Systemic Anti Cancer Therapy Protocol

Brigatinib
Non-Small Cell Lung Cancer

PROTOCOL REF: MPHABRILU
(Version No: 1.2)

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:

Brigatinib is approved as monotherapy for anaplastic lymphoma kinase (ALK) positive locally advanced or metastatic non-small cell lung cancer as **first line** treatment or as **second/third line** in patients previously treated with Crizotinib.

All patients must:

- Have a histologically or cytologically confirmed diagnosis of stage IIIB or IV non-small cell lung cancer that carries an ALK rearrangement.
- Not have treatment breaks for greater than 6 weeks – those breaks for up to six weeks are allowed but solely to allow toxicities to settle.
- Have an ECOG PS 0-2

FIRST LINE

Patients are only eligible for treatment with brigatinib if they:

- Are previously untreated with an ALK inhibitor **unless** treated with either first line alectinib or ceritinib or crizotinib which had to be stopped within 3 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression.

AND

- Are naïve to first line cytotoxic chemotherapy treatment or received cytotoxic chemotherapy containing treatment at a time when the ALK status was not known and the patient has since received no further therapy

SECOND LINE

- Has progressed on first line crizotinib or second line crizotinib after first line chemotherapy and that the patient has **not been treated with either first line alectinib or first line ceritinib**.

AND

- Have not been treated with second line ceritinib after first line crizotinib unless the ceritinib had to be stopped within three months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression.

Blueteq registration required – refer to blueteq for detailed eligibility criteria

Dosage:

Drug	Dose	Route	Frequency
Brigatinib	**90mg** ONCE daily for the first 7 days and then	ORAL	Daily for the first 7 days
	180mg ONCE daily	ORAL	To be taken continuously thereafter

Treatment should continue until progression or unacceptable toxicity.

Administration and Counselling Points:

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

- If a dose is missed or vomiting occurs after taking a dose, an additional dose should not be administered and the next dose should be taken at the scheduled time.
- Brigatinib should be swallowed whole and with water, it may be taken with or without food.
- Brigatinib contains lactose – patients with rare hereditary problems of galactose intolerance, total lactose deficiency or glucose-galactose malabsorption should not take this medicinal product.
- Women of reproductive potential should be advised to **use effective non-hormonal contraception** during treatment with Brigatinib and for at least 4 months following the final dose. Men with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 3 months after the last dose of Brigatinib.

Emetogenic risk:

Mildly emetogenic.

Supportive treatments:

- **Loperamide 2mg capsules** – take TWO capsules at once, then one capsule over each loose motion when required. Maximum of 8 capsules in 24 hours
- **Domperidone 10mg tablets** - to be taken up to three times a day as required.

Dosing in renal and hepatic impairment:

Renal	Mild or moderate renal impairment (eGFR ≥ 30 mL/min) - no dose adjustment. Severe renal impairment (eGFR < 30mL/min) - a reduced starting dose of 60mg ONCE daily for the first 7 days, then 90mg ONCE daily is recommended. **Patients with severe renal impairment should be closely monitored for new or worsening respiratory symptoms that may indicate ILD/pneumonitis particularly in the first week.**

Hepatic

Mild to moderate hepatic impairment hepatic impairment (Child-Pugh class A and B) - no dose adjustment

Severe hepatic impairment (Child-Pugh class C) - reduced starting dose of 60mg ONCE daily for the first 7 days, then 120mg ONCE daily is recommended.

Parameters	1 point	2 points	3 points
Total bilirubin (µmol/L)	< 34	34–50	> 50
Serum albumin (g/L)	> 35	28–35	< 28
Prothrombin time, prolongation (s) *Or* INR	< 4 < 1.7	4–6 1.7-2.3	> 6 >2.3
Ascites	None	Mild to Moderate (diuretic responsive)	Severe (diuretic refractory)
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory to medication)

INR: International Normalised Ratio.
Child-Pugh Class A = 5-6 points
Child-Pugh Class B = 7-9 points
Child-Pugh Class C = 10 or more points
Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.
Refer to 'Dose Modifications and Toxicity Management' section for entrectinib-induced hepatotoxicity.

