PROTOCOL

Systemic Anti Cancer Therapy Protocol

Mobocertinib
EGFR-mutated Advanced or Metastatic NSCLC

PROTOCOL REF: MPHAMEGFR
(Version No.: 1.1)

Approved for use:

As monotherapy for the treatment of adult patients who have previously received platinum-based chemotherapy for advanced or metastatic non-small cell lung cancer (squamous or non-squamous NSCLC) that is positive for an EGFR exon 20 insertion mutation.

ECOG performance status (PS) score of 0 or 1.

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

Dosage:

Drug	Dosage	Route	Frequency
Mobocertinib	160mg	Oral	Once daily continuously

Until unacceptable toxicity or disease progression whichever is first.
Four weeks supply will be issued at each SACT treatment visit.

Administration:

Mobocertinib is available as 40mg hard capsules. It should be swallowed whole with water and can be taken irrespective of food intake at roughly the same time each day.

If a dose is missed by more than 6 hours, the patient should not take a dose on that day but should resume the usual dosing on the following day at the regularly scheduled time.

If a patient vomits after taking a dose, the patient should not repeat the dose but should resume the usual dosing as prescribed on the following day.

Patients should be advised to use effective contraception throughout the treatment course. Women of childbearing potential should be advised to use highly effective **non-hormonal contraception** during treatment and for 1 month following the final dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment and for 1 week following the final dose of Mobocertinib.

Co-administration with strong CYP3A inhibitors (clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir), grapefruit or grapefruit juice, or St. John's Wort is **CONTRAINDICATED**. Refer to 'Interactions' section for full details.

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

- Cyclizine 50mg orally three times a day
- Loperamide 4mg immediately after first episode of loose stool then 2mg to be taken every 2 hours until the patient is diarrhoea-free for at least 12 hours (maximum of 8 tablets in 24 hours).

Dosing in renal and hepatic impairment:

Renal	eGFR ≥ 30 ml/min: no dose adjustment eGFR < 30 ml/min: not studied therefore not recommended, discuss with clinical team.

Hepatic	Mild hepatic impairment Bilirubin >1.0-1.5 x ULN and any AST or bilirubin ≤ULN and AST >ULN- no dose adjustment. Moderate (bilirubin 1.5-3 x ULN, with any AST) or Severe (bilirubin >3.0-10 x ULN, with any AST)- not studied therefore not recommended. discuss with clinical team.

Interactions:

This list is not exhaustive, for full list of interactions please refer to SmPC or consult with a member of the pharmacy team.

Coadministration of strong CYP3A inhibitors is CONTRAINDICATED	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), and nefazodone Grapefruit or grapefruit juice
Coadministration of moderate CYP3A inhibitors should be avoided. **If unavoidable dose reduce mobocertinib by 50%. More frequent monitoring of QTc is required. After discontinuation of moderate CYP3A inhibitor dose of mobocertinib should be resumed at the previously tolerated dose**	e.g. fluconazole and erythromycin

<table>
<tr><td>Coadministration of strong CYP3A inducers, should be avoided.

Co-administration with St John’s Wort is CONTRAINDICATED</td><td>Including but not limited to rifampicin, carbamazepine, phenytoin, rifabutin, and phenobarbital</td></tr>
<tr><td>Co-administration with drugs that prolong the QTc interval should be avoided</td><td>
<table>
<tr><th>Antimicrobials</th><th>Psychiatric Medication</th><th>Others</th></tr>
<tr><td>Erythromycin
Clarithromycin
Moxifloxacin
Fluconazole
Ketoconazole</td><td><u>Antipsychotics</u>
Risperidone
Fluphenazine
Haloperidol
Chlorpromazine
Quetiapine
Pimozide
Dronedarone
Clozapine</td><td>Methadone
Imipramine
Lofepramine
Some antimalarials</td></tr>
<tr><td><u>Antiarrhythmics</u>
Sotalol
Quinidine
Amiodarone
Flecainide</td><td><u>Antidepressants</u>
Citalopram
Escitalopram
Amitriptyline</td><td><u>Antiemetics</u>
Domperidone
Ondansetron
Granisetron</td></tr>
</table>
</td></tr>
<tr><td>Co-administration with CYP3A substrates, , can result in decreased concentrations and loss of efficacy</td><td>Including but not limited to hormonal contraceptives and midazolam</td></tr>
<tr><td>Use with caution when co-adminstering with P-gp and BCRP substrates. Potential for increased</td><td>P-gp (digoxin, dabigatran) and BCRP (sulfasalazine, rosuvastatin)</td></tr>
</table>

adverse effects from these drugs	

Main toxicities:

