Ceritinib (Zykadia®) for 2nd line treatment of ALK+ve advanced or NSCLC after Crizotinib

NHS Northern Cancer Alliance

DRUG ADMINISTRATION SCHEDULE

Day	Cycle length	Drug	Daily Dose	Route
Days 1 to 28	4 weeks	**Ceritinib**	450mg Once daily	Oral

Ceritinib is available as 150mg hard capsules. The capsules should be swallowed whole with some water on an empty stomach (no food should be eaten for at least two hours before and two hours after the dose is taken) at about the same time each day.

DOSE FREQUENCY

Clinical review after 2 weeks after starting, then every 4 weeks. continue for as long as there is clinical benefit, or unacceptable toxicity.

APROVED INDICTIONS

Ceritinib is recommended, within its marketing authorisation, as an option for treating advanced anaplastic lymphoma kinase positive non-small-cell lung cancer in adults who have previously progressed during or after crizotinib treatment.

ANTI-EMETICS AND SUPPORTIVE MEDICINES

Anti-emetics are not routinely required

INVESTIGATIONS / MONITORING REQUIRED

- FBC every month
- LFTs every 2 weeks for 2 months, then monthly
- U&Es every 4 weeks
- CT scan every 3 months
- ECG/QT interval performed by cardiology – required for patients at risk only; check pre-treatment, then after 1 month, then as indicated (See dose modifications)
- Heart rate and blood pressure every 4 weeks.
- Fasting blood glucose prior to treatment, then periodically as clinically indicated.
- Lipase & amylase prior to treatment, then periodically as clinically indicated.

REVIEW BY CLINICIAN

Review at each cycle as appropriate

NURSE / PHARMACIST LED REVIEW

Each cycle as applicable according to local protocols

ADMINISTRATION NOTES

- Elimination of Ceritinib is mainly through hepatic metabolism, with CYP3A being the major enzymes involved in its metabolism
- Concomitant use of strong CYP3A inducers (e.g. phenytoin, rifampicin, carbamazepine, dexamethasone, barbiturates, St John's Wort) with ceritinib should be avoided, as this may increase the risk of therapeutic failure.
- Co-administration of ceritinib with strong CYP3A inhibitors (e.g. itraconazole, ketoconazole, clarithromycin) should also be avoided as they will increase plasma concentration of Ceritinib. If this is not possible, reduce the ceritinib dose by approximately one third, rounded to the nearest multiple of the 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, resume the ceritinib dose that was taken prior to initiating the strong CYP3A inhibitor.

- Ceritinib is also a moderate inhibitor of CYP3A. Therefore, co-administration of Ceritinib with CYP3A substrates with a narrow therapeutic index (e.g. alfentanil, ciclosporin, fentanyl, quinidine, sirolimus and tacrolimus) should be avoided. If the combination is needed, then close clinical monitoring should be exercised.
- Ceritinib is a substrate of the efflux transporter P-glycoprotein (P-gp). If ceritinib is administered with medicinal products that inhibit P-gp, an increase in ceritinib concentration is likely. Caution should be exercised with concomitant use of P-gp inhibitors and ADRs carefully monitored.
- The bioavailability of ceritinib is increased in the presence of food depending on the fat content in the meal. Ceritinib should be taken on an empty stomach. No food should be eaten for at least two hours before and one hour after the dose is taken.

MAIN TOXCITIES

- Liver Laboratory Test Abnormalities
- Fatigue
- Nausea
- Hyperglycaemia.
- Decreased appetite
- Diarrhoea and constipation
- Rash
- Neutropenia
- Pneumonitis
- Dyspepsia, gastro-oesophageal reflux
- QT interval prolongation
- Bradycardia

DOSE MODIFICATIONS

- Dose reduction is achieved by decrements of 150 mg daily, first dose reduction to 300mg daily, second dose reduction to 150mg daily.
- Discontinue in patients unable to tolerate 150 mg daily.
- Approximately 54% of patients initiating treatment at the recommended dose of 750 mg required at least one dose adjustment due to adverse reaction, with a median time to first dose reduction of approximately 7 weeks.