Interactions:

- The concomitant use of brigatinib with strong CYP3A inhibitors should be avoided. If concomitant use of strong CYP3A inhibitors cannot be avoided, the dose of brigatinib should be reduced (see dose modification section below).
- Moderate CYP3A inhibitors may increase the AUC of brigatinib by approximately 40% on simulations from a physiologically-based pharmacokinetic model. No dose adjustment is required for brigatinib in combination with moderate CYP3A inhibitors but patients should be closely monitored.
- Grapefruit or grapefruit juice may also increase plasma concentrations of brigatinib and should be avoided.
- Coadministration of brigatinib with CYP3A substrates with a narrow therapeutic index (e.g. alfentanil, fentanyl, quinidine, cyclosporine, sirolimus, tacrolimus) should be avoided as their effectiveness may be reduced
- Coadministration of brigatinib with substrates of P-gp (e.g. digoxin, dabigatran, colchicine, and pravastatin), BRCP (e.g. methotrexate, rosuvastatin, and sulfasalazine), OCT1, MATE1, and MATE2K may increase their plasma concentration. Patients should be closely monitored when brigatinib is coadministered with substrates of these transporters with a narrow therapeutic index.
- For more information please refer to https://www.medicines.org.uk/emc/product/9691

Main toxicities:

Brigatinib

The most common adverse reactions (≥ 25%) reported in patients treated with brigatinib at the recommended dosing regimen were increased AST, hyperglycaemia, hyperinsulinaemia, anaemia, increased CPK, nausea, increased lipase, decreased lymphocyte count, increased ALT, diarrhoea, increased amylase, fatigue, cough, headache, increased alkaline phosphatase, hypophosphatemia, increased APTT, rash, vomiting, dyspnoea, hypertension, decreased white blood cell count, myalgia, and peripheral neuropathy.

The most common serious adverse reactions (≥ 2%) reported in patients treated with brigatinib at the recommended dosing regimen other than events related to neoplasm progression were pneumonitis, pneumonia, and dyspnoea.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Informed Consent	X					
Clinical Assessment	X		X	X	X	Every three cycles
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E & LFTs	X	X	X	X	X	Every Cycle
Lipid profile	X	X	X	X	X	After cycle 2 repeat lipid every 3 months
LDH	X	X	X	X	X	Every cycle – for clinician to review if raised – to be assessed in combination with symptoms and radiological progression
CT scan	X		X			Every 3 months
CPK	X	X	X	X	X	Every cycle
Amylase	X		X			Every other cycle
Counselling and assessing for visual disturbances	X					At baseline and If clinically indicated at the DISCRETION OF THE CLINICAL TEAM
Blood glucose	X	X	X	X	X	Every cycle
ECG	X		X			If clinically indicated
Blood pressure and heart rate measurement	X					Repeat if clinically indicated
Weight recorded	X	X	X	X		Every cycle
Height	X					

Dose Modifications and Toxicity Management:

Dose interruption and/or dose reduction may be required based on individual safety and tolerability. Brigatinib dose modification levels are summarised below.

Dose	Dose reduction levels		
	First	Second	Third
90mg ONCE daily (first 7 days)	Reduce to 60mg ONCE daily	Permanently discontinue	Not applicable
180mg ONCE daily	Reduce to 120mg ONCE daily	Reduce to 90mg ONCE daily	Reduce to 60mg ONCE daily

Brigatinib should be permanently discontinued if patient is unable to tolerate the 60mg once daily dose.

Recommended Brigatinib dose modification for adverse reactions:

Adverse reaction	Severity	Dose modification
Interstitial lung disease (ILD)/ pneumonitis	Grade 1	If event occurs during the first 7 days of treatment, brigatinib should be withheld until recovery to baseline, then resumed at same dose level and not escalated to 180mg once daily. If ILD/pneumonitis occurs after the first 7 days of treatment, brigatinib should be withheld until recovery to baseline, then resumed at same dose level. If ILD/pneumonitis recurs, brigatinib should be permanently discontinued.
	Grade 2	If event occurs during the first 7 days of treatment, brigatinib should be withheld until recovery to baseline, then resumed at next lower dose level and not escalated to 180mg once daily. If ILD/pneumonitis occurs after the first 7 days of treatment, brigatinib should be withheld until recovery to baseline. Brigatinib should be resumed at next lower dose level. If ILD/pneumonitis recurs, brigatinib should be permanently discontinued.
	Grade 3 or 4	Brigatinib should be permanently discontinued

