Brigatinib

Indication

Treatment of anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) in patients who have already had crizotinib.

(NICE TA571)

ICD-10 codes

Codes with a prefix C34

Regimen details

Cycle 1:

Day	Drug	Dose	Route
1-7	Brigatinib	90mg OD	PO
8-28	Brigatinib	180mg OD*	PO

* toxicity assessment should be carried out before dose increase.

Cycle 2 onwards:

Day	Drug	Dose	Route
1-28	Brigatinib	180mg OD	PO

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.

Cycle frequency

28 days, i.e. continuous

Number of cycles

Continued until disease progression or unacceptable toxicity.

Administration

Brigatinib is available as 30mg, 90mg and 180mg tablets. Tablets should be swallowed whole with water and may be taken with or without food.

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.

Grapefruit and grapefruit juice should be **avoided** whilst taking brigatinib.

Note: a washout period of at least 7 days is recommended between the last dose of crizotinib and the first dose of brigatinib.

Pre-medication

Nil

Emetogenicity

This regimen has mild emetic potential.

Additional supportive medication

Antiemetics as per local policy as required.

Extravasation

N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+Es (including CrCl)	14 days
LFTs	14 days
Glucose	14 days
CPK	14 days
Lipase	14 days
Amylase	14 days
Blood pressure	Baseline

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Monthly
U+Es (including CrCl)	Monthly
LFTs	Every 2 weeks for the first 3 months, monthly thereafter
Glucose	Monthly or as clinically indicated
CPK	Monthly
Lipase	Monthly
Amylase	Monthly
Blood pressure	Every 2 weeks for the first month then monthly.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
CrCl	≥ 30 mL/min
Bilirubin	< ULN
ALT/AST	< ULN
CPK	< 5 x ULN
Lipase	< 2 x ULN
Amylase	< 2 x ULN
Blood pressure	<140/<90mmHg

Dose modifications

Dose modifications should be made as per table below:

Dose	Dose reductions		
	First	Second	Third
90mg OD (i.e. first 7 days)	60mg OD	Discontinue	N/A
180mg OD	120mg OD	90mg OD	60mg OD

Brigatinib should be discontinued if patient cannot tolerate 60mg dose.

Once a dose has been reduced for toxicity, it should not subsequently be increased.

- **Haematological toxicity**

Brigatinib can commonly cause decreased neutrophil and platelet counts. If neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L discuss with consultant.

- **Renal impairment**

No dose adjustment is required for patients with mild-moderate renal impairment (CrCl ≥ 30 mL/min). A reduced starting dose of 60 mg OD is recommended for the first 7 days for patients with severe renal impairment (CrCl < 30 mL/min). This can then be increased to 90 mg OD as tolerated. 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 of treatment.

- **Hepatic impairment**

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

See below for management of hepatotoxicity once treatment commenced.

- **Other toxicities**

Patients should be advised to report any new or worsening respiratory symptoms, especially in the first 7 days. Patients should also be advised to report any visual symptoms or unexplained muscle pain or weakness.

Toxicity	Definition	Dose adjustment
Pneumonitis/ Interstitial lung disease (ILD)	Grade 1	If within first 7 days: - Withhold until baseline. - Resume at same dose (i.e. do not escalate to 180mg) If after first 7 days: - Withhold until baseline. - Resume at same dose If recurs permanently discontinue.
	Grade 2	If within first 7 days: - Withhold until baseline. - Resume at next lower dose (do not escalate to 180mg) If after first 7 days: - Withhold until baseline. - Resume at next lower dose If recurs permanently discontinue.
	Grade 3-4	Permanently discontinue