Haematological Toxicity

Neutrophils < 1.0 x 10^9/l **OR** Platelets < 50 x 10^9/l	Withhold Ceritinib until neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L, then re-start at the same dose
Neutrophils < 0.5 x 10^9/l **OR** Platelets < 25 x 10^9/l	Withhold Ceritinib until neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L, then re-start with dose reduced by 150mg once counts have recovered.

Hepatic Impairment

Ceritinib has not been studied in patients with hepatic impairment. Ceritinib should be used with extra caution in patients with mild or moderate hepatic impairment, and is not recommended in patients with severe hepatic impairment.

ALT	Bilirubin	Action
>5 times ULN	≤2 times ULN	Withhold ceritinib until recovery to baseline or ≤3 times ULN, then reinitiate with dose reduced by one decrement.
>3 times ULN	>2 times ULN	Permanently discontinue.

Renal Impairment
No starting dose adjustment is required in patients with CrCl ≥ 30ml/min. No data is available in patients with creatinine clearance < 30ml/min so no dosing recommendation can be made for these patients.

Pneumonitis
Ceritinib should be withheld if pneumonitis is suspected, and must be permanently discontinued if treatment related pneumonitis is diagnosed.

QT Prolongation
- If QTC interval > 500ms (milliseconds), withhold ceritinib until QTC interval ≤ 480 ms. Seek advice from cardiology, and consider re-starting ceritinib, reinitiating with dose reduced by one decrement.
- If QTC interval > 500ms or > 60 msec change from baseline and accompanied by life threatening signs, or Torsade de pointes, permanently discontinue ceritinib.
- Examples of medicines known to prolong the QT interval include anti-arrythmics, ondansetron, domperidone, clarithromycin, erythromycin, venlafaxine.

Bradycardia
- If heart rate <60 beats per minute, withhold ceritinib until recovery to a heart rate of 60 beats per minute (bpm) or above or asymptomatic (grade ≤1) bradycardia.
- If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, reinitiate ceritinib at the previous dose upon recovery to a heart rate of 60 beats per minute (bpm) or above or asymptomatic (grade ≤1) bradycardia.
- If no contributing concomitant medicinal product is identified, or if contributing concomitant medicinal products are not discontinued or dose modified, reinitiate ceritinib with dose reduced by one decrement upon recovery to a heart rate of 60 beats per minute (bpm) or above or asymptomatic (grade ≤1) bradycardia.
- If life-threatening bradycardia, permanently discontinue ceritinib.

Hyperglycaemia
Blood glucose greater than 14mmol/L, despite optimal glucose control - withhold ceritinib until hyperglycaemia is adequately controlled, then reinitiate with dose reduced by one decrement.

Pancreatitis
Lipase or amylase elevation to Grade 3 or 4, withhold until returns to grade ≤1, then re-start with dose reduced by one decrement.

EXTRAVASATION Not Applicable

TREATMENT LOCATION
Cancer Centre or Cancer Unit.

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REFERENCES:

1. Summary of Product Characteristics Ceritinib (Zykadia) https://www.medicines.org.uk/emc/medicine/30882 Last accessed 09/08/2016
2. Ceritinib for previously treated anaplastic lymphoma kinase positive non small-cell lung cancer. Technology appraisal guidance. NICE. Published: 22 June 2016 https://www.nice.org.uk/guidance/ta395
3. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Kim DW, Mehra R, Tan DS, Felip E, Chow LQ, Camidge DR et al. Lancet Oncol. 2016 Apr;17(4):452-63. doi: 10.1016/S1470-2045(15)00614-2.

Document Control

Document Title:	Ceritinib (Zykadia®) for 2nd line treatment of ALK+ve advanced or NSCLC after Crizotinib		
Document No:	CRP15 L025	**Current Version:**	1.2
Reviewer:	Chris Beck Chemotherapy Pharmacist Northern Cancer Alliance	**Date Approved:**	07.02.19
Approved by:	Steve Williamson Consultant Pharmacist Northern Cancer Alliance	**Due for Review**	07.02.22
Summary of Changes	1.0	Draft Issued	
	1.1	Updated & finalised	
	1.2	Updated with revised dosing information	