Indication	For locally advanced or metastatic non-small cell lung cancer that carries an anaplastic lymphoma kinase (ALK) rearrangement and is either previously treated with crizotinib or untreated. There must be no previous treatment with brigatinib unless brigatinib has been received as part of any compassionate use scheme or early access scheme. • For previously treated, crizotinib should be the only TKI treatment that the patient has progressed on. • For previously untreated, patients may switch to brigatinib if they have had to stop a previous ALK inhibitor (as outlined in commissioning criteria) within 3 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression. NB: for the 'untreated patient' cohort, patients may have previously received 1st line cytotoxic chemotherapy when the ALK status was not known.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 28 days Continuous until disease progression, unacceptable toxicity or patient's decision.
Monitoring Parameters pre-treatment	• FBC, U&Es, CPK levels, lipase and amylase every cycle. • LFTs, to include AST ALT and total bilirubin, at baseline and then every 2 weeks for the first 3 months of treatment and then every cycle. • Fasting serum glucose should be performed before initiation of treatment and then as clinically indicated. • ECG baseline and then as clinically indicated. • Blood pressure at baseline and then 2 weekly for first 2months, then monthly. • Heart rate at baseline and every cycle. • The patient should either have no known brain metastases or if the patient has brain metastases, the patient should be symptomatically stable prior to starting treatment. **<u>Renal Impairment:</u>** • No dose adjustment required if CrCl >/=30ml/min. If CrCl <30ml/min a reduced starting dose of 60mg OD for 7 days and then 90mg OD 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 of treatment. **<u>Hepatic Impairment:</u>** • No dose adjustment required in mild (Child-Pugh class A) to moderate (Child-Pugh class B) hepatic impairment. A reduced starting dose of 60 mg once daily for the first 7 days, then 120 mg once daily is recommended for patients with severe hepatic impairment (Child-Pugh class C). D/W consultant if bilirubin >2 x ULN. **<u>Drug interactions:</u>** • The concomitant use of moderate or strong CYP3A inducers (rifampicin, carbamazepine, phenytoin and St John's wort) and moderate (diltiazem and verapamil) or strong (clarithromycin, erythromycin, ketoconazole) inhibitors should be avoided. If the use of a strong CYP3A inhibitor cannot be avoided the following dose reduction is advised, 180mg to 90mg or from 90mg to 60mg. • Grapefruit or grapefruit juice should be avoided whilst on brigatinib. • Coadministration with CYP3A substrates with a narrow therapeutic index (e.g. alfentanil, cyclosporine) should be avoided as their effectiveness may be reduced. Patients should be closely monitored when coadministered with transporter

	substrates with a narrow therapeutic index (e.g., digoxin, dabigatran, methotrexate). • Caution should be exercised when administering brigatinib in combination with other agents known to cause bradycardia. **<u>Dose Modifications & interruptions to manage adverse reactions:</u>** • If dose reduction or interruption is required the dose modification should be: o If on 90mg OD (first 7 days) dose reduce to 60mg OD, if this is not tolerated then brigatinib should be permanently discontinued. o If on 180mg OD (day 8 onwards) first dose reduction 120mg OD, second dose reduction 90mg OD and the third dose reduction 60mg OD. o Brigatinib should be permanently discontinued if patient is unable to tolerate the 60 mg once daily dose. • If 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. **<u>Adverse reactions, see also table 1:</u>** • **Pulmonary adverse reactions:** Severe and life threating pulmonary adverse reactions have been reported including ILD/pneumonitis most commonly occurring in the first 7 days of treatment. Patients should be advised to report any new or worsening respiratory symptoms. If pneumonitis is suspected treatment should be withheld and the dose of brigatinib modified accordingly. • **Hypertension:** Hypertension should be medically controlled during treatment. Brigatinib should be withheld for severe hypertension, >/=Grade 3, until hypertension has recovered to Grade 1 or baseline. • **Bradycardia:** If symptomatic bradycardia occurs during treatment brigatinib should be withheld. In the case of life threatening bradycardia, with no concomitant medication contributing to this, or in the case of reoccurrence, brigatinib should be discontinued. • **Creatine phosphokinase (CPK) elevation:** Patients should be advised to report any unexplained muscle pain, tenderness, or weakness. Based on the severity of the CPK elevation, and if associated with muscle pain or weakness, treatment should be withheld, and the dose modified accordingly. • **Visual disturbance:** Any new or worsening visual symptoms should be evaluated by an ophthalmologist and dose reduction should be considered. • **<u>Missed doses:</u>** 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. • Patients may experience fatigue, dizziness or visual disturbances, caution when operating machinery or driving is advised.
References	SPC accessed on line 14.12.2020 KMCC protocol LUN-039v1 blueteq form accessed online 16.12.2020

