ALECTINIB

Available via an MHRA EAMS for first-line use in adults with untreated anaplastic lymphoma kinase (ALK) +ve advanced NSCLC
Blueteq registration required before treatment may start in this setting

Available via a compassionate use programme for third line use in patients with ALK+ve advanced NSCLC who have previously failed treatment (either progressed, or intolerant) with both crizotinib and ceritinib

Drug/Dosage: **Alectinib** initiate at 600mg po twice daily as continuous therapy

Administration: Alectinib is available as 150mg capsules. The capsules should be swallowed whole with food.
If a dose is missed, patients can make up that dose unless the next dose is due within 6 hours. Patients should not take two doses at the same time to make up for a missed dose. If vomiting occurs after a dose, patients should take the next dose at the scheduled time.

Frequency: continuous therapy until progression or unacceptable toxicity.

Main Toxicities: oedema (including peripheral oedema and periorbital oedema); constipation or diarrhoea; myalgia; rash or photosensitivity; hepatotoxicity; bradycardia; vision disorders; anaemia

Anti- emetics: mildly emetogenic

Regular:	FBC	every 4 weeks
Investigations:	LFTs	every 2 weeks for the first 3 months, then every 4 weeks
	U&Es	every 4 weeks
	CPK	Creatine phosphokinase levels every 2 weeks for the first month, then as indicated in patients reporting symptoms
	Pulse & Blood pressure	} baseline, then at each clinic visit for the first 2 months, then as indicated
	CT scan	every 3 months

Comments: Photosensitivity reactions are very common, so patients should avoid prolonged sun exposure while on alectinib, and for at least 7 days after stopping. Advise patients to use a sunscreen and lip balm (SPF ≥ 50) in sunny weather.

Interactions: Elimination of alectinib is mainly through hepatic metabolism, with CYP3A4 enzyme being significantly involved in its metabolism.
However, **no** dose adjustment is required when used concomitantly with strong CYP3A inducers (e.g. phenytoin, rifampicin, carbamazepine, dexamethasone, barbiturates, St John's Wort) or inhibitors (e.g. itraconazole, clarithromycin).

Dose Modifications

Dose reduction schedule	Dose level
Starting dose	600 mg twice daily
First dose reduction	450 mg twice daily
Second dose reduction	300 mg twice daily

Reason for Update: comp use programme in 3rd line setting	Approved by Consultant: Dr A Mehta
Version: 2	Approved by Lead Chemotherapy Nurse: S Wills-Percy
Supersedes: Version 1	Date: 11.10.17
Prepared by: S Taylor	Checked by: C Tucker

Hepatotoxicity:

LFTs	Management
ALT / AST > 5 x ULN with Bilirubin ≤ 2 x ULN	Temporarily withhold alectinib until ALT / AST recovery to baseline or ≤ 3 x ULN. Then resume at reduced dose.
ALT / AST > 3 x ULN with Bilirubin > 2 x ULN in the absence of cholestasis or haemolysis	Permanently discontinue alectinib

Bradycardia:

Grade 2 or 3 Pulse less than 60 beats per minute (bpm) Symptomatic, may be severe and medically significant, medical intervention indicated	Withhold alectinib 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 alectinib at previous dose. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume alectinib at reduced dose upon recovery.
Grade 4 Pulse less than 60 bpm Life-threatening consequences, urgent intervention indicated	Permanently discontinue alectinib if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume alectinib at a reduced dose, with frequent monitoring, upon recovery and heart rate ≥ 60 bpm. Permanently discontinue in case of recurrence.

Myalgia:

CPK levels	Management
CPK > 5 x ULN (> 1600iu/l)	Temporarily withhold until recovery to baseline or to ≤ 2.5 x ULN, then resume at the same dose.
CPK > 10 x ULN (> 3200iu/l) or 2nd occurrence of CPK > 5 x ULN	Temporarily withhold until recovery to baseline or to ≤ 2.5 x ULN, then resume at reduced dose as table above.

Pneumonitis: Alectinib should be withheld if pneumonitis is suspected, and must be permanently discontinued if treatment-related pneumonitis or interstitial lung disease is diagnosed.

Hepatic Impairment: Advice for before treatment is started (see above for Hepatotoxicity advice):
No dose adjustment is required in mild hepatic impairment. It has not been studied in moderate to severe hepatic impairment, and so is not recommended in these patients.

Renal Impairment: Alectinib elimination via the kidney is negligible, so no dose adjustment is required in patients with severe renal impairment.

Reference: Peters, S et al ; NEJM 2017 ; 377 : 829 - 838