Lung Pathway Group – Afatinib in Non-Small Cell Lung Cancer (NSCLC)

Indication: **NICE TA310**	First line treatment option in locally advanced or metastatic NSCLC Positive test for epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation No prior treatment with an EGFR-TK inhibitor Eligible for patients able to tolerate and comply with oral dosage forms
Regimen details:	Afatinib 40mg PO once daily continuously
Dose escalation	Dose escalation to 50mg once a day may be considered for patients who tolerate the 40mg dose (i.e. absence of diarrhoea, skin rash, stomatitis and other adverse reactions) in the first 3 weeks. maximum daily dose is 50mg.
Administration:	Afatinib available as 20mg, 30mg, 40mg and 50mg film coated tablets. Swallow whole with a glass of water on an empty stomach. Do not chew or crush. The medication should be taken at the approximately the same time each day, at least one hour before food, or three hours after food. Co-administration of a high-fat meal results in a significant decrease in exposure to afatinib. Afatinib should be taken without food. For patients unable to swallow the tablet whole, afatinib can be dispersed in approximately 100ml of non-carbonated drinking water. No other liquids should be used. The tablet should be dropped in the water, without crushing and stirred occasionally for up to 15 minutes until the tablet has broken up into very small particles. The dispersion should be consumed immediately. The glass should then be rinsed with approximately 100ml of water which should also be

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Prepared by: Lisa Yuen	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson
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	consumed. The dispersion can also be administered through gastric tubes.
Frequency:	Dosing is continuous, until disease progression or unacceptable toxicity
Pre-medication:	Not routinely required
Anti- emetics:	Minimal emetogenicity Follow local anti-emetic policy
Supportive medication:	Diarrhoea can be managed with loperamide. Mouthcare as per local policy. Various approaches may be considered to deal with skin reactions including rash, acne type reactions, erythema/ pruritus, dryness or blistering (topical emollients, clindamycin lotion, topical steroids, tetracycline antibiotics). Urea containing creams may be beneficial to treat dry skin. Support use of non-deodorant, non-fragrance products. Consider products with anti-itch additions in pruritus, and exfoliating products in hyperkeratosis. Anti-dandruff shampoo may help in management of itchy scalp. Early intervention may facilitate continuous treatment with afatinib.
Extravasation:	Not applicable
Regular investigations:	Prior to Cycle 1: EGFR mutation analysis FBC — Day 1 (within 14 days) LFTs — Day 1 (within 14 days) U&Es — Day 1 (within 14 days) Imaging — Baseline Cycle 1, Day 14 Consider LFTs and clinical toxicity review (as per local practice) Post cycle 2*: FBC — Every 2 – 3 months LFTs — Every 2 – 3 months U&Es — Every 2 – 3 months Imaging — Every 3 months

Regular clinical assessments and grading of diarrhoea, adverse skin reaction and tolerance of treatment.

* Repeat supply of afatinib does not require blood monitoring parameters to be accessible on the day. The medical team will set up treatment pathways to ensure continuous trend monitoring and timely clinical review when needed.

Toxicities: Diarrhoea, skin reactions (rash, dermatitis acneiform, acne pustular, pruritis, dry skin, palmar-plantar erythrodysaesthesia), stomatitis, paronychia, anorexia, epistaxis, occular disorders (conjunctivitis, dye eye, keratitis), elevated transaminases, interstitial lung disease.

DOSE MODIFICATIONS

Haematological Toxicity No dose modifications are required for haematological toxicity

Non-haematological Toxicities

Renal Impairment

Creatinine Clearance (ml/min)	Afatinib Dose
≥ 30	Give 100% dose
< 30	Not recommended – discuss with Consultant

Hepatic Impairment

Adjustments to the starting dose of afatinib are not necessary in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Afatinib has not been studied in patients with severe hepatic (Child-Pugh) impairment and treatment is not recommended.
Dose interruption may be necessary in patients who experience worsening of liver function.
Treatment should be discontinued in patients who develop severe hepatic impairment – discuss with Consultant.

Dose modifications for other toxicities as appropriate

Patients with poorly tolerated diarrhoea or skin adverse reactions despite maximal supportive medications may be successfully managed by treatment interruption, dose reduction or discontinuation of therapy.

CTCAE adverse reaction	Action	Recommended dosing
Grade 1 or grade 2	Continue treatment	No dose adjustment
Grade 2 (prolonged[a] or intolerable) or Grade ≥3	Interrupt until grade 0/1	Dose reduce by 10mg decrements[b] Once a dose reduction has occurred, do not re-escalate dose.

[a] > 48 hours of diarrhoea and/or >7 days of rash
[b] treatment should be discontinued in patients who are unable to tolerate 20mg/day

Location of regimen delivery:	Outpatient setting
Comments:	To be supplied to the patient for oral self-administration. Ensure that the patient has an information pack and the treatment plan. Adequate contraceptive methods should be used during therapy, and for at least 1 month after completing therapy.
Lactose	Each tablet contains 235mg lactose. Patients with rare hereditary conditions of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take afatinib.
Diarrhoea	Diarrhoea usually occurs within the first 2 weeks of treatment. Grade 3 diarrhoea most frequently occurs within the first 6 weeks of treatment. Ensure patients have an adequate supply of loperamide and are counselled on how and when to use them.
Skin reactions	Rash usually manifests as a mild or moderate erythematous and acneiform rash which may occur or worsen on sun exposed areas – advise on protective clothing and use of sunscreen. Bullous, blistering and exfoliative skin reactions have been reported – treatment must be interrupted or discontinued if severe – discuss with consultant
Keratitis	Symptoms such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred to an ophthalmologist. Treatment should be interrupted or discontinued with a diagnosis of ulcerative keratitis. Use with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.
Interstitial lung disease	Interstitial lung disease (ILD) and ILD-like adverse reactions (e.g lung infiltration, pneumonitis, acute respiratory distress syndrome, allergic alveoltis) has been reported in 0.7% of afatinib-treated patients. If patients experience acute and/or worsening of respiratory symptoms such as dyspnoea, cough and fever, afatinib

should be interrupted and the patient assessed. If ILD is confirmed, afatanib should be discontinued and appropriate treatment initiated.

Female gender, Low body weight, Underlying renal impairment

Higher exposure to afatinib has been observed in female patients, patients with lower body weight and those with underlying renal impairment may be at a higher risk of developing adverse reactions in particular diarrhoea, rash/acne and stomatitis. Closer monitoring is recommended.

Drug interactions:

- P-glycoprotein (P-gp) inducers e.g. rifampicin, carbamazepine, phenytoin, phenobarbital or St John's wort (Hypericum perforatum) – reduced exposure to afatinib
- Afatinib may increase the bioavailability of breast cancer resistance protein (BCRP) substrates e.g. rosuvastatin, sulfasalazine
- P-gp inhibitors e.g. ritonavir, cyclosporine, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, amiodarone – increased exposure to afatinib. If P-gp inhibitors need to be taken, they should be administered using staggered dosing: preferably 6 hours (for P-gp inhibitors taken twice a day), or 12 hours (for P-gp inhibitors taken once a day) apart from afatinib.

References: NICE TA310

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