CRIZOTINIB

For the treatment of anaplastic lymphoma kinase (ALK) +ve advanced NSCLC patients who have received at least one previous line of treatment.
For first-line use in adults with untreated anaplastic lymphoma kinase (ALK) +ve advanced NSCLC

Blueteq registration required before treatment with crizotinib may start

Drug/Dosage: **Crizotinib** initiate at 250mg po twice daily as continuous therapy

Administration: Crizotinib is available as 250mg and 200mg capsules. The capsules should be swallowed whole with some water, with or without food, at about the same time each day. Grapefruit and grapefruit juice should be avoided while on crizotinib.

Frequency: continuous therapy until progression or unacceptable toxicity.

Main Toxicities: vision disorders and dizziness; oedema; diarrhoea or constipation; rash; increased ALT; neutropenia; pneumonitis; QT interval prolongation

Anti- emetics: mildly emetogenic

Regular:	FBC	every 4 weeks
Investigations:	LFTs	once weekly for the first 2 months (may be reduced to every 2 weeks for the second month if no problems with raised LFTs), then every 4 weeks
	U&Es	every 4 weeks
	CT scan	every 3 months
	ECG / QTc	required for patients at risk only; check pre-treatment, then after 1 month, then as indicated (see Dose Modifications)
	Pulse &	}
	Blood pressure	} baseline, then each clinic visit for the first 2 months, then as indicated

Interactions: Elimination of crizotinib is mainly through hepatic metabolism, with CYP3A4/5 being the major enzymes involved in its metabolism.

Concomitant use of strong CYP3A inducers (e.g. phenytoin, rifampicin, carbamazepine, dexamethasone, barbiturates, St John's Wort) with crizotinib should be avoided, as this may increase the risk of therapeutic failure.

Co-administration of crizotinib with strong CYP3A inhibitors (e.g. itraconazole, clarithromycin) should also be avoided. If this is not possible, the patient needs to be closely monitored for crizotinib adverse reactions. Grapefruit should also be avoided for this reason.

Crizotinib is also a moderate inhibitor of CYP3A. Therefore, co-administration of crizotinib with CYP3A substrates with a narrow therapeutic index (e.g. alfentanil, ciclosporin, fentanyl, quinidine, sirolimus and tacrolimus) should be avoided. If the combination is needed, then close clinical monitoring should be exercised.

Of note, the effectiveness of oral contraceptives may be altered.

Dose Modifications

Haematological Toxicity:	Neutrophils 0.5 – 0.9 x 10^9/l or Platelets 25 – 49 x 10^9/l	Withhold crizotinib until neutrophils ≥ 1.0 x 10^9/l and platelets ≥ 50 x 10^9/l, then re-start at the same dose.

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Prepared by: S Taylor	Checked by: C Tucker

Neutrophils < 0.5 x 10^9/l or Platelets < 25 x 10^9/l	Withhold crizotinib until neutrophils ≥ 1.0 x10^9/l and platelets ≥ 50 x 10^9/l, then re-start at 200mg bd dose. (If this recurs, re-start at 250mg once daily dose.)

QT Prolongation: As QTc prolongation has been observed, crizotinib should be administered with caution to patients who have a history of or predisposition for QTc prolongation, or who are taking other medicines known to prolong the QT interval. When using crizotinib in these patients, periodic monitoring with ECGs and electrolytes, is advised as in the Regular Investigations section:

QTc interval (milliseconds)	Management
> 500 ms	Withhold crizotinib until QTc interval ≤ 480 ms. Seek advice from cardiology, and consider re-starting crizotinib at 200mg bd. (If it recurs, re-start at 250mg once daily dose)
> 500 ms **and** accompanied by life-threatening signs, or Torsade de pointes	Permanently discontinue crizotinib

Examples of medicines known to prolong the QT interval include anti-arrhythmics, ondansetron, domperidone, clarithromycin, erythromycin, venlafaxine.
Check with pharmacy if you require information on any other drugs.

Bradycardia:

Grade 2 or 3 Pulse less than 60 beats per minute (bpm) Symptomatic, may be severe and medically significant, medical intervention indicated	Withhold crizotinib until asymptomatic and heart rate ≥ 60 bpm. Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume crizotinib at previous dose. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery.
Grade 4 Pulse less than 60 bpm Life-threatening consequences, urgent intervention indicated	Permanently discontinue crizotinib if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume crizotinib at 250 mg once daily, with frequent monitoring, upon recovery and heart rate ≥ 60 bpm.

Pneumonitis: Crizotinib should be withheld if pneumonitis is suspected, and must be permanently discontinued if treatment-related pneumonitis is diagnosed.

Hepatic Impairment: Crizotinib should be used with extra caution in patients with mild or moderate hepatic impairment, and is not recommended in patients with severe hepatic impairment.

During treatment, if ALT or AST rises to > 5 x ULN with bilirubin ≤ 1.5 x ULN, withhold crizotinib until ALT / AST ≤ 3 x ULN. Then re-start crizotinib at 200mg bd.
(If it recurs, re-start at 250mg once daily dose.)

During treatment, if ALT or AST rises to > 3 x ULN **and** bilirubin > 1.5 x ULN, permanently discontinue crizotinib.

Renal Impairment:

CrCl (ml/min)	Crizotinib starting dose
≥ 30	250mg bd
< 30 and not requiring dialysis	250mg once daily. After 4 weeks of treatment, if well tolerated, the dose may be increased to 200mg bd.

Reference: Shaw, AT et al; NEJM 2013 ; 368 : 2385 – 2394 (2nd line)
Solomon, B et al ; NEJM 2014 ; 371 : 2167 – 2177 (1st line)

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