Ceritinib

Indication
Treatment of anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) in patients who have previously received crizotinib.

(NICE TA395)

ICD-10 codes
Codes with a prefix C34.

Regimen details

Day	Drug	Dose	Route
1-28	Ceritinib	450mg OD	PO

Cycle frequency
Continuously until disease progression or unacceptable toxicity.

Number of cycles
As above.

Administration
Ceritinib is available as 150mg capsules.
The capsules should be taken with food (from a light meal to a full meal) at the same time each day.

If a patient misses a dose it should be taken as soon as the patient remembers, unless it is less than 12 hours until the next dose is due, in which case they should omit the dose. If a patient vomits, they should not take an additional dose but should continue with the next schedules dose.

Grapefruit and grapefruit juice should be **avoided** whilst taking ceritinib.

Pre-medication
Nil

Emetogenicity
This regimen has low emetic potential (no routine antiemetics required)

Additional supportive medication
Nil

Extravasation
N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local practice)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Fasting glucose	Baseline
Lipase and amylase	Baseline

ECG at baseline and then as clinically indicated.

ALK positive status must be confirmed prior to treatment commencing.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local practice)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Fasting glucose	As clinically indicated
Lipase and amylase	As clinically indicated

LFTs should be monitored every 2 weeks for the first three months and then monthly thereafter.

Standard limits for administration to go ahead

If blood results are not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 0.5 x 10^9/L
Platelets	≥ 50 x 10^9/L
Creatinine clearance (CrCl)	≥ 30mL/min
AST/ALT*	< ULN
Bilirubin *	< 1.5 x ULN

*see below for information regarding increased LFTs during treatment

Dose modifications

Doses should be reduced by 150mg increments. Doses should not be reduced below 150mg OD. If patient is unable to tolerate 150mg OD, treatment should be discontinued.

- **Haematological toxicity**

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Dose adjustment**
≥ 0.5	and	≥ 50	Full dose
< 0.5	or	25-49	Withhold until recovery. If recovery within 7 days recommence at same dose, if > 7 days reduce dose by 150mg.
		< 25	Withhold until recovery. Reduce dose by 150mg.

If febrile neutropenia, omit until clinically resolved and then resume with 150mg dose reduction.

- **Renal impairment**

No dose adjustment necessary in mild-moderate renal impairment. Use with caution in severe renal impairment – discuss with the consultant.

- **Hepatic impairment**

Ceritinib is mainly excreted via hepatic metabolism. It has not been studied in patients with hepatic impairment. Use with caution in mild hepatic impairment and avoid in patients with moderate-severe hepatic impairment.

During treatment if AST/ALT rises to > 5 x ULN with bilirubin ≤ 2 x ULN withhold until AST/ALT ≤ 3 x ULN then recommence at a 150mg dose reduction. Close monitoring of LFTs is required. If AST/ALT rises to > 3 x ULN **and** bilirubin rises to > 2 x ULN discontinue treatment.

- **Other toxicities**

QT prolongation:
Ceritinib should be administered with caution to patients who have a history of or predisposition for QTc prolongation, or who are taking other medicines known to prolong the QT interval (see interactions below). When using ceritinib in these patients, periodic monitoring of ECG and electrolytes is advised:

- If QTc interval > 500 ms (milliseconds) on at least 2 separate ECGs, withhold ceritinib until QTc interval < 480 ms, correct any electrolyte abnormalities and recommence with one dose level reduction.
- If QTc interval > 500 ms or > 60 ms change from baseline **and** accompanied by life-threatening signs of serious arrhythmia or Torsade de pointes or polymorphic ventricular tachycardia, permanently discontinue ceritinib.

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

Bradycardia:
Grade 2-3 symptomatic bradycardia: withhold until heart rate ≥ 60 beats per minute. If any contributing medication identified, discontinue this and recommence on previous dose. If no contributing medication recommence with 150mg dose reduction.

