Regimen Monograph

A - Regimen Name

CRIZ Regimen

Crizotinib

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 locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive or ROS1-positive.

Note: Funding for ALK+ is for first or second-line. Funding for ROS1+ is in the first-line setting only. (Refer to EAP criteria for details.)

Supplementary Public Funding

crizotinib
Exceptional Access Program (crizotinib - First or second-line treatment for ALK-positive advanced NSCLC, according to specific criteria) (EAP Website)

crizotinib
Exceptional Access Program (crizotinib - First-line treatment for ROS1-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC, according to specific criteria) (EAP Website)

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B - Drug Regimen

crizotinib	250 mg	PO	BID

(outpatient prescription; available in 200 mg or 250 mg capsules)

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C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression, no evidence of further response, 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.

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E - Dose Modifications

Use only in patients with known ALK-positive or ROS1-positive NSCLC confirmed using a validated assay.

Avoid using concomitantly with strong CYP3A4 inducers/inhibitors, or CYP3A4 substrates with narrow therapeutic indices and associated with severe arrhythmias.

Electrolyte abnormalities should be corrected prior to initiating treatment.

The following recommendations have been adapted from product monographs and could be considered.

Dosage with toxicity

Dose Level	Crizotinib Dose
0	250mg twice daily
-1	200mg twice daily
-2	250 mg once daily
-3	Discontinue

Toxicity	Action
Grade 3 hematologic	Hold until recovery to ≤ grade 2; resume at same dose
Grade 4 hematologic	Hold until recovery to ≤ grade 2; resume at ↓ 1 dose level
Grade 3 or 4 AST/ALT WITH ≤ grade 1 bilirubin	Hold until recovery to ≤ grade 1 or baseline; resume at ↓ 1 dose level
Bilirubin ≥ grade 2 and AST/ALT ≥ grade 2 (in the absence of cholestasis or hemolysis)	Discontinue
QTc ≥ 500 msec without arrhythmia	Hold until ≤ 470 msec and correct electrolyte abnormalities; resume at ↓ 1 dose level
QTc ≥ 500 msec (or > 60 msec change from baseline) and Torsade de Pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmias	Discontinue
Grade 2 or 3 bradycardia (< 60 bpm; symptomatic, may be severe and medically significant, medical intervention indicated)	Hold until recovery to ≤ grade 1* Evaluate contributing medications: If contributing concomitant medication is identified and is adjusted or discontinued, resume at same dose If there is no contributing concomitant medication or if concomitant medications are <u>not</u> adjusted/ discontinued, resume at ↓ 1 dose level
Grade 4 bradycardia (life-threatening consequences, urgent intervention indicated)	Hold immediately Evaluate contributing medications: If contributing concomitant medication is

	identified and adjusted or discontinued, resume* at 250 mg once daily and monitor If no contributing concomitant medication identified, discontinue Discontinue with recurrence
Signs or symptoms of pneumonitis / interstitial lung disease	Hold and investigate; discontinue permanently if confirmed
Severe visual loss (best corrected vision < 20/200 in one or both eyes)	Discontinue and evaluate severe vision loss No data to support resuming; risk benefit must be assessed

*Do not restart until heart rate ≥ 60 bpm and asymptomatic

Hepatic Impairment

Hepatic Impairment	Crizotinib Starting dose
Mild	No dose adjustment necessary
Moderate (total bilirubin >1.5 to ≤3 x ULN and any AST)	200 mg twice daily
Severe (total bilirubin >3 x ULN and any AST)	250 mg once daily

Renal Impairment

Renal Impairment	Crizotinib Starting Dose
Mild or moderate	No dose adjustment necessary
Severe (CrCl < 30 mL/min) not requiring peritoneal dialysis or hemodialysis	250 mg once daily
Severe requiring peritoneal dialysis or hemodialysis	No data

Dosage in the Elderly

There were no overall differences in safety or efficacy between patients aged 65 or older and younger patients and dosage adjustment is not required. However, edema, constipation, dysgeusia and nausea were reported more frequently in older patients.

