Lancashire & South Cumbria Cancer Network
Systemic Anticancer Treatment Protocol

DRUG REGIMEN
Brigatinib

Indication for use
For treating anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) in adults who have already had crizotinib.

Regimen
The recommended starting dosage of brigatinib is 90 mg once daily for the first 7 days, then 180 mg once daily. Treatment should continue as long as there is clinical benefit.

If brigatinib treatment is interrupted for 14 days or longer for reasons other than adverse reactions, treatment should be resumed at 90 mg once daily for 7 days before increasing to the previously tolerated dose.

Cautions
Hepatic Impairment: No dose adjustment is required in patients with mild or moderate hepatic impairment (ChildPugh A or B). A reduced starting dose of 60mg od for the first 7 days, then 120mg od, is recommended for patients with severe hepatic impairment (Child-Pugh C).

Renal Impairment: No dose adjustment is necessary in patients with CrCl ≥ 30ml/min. If CrCl < 30ml/min, start at 60mg od for the first 7 days (monitoring closely for new or worsening respiratory symptoms), then increase to 90mg od if tolerated.

Investigations prior to initiating treatment
FBC, U&E, LFTs, Glucose, CPK, Lipase, Amylase, HR & BP

Investigations and consultations prior to each cycle

FBC	every 4 weeks
LFTs	every 2 weeks for the first 3 months, then every 4 weeks
U&Es	every 4 weeks
Glucose	baseline, after 4 weeks, then as indicated
Creatine phosphokinase	baseline, then every 4 weeks initially, then as indicated
Lipase & amylase	every 4 weeks
Blood pressure & pulse	baseline, at 2 weeks, then every 4 weeks, then as indicated

Side Effects
Most common side effects are nausea, diarrhoea, fatigue, cough, headache, rash, hypertension, bradycardia, elevated creatine phosphokinase, raised pancreatic enzymes, hyperglycaemia, hepatotoxicity, myalgia, peripheral neuropathy, reduced WBC, anaemia Most common serious side effects include pneumonitis / ILD; pneumonia; dyspnoea

Dose Modification Criteria

If dose reduction required, then reduce as follows:

- If patient on 90mg, reduce to 60mg, if further reduction needed then discontinue permanently
- If patient on 180mg, reduce to 120mg, then to 90mg, then to 60mg, then discontinue permanently
- Once dose reduced for adverse reactions, do not subsequently increase the dose

Adverse Reaction	Severity	Dose Modification
ILD/pneumonitis	Grade 1	If new pulmonary symptoms occur during the first 7 days of treatment, withhold brigatinib until recovery to baseline, then resume at same dose and do not escalate to 180mg if ILD/pneumonitis is suspected. If new pulmonary symptoms occur after the first 7 days of treatment, withhold brigatinib until recovery to baseline, then resume at same dose. If ILD/pneumonitis recurs, permanently discontinue.
	Grade 2	If new pulmonary symptoms occur during the first 7 days of treatment, withhold brigatinib until recovery to baseline. Resume at next lower dose and do not escalate if ILD/pneumonitis is suspected. If new pulmonary symptoms occur after the first 7 days of treatment, withhold brigatinib until recovery to baseline, then resume at next lower dose level. If ILD/pneumonitis recurs, permanently discontinue.
	Grade 3	Permanently discontinue
Hypertension	Grade 3 hypertension (systolic BP ≥ 160mmHg or diastolic BP ≥ 100mmHg), medical intervention indicated, more than one anti-hypertensive drug, or more intensive therapy indicated	Withhold brigatinib until hypertension has recovered to < Grade 1 (< 140/90mmHg), then resume at same dose. Recurrence: withhold brigatinib until recovery to Grade 1 or less, and resume at next lower dose or permanently discontinue treatment.
	Grade 4 hypertension (life-threatening consequences, urgent intervention needed)	Withhold brigatinib until recovery to ≤ Grade 1 (< 140/90mmHg), and then resume at next lower dose or permanently discontinue treatment. Recurrence: permanently discontinue.
Bradycardia (pulse < 60 bpm)	Grade 2 or 3 Pulse < 60 bpm Symptomatic, may be severe and medically significant, medical intervention indicated	Withhold brigatinib until asymptomatic and HR ≥ 60 bpm Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If continuing concomitant medication is identified and discontinued, or its dose is adjusted, resume brigatinib at same dose upon recovery. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume brigatinib at next lower dose upon recovery
	Grade 4 Pulse < 60 bpm Life threatening consequences, urgent	Permanently discontinue brigatinib if no contributing concomitant medication is identified.

	intervention needed	
Hepatotoxicity	ALT or AST > 5 X ULN with bilirubin ≤ 2 x ULN	Withhold brigatinib until recovery to baseline or ≤ 3 x ULN, then resume at next lower dose
	ALT or AST > 3 x ULN with concurrent bilirubin > 2 x ULN in the absence of cholestasis or haemolysis	Permanently discontinue
Visual Disturbance	Grade 2 or 3	Withhold until recovery to Grade 1 or baseline, then restart at next lower dose
	Grade 4	Permanently discontinue
CPK elevation	Grade 3 >5 x ULN	Withhold brigatinib until recovery to ≤ Grade 1 (≤2.5 x ULN) or to baseline, then resume at lower next dose. Recurrence: withhold until recovery, then resume at lower next dose.
	Grade 4 >10 x ULN Or recurrence of Grade 3 elevation	Withhold brigatibinb until recovery to ≤ Grade 1 (≤2.5 x ULN) or to baseline, then resume at next lower dose
Lipase/ Amylase elevation	Grade 3 Lipase or Amylase elevation > 2 x ULN	Withhold brigatinib until recovery to ≤ 1.5 x ULN or to baseline, then resume at next lower dose.
	Grade 4 Lipase or Amylase elevation > 5 x ULN or recurrence of G3 elevation	Withhold brigatinib until recovery to ≤ 1.5 x ULN or to baseline, then resume at next lower dose
Hyperglycaemia	Grade 3 (≥ 14 mmol/L)	If adequate hyperglycaemic control cannot be achieved with optimal medical management, withhold brigatinib until adequate control is achieved and then consider reduction at next lower dose, or permanently discontinue.
Other	Grade 3	Withhold brigatinib until recovery to baseline, then resume at next lower dose. Recurrence: withhold brigatinib until recovery to baseline, then resume at next lower dose or discontinue
	Grade 4	Withhold brigatinib until recovery to baseline, then resume at next lower dose. Recurrence: discontinue

Specific Information on Administration

Brigatinib is available as 30mg, 90mg and 180mg tablets. The tablets should be swallowed whole with some water at about the same time each day, with or without food. Grapefruit and grapefruit juice should be avoided while on brigatinib. A “washout period” of at least 7 days is recommended between the last crizotinib dose and the first brigatinib dose

Drug Interactions

CYP3A is the major enzyme involved in the metabolic clearance of brigatinib. Co-administration of brigatinib with strong CYP3A inhibitors (e.g. itraconazole, posaconazole, voriconazole, clarithromycin) should be avoided. If this is not possible, reduce the brigatinib dose from 180mg to 90mg, or from 90mg to 60mg. After discontinuation of a strong CYP3A inhibitor, resume the brigatinib dose that was taken prior to initiating the strong CYP3A inhibitor. Grapefruit should also be avoided for this reason

THIS PROTOCOL HAS BEEN DIRECTED BY DRs YOUSIF and Dr Yiannakis, CLINICIAN FOR LUNG CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

Reference:
St Lukes Cancer Alliance
https://stlukescanceralliance.co.uk/wp-content/uploads/2019/03/Brigatinib-V2-3.19.pdf

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