Grade 4 life threatening bradycardia: withhold until complete recovery. If any contributing medication identified, discontinue this and recommence with 300mg dose reduction with frequent monitoring. If no contributing medication or reoccurrence, permanently discontinue.

Nausea, vomiting or diarrhoea:
Grade 3 (despite antiemetics/antidiarrhoeals): withhold until improved, then recommence with 150mg dose reduction.

Hyperglycaemia:
Persistent hyperglycaemia (greater than 13.9mmol/L) despite antihyperglycaemics): withhold until adequate control, then recommence with 150mg dose reduction. If adequate control cannot be achieved then permanently discontinue.

Elevation in lipase or amylase:
≥ Grade 3 elevations in lipase or amylase: withhold until ≤ grade 1 and then recommence with 150mg dose reduction.

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

- **Serious side effects**

Pneumonitis
QT prolongation
Bradycardia
Myelosuppression
GI perforation
Hepatotoxicity

- **Frequently occurring side effects**

Visual disturbances
Bradycardia
Oedema
Nausea and vomiting
Diarrhoea, constipation
Rash
Anorexia
Abdominal pain
Anaemia
Elevated LFTs
Increased creatinine
Hyperglycaemia

- **Other side effects**

Fatigue
Elevations in lipase and/or amylase, pancreatitis
Hypophosphataemia
Pericarditis

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

Coumarin anticoagulants, e.g. warfarin: Avoid if possible as may cause elevation and fluctuation in INR. Consider switching to low molecular weight heparin.
Medications which prolong the QT interval (e.g. anti-arrhythmics, ondansetron, domperidone, clarithromycin, erythromycin, venlafaxine) use with caution and close monitoring (see above).
CYP3A inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin): avoid co-administration these may increase plasma concentrations of ceritinib. If concomitant use is unavoidable reduce ceritinib dose by 33% to the nearest 150mg (dose not clinically verified, use at the consultants discretion) and closely monitor.
Inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration as these may reduce exposure to ceritinib.
Grapefruit and grapefruit juice: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of ceritinib.
CYP3A substrates (midazolam, diclofenac): ceritinib may inhibit clearance.
CYP3A substrates with a narrow therapeutic index (e.g. alfentanil, ciclosporin, fentanyl, quinidine, sirolimus and tacrolimus) should be avoided as ceritinib is an inhibitor of CYP3A. If this is not possible, then close monitoring is required.
P-gp inhibitors: likely to increase ceritinib concentration: use with caution and close monitoring for adverse effects.
Bradycardic agents (e.g. beta blockers, calcium channel blockers, digoxin) use with caution due to risk of excessive bradycardia.
H_2 antagonists and **antacids**: do not take at the same time as ceritinib. H_2 antagonists should be administered 10 hours before or 2 hours after ceritinib and antacids 2 hours before or 2 hours after the dose.
PPIs: use with caution, may reduce exposure to ceritinib.

Additional comments

Women of childbearing potential should be advised to use a highly effective form of contraception during and for 3 months after completion of treatment.

Ceritinib should be taken with food. The bioavailability of ceritinib is increased in the presence of food. For patients unable to take the dose with food refer to product literature for dose adjustments for administration in a fasted state.

References

- Summary of Product Characteristics – Ceritinib (Novartis) accessed 13 June 2018 via www.medicines.org.uk
- National Institute for Health and Clinical Excellence TA395. Accessed 13 June 2018 via www.nice.org.uk
- Alice T. Shaw, et al. Ceritinib in ALK-rearranged non-small cell lung cancer. N Engl J Med 2014; 370:1189-1197
- Mok, T. et al. ASCEND-2: a single-arm, open-label, multicenter Phase 2 study of ceritinib in adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) previously treated with chemotherapy and crizotinib (CRZ). Abstract #8059. 2015 American Society of Clinical Oncology (ASCO) Annual Meeting.

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