Regimen Monograph

Regimen Name | Drug Regimen | Cycle Frequency | Premedication and Supportive Measures | Dose Modifications | Adverse Effects | Interactions | Drug Administration and Special Precautions | Recommended Clinical Monitoring | Administrative Information | References | Other Notes | Disclaimer

A - Regimen Name

ENTR Regimen

entrectinib

Disease Site
Lung
Non-Small Cell

Intent
Palliative

Regimen Category
Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses
First-line monotherapy for locally advanced (not amenable to curative therapy) or metastatic ROS1-positive non-small cell lung cancer (NSCLC), in patients who have good performance status

Supplementary Public Funding
entrectinib
Exceptional Access Program (entrectinib - For the treatment of locally advanced (not amenable to curative therapy) or metastatic NSCLC, according to clinical criteria) (EAP Website)

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B - Drug Regimen

entrectinib	600 mg	PO	Daily

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C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low – No routine prophylaxis; PRN recommended

- Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

ROS1-positive status should be established using a validated test prior to initiation of entrectinib.

In patients with symptoms or known risk factors of CHF, LVEF should be assessed prior to initiation of entrectinib.

Dosage with toxicity

Dose Level	Entrectinib Dose (mg/day)
0	600
-1	400
-2	200
-3	Discontinue

Refer to interactions section for dosing recommendations when co-administered with CYP3A inhibitors.

Toxicity	Grade	Action
Anemia or Neutropenia	≥ Grade 3	Hold*; resume at same dose level or 1 dose level ↓.
CNS Effects	≥ Grade 2	Hold*; resume at 1 dose level ↓. If recurs, hold*; further ↓ 1 dose level. Discontinue if prolonged, severe, or intolerable events occur.
Hepatotoxicity	Grade 3	Hold*. If recovery in: • ≤ 4 weeks; resume at same dose level • > 4 weeks; discontinue If recurs, and recovery in: • ≤ 4 weeks; resume at 1 dose level ↓ • > 4 weeks; discontinue

	Grade 4	Hold*. If recovery in: • ≤ 4 weeks; resume at 1 dose level ↓ • > 4 weeks; discontinue If recurs; discontinue.
	ALT or AST > 3 x ULN with total bilirubin > 1.5 x ULN (in the absence of cholestasis or hemolysis)	Discontinue.
Hyperuricemia	Symptomatic or Grade 4	Hold until improvement of signs and/or symptoms. Initiate urate-lowering medication. Resume at same dose level or 1 dose level ↓.
Syncope	Any	Hold until recovered; resume at 1 dose level ↓. If recurs, hold until recovered; further ↓ 1 dose level or discontinue.
Congestive Heart Failure	Grade 2 or 3	Hold until recovery to ≤ grade 1; resume at 1 dose level ↓.
	Grade 4	Discontinue.
QT Interval Prolongation	QTc 481 to 500 msec	Hold until recovery to baseline; resume at same dose level.
	QTc >500 msec	Hold until recovery to baseline; If QT prolongation risk factors are: • Identified and corrected; resume at same dose level • **NOT** identified; resume at 1 dose level ↓
	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	Discontinue.
Vision Disorders	≥ Grade 2	Hold until improvement or stabilization; resume at same dose level or 1 dose level ↓.

All other toxicities	≥ Grade 3	Hold*. If recovery in: • ≤ 4 weeks; resume at same dose level or 1 dose level ↓ • > 4 weeks; discontinue
	Recurrent Grade 4	Discontinue.

*Resume when hematologic toxicities recovered to ≤ grade 2 or baseline and other specified toxicities recovered to ≤ grade 1 or baseline.

Hepatic Impairment

Hepatic impairment may increase the plasma concentration of entrectinib and/or its major active metabolite as entrectinib is primarily eliminated through metabolism in the liver.

Hepatic Impairment	Entrectinib Dose
Child-Pugh A	No dose adjustment required
Child-Pugh B	
Child-Pugh C	No dose adjustment required; closely monitor hepatic function and toxicities

Renal Impairment

The pharmacokinetics of entrectinib are not significantly affected by renal impairment.

