Regimen Monograph

A - Regimen Name

CERI Regimen

ceritinib

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
Monotherapy for the treatment of patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC who have progressed on, or were intolerant to crizotinib.

Supplementary Public Funding
ceritinib
Exceptional Access Program (ceritinib - Second-line monotherapy of ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC, in patients who have experienced disease progression or intolerance to crizotinib, according to specific criteria)

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B - Drug Regimen

ceritinib	450 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: Moderate – Consider prophylaxis daily

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

A supply of loperamide should be provided for diarrhea.

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E - Dose Modifications

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

Electrolyte abnormalities (hypokalemia, hypomagnesemia, and hypocalcemia) should be corrected prior to starting treatment.

Patients must have documented ALK-positive status based on a validated ALK assay.

Dosage with toxicity

Dose level	Ceritinib dose (mg/day)
0	450
-1	300

-2	150
-3	Discontinue

Toxicity	Severity	Ceritinib Dose
Nausea, vomiting or diarrhea	Grade 3 or intolerable, despite optimal antiemetic and antidiarrheal therapy.	Hold until improved, restart at ↓ 1 dose level.
Hyperglycemia (> 250 mg/dL or 14 mmol/L)	Persistent hyperglycemia despite optimal anti-hyperglycemic therapy.	Hold until controlled, restart at ↓ 1 dose level. Discontinue if adequate control cannot be achieved with optimal medical management.
Bradycardia (HR < 60 bpm)	Symptomatic, non-life-threatening	Hold until asymptomatic or heart rate ≥ 60 bpm. If medication(s) contributing to bradycardia/hypotension is discontinued or dose adjusted, restart ceritinib at same dose. If no contributing medication(s) is identified or cannot be discontinued/dose adjusted, restart ceritinib at ↓ 1 dose level.
	Life-threatening	Hold until asymptomatic or heart rate ≥ 60 bpm. If medication(s) contributing to bradycardia/hypotension is discontinued or dose adjusted, restart ceritinib at ↓ 1 dose level. Discontinue permanently: • If potentiating medications cannot be identified and discontinued • For recurrence
Prolonged QTcF	> 500 msec on at least 2 separate ECGs	Hold until baseline or < 481 msec, restart at ↓ 1 dose level.
	Torsades de pointes or polymorphic ventricular tachycardia or signs and symptoms of other serious arrhythmia	Discontinue.
Elevated LFTs	AST or ALT > 5 x ULN AND total bilirubin ≤ 1.5 x ULN	Hold until baseline or ≤ 3 x ULN, restart at ↓ 1 dose level.

	AST or ALT > 3 x ULN AND total bilirubin > 2 x ULN (without cholestasis or hemolysis)	Discontinue.
Elevated lipase or amylase	> 2 x ULN	Hold until ≤ 1.5 x ULN, restart at ↓ 1 dose level if pancreatitis is ruled out. If pancreatitis is confirmed, discontinue and manage appropriately.
Suspected ILD/pneumonitis	Any grade	Hold and investigate; discontinue if confirmed.

Hepatic Impairment

Hepatic Impairment	Ceritinib Dose
Mild to moderate impairment (Child-Pugh classes A and B)	No dosage adjustment necessary.
Severe impairment (Child-Pugh class C)	Reduce the dose by approximately one-third (rounded to the nearest multiple of the 150 mg strength).

Renal Impairment

Creatinine Clearance	Ceritinib Dose
≥ 30 to 90 mL/minute	No dosage adjustment necessary.
< 30 mL/minute; patients on dialysis	Use with caution; No data available.

Dosage in the Elderly

No overall differences in efficacy were observed between patients ≥ 65 years and younger patients.