Hypertension	Grade 3 (≥160/≥100mmHg, medical intervention required, more than one antihypertensive required, or more intensive therapy than previously required)	Withhold until ≤Grade 1 (<140/<90mmHg) then resume at same dose. If recurs withhold until ≤Grade 1, then resume at next lower dose or permanently discontinue.
	Grade 4 (life threatening)	Withhold until ≤Grade 1 (<140/<90mmHg) then resume at next lower dose or permanently discontinue. If recurs permanently discontinue.
Bradycardia (HR < 60 bpm)	Symptomatic	Withhold until asymptomatic or HR > 60bpm - If concomitant medication known to cause bradycardia, this should be discontinued or dose reduced. Resume at same dose on recovery. - If no contributing cause or recurs withhold until recovery, then resume at next lower dose or permanently discontinue.
	With life-threatening consequences	If concomitant medication known to cause bradycardia, this should be discontinued or dose reduced. Withhold until asymptomatic or HR > 60bpm, then resume at next lower dose. If no contributing cause or recurs permanently discontinue.
Elevation of CPK	Grade 3 (>5 x ULN)	Withhold until ≤Grade 1 then resume at same dose. If recurs withhold until ≤Grade 1, then resume at next lower dose.
	Grade 4 (>10 x ULN)	Withhold until ≤Grade 1, then resume at next lower dose.
Elevation of lipase or amylase	Grade 3 (> 2 x ULN)	Withhold until ≤Grade 1 then resume at same dose. If recurs withhold until ≤Grade 1, then resume at next lower dose.
	Grade 4 (> 5 x ULN)	Withhold until ≤Grade 1, then resume at next lower dose.
Hepatotoxicity	ALT/AST > 5 x ULN with bilirubin ≤ 2 x ULN	Withhold until recover to baseline or ≤ 3 x ULN, then resume at next lower dose.
	ALT/AST > 3 x ULN with bilirubin > 2 x ULN	Permanently discontinue
Hyperglycaemia	Grade 3	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.
Visual disturbances	Grade 2-3	Withhold until ≤Grade 1 or baseline, then resume at next lower dose.
	Grade 4	Permanently discontinue
Other toxicity	Grade 3	Withhold until recovery to baseline then resume at same dose. If recurs withhold until baseline, then resume at next lower dose or permanently discontinue.
	Grade 4	Withhold until recovery to baseline then resume at next lower dose. If recurs withhold until baseline, then resume at next lower dose or permanently discontinue.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Pneumonitis
Interstitial lung disease
Peripheral neuropathy
Hepatotoxicity
Bradycardia

- **Frequently occurring side effects**

Nausea
Diarrhoea
Visual disturbance
Fatigue
Cough
Headache, dizziness
Rash
Hypertension
Myalgia
Reduced WCC
Anaemia

- **Other side effects**

Elevations in pancreatic enzymes and CPK
Hyperglycaemia
Deranged electrolytes

Significant drug interactions – for full details consult product literature/ reference texts

Strong CYP3A inhibitors, including but not limited to certain antivirals (e.g., indinavir, nelfinavir, ritonavir, saquinavir), macrolide antibiotics (e.g., clarithromycin, telithromycin, troleandomycin), antifungals (e.g., ketoconazole, voriconazole), mibefradil, and nefazodone: avoid concomitant use. Increased risk of toxicity. If cannot be avoided consider dose reduction of 50%.

Moderate CYP3A inhibitors (e.g., diltiazem and verapamil): use with caution and close monitoring.

Strong and moderate CYP3A inducers including but not limited to rifampicin, carbamazepine, phenytoin, rifabutin, phenobarbital, and St. John's wort: avoid concomitant use.

CYP3A sensitive substrates Brigatinib may reduce plasma levels of coadministered medicinal products that are predominantly metabolised by CYP3A. Therefore, coadministration CYP3A substrates with a narrow therapeutic index (e.g., alfentanil, fentanyl, quinidine, cyclosporine, sirolimus, tacrolimus) should be avoided as their effectiveness may be reduced.

Substrates of P-gp (e.g., digoxin, dabigatran, colchicine, pravastatin), BCRP (e.g., methotrexate, rosuvastatin, sulfasalazine), organic cation transporter 1 (OCT1), multidrug and toxin extrusion protein 1 (MATE1), and 2K (MATE2K): concomitant use may increase their plasma concentrations. Patients should be closely monitored when Brigatinib is co-administered with substrates of these transporters with a narrow therapeutic index (e.g., digoxin, dabigatran, methotrexate).

Additional comments

Women of childbearing potential should be advised to use effective non-hormonal contraception during treatment for at least 4 months following the final dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment and for at least 3 months after the last dose.

References

- Summary of Product Characteristics Brigatinib (Takeda) accessed 7 August 2019 via www.medicines.org.uk
- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 571 accessed 7 August 2019 via www.nice.org.uk
- Dong-Wan, K et al; Brigatinib in Patients with Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial. JCO 2017; 35 (22): 2490 – 2498

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