Creatinine Clearance (mL/min)	Entrectinib Dose
≥ 30	No dose adjustment required
< 30	Has not been studied

Dosage in the Elderly

No dose adjustment required. No differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients.

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F - Adverse Effects

Refer to entrectinib drug monograph(s) for additional details of adverse effects.

Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Fatigue • Constipation • Dysgeusia • Edema • Dizziness • Diarrhea • Nausea, vomiting • Cough, dyspnea • Dysesthesia (including peripheral neuropathy) • Myelosuppression ± infection • Cognitive disturbance • Weight gain	• Creatinine increased • Eye disorders • Musculoskeletal pain • Headache • Hypotension • Ataxia • ↑ LFTs • Sleep disorder • Anorexia • Rash • Mood changes	• Cardiotoxicity • QT interval prolonged • Syncope • Hyperuricemia • Fracture

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G - Interactions

Refer to entrectinib drug monograph(s) for additional details.

- Avoid co-administration or limit concomitant use with strong or moderate CYP3A4 inhibitors to ≤14 days as combination may increase entrectinib concentration and/or toxicity.
    - If concomitant use of **strong** inhibitors cannot be avoided, reduce entrectinib dose to 100mg daily.
    - If concomitant use of **moderate** inhibitors cannot be avoided, reduce entrectinib dose to 200mg daily.
    - After discontinuation of strong or moderate CYP3A4 inhibitor for 3 to 5 half-lives, resume entrectinib dose from prior to initiating the inhibitor.

- Avoid concomitant use with CYP3A4 inducers as combination may decrease entrectinib concentration and/or efficacy.
- Avoid concomitant use of with drugs that may prolong QT interval as combination may enhance QT-prolonging effects.

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H - Drug Administration and Special Precautions

Refer to entrectinib drug monograph(s) for additional details.

Administration

- Administer with or without food.
- Capsules should be swallowed whole and not opened, crushed, chewed, or dissolved.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- If a dose is missed, a make-up dose can be administered unless the next dose is within 12 hours.
- If vomiting occurs immediately after the dose, the dose may be repeated.
- Store at room temperature (15-30°C).

Contraindications

- Patients who have a hypersensitivity to this drug or any components of the formulation.

Other Warnings/Precautions

- Entrectinib contains lactose; consider use in patients with lactose intolerance, hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.
- Patients with symptomatic CHF, myocardial infarction, unstable angina, or coronary artery bypass graft within three to six months of study entry were excluded from clinical trials.
- Entrectinib should be avoided in patients with congenital long QT syndrome.
- Caution with driving or using machinery as visual disturbances, dizziness, and syncope may occur with treatment.

Pregnancy/Lactation

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility Effects: Probable

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC: Baseline, at each visit, and as clinically indicated
- ECG; Baseline and as clinically indicated; more frequently in patients with risk factors such as CHF, electrolyte abnormalities, or concomitant medications known to prolong QT interval
- LVEF; Baseline in patients with symptoms or known risk factors for CHF, and as clinically indicated
- Liver function tests; Every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated
- Electrolytes, uric acid levels; Baseline and as clinically indicated
- Renal function tests; Baseline and as clinically indicated
- Clinical toxicity assessment for signs/symptoms of edema, fatigue, fractures, cardiotoxicity, tumor lysis syndrome, visual changes, GI and CNS effects; As clinically indicated

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Dziadziuszko R, Krebs MG, De Braud F, et al. Updated integrated analysis of the efficacy and safety of entrectinib in locally advanced or metastatic *ROS1* fusion-positive non-small-cell lung cancer. J Clin Oncol. 2021 Apr 10;39(11):1253-1263. doi: 10.1200/JCO.20.03025.

Entrectinib Drug Monograph, Ontario Health (Cancer Care Ontario).

pCODR expert review committee: final recommendation (entrectinib: Rozlytrek), January 27, 2021.

March 2024 Modified Dosage with toxicity and Dosage with hepatic toxicity section

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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