Dosage based on ethnicity

Although exposure is higher in Asian patients, there is no increase in the incidence of grade 3 or 4 adverse events.

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F - Adverse Effects

Refer to crizotinib 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
• Visual disorders (may be severe) • Diarrhea • Nausea, vomiting	• Edema • Constipation • Increased LFTs (may be severe) • Anorexia • Fatigue • Abdominal pain • Dysgeusia • Upper respiratory tract infections	• Neuropathy • Fever • Cough, dyspnea • Dizziness • Musculoskeletal pain • Bradycardia • Dyspepsia • Myelosuppression +/- infection or bleeding (may be severe) • Rash	• QT interval prolonged • Arterial/venous thromboembolism • Hypotension, syncope • DIC • Pneumonitis • Renal failure

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G - Interactions

Refer to crizotinib drug monograph(s) for additional details

- Avoid use with strong CYP3A4 inhibitors and inducers
- Avoid CYP3A4 substrates with narrow therapeutic index and associated with severe arrhythmias
- Avoid (where possible) drugs that disrupt electrolyte levels and those that prolong the QT interval
- Avoid (where possible) drugs that decrease heart rate

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H - Drug Administration and Special Precautions

Refer to crizotinib drug monograph(s) for additional details

Administration

- Swallow capsules whole with a glass of water. Do not crush, dissolve, or open capsules.
- Administer crizotinib with or without food.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during crizotinib treatment
- If a dose is missed, patient may take within 6 hours of missed dose. If more than 6 hours, the dose should be skipped and taken at the next planned time.
- Store at room temperature and away from children or pets.

Contraindications/Precautions

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

Warnings/Precautions

- Use with caution in patients who are at risk of QT prolongation or bradycardia (low potassium/magnesium, congenital QT prolongation, CHF, anti-arrhythmics, other QTc prolonging agents, prior anthracyclines, AV block, sick sinus, sinoatrial block or drugs leading

to bradycardia etc.).

- Use with caution in patients who have bradycardia at baseline (< 60 bpm), and in patients with cardiac disease, history of arrhythmias or who are on medications that may reduce heart rate.
- Caution with driving or using machinery due to vision disorder including diplopia, photopsia, blurred vision, visual impairment and vitreous floaters.
- Caution in patients with a history of thrombotic events. Crizotinib has not been studied in patients who have had arterial thromboembolism or CHF within the last 3 months.
- Exercise caution in patients with hepatic impairment or severe renal impairment requiring dialysis.

Pregnancy/Lactation:

- Crizotinib 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: Not recommended
- 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.

Recommended Clinical Monitoring

- CBC; baseline and at each visit; more frequent if severe myelosuppression, fever and/or infection
- Creatinine, electrolytes, including calcium, potassium and magnesium; baseline and as clinically indicated
- ECG, heart rate and blood pressure; baseline and as clinically indicated
- Liver function tests; baseline, every 2 weeks during the first 2 months, then monthly and as clinically indicated (more frequent with hepatotoxicity)
- Ophthalmoscopy and assessment of visual loss; As clinically indicated

- Renal imaging and urinalysis if renal cysts develop; As clinically indicated
- Clinical toxicity assessment for signs of bleeding or infection and GI, ocular, hepatic, cardiac and nervous system effects, pneumonitis and venous thromboembolism; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- MUGA, especially for patients with cardiac risk factors; baseline and as clinically indicated

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Crizotinib drug monograph, Cancer Care Ontario.

Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368(25):2385-94.

Shaw, AT, Ou S, Bang Y, et al. Crizotinib in ROS1-rearrangd non-small cell lung cancer. N Eng J Med 2014; 371(21): 1963-71.

Solomon BJ, Mok T, Kim DW; PROFILE1014 Investigators. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014 Dec 4;371(23):2167-77.

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

March 2021 Added PEBC guideline link

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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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