Indication	• 1st or subsequent line systemic therapy for ROS1-positive inoperable locally advanced/metastatic non-squamous non-small cell lung cancer. • For the treatment of ALK +ve advanced non-small cell lung cancer previously untreated with an ALK inhibitor NB: The patient should either be naïve to 1st line cytotoxic chemotherapy-containing systemic treatment for this locally advanced or metastatic NSCLC indication or the patient received 1st line cytotoxic chemotherapy-containing treatment for locally advanced/metastatic non-small cell lung cancer at a time when the ALK status was not known and the patient has since received no further therapy.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 28 days Continuous until disease progression or unacceptable toxicity.
Monitoring parameters	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor **FBC** and **U&Es** prior to each cycle. Correct abnormalities in potassium, calcium and magnesium prior to initiating treatment and as clinically indicated. • Monitor **LFTs** once a week for the first 2 months of treatment then once a month and as clinically indicated. • If neuts <1.0 and/or PLT <50 d/w consultant. • Monitor **pulse** and **BP** prior to each cycle or as clinically indicated. • **ECG** prior to treatment and as clinically indicated thereafter. • **Hepatic impairment:** Crizotinib should be used with caution in patients with hepatic impairment. The recommended starting dose for patients with moderate hepatic impairment (any AST and total bilirubin >1.5 × ULN and </=3 × ULN) is 200 mg twice daily. The recommended starting dose for patients with severe hepatic impairment (any AST and total bilirubin >3 × ULN) is 250 mg once daily. • **Renal impairment:** No dose reduction if CrCl >/= 30ml/min. If CrCl <30ml/min recommended dose reduction to 250 mg once daily in patients 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. • **Dose adjustments & management of adverse events:** • If dose reduction is necessary, reduce to 200 mg twice daily. If further dose reduction is necessary, then the dose should be modified to 250 mg once daily. • Permanently discontinue if unable to tolerate 250mg once daily. • <u>Dose modifications in haematological toxicities (except lymphopenia unless associated with clinical events such as opportunistic infection):</u> o Grade 3 (neuts 0.5 - <1, PLT 25 - <50): withhold until recovery to Grade </=2, then resume at the same dose schedule. o Grade 4 (neuts<0.5, PLT <25): withhold until recovery to Grade </=2, then resume at 200 mg twice daily. In case of recurrence, dosing should be withheld until recovery to Grade </=2,

	then dosing should be resumed at 250 mg once daily. Crizotinib must be permanently discontinued in case of further Grade 4 recurrence. • Dose modifications in non-haematological toxicities: see table 1 below • Crizotinib has been associated with life-threatening ILD / pneumonitis. Patients with pulmonary symptoms indicative of ILD / pneumonitis should be monitored and treatment permanently discontinued if diagnosis is treatment related. • Crizotinib should be administered with caution to patients who have a history of or predisposition for **QTc prolongation**, or who are taking medicinal products that are known to prolong the QT interval. • Crizotinib should be used with caution in patients at risk for gastrointestinal perforation. Crizotinib should be discontinued in patients who develop gastrointestinal perforation. Electrolyte disturbances, dehydration and bradycardia may increase the risk of QTc prolongation and thus, periodic monitoring of ECG and electrolyte levels is recommended in patients with GI toxicity. • **Visual disturbance:** Ophthalmological evaluation should be performed for new onset of visual loss and for other visual symptoms. In any patient with new onset of severe visual loss (best corrected visual acuity less than 6/60 in one or both eyes), crizotinib treatment should be discontinued. • **Photosensitivity:** Patients should be advised to avoid prolonged sun exposure while taking crizotinib and, when outdoors, to take protective measures (e.g. use of protective clothing and/or sunscreen). • **Missed doses**: If a dose is missed, patients should take as soon as possible unless it is less than 6 hours until the next dose, in which case the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** • Avoid concomitant treatment with potent CYP3A inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin, grapefruit juice) or strong or moderate inducers (e.g. rifampicin, dexamethasone, phenytoin, carbamazepine and St John's wort) or CYP3A4 substrates with narrow therapeutic indices. Avoid using in combination with other bradycardic agents *(*e.g. beta-blockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin*),* medicinal products that are known to prolong QT interval and/or antiarrhythmics. - see SPC for a full list of drug interactions. • The effectiveness of concomitant administration of oral contraceptives may be reduced. • **Driving:** Patients should be advised to be cautious when driving or using machines in case they experience fatigue, vision disorder or symptomatic bradycardia during treatment. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Cancerbackup information sheet.
Reference(s)	KMCC protocol LUN-027 V5 SPC accessed online 24.02.2025 CDF list accessed online 24.02.2025

NB for funding information, refer to CDF and NICE Drugs Funding List

Table 1. Crizotinib dose modification – non-haematological toxicities

CTCAE Grade	**Crizotinib treatment**
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. Discontinue in case of further Grade ≥3 recurrence.
Grade 2, 3 or 4 ALT or AST elevation with concurrent Grade 2, 3 or 4 total bilirubin elevation (in the absence of cholestasis or haemolysis)	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 [c]
Grade 3 QTc prolongation	Withhold until recovery to Grade ≤1, check and if necessary correct electrolytes, then resume at 200 mg twice daily. Discontinue in case of further Grade ≥3 recurrence.
Grade 4 QTc prolongation	Permanently discontinue
Grade 2, 3 Bradycardia (Heart rate less than 60 beats per minute (bpm)). 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 (bpm)). 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. Permanently ddiscontinue in case of recurrence.
Grade 4 Ocular Disorder (Visual Loss)	Discontinue during evaluation of severe vision loss

Repeat every 28 days

TTO	Drug	Dose	Route	Directions
Day 1	**CRIZOTINIB**	**250mg**	PO	**Twice daily taken continuously**. Swallow whole with a glass of water. **Do not take with grapefruit juice.** **Available as 200mg and 250mg capsules in a pack size of 60**
	Metoclopramide	10mg	PO	TDS when required (dispense 28 tablets on cycle 1, then only if specified). Do not take for more than 5 days continuously.