The most common (all grades) (≥ 25%)	Diarrhoea (94%) Rash (77%) Anaemia (69%), Blood creatinine increased (57%) Nausea (49%), Stomatitis (47%) Amylase increased (42%) Vomiting (37%) Decreased appetite (37%) Lipase increased (37%) Fatigue (31%) Dry skin (32%) Paronychia (36%) Dry skin (32%) Hypokalaemia (30%) Hypomagnesaemia (31%) Hyponatraemia (28%) Decreased platelet count (29%) Decreased lymphocyte (51%) ALT increased (28%) AST increased (28%)
Serious adverse reactions occurred in ~ 50% of patients	Dyspnoea Diarrhoea Vomiting Pneumonia AKI Decreased Appetite Dehydration Nausea Respiratory failure
The most common laboratory abnormalities	Anaemia Serum creatinine increase Amylase increase Lipase increase Hypokalaemia Hypomagnesaemia

	Hyponatraemia Thrombocytopenia Leukopenia Elevated ALT and AST

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Informed Consent	x					
Clinical Assessment	x		x		x	As clinically indicated or every 3 months
SACT Assessment (to include PS and toxicities*)	x	x	x	x	x	Every cycle
FBC	x	x	x	x	x	Every cycle
LFTs (ALT, AST and Bilirubin)	x	x	x	x	x	Every cycle.
U&E & Magnesium*	x	x	x	x	x	Every Cycle
eGFR	x	x	x	x	x	Every cycle
CT scan	x				x	Every 3 months or as clinically indicated
ECHO/MUGA	x				x	Assess LVEF at baseline then after 3 and 6 months or as clinically indicated Monitor for symptoms of heart failure**
ECG	x				x	At baseline then after 3 and 6 months as clinically indicated QTc > 450 msec in males or 470 msec in females at baseline to be inititated at the discretion of the clinical team with regular ECG monitoring for the first 2 months and/or stablilised on mobocertinib dose
Full Observations *(HR, RR, BP and O_2 Sats)*		x	x	x	x	Every cycle***
Weight recorded	x	x	x	x	x	Every cycle
Height	x					

* Monitor for hypokalaemia, hyponatraemia and hypocalcaemia and supplement accordingly. Deficiencies in any of these electrolyte predisposes to QT prolongation.

** Persistent cough, which may be worse at night, wheezing, confusion, fast heart rate, pounding, fluttering or irregular heartbeat.

***Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g. shortness of breath, cough, and fever), refer to 'Non-haematological Toxicity 'section.

Dose Modifications and Toxicity Management:

Dosing should be modified based on Mobocertinib toxicity.

Table 1. Recommended Mobocertinib dose reduction levels

Dose reduction level	Dose
First dose reduction	120 mg (three 40 mg tablets) once daily
Second dose reduction	80 mg (two 40 mg tablets) once daily

Table 2. Recommended dose modifications for Mobocertinib

Adverse Reaction	Severity*	Dose Modification
QTc Interval Prolongation	Grade 2 (QTc interval 481-500 msec)	First Occurrence Withhold until ≤ Grade 1 or baseline. Upon recovery, resume at the same dose. Recurrence Withhold until ≤ Grade 1 or baseline Upon recovery, resume at the next lower dose or permanently discontinue treatment.
	Grade 3 (QTc interval ≥ 501 msec or QTc interval > 60 msec increase from baseline)	First Occurrence Withhold until ≤ Grade 1 or baseline. Upon recovery, resume at the next lower dose or permanently discontinue. Recurrence Permanently discontinue treatment.
	Grade 4 (Torsades de Pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)	Permanently discontinue treatment.
Interstitial Lung Disease (ILD)/Pneumonitis	Any grade	Withhold if ILD/pneumonitis is suspected. Permanently discontinue mobocertinibif ILD/pneumonitis is confirmed.

Decreased Ejection Fraction or Heart Failure	Grade 2 decreased ejection fraction	Withhold until ≤ Grade 1 or baseline. If recovered to baseline within 2 weeks, resume at the same dose or the next lower dose. If not recovered to baseline within 2 weeks, permanently discontinue treatment.
	≥ Grade 2 heart failure or Grade 3 or 4 decreased ejection fraction	Permanently discontinue treatment.
Diarrhoea	Grade 1 or Grade 2	No dose modification is required. Initiate treatment with anti-diarrheal medicinal products (loperamide) at first onset of diarrhoea.
	Intolerable or recurrent Grade 2 or Grade 3	Withhold until recovery to Grade 1 or lower; then resume at the same dose or at the next lower dose.
	Grade 4	First Occurrence Withhold until recovery to Grade 1 or lower. If recovered within 2 weeks, resume at the next lower dose. If not recovered to Grade 1 or lower within 2 weeks, permanently discontinue treatment. <u>Recurrence</u> Permanently discontinue treatment
Amylase/lipase elevation	Grade 2 (> 1.5 to ≤ 2x ULN) and asymptomatic Grade 3 (> 5.0 × ULN)	Withhold until recovery to ≤ Grade 1 If recovered within 2 weeks, resume at the same dose or at the next lower dose. If not recovered to ≤ Grade 1within 2 weeks, permanently discontinue treatment.
	Symptomatic Grade 3 and Grade 4	Withhold until recovery to ≤ Grade 1. If recovered within 2 weeks, resume at the next lower dose. If not recovered to ≤ Grade 1 within 2 weeks, permanently discontinue treatment.
Other Non-haematologic toxicity	Grade 2	No dose modification is required. For intolerable or recurrent Grade 2 toxicity, withhold until symptoms resolve and resume at the next lower dose.
	Grade 3 or 4	Withhold until recovery to Grade 1 or lower; then resume at the same dose or at the next lower dose. For Grade 4 toxicity, consider permanent discontinuation of treatment.

