Crizotinib (NSCLC)

Indication
Second line (or subsequent) treatment of anaplastic lymphoma kinase (ALK) positive advanced or metastatic non-small cell lung cancer (NSCLC).

(Funding via CDF)

ICD-10 codes
Codes with a prefix C34

Regimen details

Day	Drug	Dose	Route
1-28	Crizotinib	250mg BD	PO

Cycle frequency
Continuously until disease progression or unacceptable toxicity.

Number of cycles
As above

Administration
Crizotinib is available as 250mg and 200 mg capsules.
The capsules should be swallowed whole with a glass of water, with or without food, at about the same time each day. If a patient misses a dose it should be taken as soon as the patient remembers, unless it is less than 6 hours until the next dose is due, in which case they should omit the dose.

Grapefruit and grapefruit juice should be **avoided** whilst taking crizotinib.

Pre-medication
Nil

Emetogenicity
This regimen has low emetic potential (no routine antiemetics required)

Additional supportive medication
Nil

Extravasation
N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local practice)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days

ECG for patients with significant cardiac risk, pre-treatment and then monthly or as clinically indicated.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local practice)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days

LFTs should be monitored every 2 weeks for the first 2 months and then monthly (or as clinically indicated) thereafter.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L
Creatinine clearance (CrCl)	≥ 30mL/min
AST/ALT	< 2.5 x ULN
Bilirubin	< 1.5 x ULN

Dose modifications

- **Haematological toxicity**

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Dose adjustment**
0.5-0.9	or	25-49	Withhold until recovery and recommence at same dose
< 0.5	or	< 25	Withhold until recovery and recommence at 200mg BD (if reoccurs then wait until recovery and recommence at 250mg OD)

- **Renal impairment**

Plasma concentration of crizotinib may be increased in patients with severe renal impairment (CrCl < 30 mL/min). In patients not requiring dialysis, the starting dose should be reduced to 250mg OD. This may be increased to 200mg BD depending on tolerability after a minimum of 4 weeks treatment.

- **Hepatic impairment**

Crizotinib is mainly excreted via hepatic metabolism. It has not been studied in patients with hepatic impairment. Use with caution in mild-moderate hepatic impairment and avoid in patients with severe hepatic impairment.

During treatment if AST/ALT rises to > 5 x ULN with bilirubin <1 x ULN withhold until AST/ALT ≤ 2.5 x ULN then recommence at a dose of 200mg BD. (If reoccurs recommence at 250mg OD). If AST/ALT rises to > 2.5 x ULN and bilirubin rises to > 1.5 x ULN discontinue treatment.

- **Other toxicities**

QT prolongation:

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 (see interactions below). When using crizotinib in these patients, periodic monitoring of ECG and electrolytes is advised:

- If QTc interval > 500 ms (milliseconds), withhold crizotinib until QTc interval < 470 ms. Seek advice from cardiology, and consider re-starting crizotinib at 200mg BD. (If reoccurs recommence at 250mg OD).
- If QTc interval > 500 ms **and** accompanied by life-threatening signs, or Torsade de pointes, permanently discontinue crizotinib.

Pneumonitis:

Crizotinib should be withheld if pneumonitis is suspected, and must be permanently discontinued if treatment-

related pneumonitis is diagnosed.

Bradycardia:
Grade 2-3 symptomatic bradycardia: withhold until heart rate ≥ 60. If any contributing medication identified, discontinue this and recommence on previous dose. If no contributing medication recommence on reduced dose.
Grade 4 life threatening bradycardia: withhold until complete recovery. If any contributing medication identified, discontinue this and recommence at dose of 250mg OD. If no contributing medication, permanently discontinue.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Pneumonitis
QT prolongation
Myelosuppression
GI perforation

- **Frequently occurring side effects**

Visual disturbances
Bradycardia
Oedema
Diarrhoea, constipation
Rash
Anorexia
Elevated LFTs

- **Other side effects**

Fatigue

Significant drug interactions – for full details consult product literature/ reference texts

Coumarin anticoagulants, e.g. warfarin: Avoid if possible as may cause elevation and fluctuation in INR. Consider switching to low molecular weight heparin.
Medications which prolong the QT interval (e.g. anti-arrhythmics, ondansetron, domperidone, clarithromycin, erythromycin, venlafaxine) use with caution and close monitoring (see above).
CYP3A inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin): avoid co-administration these may increase plasma concentrations of crizotinib.
Inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration as these may reduce exposure to crizotinib.
Grapefruit and grapefruit juice: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of crizotinib.
CYP3A substrates with a narrow therapeutic index (e.g. alfentanil, ciclosporin, fentanyl, quinidine, sirolimus and tacrolimus) should be avoided as crizotinib is a moderate inhibitor of CYP3A. If this is not possible, then close monitoring is required.
Bradycardic agents (e.g. beta blockers, calcium channel blockers, digoxin) use with caution due to risk of excessive bradycardia.

Additional comments

Crizotinib may alter the effectiveness of the oral contraceptive pill.

References

- Summary of Product Characteristics – Crizotinib (Pfizer) accessed 25 Sept 2014 via www.medicines.org.uk
- NHS England Cancer Drug Fund List. Accessed 25 Sept 2014 via www.england.nhs.uk
- Shaw, AT et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. NEJM. 2013. 368 (25) p2385-94

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