BRIGATINIB (Alunbrig)

INDICATION (ICD10) C34

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (BRI1) (BRI2)

1. Brigatinib monotherapy for anaplastic lymphoma kinase-positive rearrangement advanced non-small-cell lung cancer previously treated with crizotinib. The only TKI treatment that 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 or brigatinib. No brain metastases or, if the patient has brain metastases, the patient is symptomatically stable prior to starting brigatinib. PS 0, 1 or 2. (TA571)
2. Brigatinib monotherapy for anaplastic lymphoma kinase-positive rearrangement locally advanced or metastatic non-small cell lung cancer previously untreated with an ALK inhibitor. Either the patient is naïve to 1st line cytotoxic chemotherapy-containing systemic treatment for this locally advanced or metastatic NSCLC indication or the patient received 1st line cytotoxic chemotherapy-containing treatment for locally advanced/metastatic non-small cell lung cancer at a time when the ALK status was not known and the patient has since received no further therapy. No brain metastases or, if the patient has brain metastases, the patient is symptomatically stable prior to starting brigatinib. PS 0, 1 or 2. (TA670)

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REGIMEN

Cycle 1

Days 1 to 7 BRIGATINIB 90mg orally daily
Days 8 to 28 BRIGATINIB 180mg orally daily

Cycle 2 onwards

BRIGATINIB 180mg orally daily continuously

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 previously tolerated dose.

CYCLE FREQUENCY AND NUMBER OF CYCLES

Until disease progression. A formal medical review as to whether treatment with brigatinib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment.

ADMINISTRATION

Available as 30mg, 90mg and 180mg tablets
Swallowed whole with water once daily with or without food
Grapefruit and grapefruit juice should be avoided while on brigatinib

ANTI-EMETICS

Low risk

CONCURRENT MEDICATION REQUIRED

Brigatinib	Diarrhoea – Loperamide required

EXTRAVASATION AND TYPE OF LINE / FILTERS

Not applicable

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E every cycle
LFTs every 2 weeks for 3 cycles then every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Creatinine phosphokinase every cycle
Glucose baseline and every cycle
Lipase and amylase every cycle
Blood pressure and pulse baseline, at 2 weeks, then every cycle
ECG baseline
Baseline weight

MAIN TOXICITES AND ADVERSE REACTIONS

Brigatinib	Pulmonary adverse reactions Hypertension Bradycardia Visual disturbance

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS

(not exhaustive list check SPC/BNF/Stockleys)

Brigatinib	Co-administration 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. Moderate CYP3A inhibitors monitor.

DOSE MODIFICATIONS

Non-haematological

Brigatinib

Dose	1st dose reduction	2nd dose reduction	3rd dose reduction
90mg once daily (first 7 days)	reduce to 60mg once daily	permanently discontinue	NA
180mg once daily	reduce to 120mg once daily	reduce to 90mg once daily	reduce to 60mg once daily

Bradycardia (HR less than 60 bpm)

Symptomatic bradycardia	• Withhold until recovery to asymptomatic bradycardia or to a resting heart rate of ≥60bpm • 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 60bpm 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 60bpm 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 60bpm or above, with frequent monitoring as clinically indicated. • Permanently discontinue if no contributing concomitant medicinal product is identified. • Permanently discontinue in case of recurrence.

Elevation of CPK

Grade 3 elevation of CPK (>5.0×ULN)	• Withhold until recovery to grade ≤1 (≤2.5×ULN) or to baseline, then resume at the same dose. • If grade 3 elevation of CPK recurs, withhold until recovery to grade ≤1 (≤2.5×ULN) or to baseline, then resume at the next lower dose level.
Grade 4 elevation of CPK (>10.0×ULN)	• Withhold until recovery to grade ≤1 (≤2.5×ULN) or to baseline, then resume at the next lower dose level.

Elevation of lipase or amylase

Grade 3 elevation of lipase or amylase (>2.0×ULN)	• Withhold until recovery to grade ≤1 (≤1.5×ULN) or to baseline, then resume at same dose. • If grade 3 elevation of lipase or amylase recurs, withhold until recovery to grade ≤1 (≤1.5×ULN) or to baseline, then resume at the next lower dose level.
Grade 4 elevation of lipase or amylase (>5.0xULN)	• Withhold until recovery to grade ≤1 (≤1.5×ULN), then resume at the next lower dose level.

Hepatoxicity

Grade ≥3 elevation (>5.0×ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with bilirubin ≤2×ULN	• Withhold until recovery to baseline or less than or equal to 3×ULN, then resume 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	• Permanently discontinue.

Hyperglycaemia

For grade 3 (greater than 250mg/dL or 13.9mmol/L) or greater	• If adequate hyperglycaemic control cannot be achieved with optimal medical management, withhold until adequate hyperglycaemic control is achieved. Upon recovery, Resume at the next lower dose or permanently discontinued.

Hypertension

Grade 3 hypertension (SBP ≥160mmHg or DBP ≥100mmHg, medical intervention indicated, more than one anti-hypertensive medicinal product, or more intensive therapy than previously used indicated)	• Withhold until hypertension has recovered to grade ≤1 (SBP <140mmHg and DBP <90mmHg), then resume at same dose. • If grade 3 hypertension recurs, withhold until hypertension has recovered to Grade ≤1 then resume at the next lower dose level or permanently discontinue
Grade 4 hypertension (life threatening consequences, urgent intervention indicated)	• Withhold until hypertension has recovered to grade ≤1 (SBP <140mmHg and DBP <90mmHg), then resume at the next lower dose level or permanently discontinued. • If grade 4 hypertension recurs, permanently discontinue.

Interstitial lung disease (ILD) /pneumonitis

Grade 1	• If event occurs during the first 7 days of treatment, withhold until recovery to baseline, then resume at same dose level and not escalated to 180mg once daily. • If ILD/pneumonitis occurs after the first 7 days of treatment, withhold until recovery to baseline, then resume at same dose level. • If ILD/pneumonitis recurs, permanently discontinue.
Grade 2	• If ILD/pneumonitis occurs during the first 7 days of treatment, withhold until recovery to baseline, then resume at next lower dose level and not escalated to 180mg once daily. • If ILD/pneumonitis occurs after the first 7 days of treatment, withhold until recovery to baseline. Resume at next lower dose level. • If ILD/pneumonitis recurs, permanently discontinue.
Grade 3 or 4	• Permanently discontinue.

Other adverse reactions

Grade 3	• Withhold until recovery to baseline, then resume at the same dose level. • If the grade 3 event recurs, withhold until recovery to baseline, then resume at the next lower dose level or permanently discontinue.
Grade 4	• withhold until recovery to baseline, then resume at the next lower dose level. • If the grade 4 event recurs, withhold until recovery to baseline, then resume at the next lower dose level or permanently discontinue.

Visual disturbance

Grade 2 or 3	Withhold until recovery to grade 1 or baseline, then resume at the next lower dose level.
Grade 4	Permanently discontinue.

Hepatic impairment

Brigatinib

Child-Pugh scores are based on ascites, encephalopathy, INR, albumin, total bilirubin

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 60mg once daily for the first 7 days, then 120mg once daily is recommended for patients with severe hepatic impairment (Child-Pugh class C).

Renal impairment

Brigatinib

CrCl >30ml/min	Give 100% dose
CrCl <30ml/min	Start dose 60mg once daily for the first 7 days, then 90mg once daily and monitor for new or worsening respiratory symptoms that may indicate ILD/pneumonitis (eg dyspnoea, cough etc) particularly in the first week

REFERENCES

1. Dong-Wan, K et al; JCO 2017; 35 (22): 2490–2498