Chemotherapy Protocol

Lung Cancer

Brigatinib

Regimen

- NSCLC – Brigatinib

Indication

- Brigatinib is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib;
    - where the patient has progressed on is 1st line crizotinib or 2nd line crizotinib after 1st line chemotherapy and that the patient has not been treated with either 1st line alectinib or 1st line ceritinib.
    - where the patient has not been treated with 2nd line ceritinib after 1st line crizotinib unless the ceritinib 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.
    - where the patient has not been previously treated with brigatinib unless brigatinib has been received as part of any compassionate use scheme and the patient meets all the other criteria set out here
    - where brigatinib will be used only as monotherapy
    - where the patient either has no brain metastases or, if the patient has brain metastases, the patient is symptomatically stable prior to starting brigatinib
    - where the patient will be treated with brigatinib until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment, whichever is the sooner.
    - where treatment breaks of up to 6 weeks are allowed but solely to allow toxicities to settle
    - where the ECOG performance status is 0, 1 or 2

Toxicity

Drug	Adverse Effect
Brigatinib	Pneumonia, upper respiratory tract infections, pneumonitis, haematological toxicity, electrolyte disturbances, hyperglycaemia, headache, peripheral neuropathy, dizziness, insomnia, visual disturbance, hypertension, cough, dyspnoea, GI disturbances, increased LFTs, blood CPK increased, myalgia, arthralgia, musculoskeletal chest pain, blood creatinine increase, fatigue, oedema, pyrexia, nausea, rash, bradycardia

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

- FBC, U&Es, LFTs at baseline, then LFTs every 2 weeks during the first 3 months of treatment then prior to each cycle or as clinically indicated.
- Fasting serum glucose at baseline then prior to each cycle or as clinically indicated.
- Lipase and amylase at baseline then prior to each cycle or as clinically indicated.
- Heart rate and blood pressure at baseline then prior to each cycle or as clinically indicated.

  Heart rate should be monitored more frequently in patients if concomitant use of a medicinal product known to cause bradycardia cannot be avoided.
- CPK levels at baseline then prior to each cycle or as clinically indicated.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and certain drug specific toxicities. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Brigatinib Dose Reduction levels

Dose Level	Brigatinib Dose (mg/day)	
	Days 1-7	Day 8+
0	90	180
-1	60	120
-2	Permanently Discontinue	90
-3	N/A	60

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

If brigatinib 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.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent.

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if patient symptomatic of anaemia or has haemoglobin of less than 8g/dL (80g/L)

Prior to prescribing cycle 1 the following criteria must be met;

Criteria	Eligible Level
Neutrophils	Equal to or more than $1x10^9$/L
Platelets	Equal to or more than $100x10^9$/L

For subsequent cycles;

Haematological toxicity ($x10^9$/L)	Dose Modifications
Grade 3 Neutrophils less than 1 or Lymphocytes less than 0.5 or Platelets less than 50	First occurrence - withhold brigatinib until recovery to baseline, then resume at same dose. Recurrence - withhold brigatinib until recovery to baseline then resume at the next lower dose level or permanently discontinue brigatinib.
Grade 4 Neutrophils less than 0.5 or Lymphocytes less than 0.2 or Platelets less than 25	For other Grade 4 adverse reactions First occurrence - withhold brigatinib until recovery to baseline, then resume at the next lower dose level. Recurrence - withhold brigatinib until recovery to baseline then resume at the next lower dose level or permanently discontinue brigatinib.

Hepatic Impairment

No dose adjustment of brigatinib is required for patients with mild hepatic impairment (Child-Pugh class A) or moderate hepatic impairment (Child-Pugh class B). 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)

AST/ALT (units/L)		**Bilirubin (µmol/L)**	**Brigatinib dose adjustment**
Grade 3 or above	and	2xULN or less	Withhold until recovery to baseline or less than or equal to 3×ULN (AST/ALT) then resume at next lower dose.
Grade 2 or above	and	Greater than 2x ULN in the absence of cholestasis or haemolysis	Permanently discontinue brigatinib.

