PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Osimertinib Adjuvant Use

NSCLC EGFR exon 19 deletion or exon 21 (L858R) Substitution Mutation

PROTOCOL REF: MPHAOSAULU
(Version No. 1.1)

Approved for use in:

As monotherapy for the adjuvant treatment of adult patients with stage IB–IIIA or N2 only IIIB non-small cell lung cancer (NSCLC) following complete tumour resection, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations where the following criteria are fulfilled:

- No prior adjuvant SACT-Osimertinib commenced within 10 weeks of surgery. Prior treatment with EGFR inhibitor NOT permitted.
- Adjuvant SACT administered- Osimertinib commenced within 26 weeks of surgery.
- Neo-adjuvant SACT treatment is NOT permitted.
- Neoadjuvant or adjuvant radiotherapy is NOT permitted.
- ECOG performance status (PS) of 0 or 1.

**********Blueteq Form Required**********

Dosage:

Drug	Dosage	Route	Frequency
Osimertinib	80mg	Oral	Once daily

Treatment is continuous for 3 years or until unacceptable toxicity or disease progression whichever is first.

Four weeks supply will be issued at each SACT treatment visit.

Administration:

- Osimertinib is available as 40mg and 80mg film-coated tablets. It should be swallowed whole with water and can be taken irrespective of food intake.
- If a dose of Osimertinib is missed, the dose should be made up unless the next dose is due within 12 hours.
- If the patient is unable to swallow the tablet whole it may first be dispersed in 50ml of non-carbonated water. The tablet should be dropped into water without crushing, stirred until dispersed and immediately swallowed. An additional half glass of water should be added to the empty glass to ensure that no reside remains and then immediately swallowed. No other liquids can be used.
- If administration via the nasogastric tube is required the same process as above should be followed but using 15ml of water for the initial dispersion and 15ml for the residue rinses. The resulting 30ml of liquid should be administered as per the naso-gastric tube manufactures instruction with appropriate flushes.
- Patients should be advised to use effective contraception for the following periods after completion of treatment with this Osimertinib: at least 2 months for females and 4 months for males. A risk for decreased exposure of hormonal contraceptives cannot be exclude

Emetogenic risk:

Not emetogenic.

Supportive treatments:

Loperamide 4mg immediately after first episode of loose stool then 2mg to be taken after each subsequent episode (maximum of 8 tablets in 24 hours) as required for management of diarrhoea.

Dosing in renal and hepatic impairment:

Renal	CrCl ≥ 15 ml/min: no dose adjustment CrCL < 15 ml/min: not studied discuss with clinical team. Haemodialysis: not studied discuss with clinical team Creatinine Clearance (CrCL) calculated using Cockcroft and Gault formula (please use the application available on the Remote Citrix Web Portal).

Hepatic	**Osimertinib is eliminated mainly via the liver.** No dose adjustment required Total bilirubin ≤ ULN and AST >ULN OR Total bilirubin ≥1-3 x ULN and any AST (whether raised or normal). Not studied in severe hepatic impairment- discuss with clinical team Bilirubin ≥ 3-10 times ULN and any AST (whether raised or normal). Commencing on 40mg OD may be considered.

Drug Interactions

Concomitant use of strong CYP3A inducers (e.g. phenytoin, rifampicin and carbamazepine) should be avoided. Moderate CYP3A4 inducers (e.g. bosentan, efavirenz, etravirine, modafinil) should be used with caution, or avoided when possible. Closely monitor patients taking concomitant medications with disposition dependent upon breast cancer resistant protein (BCRP) and P-glycoprotein (P-gb) and with narrow therapeutic index.

Please refer to SmPC for full list of interactions or discuss with a member of the pharmacy team.

Main Toxicities:

Please refer to SmPC for full details.

Very common (all grades)	Diarrhoea, stomatitis, rash, dry skin, paronychia, pruritus, platelet count decreased, leucocytes decreased, lymphocytes decreased, neutrophils decreased.
Common (all grades)	Interstitial lung disease, epistaxis, palmar-plantar erythrodysaesthesia syndrome, alopecia, urticaria, blood creatinine increased.
Uncommon (all grades	Keratitis, QTc interval prolongation, erythema multiforme, cutaneous vasculitis.
Rare (all grades)	Stevens-Johnson syndrome.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Clinical Assessment	X		X	X	X	Every 3 cycles
SACT Assessment (to include PS and toxicities*)	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E (including magnesium) & LFT	X	X	X	X	X	Every cycle
CrCl (Cockcroft and Gault)	X	X	X	X	X	Every cycle
LDH	X	X	X	X	X	Every cycle**--for clinician to review if raised. To be assessed in combination with symptoms and radiological progression.
CT scan and MRI brain	X					To be carried out at baseline then every six months for the 3 year duration of treatment or as clinically indicated. Following completion of treatment this should continue at 3 monthly intervals for a further 2 years (5 years in total)
Informed Consent	X					
ECG***	X			X		ECG to be carried out at baseline and then on cycle 3 at clinical assessment, then as clinically indicated
Full Observations	X					Repeat if clinically indicated
Weight recorded	X	X	X	X	X	Every cycle
Height	X					