Other Haematologic toxicity	Grade 3 or 4	Withhold until recovery to Grade 2 or lower; then resume at the same dose or at the next lower dose. For Grade 4 toxicity, consider permanent discontinuation of EXKIVITY.
ULN = upper limit of normal * Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 5.0 (NCI CTCAE v5)		

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

Non- Haematological toxicity:

QTc Interval Prolongation

Heart rate-corrected QT (QTc) interval prolongation, including resultant life-threatening arrhythmias such as Torsades de Pointes have occurred in patients treated with Mobocertinib.

Clinical trials did not enrol patients with a prolonged baseline QTc > 450 msec in males or 470 msec in females. Where possible, the use of mobocertinib in patients with congenital long QT syndrome should be avoided. Assess QTc and electrolytes at baseline and correct abnormalities in sodium, potassium, calcium, and magnesium prior to initiating Mobocertinib. Monitor QTc and electrolytes periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation, such as patients with congenital long QTc syndrome, cardiac

failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval (e.g., ondansetron).

Co-administration of strong CYP3A inhibitors with Mobocertinib is contraindicated (Refer to 'Interactions' section for further details). Avoid coadministration of moderate CYP3A inhibitors and medications known to prolong QTc interval with Mobocertinib, as they may further prolong the QTc interval.

Permanently discontinue Mobocertinib in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis have occurred in patients treated with Mobocertinib.

Patients with a history of ILD, dyspnoea at rest, drug-related pneumonitis, radiation pneumonitis that required steroid treatment were excluded from enrolment in the mobocertinib clinical trials.

Withhold Mobocertinib for acute onset of new or progressive unexplained pulmonary symptoms such as dyspnoea, cough, and fever pending diagnostic evaluation and

diagnosis confirmation. Permanently discontinue treatment f ILD/pneumonitis is confirmed and initiate appropriate treatment as necessary.

Cardiac failure

Severe, life-threatening, and fatal cardiac failure (including congestive cardiac failure, decreased ejection fraction, and cardiomyopathy) have occurred in patients treated with Mobocertinib.

Patients with a history of significant, uncontrolled, active cardiovascular disease were excluded from enrolment in the mobocertinib clinical trials.

Diarrhoea

In clinical studies, most patients experienced mild to moderate diarrhoea. In some cases diarrhoea was severe or life threatening. The median time to first onset of diarrhoea was 5 days but could occur as soon as 24 hours after administration of mobocertinib. Diarrhoea was usually transient and had a median time to resolution of 3 days. Over a third of patients in the clinical studies experienced recurrent diarrhoea. Prolonged diarrhoea led to dehydration or electrolyte imbalance, with or without renal impairment.

Early and compliant diarrhoea management such as prescribed anti-diarrheal medicinal products (e.g., loperamide), diet, adequate fluid intake (~2L clear liquids per day), and patient education is essential. Patients should be advised to have anti-diarrheal medicinal products (e.g., loperamide) readily available. Begin anti-diarrheal treatment at

the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normal.

References:

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Published: November 27, 2017

Mobocertinib 40 mg hard capsules, summary of Product Characteristics, Takeda UK Ltd available via https://www.medicines.org.uk/emc (last updated 9th Jan 2023).

NICE TA855: Mobocertinib for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy. Published 4th January 2023.

Zhou, C., et al. (2021). Treatment outcomes and safety of mobocertinib in platinum-pretreated patients with EGFR exon 20 insertion–positive metastatic non–small cell lung cancer: a phase 1/2 open-label nonrandomized clinical trial. *JAMA oncology*, 7(12), e214761-e214761.

Circulation/Dissemination

Date added into Q-Pulse	20th July 2022
Date document posted on the Intranet	N/A

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**	**Updated in line with funding and licensing changes (dosing in hepatic impairment, toxicity profile and supportive treatments, investigations table)** **V1.1**