Hypertension (HTN)	Grade 3 HTN (≥160/≥100, medical intervention indicated, >1 anti-hypertensive medicinal product, or more intensive therapy than previously used indicated)	Brigatinib should be withheld until hypertension as recovered to Grade ≤ 1 (<140/90), then resumed at same dose. If Grade 3 hypertension recurs, brigatinib should be withheld until hypertension has recovered to Grade ≤ 1 then resumed at the next lower dose level or permanently discontinued.
	Grade 4 HTN (life threatening consequences urgent intervention indicated)	Brigatinib should be withheld until hypertension has recovered to Grade ≤ 1 (<140/90), then resumed at the lower dose or permanently discontinued. If Grade 4 hypertension recurs, brigatinib should be permanently discontinued.
Bradycardia (HR less than 60 bpm)	Symptomatic bradycardia	Brigatinib should be withheld until recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. If a concomitant medicinal product known to cause bradycardia is identified and discontinued, or its dose is adjusted, brigatinib should be resumed at same dose upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. If no concomitant medicinal product known to cause bradycardia is identified, or if contributing concomitant medications are not discontinued or dose modified, brigatinib should be resumed at the next lower dose level upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above.
	Bradycardia with lifer-threatening consequences, urgent intervention indicated	If contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, brigatinib should be resumed at the next lower dose level upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. Brigatinib should be permanently discontinued if no contributing concomitant medicinal product is identified. Brigatinib is permanently discontinued in case of recurrence.

Elevation of CPK	Grade 3 elevation of CPK (>5xULN)	Brigatinib should be withheld until recovery to Grade ≤1 (≤2.5xULN) or to baseline, then resumed at same dose. If Grade 3 elevation of CPK recurs, brigatinib should be withheld until recovery to Grade ≤1 (≤2.5xULN) or to baseline, then resumed at the next lower dose level.
	Grade 4 elevation of CPK (>10xULN)	Brigatinib should be withheld until recovery to Grade ≤ 1(≤2.5xULN) or to baseline, then resumed at the next lower dose level.
Elevation of lipase or amylase	Grade 3 elevation of lipase or amylase (>2.0xULN)	Brigatinib should be withheld until recovery to Grade ≤1 (≤1.5xULN) or to baseline, then resumed at same dose. If Grade 3 elevation of lipase or amylase recurs, brigatinib should be withheld until recovery to Grade ≤1 (≤1.5xULN) or to baseline, then resumed at the next lower dose level.
	Grade 4 elevation of lipase or amylase (>5.0xULN)	Brigatinib should be withheld until recovery to Grade ≤ 1(≤1.5xULN), then resumed at the next lower dose level.
Hepatotoxicity	Grade ≥ 3 elevation (>5xULN) of either ALT or AST with bilirubin ≤ 2 x ULN	Brigatinib should be withheld until recovery to baseline or less than or equal to 3xULN, then resumed at next lower dose level.
	Grade ≥2 elevation (>3xULN) or ALT or AST with concurrent total bilirubin elevation > 2xULN in the absence of cholestasis or haemolysis.	Brigatinib should be permanently discontinued.
Hyperglycaemia	For Grade 3 (>13.9mmol/L) or greater	If adequate hyperglycaemic control cannot be achieved with optimal medical management, brigatinib should be withheld until adequate hyperglycaemic control is achieved. Upon recover, brigatinib may either be resumed at the next lower dose level or permanently discontinued.
Visual disturbance	Grade 2 or 3	Brigatinib should be withheld until recovery to Grade 1 or baseline, then resumed at the next dose level.
	Grade 4	Brigatinib should be permanently discontinued.
Other adverse reactions	Grade 3	Brigatinib should be withheld until recovery to baseline, then resumed at the same dose level.

		If the Grade 3 event recurs, brigatinib should be withheld until recovery to baseline, then resumed at the next lower dose level or permanently discontinued.
	Grade 4	Brigatinib should be withheld until recovery to baseline, then resumed at the next lower dose level. If the Grade 4 event recurs, brigatinib should be withheld until recovery to baseline, then resumed at the next lower dose level or permanently discontinued.

References:

1. Summary of Product Characteristics, Alunbrig, Brigatinib, Takeda UK Ltd, https://www.medicines.org.uk/emc [accessed on 12th January 2021]
2. NICE TA 571, Brigatinib for treating ALK-positive advanced non-small cell lung cancer after crizotinib, published on 20th March 2019.