LONDON CANCER ALLIANCE West and South

Lung Pathway Group – Crizotinib in Non-Small Cell Lung Cancer (NSCLC)

Indication:	Treatment option in previously treated Anaplastic Lymphoma Kinase (ALK) positive advanced NSCLC
NCDF criteria	ALK +ve advanced or metastatic non-small cell lung cancer 2nd or subsequent line treatment post 1st line combination chemotherapy Eligible for patients able to tolerate and comply with oral dosage forms.
Regimen details:	Crizotinib 250mg PO Twice daily continuously
Administration:	Crizotinib available as 200mg and 250mg hard capsules. Swallow whole. Take with or without food
Frequency:	Dosing is continuous, until disease progression or unacceptable toxicity
Pre-medication:	Not routinely required
Anti- emetics:	Minimal emetogenicity Follow local anti-emetic policy
Supportive medication:	Diarrhoea can be managed with loperamide. Mouthcare as per local policy. Various approaches may be considered to deal with skin reactions including rash, acne type reactions, erythema/ pruritus, dryness or blistering (topical emollients, cleansers or possibly anti-infective creams). Urea containing creams may be beneficial to treat dry skin. Support use of non-deodorant, non-fragrance products. Consider

Version: 2.0 Supersedes: all other versions	Approved by LCA Lung Pathway Chemotherapy Lead: Ro Lal 15/12/2015
Reason for Update: MHRA update	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla and Rebecca Johl 21/01/2016
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Second check by: Lisa Yuen 09/12/15	Date prepared: December 2015 Review Date: December 2017

products with anti-itch additions in pruritus, and exfoliating products in hyperkeratosis. Anti-dandruff shampoo may help in management of itchy scalp. Analgesia may help but a 1-2 week dose interruption may be necessary for painful and severe symptoms. Rashes usually resolve rapidly upon cessation of treatment.

Extravasation: Not applicable

Regular investigations:

Prior to Cycle 1:	
ALK or ROS1 assay	
FBC	Day 1 (within 14 days)
LFTs (incl. AST, ALT)	Day 1 (within 14 days)
U&Es	Day 1 (within 14 days)
Imaging	Baseline
ECG	Baseline and periodic monitoring as clinically indicated
LFTs (incl. AST, ALT)	Every 2 weeks for the first 2 cycles
Prior to Day 1 (all cycles):	
FBC	Monthly
LFTs (incl. AST, ALT)	Monthly
U&Es	Monthly
Imaging	After 3 months

Toxicities: Hepatic failure and increased transaminases, risk of QT prolongation, heart failure, neutropenia, pneumonia, visual effects, nausea, vomiting, decreased appetite, diarrhoea, oedema, constipation, fatigue, neuropathy, dysgeusia.

DOSE MODIFICATIONS

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability.
If dose reductions are necessary, then the dose of Crizotinib should be reduced to **200mg twice daily**.
If further dose reduction is necessary, then reduce to **250mg once daily**.

Haematological Toxicity

Any haematological toxicity (except lymphopenia)	Dose Modification Algorithms
Grade 1 or 2 (Platelets ≥ 50 x 10^9/L), (Neut ≥ 1.0 x 10^9/L)	Continue treatment at same dose; monitor as clinically indicated.
Grade 3 (Platelets 25- 49 x 10^9/L), (Neut 0.5- 0.9 x 10^9/L)	Step 1. Interrupt treatment until toxicity reduced to ≤ Grade 2 (Platelets > 50 x 10^9/L), (Neut > 1.0 x 10^9/L) Step 2. Restart treatment at same dose.
Grade 4 (1^{st} & 2^{nd} occurrence) (Platelets < 25 x 10^9/L), (Neut < 0.5 x 10^9/L)	Step 1. Interrupt treatment until toxicity reduced to ≤ Grade 2 (Platelets > 50 x 10^9/L), (Neut > 1.0 x 10^9/L) Step 2. Restart treatment with lower dose
Grade 4 further recurrence	Discontinue permanently

Non-haematological Toxicities

Renal Impairment

No dose adjustment is recommended for patients with mild (creatinine clearance 60 to 90 ml/min) and moderate renal impairment (CrCl 30 to 60 ml/min).
Studies have excluded patients with calculated CrCl <30ml/min. Discuss the management of the treatment for such patients with the consultant.