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F - Adverse Effects

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

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Diarrhea (maybe severe) • Nausea, vomiting • ↑ LFTs (maybe severe)	• Fatigue • Abdominal pain • Anorexia, weight loss	• Creatinine increased (maybe severe) • Rash • Constipation • Musculoskeletal pain • Anemia • QT interval prolonged • Hyperglycemia (maybe severe) • ↑Amylase / lipase (maybe severe)	• Pericarditis • Bradycardia • Venous thromboembolism • Atrial fibrillation • ↓ PO4 • Visual disorders • Pneumonitis

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G - Interactions

Refer to ceritinib drug monograph(s) for additional details

- Avoid concomitant use with QT prolonging agents if possible, due to the increased risk of prolonged QT or Torsades de Pointes; closely monitor QT.
- Avoid co-administration with agents that lower heart rate if possible, due to the increased risk of bradycardia; closely monitor HR.
- Avoid strong CYP3A4 inhibitors, which may increase ceritinib concentration and/or toxicity; if unavoidable, consider ceritinib dose reduction.

- Avoid strong CYP3A4 inducers, which may decrease ceritinib concentration and/or efficacy.
- Avoid co-administration with CYP3A4 or CYP2C9 substrates that have narrow therapeutic indices, due to the potential of increased substrate concentration and/or toxicity. Consider substrate dose reduction if concurrent use of ceritinib and CYP3A4 or CYP2C9 substrates cannot be avoided. Increase INR monitoring with warfarin
- Drugs that reduce gastric acid (antacids, H_2-receptor blockers, proton pump inhibitors) may result in decreased ceritinib concentrations. If concurrent use is necessary, give H_2-blocker 10 hours before or 2 hours after ceritinib dose. Give antacids 2 hours before or 2 hours after ceritinib dose.

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H - Drug Administration and Special Precautions

Refer to ceritinib drug monograph(s) for additional details

Administration

- Administer ceritinib at the same time each day with food. Food can range from a snack to a full meal.
- Capsules should be swallowed whole with water and not be chewed or crushed.
- Avoid fruit or juice from grapefruit, Seville oranges or starfruit as they may inhibit CYP3A in the gut wall and may increase the bioavailability of ceritinib.
- If a dose is missed it may be taken as soon as possible, unless the next dose is due within 12 hours.
- If vomiting occurs after taking the dose, do not take a replacement dose. Continue with the next scheduled dose.
- Store at room temperature, between 15^{o}C to 30^{o}C

Contraindications

- Patients who have a hypersensitivity to this drug or any of its components
- Patients with congenital long QT syndrome or with a persistent QTcF > 500 msec

Warnings/Precautions

Not recommended for use in:

- ALK-negative patients
- Patients who are taking medications known for QT prolongation

Use with caution in:

- Patients who are at risk of prolonged QT (electrolyte imbalances, cardiovascular disease, diabetes, autonomic neuropathy, females, older patients).
- Patients with baseline bradycardia (HR < 60 bpm), history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular block, ischemic heart disease or congestive heart failure, or taking agents known to cause bradycardia or hypotension.
- Patients with severe renal impairment requiring peritoneal dialysis or hemodialysis (ceritinib has not been studied in these patients).

Pregnancy and Lactation

- Ceritinib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **3 months** after the last dose.
- Breastfeeding is not recommended.
- Fertility effects: Unknown

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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.

Recommended Clinical Monitoring

- ECG; Baseline and as clinically indicated; more frequent in patients at risk for QT prolongation
- Blood glucose; Baseline and as clinically indicated; more frequent if diabetic
- Lipase, amylase; Baseline and as clinically indicated; more frequently if abnormal or symptoms of pancreatitis
- Liver function tests; Baseline and monthly thereafter; more frequently in patients that develop liver enzyme elevations during treatment
- Renal function tests and electrolytes; Baseline and as clinically indicated
- Clinical toxicity assessment for gastrointestinal, skin, cardiac (blood pressure and heart rate), and respiratory toxicity; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Ceritinib drug monograph, Cancer Care Ontario.

Shaw AT, Engelman JA. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med. 2014 Jun 26;370(26):2537-9.

PEBC Advice Documents or Guidelines

- Systemic Treatment for Patients with Advanced Non-Small Cell Lung Cancer
- Therapy for Stage IV Non-Small-Cell Lung Cancer With Driver Alterations: ASCO and OH(CCO) Joint Guideline Update

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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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