North West Coast
Strategic Clinical Networks

Chemotherapy Protocol

DRUG REGIMEN
Ceritinib

Indication for use
ALK positive advanced or metastatic Non-Small Cell Lung Cancer

Regimen
Ceritinib 450mg daily until disease progression or intolerable side effects

Treatment is continuous but cycles are defined as 28 days
Treatment should be continued until disease progression or unacceptable toxicity

Investigation prior to initiating treatment
ALK, FBC, U&Es, LFTs

Cautions
Use in caution in patients with mild to moderate hepatic impairment. Reduce dose by one third in patients with severe hepatic impairment
Use in caution in patients with pre-existing cardiac disease or who are taking medicines known to prolong the QT interval
Ceritinib may interact with other medication which induces or inhibits cytochrome-P450
H_2 antagonists or antacids must not be taken at the same time as ceritinib. PPIs should be used with caution

Investigations and consultations prior to each cycle
FBC, U&Es
Check LFTs every 2 weeks for the first 3 months of treatment then monthly thereafter. In patients who develop transaminase elevations, more frequent monitoring of LFTs should be carried out.

Acceptable levels for treatment to proceed (if outside these levels defer one week or contact consultant)
Neutrophils >0.5, Platelets >50

Side Effects
Vision disorder, nausea, diarrhoea, vomiting, oedema, constipation, fatigue, hepatotoxicity, pneumonitis

Dose Modification Criteria

Dose reduction steps for Ceritinib

Dose levels	Dose* and schedule
Starting dose level	450 mg daily continuously
Dose level – 1	300 mg daily continuously
Dose level – 2	150 mg daily continuously**

*Dose reduction should be based on the worst preceding toxicity as per NCI-CTCAE version 4.03
**Dose reduction below 150mg/day is not allowed. If a dose reduction below 150mg/day is required, the patient should be permanently discontinued from ceritinib

General Guidelines

- For grade 1 and tolerable grade 2 treatment-related toxicities, with the exception of pneumonitis, patients may continue at the current dose of ceritinib treatment
- For intolerable grade 2 treatment-related toxicities or any grade 3 toxicities dosing should be interrupted until resolution to grade 1 or lower followed by dose reduction to the next dose level
- For any grade 4 toxicity, dosing should be interrupted and the patients should be followed until the toxicity resolves to baseline levels, grade 1, or become stable. Following recovery from grade 4 events, **no additional ceritinib treatment** should be given to the patient unless specified below

Worst toxicity (CTCAE 4.03 Grade)*	Dose Modifications for Ceritinib
HEMATOLOGICAL	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 109/L)	Maintain dose level
Grade 2 (ANC < 1.5 and ≥ 1.0 x 109/L)	
Grade 3 (ANC < 1.0 and ≥0.5 x 109/L)	
Grade 4 (ANC < 0.5 x 109/L)	Omit dose until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓1 dose level
Febrile neutropenia (ANC < 1.0 x 109/L, with a **single** temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour)	Omit dose until clinically resolved and neutropenia ≤ Grade 2, then ↓1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 109/L)	Maintain dose level
Grade 2 (PLT < 75 and ≥ 50 x 109/L)	
Grade 3 (PLT < 50 and ≥ 25 x 109/L)	If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓1 dose level
Grade 4 (PLT < 25 x 109/L)	Omit dose until resolved to ≤ Grade 2, then ↓1 dose level
HEPATIC	
Alkaline phosphatase and/or Gamma-glutamyl transpeptidase (GGT)	
Isolated elevations of any grade	Maintain dose level
Total Bilirubin** (for patients with Gilbert Syndrome these dose modifications apply to changes in direct (conjugated) bilirubin only)	
Grade 1 (> ULN and ≤ 1.5 x ULN)	Maintain dose level with LFTs*** monitored as per treatment plan
Grade 2 (> 1.5 and ≤ 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 and ≤ 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days discontinue patient from ceritinib

