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

***Protocol Code**:*	*UTAAVENT*
***Tumour Group**:*	*Tumour-Agnostic*
***Contact Physician**:*	*Dr. Howard Lim*

ELIGIBILITY:

Patients must have:

- Locally advanced or metastatic extracranial 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:

- Entrectinib to be used as monotherapy only. Combination of entrectinib with other treatments is not funded.
- Patients are eligible for one line of NTRK inhibitor therapy (One of either entrectinib (UTAAVENT) or larotrectinib (UTAAVLAR) will be funded.

Patients should have:

- Good performance status

EXCLUSIONS:

Patients must not have:

- Primary central nervous system (CNS) tumours,
- Congenital long QT syndrome or a persistent corrected electrocardiogram interval (QTc) 500 ms or longer, or
- Symptomatic or unstable brain metastases. Previously treated, stable, or asymptomatic brain metastases permitted

CAUTIONS:

- Patients with symptomatic congestive heart failure, myocardial infarction, unstable angina, or coronary artery bypass graft within 3 to 6 months
- 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, calcium, albumin, sodium, potassium, phosphorus, magnesium, uric acid, ECG, muga scan or echocardiogram to assess LVEF
- During treatment: CBC & Diff, platelets, alkaline phosphatase, ALT, total bilirubin and LDH should be checked two weeks after starting entrectinib and at each subsequent visit thereafter
- If clinically indicated: calcium, albumin, sodium, potassium, phosphorus, magnesium, ECG, muga scan or echocardiogram to assess LVEF, uric acid, creatinine, GGT, alkaline phosphatase

PREMEDICATIONS:

- No premedications needed

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
entrectinib	600 mg once daily	PO

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

DOSE MODIFICATIONS:

Entrectinib dose levels:

Dose Level	Entrectinib Dose
0	600 mg once daily
-1	400 mg once daily
-2	200 mg once daily

1. Neutropenia:

ANC (x 10^9/L)	Entrectinib 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 1.0 or baseline, then restart at same dose or reduce by one dose level

2. Hepatic Dysfunction:

ALT or AST increased		Total Bilirubin	Entrectinib Dose
Less than or equal to 3 x ULN	or	1.5 x ULN or less	100 %
Greater than 3 to 5 x ULN	or	Greater than 1.5 to 3 x ULN	100%. Monitor ALT and total bilirubin as clinically appropriate
ALT or AST greater than 3 x ULN	**and**	Greater than 1.5 x ULN	▪ Hold ▪ Discontinue if no cholestasis or hemolysis ▪ Once recovered, resume per provider discretion
Greater than 5 to 20 x ULN	or	Greater than 3 to 10 x ULN	▪ Hold until less than or equal to ALT/AST 3 x ULN and total bilirubin 1.5 x ULN or baseline, then if recovery within 4 weeks: ○ First occurrence: restart at previous dose ○ Recurrent: restart at reduced dose ▪ If no recovery within 4 weeks, discontinue
Greater than 20 x ULN	or	Greater than 10 x ULN	▪ Hold until less than or equal to ALT/AST 3 x ULN and total bilirubin 1.5 x ULN or baseline, then if recovery within 4 weeks, restart at reduced dose ▪ Discontinue if recurrent or if no recovery within 4 weeks

3. Syncope:

- Hold entrectinib for any grade syncope until recovered, then restart at 1 dose level lower
- If recurrence, hold until recovery and reduce again by another dose level, or consider discontinuation

4. Heart failure:

Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with moderate activity or exertion	Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)

- Hold entrectinib for Grade 2 or 3 heart failure until recovered to Grade 1 or less, then restart at reduced dose
- Discontinue for Grade 4 heart failure

5. QT prolongation:

Toxicity	Entrectinib Dose
QTc 450 to 480 ms	Maintain Dose
QTc 481 to 500 ms	Hold until recovered to baseline, then restart at same dose.
QTc greater than or equal to 501 ms	Hold until recovered to baseline, and: ▪ Identify and correct causes, then restart at same dose ▪ If no cause identified, restart at reduced dose
Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Discontinue

6. CNS Effects: treatment interruption and subsequent dose reduction is required for events Grade 2 or higher.

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

8. Other Toxicities:

Other Toxicity	Entrectinib Dose
Any Grade 3 or 4 adverse reaction	▪ Hold until resolution to Grade 1 or baseline ○ If improvement within 4 weeks, restart at same or lower dose ○ Consider discontinuation if no improvement within 4 weeks ▪ Discontinue for recurrent Grade 4 events

PRECAUTIONS:

1. **Anemia:** in patients with hemoglobin less than 80 g/L, consider correction of anemia prior to beginning/continuing entrectinib treatment.
2. **Central Nervous System:** a broad spectrum of CNS adverse reactions are reported. Patients with brain metastases previously treated with CNS irradiation may be at increased risk of dizziness, headache, balance disorder, paresthesia, and confusional state. Patients should not drive or operate potentially hazardous machinery if they are experiencing CNS symptoms. Cognitive disorders may occur and usually start within 3 months of starting treatment. Dose interruption, reduction, or treatment discontinuation may be required.
3. **Hyperuricemia:** initiate urate-lowering medication and hold entrectinib for symptomatic elevations in uric acid, or for Grade 4 hyperuricemia. When signs or symptoms have improved, may restart at same or reduced dose.
4. **Vision disorders** are reported in 21% of patients and can include blurred vision, photophobia, diplopia, visual impairment, photopsia, cataract, and vitreous floaters. Consider ophthalmological evaluation in patients with new visual changes or changes that interfere with activities of daily living. Entrectinib should be held until improved or stabilized, then restarted at same or reduced dose as appropriate.
5. **Drug interactions**: the concomitant use of moderate or strong CYP 3A4 inhibitors should be avoided or limited to 14 days or less. If concomitant use cannot be avoided, dose reduction is required. After discontinuation of the inhibitor, entrectinib may be resumed at the prior dose. A wash out period may be required for inhibitors

with long half-lives. CYP 3A4 inducers may decrease the plasma concentrations of entrectinib; avoid concurrent use. See Cancer Drug Manual. Avoid grapefruit juice for 48 hours before and for duration of entrectinib therapy

Call Dr. Howard Lim or tumour group delegate at 604-682-2344 or 1-800-663-3333 with any problems or questions regarding this treatment program.

REFERENCES:

1. Demetri GD, De Braud F, Drilon A, et al. Updated Integrated Analysis of the Efficacy and Safety of Entrectinib in Patients With NTRK Fusion-Positive Solid Tumors. Clin Cancer Res. 2022 Apr 1;28(7):1302-1312.
2. CADTH Reimbursement Review Entrectinib (Rozlytrek). Canadian Journal of Health Technologies November 2022 Volume 2 Issue 11.