BC Cancer Protocol Summary for First-Line Treatment of ROS1-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Entrectinib

Protocol Code:	*ULUAVENT*
Tumour Group:	*Lung*
Contact Physician:	*Dr. Sophie Sun*

ELIGIBILITY:

Patients must have:
- Stage IIIB or IV non-small cell lung cancer,
- Laboratory confirmed ROS1-positive tumour based on FISH or next-generation sequencing (NGS) testing,
- No prior systemic therapy, and
- BC Cancer Compassionate Access Program (CAP) approval

Patients should have:
- Asymptomatic/stable brain metastases (if applicable)
- ECOG performance status 0-2

Note:
- Patients who were started on, or had completed first-line chemotherapy and/or immunotherapy prior to 1 April 2022 may receive entrectinib (ULUAVENT) if all other eligibility criteria are met
- If crizotinib (LUAVCRIZR) was discontinued for intolerable toxicity, patients may switch to entrectinib (ULUAVENT)

EXCLUSIONS:
- Congenital long QT syndrome or a persistent corrected electrocardiogram interval (QTc) of ≥ 500 msec

CAUTION:
- Patients with symptomatic CHF, myocardial infarction, unstable angina, or coronary artery bypass graft within 3 to 6 months

TESTS:

- Baseline: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, calcium, magnesium, uric acid, sodium, potassium, ECG, muga scan or echocardiogram to assess LVEF
    - C-reactive protein and albumin (optional, and results do not have to be available to proceed with first treatment)
- During treatment: CBC & differential, platelets, alkaline phosphatase, ALT, total bilirubin and LDH should be checked two weeks after starting entrectinib and at each subsequent visit thereafter
- As required: muga scan or echocardiogram to assess LVEF, ECG, uric acid, calcium, magnesium, sodium, potassium, creatinine; chest X-ray and scans to monitor index lesions

PREMEDICATIONS:

- no premedications needed

TREATMENT:

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

Dose reduction:

Dose level -1: 400 mg once daily

Dose level -2: 200 mg once daily

- Careful re-evaluation after initiation of therapy is essential as entrectinib should be continued *only if* tumour regression continues or the disease is stable and cancer-related symptoms have improved. Continued entrectinib for “psychological” palliation in the face of progressive disease is inappropriate.

DOSE MODICATIONS:

1. Hematological:

ANC ($x10^9$/L)	Dose
greater than or equal to 1.0	600 mg once daily
less than 1.0	Withhold until recovery, then resume at same or reduced dose level as clinically appropriate

2. **Hepatic Dysfunction:**

Severity	Dose
Grade 3 elevation	Withhold until recovery to ≤ Grade 1 or baseline. Resume at same dose if resolution occurs within 4 weeks. Permanently discontinue if no resolution within 4 weeks. Resume at reduced dose for recurrent Grade 3 events that resolve within 4 weeks.
Grade 4 elevation	Withhold until recovery of to ≤ Grade 1 or baseline. Resume at reduced dose if resolution occurs within 4 weeks. Permanently discontinue if no resolution within 4 weeks. Permanently discontinue for recurrent Grade 4 events.
ALT elevation to > 3.0 x ULN and concurrent bilirubin elevation to > 1.5 x ULN	Permanently discontinue

3. **QTc Prolongation:** treatment interruption is required for QTc > 481 msec.
4. **Congestive Heart Failure:** treatment interruption and subsequent dose reduction is required for Grade 2 or Grade 3 CHF. Permanently discontinue treatment for Grade 4 CHF.
5. **Drug interactions:** dose modification is required for concurrent use with moderate or strong CYP 3A4 inhibitors. Refer to BC Cancer Drug Manual.
6. **CNS Effects:** treatment interruption and subsequent dose reduction is required for Grade ≥ 2 events.

PRECAUTIONS:

1. **Cardiovascular**: Congestive heart failure (CHF) has been reported and may occur in patients with or without a history of cardiac disease. Patients should be carefully monitored; patients with clinical signs and symptoms of CHF, including shortness of breath or edema, should be evaluated and treated as clinically appropriate.
2. **Hyperuricemia**: monitor for signs and symptoms of hyperuricemia; urate-lowering medications may be required as clinically indicated.
3. **Skeletal fractures**: entrectinib increases the risk of fractures.
4. **Vision disorders**: vision disorders may include blurred vision, photophobia, diplopia, visual impairment, photopsia, or other changes. Consider ophthalmological exam for patients with new visual changes. Ability to drive or operate machinery may be compromised.

5. **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. Cognitive disorders may occur and usually start within 3 months of starting treatment. Dose interruption, reduction, or treatment discontinuation may be required.
6. **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.

Call Dr. Sophie Sun or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

REFERENCES:

1. Hoffmann-La Roche Ltd. Entrectinib (ROZLYTREK®) product monograph. Mississauga, Ontario; 7 January 2021.
2. Drilon A, Siena S, Dziadziuszko R, et al. Entrectinib in ROS1 fusion-positive non-small cell lung cancer: intergrated analysis of three phase 1-2 trials. Lancet Oncol 2020; 21(2): 261-270.