CRIZOTINIB (Xalkori)

INDICATION (ICD10) C34

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (CRI1) (CRI3)

1. Crizotinib monotherapy for anaplastic lymphoma kinase-positive rearrangement locally advanced or metastatic non-small cell lung cancer previously untreated with an ALK inhibitor. The patient is 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. No known brain metastases or if the patient has brain metastases, the patient is symptomatically stable prior to starting crizotinib. PS 0, 1 or 2. (TA422)
2. Crizotinib monotherapy for 1st or subsequent line systemic therapy for ROS1-positive rearrangement inoperable locally advanced/metastatic stage IIIB or stage IV non squamous non-small cell lung cancer, no previous ROS1-targeted therapy. No known brain metastases or if the patient has brain metastases, the patient is symptomatically stable prior to starting crizotinib. PS 0, 1 or 2.

REGIMEN

CRIZOTINIB 250mg orally twice daily continuously

CYCLE FREQUENCY AND NUMBER OF CYCLES

Until disease progression. A formal medical review as to whether treatment with crizotinib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment.

ADMINISTRATION

Available as 200mg and 250mg capsules
Swallow whole with food.
Grapefruit and grapefruit juice and Seville Oranges should be avoided while on crizotinib.

ANTI-EMETICS

Low risk

CONCURRENT MEDICATION REQUIRED

Crizotinib	None required

EXTRAVASATION AND TYPE OF LINE / FILTERS

Not applicable

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E every cycle
LFTs every 2 weeks for 2 cycles then every cycle
Neutrophils x 10^9/L ≥1.0
Platelets x 10^9/L ≥50
Creatinine every cycle
Baseline ECG
Baseline weight

MAIN TOXICITES AND ADVERSE REACTIONS

Crizotinib	Increased LFTs Diarrhoea QT prolongation Interstial lung disease

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Crizotinib	Strong CYP3A inducers and inhbitorsm- use of these drugs are cautioned with the use of ceritinib eg ketoconazole, ritonavir, itraconazole, voriconazole and posaconazole. QT prolongation use with caution in patients who have or may develop prolongation of the QT interval eg patients taking anti-arrhythmics, domperidone, droperidol, clarithromycin, amiodarone, haloperidol and methadone. Avoid grapefruit and Seville oranges, and St Johns wort.

DOSE MODIFICATIONS

Level	Crizotinib dose
Starting dose	250mg twice daily
First dose reduction	200mg twice daily
Second dose reduction	250mg once daily

Haematological
Crizotinib

Grade 3	Withhold until recovery to grade ≤2, then resume at the same dose schedule.
Grade 4	Withhold until recovery to grade ≤2, then resume at the next lower dose. In case of recurrence, dosing should be withheld until recovery to grade ≤2, then dosing should be resumed at 250mg once daily. crizotinib must be permanently discontinued in case of further grade 4 recurrence. For patients treated with 250mg once daily or whose dose was reduced to 250mg once daily, discontinue during evaluation.

Non-haematological

Crizotinib

Cardiac

Grade 3 QTc prolongation	Withhold until recovery to grade ≤1, check and if necessary correct electrolytes, then resume at the next lower dose.
Grade 4 QTc prolongation	Permanently discontinue
Grade 2, 3 bradycardia 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 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 250mg once daily upon recovery to grade ≤1 or to heart rate 60 or above, with frequent monitoring.

Hepatotoxicity

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 250mg once daily and escalate to 200mg twice daily if clinically tolerated.
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

Interstitial lung disease (ILD) / Pneumonitis

Any grade interstitial lung disease (ILD)/pneumonitis	Withhold if ILD/pneumonitis is suspected, and permanently discontinue if treatment related ILD/pneumonitis is diagnosed.

Ocular disorder (visual loss)

Grade 4	Discontinue during evaluation of severe vision loss.

Hepatic impairment

Crizotinib starting dose

Any ALT or AST and total bilirubin elevation >1.5 to ≤3xULN	200mg bd
Any ALT or AST and total bilirubin elevation >3xULN	250mg od

Renal impairment

Crizotinib

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

REFERENCES

1. Shaw, A et al; NEJM 2013; 368: 2385–2394 (2nd line)
2. Solomon, B et al; NEJM 2014; 371: 2167–2177 (1st line)
3. Shaw, A et al; Annals of Oncology 2016; 27 suppl 6 (ROS-1)