Alectinib

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

(NICE TA 536)

ICD-10 codes
Codes with a prefix C34

Regimen details

Day	Drug	Dose	Route
1-28	Alectinib	600mg BD	PO

Cycle frequency
28 days, i.e. continuous.

Number of cycles
Continuous until disease progression or unacceptable toxicity.

Administration
Alectinib is available as 150mg capsules. Capsules should be swallowed whole and taken with food.

If a planned dose is missed, patients should be advised to take the dose if it is more than 6 hours until the next dose is due. If it is less than 6 hours the dose should be missed. Patients should not take two doses at the same time to make up for a missed dose. If vomiting occurs after taking a dose, patients should not take an extra dose and take the next dose at the scheduled time.

Pre-medication
Nil

Emetogenicity
This regimen has mild emetic potential.

Additional supportive medication
Not routinely required.

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+Es (including creatinine)	14 days
LFTs	14 days
CPK	14 days
Blood pressure	Baseline
Heart rate	Baseline

A validated ALK assay is necessary for the selection of ALK-positive NSCLC patients. ALK-positive NSCLC status must be established prior to initiation of alectinib.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Monthly
U+Es (including creatinine)	Monthly
LFTs	Every 2 weeks for the first 3 months, monthly thereafter
CPK	Every 2 weeks for the first month, monthly or as clinically indicated thereafter
Blood pressure and heart rate	As clinically indicated

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	≥ 100 x 10^9/L
ALT/AST	< 3 x ULN
Bilirubin	< 2 x ULN
CPK	< 5 x ULN

Dose modifications

Management of adverse events may require dose reduction, temporary interruption, or discontinuation of treatment. The dose should be reduced in steps of 150 mg twice daily based on tolerability as per table below:

Dose level	Dose
Full dose	600mg BD
First dose reduction	450mg BD
Second dose reduction	300mg BD

Treatment should be permanently discontinued if patients are unable to tolerate the 300 mg twice daily dose.

- **Haematological toxicity**

Discuss with consultant if neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L
Alectinib is not myelosuppressive. Patients may continue to take during periods of mild myelosuppression.

- **Renal impairment**

No dose adjustment is required in patients with mild or moderate renal impairment. Alectinib has not been studied in patients with severe renal impairment. However, since alectinib elimination via the kidney is negligible, no dose adjustment is required in patients with severe renal impairment.

- **Hepatic impairment**

No starting dose adjustment is required in patients with underlying mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Patients with underlying severe hepatic impairment (Child-Pugh C) should receive a starting dose of 450 mg BD. For all patients with hepatic impairment close monitoring of LFTs is recommended.

See below for management of hepatotoxicity.

- **Other toxicities**

Interstitial lung disease (ILD)/pneumonitis:
Patients should be closely monitored for pulmonary symptoms. If symptoms of ILD/pneumonitis of any grade develop, treatment should be withheld and if no other cause is identified Alectinib should be permanently discontinued.

Hepatotoxicity:
Hepatotoxicity usually occurs within the first 3 months of treatment, although can occur after this time period.
If ALT/AST > 5 x ULN and bilirubin ≤ 2 x ULN: withhold treatment until recovery to ALT/AST ≤ 3 x ULN or baseline and then continue with one dose level reduction.

If ALT/AST > 3 x ULN and bilirubin > 2 times ULN: permanently discontinue treatment.

Myalgia and CPK elevation:
Patients should be advised to report any unexplained muscle pain, tenderness, or weakness.
If CPK > 5 x ULN: withhold until ≤ 2.5 x ULN or baseline and then continue with same dose.
If second occurrence or CPK > 10 x ULN: withhold until ≤ 2.5 x ULN or baseline and then continue with one dose level reduction.

Bradycardia:
Heart rate and blood pressure should be monitored as clinically indicated. Dose modification is not required in cases of asymptomatic bradycardia.
If symptomatic bradycardia (Grade 2-3): withhold until asymptomatic or heart rate ≥ 60bpm. Review concomitant medication including antihypertensives. If contributing concomitant medication identified and discontinued or dose reduced, continue with same dose on recovery. If no other cause identified continue with one dose level reduction on recovery.

If life-threatening bradycardia: Review concomitant medication including antihypertensives. If contributing concomitant medication identified and discontinued or dose reduced, continue with one dose level reduction on recovery. If no other cause identified or if recurrence permanently discontinue alectinib.

Photosensitivity:
Patients should be advised to avoid prolonged sun exposure and use broad spectrum sun screen and lip balm during treatment and for at least 7 days after discontinuation of treatment.

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

- **Serious side effects**

ILD and pneumonitis
Bradycardia
Myalgia
Hepatotoxicity

- **Frequently occurring side effects**

Anaemia
Dysgeusia
Visual disorders
Constipation, diarrhoea
Nausea, vomiting
Stomatitis
Oedema
Weight gain

- **Other side effects**

Rash
Photosensitivity
Raised creatinine

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

Strong CYP3A inducers (including carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort): no dose adjustments required but close monitoring is recommended.

Strong CYP3A inhibitors (including ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole nefazodone, grapefruit or Seville oranges): no dose adjustments required but close monitoring is recommended.

P-gp substrates (including digoxin, dabigatran etexilate, topotecan, sirolimus, everolimus, nilotinib and lapatinib): potential to increase plasma level of P-gp substrate – close monitoring recommended.

BCRP substrates (including methotrexate, mitoxantrone, topotecan and lapatinib): potential to increase plasma level of BCRP substrate – close monitoring recommended.

The effectiveness of oral contraceptives may be reduced.

Use with caution with agents which may also cause bradycardia.

Additional comments

Alectinib may cause foetal harm when administered to a pregnant woman. Female patients of child-bearing potential must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, a congenital lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

References

- Summary of Product Characteristics Alectinib (Roche) accessed 4 September 2019 via www.medicines.org.uk
- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 536 accessed 4 September 2019 via www.nice.org.uk
- Peters, S., et al. Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer. N Engl J Med 2017; 377:829-838.

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