inhibitor therapy (One of either larotrectinib (UTAAVLAR) or entrectinib (UTAAVENT) will be funded)

Patients should have:

- ECOG 0 to 2

EXCLUSIONS:

Patients must not have:

- Symptomatic or unstable brain metastases. Previously treated, stable, or asymptomatic brain metastases permitted

CAUTIONS:

- Unstable cardiovascular disease, or
- Concurrent treatment with a strong CYP3A4 inhibitor or inducer before treatment initiation and unable to discontinue

TESTS:

- Baseline: CBC & Diff, platelets, creatinine, total bilirubin, ALT, alkaline phosphatase, LDH, albumin, calcium, sodium, potassium, phosphorus, random glucose
  - If clinically indicated: INR
- During treatment:
  - total bilirubin, ALT, alkaline phosphatase should be checked two weeks after starting larotrectinib
  - At each physician visit: CBC & Diff, platelets, total bilirubin, ALT, alkaline phosphatase
  - If clinically indicated: calcium, albumin, sodium, potassium, phosphorus, creatinine, LDH, random glucose, INR

PREMEDICATIONS:

- No premedications needed

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
larotrectinib	100 mg twice daily	PO

Repeat every 28 days continuously until disease progression or unacceptable toxicity.

Starting Dose for Pre-Existing Hepatic impairment:

Pre-Existing Hepatic impairment	Larotrectinib Starting Dose
Child-Pugh A	No initial dose adjustment required
Child-Pugh B or C	Start at dose level -2

DOSE MODIFICATIONS:

Dose Levels:

Dose Level	Larotrectinib Dose
0	100 mg BID
-1	75 mg BID
-2	50 mg BID
-3	100 mg **once daily**

1. Neutropenia:

ANC (x 10^9/L)	Larotrectinib Dose
Greater than or equal to 1.5	100%
1.0 to 1.49	100% Monitor CBC & Diff as clinically appropriate
Less than 1.0	Hold until ANC greater than or equal to 1.5 or baseline, then restart at next lower dose level

2. Hepatic dysfunction:

Transaminase elevation during treatment

ALT or AST increased	Larotrectinib Dose
Less than or equal to 3 x ULN	100%
Greater than 3 to 5 x ULN	100% Monitor as clinically appropriate
Greater than 5 x ULN	Hold until less than or equal to 3 x ULN or baseline, then restart at next lower dose level

3. Other toxicities:

Other Toxicity	Larotrectinib Dose
Any Grade 3 or 4 adverse reaction	▪ Hold. Re-evaluate at least weekly. ▪ If improvement to Grade 1 or baseline within 4 weeks, restart at next lower dose ▪ Discontinue if no improvement within 4 weeks

4. **Drug Interactions:** dose modification is required for concurrent use with moderate or strong CYP 3A4 inhibitors. Refer to BC Cancer Drug Manual.

PRECAUTIONS:

1. **Neurologic/psychiatric** adverse events are reported in up to 63% of patients and include dizziness, cognitive impairment, mood disorders, and sleep disorders. The majority of events occur within the first three to six months of treatment. Patients should not drive or operate potentially hazardous machinery if they are experiencing neurologic symptoms. Cognitive impairment has a median time to onset of 5 to 6 months and may include memory impairment, confusion, disturbance in attention, and delirium. Mood disorders have a median time to onset of ~4 months and may include anxiety, depression, agitation, and irritability. Sleep disorders may include insomnia, somnolence, and other sleep disturbances. Based on the severity of the symptoms, larotrectinib dose interruption, dose reduction, or treatment discontinuation may be required.
2. **Drug interactions:** larotrectinib is a substrate of CYP3A4. Concurrent use with strong CYP3A4 inhibitors may increase the plasma concentration of larotrectinib. Concurrent use with strong CYP3A4 inducers may decrease the plasma concentration of larotrectinib. Avoid if possible. If coadministration is required, dose adjustment may be required. See Cancer Drug Manual. Avoid grapefruit juice for 48 hours before and for duration of larotrectinib therapy.
3. **Gastrointestinal effects** such as constipation, diarrhea, nausea and vomiting are reported during treatment with larotrectinib. Monitor during treatment and treat with supportive care measures as appropriate.

Call Dr. Cheryl Ho or tumour group delegate at 604- 930-2098 or 1-800-523-2885 with any problems or questions regarding this treatment program.

REFERENCES:

1. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol. 2020 Apr;21(4):531-540.
2. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med. 2018 Feb 22;378(8):731-739.
3. Kummar S, Berlin J, Mascarenhas L, et al. Quality of Life in Adult and Pediatric Patients with Tropomyosin Receptor Kinase Fusion Cancer Receiving Larotrectinib. Curr Probl Cancer. 2021 Dec;45(6):100734.
4. CADTH Reimbursement Review Larotrectinib (Vitrakvi). Canadian Journal of Health Technologies November 2021 Volume 1 Issue 11.
5. Waguespack SG, Drilon A, Lin JJ, et al. Efficacy and safety of larotrectinib in patients with TRK fusion-positive thyroid carcinoma. Eur J Endocrinol. 2022 Apr 29;186(6):631-643.