CRIZOTINIB (XALKORI®) for ALK+ve advanced or metastatic NSCLCCRIZOTINIB (XALKORI®) for ALK+ve advanced or metastatic NSCLC

NHS Northern Cancer Alliance

DRUG ADMINISTRATION SCHEDULE

Day	Cycle length	Drug	Daily Dose	Route
Days 1 to 28	4 weeks	**Crizotinib**	250mg twice daily	Oral

DOSE FREQUENCY
Clinical review after 2 weeks after starting, then every 4 weeks. Continue for as long as there is clinical benefit, or unacceptable toxicity.

APROVED INDICTIONS
Crizotinib is recommended, within its marketing authorisation, as an option for treatment of anaplastic lymphoma kinase-positive (ALK+ve) advanced non-small-cell lung cancer in adults.

ANTI-EMETICS AND SUPPORTIVE MEDICINES
Anti-emetics are not routinely required

INVESTIGATIONS / MONITORING REQUIRED
- FBC every month
- LFTs every 2 weeks for 2 months, then monthly
- U&Es every 4 weeks
- CT scan every 3 months
- ECG/QT interval performed by cardiology – required for patients at risk only; check pre-treatment, then after 1 month, then as indicated (See dose modifications)
- Heart rate and blood pressure every 4 weeks.

REVIEW BY CLINICIAN
Review at each cycle as appropriate

NURSE / PHARMACIST LED REVIEW
Each cycle as applicable according to local protocols

ADMINISTRATION NOTES
- 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
- 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, ketoconazole, 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.

MAIN TOXCITIES

- Vision disorders and dizziness
- Oedema
- Diarrhoea and constipation
- Rash
- Increased ALT
- Neutropenia
- Pneumonitis
- QT interval prolongation
- Bradycardia

DOSE MODIFICATIONS

Haematological Toxicity

Neutrophils > 0.5 and < 1.0 x 10^9/L **OR** Platelets >25 and < 50 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
Neutrophils < 0.5 x 10^9/L **OR** Platelets < 25 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 200mg bd dose. (if this recurs, wait until counts have recovered again, then re-start at 250mg once daily dose).

Hepatic Impairment

- Crizotinib has not been studied in patients with 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 ≤ 2.5 x ULN. Then re-start crizotinib at 200mg twice daily (In case of recurrence, re-start at 250mg once daily).
- During treatment, if ALT or AST rises to > 2.5 x ULN and bilirubin > 1.5 x ULN, permanently discontinue crizotinib.

Renal Impairment

No starting dose adjustment is required in patients with CrCl ≥ 30ml/min. No data is available in patients with creatinine clearance < 30ml/min so no dosing recommendation can be made for these patients.

Pneumonitis

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

QT Prolongation

- If QTC interval > 500ms (milliseconds), withhold crizotinib until QTC interval ≤ 470ms.

Seek advice from cardiology, and consider re-starting crizotinib at 200mg bd. (In case of recurrence, re-start at 250mg once daily dose).

- If QTC interval > 500ms 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.

Bradycardia

- If heart rate <60 beats per minute, withhold crizotinib until recovery to a heart rate of 60 beats per minute (bpm) or above or asymptomatic (grade ≤1) bradycardia.
- If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, reinitiate crizotinib at the previous dose upon recovery to a heart rate of 60 beats per minute (bpm) or above or asymptomatic (grade ≤1) bradycardia.
- If no contributing concomitant medicinal product is identified, or if contributing concomitant medicinal products are not discontinued or dose modified, reinitiate crizotinib at reduced dose upon recovery to a heart rate of 60 beats per minute (bpm) or above or asymptomatic (grade ≤1) bradycardia.
- If life-threatening bradycardia, permanently discontinue crizotinib 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.

EXTRAVASATION Not Applicable

TREATMENT LOCATION

Cancer Centre or Cancer Unit.

REFERENCES:

1. Crizotinib (XALKORI®) - Summary of Product Characteristics SPC. Date: April 2014. Available at http://www.medicines.org.uk/emc/medicine/27168 Last accessed 04/10/17
2. Crizotinib versus Chemotherapy in Advanced ALK-Positive Lung Cancer; Shaw et al. N Engl J Med 2012; 367:1187-1197

Document Control

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