Systemic Anti Cancer Treatment Protocol

Crizotinib

PROTOCOL REF: MPHACRIZLU
(Version No: 1.2)

This protocol has been temporarily amended-please see the ORAL SACT OPERATIONAL CHANGES DURING COVID -19

Amendments may include less frequent blood monitoring, telephone SACT assessments and longer durations of treatment being dispensed.

Approved for use in:

First line treatment of ALK positive advanced or metastatic non-small-cell lung cancer

Second and subsequent line treatment of ALK positive advanced or metastatic non-small cell lung cancer (post 1st line platinum based combination chemotherapy)

First or subsequent line systemic therapy for ROS1-positive inoperable locally advanced/metastatic non squamous non-small cell lung cancer

Blueteq registration required

Dosage:

Drug	Dosage	Route	Frequency
Crizotinib	250mg	Oral	Twice daily

Treatment is continuous until disease progression or unacceptable toxicity.

Supportive treatments:

Loperamide 2mg Take 2 capsules at once, then one capsule over each loose motion when required. Maximum of 8 capsules in 24 hours.

Metoclopramide 10mg tablets, to be taken up to three times a day as required

Extravasation risk:

Not applicable

Administration:

Crizotinib capsules should be swallowed whole preferably with water and should not be crushed, dissolved or opened.

They may be taken with or without food.

Drug Interactions

- Grapefruit or grapefruit juice should be avoided as it may increase crizotinib plasma concentration.
- St John's wort should be avoided as it may decrease crizotinib plasma concentration.
- Strong CYP3A inhibitors should be avoided as can increase crizotinib plasma concentrations. Examples include: atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, itraconazole, ketoconazole, voriconazole, clarithromycin, telithromycin, and troleandomycin. Consult SPC for full list of potential interactions
- Domperidone: Crizotinib increases the risk of QT prolongation when given with domperidone. Manufacturer advises avoid.
- **Please consult SPC for full list of interactions: available via medicines.org.uk or discuss with a pharmacist.**

Main Toxicities:

Nausea and vomiting, diarrhoea, neutropenia and elevated transaminases, QTc prolongation

Interstitial Lung Disease

Interstitial Lung Disease (ILD) should be suspected in patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms such as dyspnoea, cough and fever, and should have their crizotinib interrupted pending diagnostic evaluation.

Investigations:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Medical Assessment	X		X	X	X	Every three cycles
Nursing Assessment	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E & LFT (**including CK**)	X	X	X	X	X	Every cycle
Lipid profile	X		X			After cycle 2 repeat lipid profile every 3 months
LDH		X	X	X	X	Every cycle
CT scan	X			X*		*CT scan to be carried out prior to cycle 3 then every three months or as clinically indicated
ECG	X			X		ECG to be carried out at baseline and then on cycle 3 at medical assessment, then as clinically indicated
Blood pressure and heart rate measurement	X	X	X			Repeat if clinically indicated
Informed Consent	X					
PS recorded	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

Proceed on day 1 if:

Plt ≥ 50 x 10^9/L	ANC ≥ 1.0 x 10^9/L

Haematological toxicity

CTCAE Grade	Action
Grade 3	Withhold until recovery to Grade ≤2, then resume at the same dose schedule
Grade 4	Withhold until recovery to Grade ≤2, then resume at reduced dose as per reduction table

Non-haematological toxicities

CTCAE Grade	Action
Grade 3 or 4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation with Grade ≤1 total bilirubin	Withhold until recovery to Grade ≤1 or baseline, then resume at 250 mg once daily and escalate to 200 mg twice daily if clinically tolerated. Crizotinib should be permanently discontinued in case of further grade ≥3 recurrence.
Grade 2 to 4 ALT or AST elevation with concurrent Grade 2 to 4 total bilirubin elevation	Permanently discontinue
Any Grade interstitial lung disease (ILD)/pneumonitis	Withhold if ILD/pneumonitis is suspected, and permanently discontinue if treatment-related ILD/pneumonitis is diagnosed
Grade 3 QTc prolongation	Withhold until recovery to Grade ≤1, check and if necessary correct electrolytes, then resume at 200 mg twice daily. Crizotinib should be permanently discontinued in case of further grade ≥3 recurrence.
Grade 4 QTc prolongation	Permanently discontinue

Grade 2, 3 Bradycardia Symptomatic, may be severe and medically significant, medical intervention indicated	Withhold until recovery to Grade ≤1 or to heart rate 60 or above. Evaluate concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products. If contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to Grade ≤1 or to heart rate 60 or above. If no contributing concomitant medicinal product is identified, or if contributing concomitant medicinal products are not discontinued or dose modified, resume at reduced dose upon recovery to Grade ≤1 or to heart rate 60 or above.
Grade 4 Bradycardia (heart rate less than 60 beats per minute) Life-threatening consequences, urgent intervention indicated	Permanently discontinue if no contributing concomitant medicinal product is identified If contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at 250 mg once daily upon recovery to Grade ≤1 or to heart rate 60 or above, with frequent monitoring
Grade 4 Ocular Disorder (Visual Loss)	Discontinue during evaluation of severe vision loss

Dose Reduction Table

Level	Crizotinib Dose
Starting Dose	**250mg twice daily**
1st Reduction	200mg twice daily
2nd Reduction	250mg once daily

Hepatic Impairment

Crizotinib is extensively metabolized in the liver. Treatment with crizotinib should be used with caution in patients with hepatic impairment (see tables above)

Based on the National Cancer Institute (NCI) classification, no starting dose adjustment of crizotinib is recommended for patients with mild hepatic impairment (either AST >

Upper Limit of Normal (ULN) and total bilirubin ≤ULN or any AST and total bilirubin >ULN but ≤1.5 × ULN).

The starting crizotinib dose for patients with moderate hepatic impairment (any AST and total bilirubin >1.5 × ULN and ≤3 × ULN) is recommended to be 200 mg twice daily.

The starting crizotinib dose for patients with severe hepatic impairment (any AST and total bilirubin >3 × ULN) is recommended to be 250 mg once daily.

Crizotinib dose adjustment according to Child-Pugh classification has not been studied in patients with hepatic impairment.

Renal Impairment

No starting dose adjustment is recommended for patients with mild (creatinine clearance: 60-90 mL/min) or moderate (creatinine clearance 30-60 mL/min) renal impairment, since the population pharmacokinetic analysis indicated no clinically meaningful changes in steady-state crizotinib exposure in these patients.

Crizotinib plasma concentrations may be increased in patients with severe renal impairment (CL_{cr} <30 mL/min). The crizotinib starting dose should be adjusted to 250 mg taken orally once daily in patients with severe renal impairment not requiring peritoneal dialysis or haemodialysis. The dose may be increased to 200 mg twice daily based on individual safety and tolerability after at least 4 weeks of treatment.

References:

- NICE TA 422 Crizotinib for previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer
- NICE TA 406 Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer
- NICE TA529 Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer
- https://www.medicines.org.uk/emc/