Renal Impairment

GFR / eGFR	**Brigatinib dose adjustment**
Greater than or equal to 30ml/min	No dose adjustment required
Less than 30ml/min	Reduce starting dose to 60 mg once daily for the first 7 days, then increase to 90 mg once daily

Patients with severe renal impairment should be closely monitored for new or worsening respiratory symptoms that may indicate ILD/pneumonitis (e.g., dyspnoea, cough, etc) particularly in the first week.

Other

Interstitial lung disease (ILD)/pneumonitis

Grade	Occurrence	Dose Modification
Grade 1	During the first 7 days of treatment	Withhold until recovery to baseline, then resumed at same dose level. Do NOT escalate to 180 mg once daily
	After the first 7 days of treatment	Withhold until recovery to baseline, then resumed at same dose level.
	Recurrence	Permanently discontinue brigatinib.
Grade 2	During the first 7 days of treatment	Withhold until recovery to baseline, then resume at next lower dose level. Do NOT escalate to 180 mg once daily
	After the first 7 days of treatment	Withhold until recovery to baseline, then resume at next lower dose level.
	Recurrence	Permanently discontinue brigatinib.
Grade 3 or 4	Any	Permanently discontinue brigatinib.

Hypertension

For NCI-CTC grade 3 hypertension withhold brigatinib until hypertension has recovered to NCI-CTC grade 1 or below (SBP less than 140 mmHg and DBP less than 90 mmHg), then resumed at same dose.

If NCI-CTC grade 3 hypertension recurs, withhold brigatinib until hypertension has recovered to NCI-CTC grade 1 or below then resume at the next lower dose level or permanently discontinue.

For NCI-CTC grade 4 hypertension withhold brigatinib until hypertension has recovered to NCI-CTC grade 1 or below (SBP less than 140mmHg and DBP less than 90mmHg), then resumed at the next lower dose level or permanently discontinue.

If NCI-CTC grade 4 hypertension recurs permanently discontinue brigatinib.

Bradycardia (heart rate less than 60 bpm)

For symptomatic bradycardia withhold brigatinib 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, resume brigatinib at the 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, resume brigatinib at the next lower dose upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above.

For bradycardia with life-threatening consequences / urgent intervention indicated.

If contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume brigatinib 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. If no contributing concomitant medicinal product is identified, or in the case of recurrence, permanently discontinue brigatinib.

CPK Elevation

For Grade 3 elevation of CPK;

1. First occurrence - withhold until recovery to NCI-CTC grade 1 or below or to baseline, then resume at the same dose.

2. Recurrence - withhold until recovery toNCI-CTC grade 1 or below or to baseline, then resumed at the next lower dose level.

For Grade 4 elevation of CPK;

Withhold until recovery to NCI-CTC grade 1 or below or to baseline, then resume at the next lower dose.

Elevation of lipase or amylase

For NCI-CTC grade 3 elevation of lipase or amylase;

1. First occurrence - withhold brigatinib until recovery to NCI-CTC grade1 or below or to baseline, then resume at same dose.

2. Recurrence - withhold brigatinib until recovery to NCI-CTC grade 1 or below or to baseline, then resume at the next lower dose level.

For NCI-CTC grade 4 elevation of lipase or amylase then withhold brigatinib until recovery to NCI-CTC grade 1 or below, then resume at the next lower dose level.

Hyperglycaemia

For NCI-CTC grade 3 or greater, if adequate hyperglycaemic control cannot be achieved with optimal medical management, withhold brigatinib until adequate hyperglycaemic control is achieved. Upon recovery, either resume at the next lower dose or permanently discontinue.

Visual Disturbance

For NCI-CTC grade 2 or 3 visual disturbance withhold brigatinib until recovery to NCI-CTC grade 1 or baseline, then resumed at the next lower dose level.