Grade 4 (> 10.0 x ULN)	Permanently discontinue patient from ceritinib
AST or ALT	
Grade 1 (> ULN and ≤ 3.0 x ULN)	Maintain dose level with LFTs*** monitored per treatment plan
Grade 2 (> 3.0 and ≤ 5.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Maintain dose level with LFTs*** monitored per treatment plan
Grade 3 (> 5.0 and ≤ 20.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ Grade 1, then ↓1 dose level
Grade 4 (> 20.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ Grade 1, then ↓1 dose level
AST or ALT and concurrent Total Bilirubin	
AST or ALT > 3.0 x ULN with total bilirubin > 2.0 x ULN in the absence of cholestasis or hemolysis	Permanently discontinue patient from ceritinib
RENAL	
Serum creatinine	
Grade 1 (>ULN and < 1.5 x ULN)	Maintain dose level
Grade 2 (≥ 1.5 and ≤ 3 x ULN)	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓1 dose level
Grade 3 (> 3.0 and ≤ 6.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then ↓1 dose level
Grade 4 (> 6.0 x ULN)	Permanently discontinue patient from ceritinib
GASTROINTESTINAL	
Diarrhea**	
Grade 1	Maintain dose level but adjust anti-diarrhea treatment
Grade 2 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, and then maintain dose level. If diarrhea returns as ≥ Grade 2, then omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 3 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Nausea***	
Grade 1 or 2	Maintain dose level but adjust anti-emetic treatment
Grade 3 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Vomiting***	
Grade 1	Maintain dose level but adjust anti-emetic treatment
Grade 2 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, and then maintain dose level. If vomiting returns as ≥ Grade 2, then suspend dose until resolved to ≤ Grade 1, then ↓ 1 dose level.
Grade 3 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
METABOLIC	
Any Grade **hypophosphatemia**	Treatment with phosphate supplements as clinically indicated and maintain dose level
Persistent **hyperglycaemia >250 mg/dL** (despite optimal anti-hyperglycaemic therapy)	Omit dose until hyperglycemia is adequately controlled then resume ceritinib at ↓ 1 dose level If adequate hyperglycemic control cannot be achieved with optimal medical management permanently discontinue patient from ceritinib
CARDIAC INVESTIGATIONS	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTc 450-480 ms)	Maintain dose level
Grade 2 (QTc 481-500 ms)	Maintain dose level
Grade 3 (QTc ≥ 501 ms on at least two separate ECGs)	Omit dose until QTC is less than 481 ms or recovery to baseline if baseline QTC is ≥481 ms and then ↓□1 dose level
Grade 4 (QTc ≥ 501 or > 60ms change from baseline	Permanently discontinue patient from ceritinib

and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	
BRADYCARDIA	
Grade 1 or Grade 2	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm Evaluate concomitant medications known to cause bradycardia and adjust the dose of ceritinib
Grade 3 Grade 4 (in patients taking a concomitant medication also known to cause bradycardia or a medication known to cause hypotension)	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm If the concomitant medication can be adjusted or discontinued, resume ceritinib at ↓ 1 dose level with frequent monitoring
Grade 4 (in patients who are not taking a concomitant medication also known to cause bradycardia or known to cause hypotension)	Permanently discontinue ceritinib
Pulmonary	
Notes: ● Withhold ceritinib for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnoea, cough and fever and during diagnostic workup for pneumonitis/ILD. ● During evaluation of potential grade 2, 3, and 4 pneumonitis, if an infectious aetiology is confirmed (i.e., pneumonia) and pneumonitis is excluded, then consider resuming ceritinib at current dose level after the pneumonia resolves.	
Pneumonitis	
Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for ceritinib**
Any Grade treatment-related ILD /pneumonitis	Permanently discontinue patient from ceritinib
GENERAL DISORDERS	
Fatigue (asthenia)	
Grade 1 or 2	Maintain dose level
Grade 3	If grade 3 fatigue resolves to Grade 2 in ≤ 7 days, maintain dose level If grade 3 fatigue lasts > 7 days, omit dose until resolved to ≤ Grade 2 and then↓ dose level

* Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All dose modifications should be based on the worst preceding toxicity.
** If Grade 3 or 4 hyperbilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the Treating Physician
***Liver function tests include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase and GGT
**** Dose modifications apply to patients who experience diarrhoea despite appropriate antidiarrheal medication. This medication should be started at the first sign of abdominal cramping, loose stools or overt diarrhoea
***** Dose modifications apply to patients who experience nausea and/or vomiting despite appropriate antiemetic medication. This medication should be started at the first sign of nausea and/or vomiting

Specific Information on Administration

Ceritinib must be taken at approximately the same time each day
It is essential that Ceritinib be taken with food to ensure sufficient absorption of the drug.
For patients who are unable to take Ceritinib with food, consult the SPC for alternative dosing regimen
Patients should avoid grapefruit and grapefruit juice
Patients must not make up missed or partial doses. If the patient vomits after taking a dose, no re-dosing is allowed.

This protocol has been reviewed by the Lancashire & South Cumbria Lung Oncology Consultants' Group and responsibility for the template lies with the Head of Service.

Date: July 2018

Next review: July 2020