***Refer to 'Dose Modifications and Toxicity Management' section for full details**

****DO NOT DEFER TREATMENT if LDH has been omitted from laboratory tests.**

****ECGs to be requested and reviewed by clinical teams. The occurrence of QTc prolongation can be managed with dose reduction, interruption or discontinuation with correction of abnormal electrolytes and control of risk factors (refer to relevant sections in 'Main Toxicities' and 'Dose Modifications and Toxicity Management Section').**

Dose Modifications and Toxicity Management:

Haematological toxicity

Osimertinib causes decreased platelets, leucocytes, lymphocytes and neutrophils.

Proceed on day 1 if:

Plt ≥ 100 x 10^9/L	ANC ≥ 1.0 x 10^9/L

Dose adjustments for Osimertinib are required for CTCAE Grade 3 or higher haematological toxicities (see Table 1).

Non-haematological toxicities

Any patient with grade 3 or higher toxicity will require a dose reduction as per the table below.

Table 1

CTCAE Grade	Dose Modification
Grade 3 or higher	Withold Osimertinib for up to 3 weeks
If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding Osimertinib for up to 3 weeks	Osimertinib may be restarted at the same dose (80mg) or lowered dose (40mg)
Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue Osimertinib

Dose adjustment for skin rash:

Rash is a commonly reported adverse effect of Osimertinib, in general it manifests as mild or moderate erythematous and acneiform rash, which may occur or worsen in areas exposed to the sun. Dry skin and pruritis may also occur.

Bullous, blistering and exfoliative skin conditions can occur and treatment should be interrupted or discontinued if severe.

Use of emollients such as Aquamax cream may be used in the case of rash and dry skin for Grade 0-2 toxicities. For Grade 3 or higher refer to Table 1.

Dose adjustment for diarrhoea

Diarrhoea is a common side effect of Osimertinib. Dose adjustment as per Table 2.

Table 2

Toxicity	Management
Grade 1 or 2	Loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) Encourage fluid intake Continue loperamide until normal bowel function restored for at least 12 hours
Grade 3	Withhold until resolved, refer to Table 1.

Interstitial Lung

Interstitial Lung Disease (ILD) should be suspected in patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms such as dyspnoea, cough and fever, and should have their Osimertinib interrupted pending diagnostic evaluation. **If ILD/pneumonitis confirmed then Osimertinib should be discontinued.**

QT Interval Prolongation

QTc interval prolongation occurs in patients treated with Osimertinib. When possible, avoid use of Osimertinib in patients with congenital long QT syndrome. Caution is required in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medications that are known to prolong the QTc interval, periodic monitoring with electrocardiograms (ECGs) and electrolytes is recommended in these individuals Withhold Osimertinib in patients who develop a QTc prolongation, then resume Osimertinib at a reduced dose as described in Table 3. Permanently discontinue Osimertinib in patients who develop QTc interval prolongation in combination with any of the following: Torsade de pointes, polymorphic ventricular tachycardia, signs/symptoms of serious arrhythmia.

Table 3

Toxicity	Management
QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold Osimertinib until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then restart at a reduced dose (40 mg)
QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue Osimertinib.

Additional Information

Reporting of all suspected adverse reactions for patients on Osimertinib is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions in accordance with the training provided and the pharmacovigilance protocol.

References:

Formulary application support tool for use of adjuvant TAGRISSO®▼ (osimertinib) produced by AstraZeneca UK Limited. JBN: GB-26306. Date of publication: May 2021

Osimertinib 40 mg film-coated tablets, summary of Product Characteristics, AstraZeneca UK Limited available via https://www.medicines.org.uk/emc (last updated 14th May 2021).

Supplement to: Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.

Wu et al. (2020). Osimertinib in Resected EGFR-Mutated Non–Small-Cell Lung Cancer.

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
Date document posted on the Intranet	For completion by DCM

Version History

		Author name and designation	Summary of main changes
		Hala Ghoz Lung SRG Pharmacist	New Regimen Protocol V1.0
		Hala Ghoz Lung SRG Pharmacist	Funding criteria changed (Orbis EAS closed and funded under CDF) V1.1