Hepatic Impairment

Crizotinib should be used with caution in patients with mild and moderate hepatic impairment. See table below for dose modifications.
Crizotinib should not be used in severe hepatic impairment.

Dose modifications for other toxicities as appropriate

Pneumonitis

Crizotinib has been associated with severe, life-threatening, or fatal treatment-related pneumonitis in clinical trials. All of these cases occurred within 2 months after the initiation of treatment. Patients with pulmonary symptoms indicative of pneumonitis should be monitored and treatment withheld if pneumonitis is suspected. Other causes of pneumonitis should be excluded, and crizotinib should be permanently discontinued in patients diagnosed with treatment-related pneumonitis. (see table below).

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Cardiotoxicity

QTc prolongation has been observed, which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de Pointes) or sudden death. The risk of QTc prolongation may be increased in patients concomitantly taking antiarrhythmics and in patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances (e.g., secondary to diarrhoea or vomiting). 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 (see table below).

The MHRA have produced a drug safety update due to reports of severe and sometimes fatal cases of heart failure in patients treated with crizotinib. Patients should be monitored for signs of heart failure including dyspnoea, oedema or rapid weight gain from fluid retention. Consider reducing the dose, or interrupting or stopping treatment if symptoms of heart failure occur.

Non-haematological Toxicity:	**Dose Modification Algorithms**
AST or ALT > 5.0 x ULN and Bilirubin ULN < 1.5 x ULN	Step 1. Interrupt treatment until toxicity reduced to ≤Grade 1 or baseline. (AST or ALT ≤ 3.0 x ULN, Bilirubin ≤ 1.5 x ULN) Step 2. Restart treatment with lower dose. If recurrence of toxicity, discontinue. Step 3. In 3rd recurrence, discontinue permanently.
AST or ALT > 3.0 x ULN and Bilirubin > 1.5 x ULN (in the absence of cholestasis or hemolysis)	Discontinue permanently
Any grade, treatment related pneumonitis	Discontinue permanently
Grade 3 QTc prolongation QTc >= 501 ms on at least two separate ECGs	Step 1. Interrupt treatment until toxicity reduced to ≤Grade 1 (QTc 450 - 480 ms) Step 2. Restart treatment with lower dose.
Grade 4 QTc prolongation QTc >= 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Discontinue permanently

Location of regimen delivery: Outpatient setting

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Comments:

To be supplied to the patient for oral self-administration.
Ensure that the patient has an information pack and the treatment plan.
Adequate contraception methods to be applied during and at least 90 days after therapy. The effectiveness of concomitant administration of oral contraceptives may be altered with crizotinib.

Drug interactions:

Caution with a history of QT interval prolongation or relevant pre-existing cardiac disease, and concurrent antiarrhythmics or other medicines that may prolong the QT interval / bradycardic agents e.g.

- non-dihydropyridine calcium channel blockers e.g. verapamil & diltiazem
- beta-blockers
- clonidine
- guanfacine
- digoxin
- mefloquine
- anticholinesterases
- pilocarpine

CYP3A4 inducers can decrease crizotinib plasma concentration and reduce efficacy:	CYP3A4 inhibitors can increase crizotinib plasma concentration and increase toxicity:
phenytoin	ketoconazole
carbamazepine	itraconazole
rifampicin	erythromycin
barbiturates	clarithromycin
dexamethasone	grapefruit juice
St John's Wort	

The inhibitory effect of crizotinib on UGTs, notably UGT1A1, is not established. Therefore, caution should be exercised when crizotinib and substrates of UGTs, such as paracetamol or morphine are combined.
Administration of crizotinib with medicinal products that are substrates of P-gp (e.g., digoxin, dabigatran, colchicine, pravastatin) may increase their therapeutic effect and adverse reactions. Close clinical surveillance is recommended when crizotinib is administered with these medicinal products.

References:

Pfizer ltd. 2013. Summary of product characteristics: Xalkori (crizotinib). Available at www.medicines.org.uk [accessed 21/01/2014]

Kwak E.L. (2010);NEJM 363(18): 1693-1703

MHRA Drug Safety Update: Crizotinib (Xalkori): Risk of cardiac failure (12 November 2015)

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