Systemic Anti Cancer Treatment Protocol

Ceritinib
Non-Small Cell Lung Cancer

PROTOCOL REF: MPHACERILU
(Version No: 2.1)

This protocol has been temporarily amended-please see the ORAL SACT OPERATIONAL CHANGES DURING COVID -19

Amendments may include less frequent blood monitoring, telephone SACT assessments and longer durations of treatment being dispensed.

Approved for use in:

Ceritinib is recommended as a **1st line option** for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive stage IIIB or IV non-small cell lung cancer (NSCLC) where the following conditions are met:

- The patient has received no previous ALK-targeted therapy
- The patient has received no previous cytotoxic chemotherapy for locally advanced or metastatic NSCLC i.e. no previous systemic treatment except when this has been given as neoadjuvant or adjuvant therapy or concurrently with radiotherapy
- Performance status must be 0-2.
- The patient either has no brain metastases or, if the patient has brain metastases, the patient is symptomatically stable prior to starting ceritinib

Ceritinib is recommended as a **2nd line option** for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive stage IIIB or IV non-small cell lung cancer (NSCLC) only after crizotinib treatment; where disease has progressed during or after therapy.

Blueteq registration required

Starting Dosage:

Drug	Dosage	Route	Frequency
Ceritinib	450mg	Oral	Once daily

If a dose is missed, the patient should make up that dose, unless the next dose is due within 12 hours. Treatment will be supplied every 28 days.

Note: the tablets are available as 150mg film-coated tablets and therefore the standard dose is 3 x 150mg tablets. Please ensure that the patient can swallow this amount of treatment before prescribing.

Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity.

Supportive treatments:

Loperamide 2 to 4mg four times a day as required for management of diarrhoea. Max: 16mg in 24 hours.

Extravasation risk:

Oral therapy therefore not applicable

Administration:

- Ceritinib should be administered orally once daily at the same time every day.
- The tablets should be swallowed whole with water and should not be chewed or crushed.
- If vomiting occurs during the course of treatment, the patient should not take an additional dose, but should continue with the next scheduled dose
- **The tablets must be taken with food.** It is important that ceritinib is taken with food to reach the appropriate exposure. Food can range from a light to a full meal (note if patient is unable to take ceritinib with food then the dose may need adjusting and may differ to the doses recommended in this protocol. Please consult SPC or discuss with a pharmacist for details and advice).

Drug Interactions

Ceritinib is a substrate for CYP3A/PgP and is affected by strong CYP3A inducers and inhbitors. Avoid concomitant use of strong CYP3A inhibitors. If it is not possible to avoid concomitant use with strong CYP3A inhibitors (including, but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole and nefazodone), 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.

Co-administration of ceritinib with strong CYP3A/P-gp inducers decreases ceritinib plasma concentrations. Concomitant use of strong CYP3A inducers should be avoided; this includes, but is not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort (*Hypericum perforatum*).

Caution should be exercised with concomitant use of P-gp inducers.

Co-administration of ceritinib with substrates primarily metabolised by CYP2C9 or CYP2C9 substrates known to have narrow therapeutic indices (e.g. phenytoin and warfarin) should be avoided. If unavoidable, dose reduction for co-administered medicinal products that are CYP2C9 substrates with narrow therapeutic indices should be considered. Increasing the frequency of international normalised ratio (INR) monitoring may be considered if co-administration with warfarin is unavoidable.

QT prolongation has been observed with ceritinib in clinical studies. Therefore, ceritinib should be used with caution in patients who have or may develop prolongation of the QT interval, including those patients taking anti-arrhythmics or other medicinal products that may lead to QT prolongation, such as domperidone, droperidol, clarithromycin, amiodarone, haloperidol, methadone, chloroquine and moxifloxacin. Monitoring of the QT interval is indicated in the event of combinations of such medicinal products.

Ceritinib should be taken with food. The bioavailability of ceritinib is increased in the presence of food.

Patients should be instructed to avoid grapefruit and grapefruit juice as they may inhibit CYP3A in the gut wall and may increase the bioavailability of ceritinib

Please consult SPC for full list of interactions: available via medicines.org.uk or discuss with a pharmacist.

Main Toxicities:

Diarrhoea, nausea, vomiting, fatigue, liver laboratory test abnormalities, abdominal pain, decreased appetite, constipation, rash, blood creatinine increased, QT prolongation, gastric reflux, oesophageal disorder, weight decrease and anaemia.