NB For funding information, refer to the SACT funding spread sheet

Table 1: Recommended dose modifications 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 180 mg 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 ILD/pneumonitis 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 180 mg 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	Grade 3 hypertension (SBP ≥ 160 mmHg or DBP ≥ 100 mmHg, medical intervention indicated, more than one anti-hypertensive medicinal product, or more intensive therapy than previously used indicated)	• Brigatinib should be withheld until hypertension has recovered to Grade ≤ 1 (SBP < 140 mmHg and DBP < 90 mmHg), 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 hypertension (life threatening consequences, urgent intervention indicated)	• Brigatinib should be withheld until hypertension has recovered to Grade ≤ 1 (SBP < 140 mmHg and DBP < 90 mmHg), then resumed at the next lower dose level 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 life-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 should be permanently discontinued in case of recurrence.
Elevation of CPK	Grade 3 or 4 elevation of CPK (> 5.0 × ULN) with Grade ≥ 2 muscle pain or weakness	• Brigatinib should be withheld until recovery to Grade ≤ 1 (≤ 2.5 × ULN) elevation of CPK or to baseline, then resumed at the same dose. • If Grade 3 or 4 elevation of CPK recurs with Grade ≥ 2 muscle pain or weakness, brigatinib should be withheld until recovery to Grade ≤ 1 (≤ 2.5 × ULN) elevation of CPK or to baseline, then resumed at the next lower dose level
Elevation of lipase or amylase	Grade 3 elevation of lipase or amylase (> 2.0 × ULN)	• Brigatinib should be withheld until recovery to Grade ≤ 1 (≤ 1.5 × ULN) 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 (≤ 1.5 × ULN) or to baseline, then resumed at the next lower dose level.
	Grade 4 elevation of lipase or amylase (> 5.0 x ULN)	• Brigatinib should be withheld until recovery to Grade ≤ 1 (≤ 1.5 × ULN), then resumed at the next lower dose level.
Hepatotoxicity	Grade **≥** 3 elevation (> 5.0 × ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with bilirubin ≤ 2 × ULN	• Brigatinib should be withheld until recovery to baseline or less than or equal to 3 × ULN, then resumed at next lower dose.
	Grade **≥** 2 elevation (> 3 × ULN) of ALT or AST with concurrent total bilirubin elevation **>** 2 × ULN in the absence of cholestasis or haemolysis	• Brigatinib should be permanently discontinued.

Hyperglycaemia	For Grade 3 (greater than 250 mg/dL or 13.9 mmol/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 recovery, Brigatinib may either be resumed at the next lower dose 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 lower 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 • 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.
bpm = beats per minute; CPK = Creatine Phosphokinase; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure; ULN = upper limit of normal		

Repeat every 28 days

Cycle 1

TTO	Drug	Dose	Route	Administration
Day 1-7	**BRIGATINIB**	**90mg**	PO	OD at the same time every day. The tablets should be swallowed whole and with water. Available as 30mg, 90mg and 180mg tablets.
Day 8 - 28	**BRIGATINIB**	**180mg**	PO	OD at the same time every day. The tablets should be swallowed whole and with water. Available as 30mg, 90mg and 180mg tablets.
	Metoclopramide	10mg	PO	Take 10mg TDS PRN. Do not take for more than 5 days continuously.
	Loperamide	2mg-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if specified.

Cycle 2 onwards

TTO	Drug	Dose	Route	Administration
Day 1-28	**BRIGATINIB**	**180mg**	PO	OD at the same time every day. The tablets should be swallowed whole and with water. Available as 30mg, 90mg and 180mg tablets.
	Metoclopramide	10mg	PO	Take 10mg TDS PRN. Do not take for more than 5 days continuously.
	Loperamide	2mg-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if specified.