For NCI-CTC grade 4 visual disturbance permanently discontinue brigatinib.

Other adverse reactions not listed above

For other NCI-CTC grade 3 adverse reactions;

1. First occurrence - withhold brigatinib until recovery to baseline, then resume at same dose.

2. Recurrence - withhold brigatinib until recovery to baseline then resume at the next lower dose level or permanently discontinue brigatinib.

For other NCI-CTC grade 4 adverse reactions;

1. First occurrence - withhold brigatinib until recovery to baseline, then resume at the next lower dose level.

2. Recurrence - withhold brigatinib until recovery to baseline then resume at the next lower dose level or permanently discontinue brigatinib.

Regimen

28 day cycle continued as long as benefit is observed or until unacceptable toxicity occurs (twelve cycles will be set in ARIA)

Cycle 1

Drug	Dose	Days	Route
Brigatinib	90mg once a day	1-7	Oral
Brigatinib	180mg once a day	8-28	Oral

Cycle 2 onwards

Drug	Dose	Days	Route
Brigatinib	180mg once a day	1-28	Oral

Dose Information

- Brigatinib is available as 30mg, 90mg and 180mg tablets

- If brigatinib 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.

- If concomitant use of strong CYP3A inhibitors cannot be avoided, the dose of brigatinib should be reduced from 180mg to 90mg or from 90mg to 60mg. After discontinuation of a strong CYP3A inhibitor, brigatinib should be resumed at the dose that was tolerated prior to the initiation of the strong CYP3A inhibitor.

Administration Information

- Brigatinib tablets should be swallowed whole and with water. Brigatinib may be taken with or without food.

- Grapefruit or grapefruit juice may increase plasma concentrations of brigatinib and should be avoided.

- The concomitant use of brigatinib with strong and moderate CYP3A inducers should be avoided.

- 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.

- If possible a 7 day interval should occur between discontinuation of crizotinib and start of brigatinib.

Supportive Treatments

As take home medication (cycle 1 only)

- Metoclopramide 10mg oral up to three times a day when required for the relief of nausea and vomiting

- Loperamide 4mg after the first loose stool and 2mg after each subsequent loose stool to a maximum of 16mg in 24 hours.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to brigatinib.

- It must be made clear to all staff, including those in the community, that brigatinib should only be prescribed under the supervision of a consultant oncologist

- Brigatinib interacts with many other agents. Always check for drug interactions.

References

1. Brigatinib in Patients with Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial. Kim DW, Tiseo M, Ahn M et al; J Clin Oncol, 2017; 35 (22): 2490 – 2498.
2. Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib. NICE TA571 20/03/2019

REGIMEN SUMMARY

Brigatinib

Cycle 1 only

Day One

1. Brigatinib 90mg once a day for 7 days oral
   Administration Instructions
   Oral SACT.
   This supply together with the 180mg supply for this cycle may be dispensed as treatment starter pack. This is a 28 day cycle. Take 90mg once a day for 7 days then increase to 180mg once a day days 8-28.

2. Brigatinib 180mg once a day for 21 days oral
   Administration Instructions
   Oral SACT.
   This supply together with the 90mg supply for days 1-7 may be dispensed as treatment starter pack. This is a 28 day cycle. Take 90mg once a day for 7 days then increase to 180mg once a day days 8-28.

3. Metoclopramide 10mg three times a day when required
   Administration Instructions
   Take 10mg up to three times a day when required for the relief of nausea and vomiting. Please supply 28x10mg tablets or nearest equivalent original pack size.

4. Loperamide as directed
   Administration instructions
   Loperamide 4mg after the first loose stool and 2mg after each subsequent loose stool to a maximum of 16mg in 24 hours

Cycle 2 onwards

Day One

5. Brigatinib 180mg once a day for 28 days oral
   Administration Instructions
   Oral SACT.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	Sept 2020	None	Rebecca Wills Pharmacist	Dr Luke Nolan Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.