Investigations and Treatment Plan:

	Pre	Cycle 1	Cycle 1 Day 14	Cycle 2	Cycle 2 Day 14	Cycle 3	Cycle 3 Day 14	Cycle 4	Ongoing
Medical Assessment	X			X		X			Every three cycles
Nursing Assessment	X	X	X	X		X		X	Every cycle
FBC	X	X		X		X		X	Every cycle
U&E & LFT (including CK)	X	X	X	X	X	X	X	X	Every two weeks during the first three months then monthly thereafter
LDH		x	x	x		x		x	Every cycle
Lipid profile		x		x		x			Every cycle
Amylase and/or lipase		X		X				X	As clinically indicated
CT scan	X					X*			*CT scan to be carried out prior to cycle 3 then every three months or as clinically indicated
Informed Consent	X								
ECG	X					X			ECG to be carried out at baseline and then on cycle 3 at medical assessment, then as clinically indicated
Blood Glucose	X								Repeat if clinically indicated
Blood pressure measurement	X								Repeat if clinically indicated
PS recorded	X	X	X	X		X		X	Every cycle
Toxicities documented	X	X	X	X		X		X	Every cycle
Weight recorded	X	X		X		X		X	Every cycle

Dose Modifications and Toxicity Management:

Haematological toxicity

Ceritinib is not myelosuppressive; however, FBC should be reviewed prior to each cycle and clinical team notified if neutrophil count is below 1.0 x 10^9/L or platelets below 100 x 10^9/L. Treatment can continue.

Non-haematological toxicities

Any patient with a grade 3 or 4 toxicity not controlled by optimum supportive care will require a dose reduction as per the table below.

Level	Ceritinib dose
Starting Dose	450mg daily
1st Reduction	300mg daily
2nd Reduction	150mg daily

If 150mg daily is not tolerated then treatment should be discontinued

Cardiac

Toxicity	Ceritinib dose
QTc > 500 msec on at least 2 separate ECGs	Withhold ceritinib until recovery to baseline or to a QTc ≤480 msec. Correct electrolyte abnormalities, then reinitiate with a dose reduction of one decrement
QTc > 500 msec or > 60 msec change from baseline and torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue ceritinib.

Bradycardia[a] (symptomatic, may be severe and medically significant, medical intervention indicated)	Withhold ceritinib until recovery to grade ≤1 bradycardia or to a heart rate of 60 bpm or above. Evaluate concomitant medicines known to cause bradycardia and/or anti-hypertensives. If a contributing medicine is identified and adjusted reinitiate ceritinib at the previous dose. If no contributing medicine is identified, or dose modified, reinitiate ceritinib with dose reduced by one decrement upon recovery.
Bradycardia[a] (life-threatening consequences, urgent intervention indicated)	Permanently discontinue ceritinib if no contributing concomitant medicine is identified. If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, reinitiate ceritinib with dose reduced by two decrements upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring[b].

[a] Heart rate less than 60 beats per minutes (bpm)

[b] Permanently discontinue in the event of recurrence.

Other

Toxicity	Ceritinib dose
Any grade treatment-related pneumonitis	Permanently discontinue ceritinib.
Severe (grade 3) or intolerable nausea, vomiting or diarrhoea despite optimal anti-emetic or anti-diarrhoeal therapy	Withhold ceritinib until improved. Then reinitiate ceritinib with dose reduced by one decrement.
Persistent hyperglycaemia greater than 250 mg/dL despite optimal anti-hyperglycaemic therapy	Withhold ceritinib until hyperglycaemia is adequately controlled, then reinitiate ceritinib with dose reduced by one decrement. If adequate glucose control cannot be achieved with optimal medical management, permanently discontinue ceritinib
Lipase or amylase elevation grade ≥3	Withhold ceritinib until lipase or amylase returns to grade ≤1, then reinitiate with dose reduced by one decrement.

Other supportive medicines

Consider adding ondansetron 4mg orally twice daily if patient reports nausea and or vomiting grade 2 or above. Please note ondansetron may also cause QT prolongation- use with caution.

Hepatic Impairment

Toxicity	Ceritinib dose
ALT or AST elevation >5 times ULN with total bilirubin ≤2 times ULN	Withhold ceritinib until recovery to baseline or ≤3 times ULN, then reinitiate with dose reduced by one decrement.
ALT or AST elevation >3 times ULN with concurrent total bilirubin elevation >2 times ULN	Permanently discontinue ceritinib

Raised LFTs occur in less than 1% of patients; however it is important that LFTs are monitored as per the investigations and treatment plan.

No dose adjustments required for mild to moderate hepatic impairment.

Particular caution should be exercised when treating patients with severe hepatic impairment and the dose should be reduced by approximately one third, rounded to the nearest multiple of the 150 mg dosage strength.

Renal Impairment

No dose adjustments are required in patients with mild to moderate renal impairment.

There is limited data for patients with severe renal impairment, and treatment in patients with CrCl <30mL/min is not recommended

References:

NICE TA 395 Ceritinib for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer. Published 22nd of June 2016

NICE TA 500 Ceritinib for untreated ALK-positive non-small-cell lung cancer. Published 24th of January 2018

https://www.medicines.org.uk/emc/