Systemic Anti Cancer Therapy Protocol

Dacomitinib
EGFR +ve Non-Small Cell Lung Cancer (NSCLC)

PROTOCOL REF: MPHADACLU
(Version No: 1.1)

This protocol has been temporarily amended-please see the ORAL SACT OPERATIONAL CHANGES DURING COVID -19

Amendments may include less frequent blood monitoring, telephone SACT assessments and longer durations of treatment being dispensed.

Approved for use in:

- Stage IIIB or stage IV EGFR +ve NSCLC
- Patient has received no previous EGFR-targeted therapy unless this has had to be stopped within 3 months of its start solely as a consequence of dose limiting toxicity and in clear absence of disease progression
- Patient has received no previous cytotoxic chemotherapy for locally advanced or metastatic NSCLC
- Performance status of 0 or 1

Blueteq registration required: see Blueteq for more detailed eligibility criteria

Dosage:

Drug	Dose	Route	Frequency
Dacomitinib	**45mg**	Oral	Once daily

Tablets will be supplied at 28 day intervals.

Treatment will be continued until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment, whichever is sooner.

Administration (+/- Counselling Points):

Patients should be encouraged to take their dose at approximately the same time each day.

If the patient vomits or misses a dose, an additional dose should not be taken and the next prescribed dose should be taken at the usual time the next day.

Tablets should be swallowed with water and can be taken with or without meals.

Supportive treatments:

Domperidone 10mg, THREE times a day when required

Loperamide 4mg immediately, then 2mg after each loose stool when required up to a maximum of 16mg in 24 hours

Dosing in renal and hepatic impairment:

Renal	No starting dose adjustments are required when administering to patients with mild or moderate renal impairment (creatinine clearance ≥ 30ml/min). Limited data are available in patients with severe renal impairment (creatinine clearance < 30ml/min). No data are available in patients requiring haemodialysis.

Hepatic	No starting dose adjustments are required in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. Dacomitinib has not been studied in patients with severe (Child-Pugh class C) hepatic impairment. Treatment in this population is not recommended.

Interactions:

Proton Pump Inhibitors (PPIs): Concomitant use of PPIs should be avoided. The aqueous solubility of dacomitinib is pH dependent and therefore PPIs were found to decrease the concentration of dacomitinib. Local antacids and H2 receptor antagonists may be used if need. Dacomitinib should be administered 2 hours before or at least 10 hours after taking H2 receptor antagonists.

Please consult SPC available via medicines.org.uk for full list of interactions

Main toxicities:

Decreased appetite, hypokalaemia, conjunctivitis, stomatitis, nausea, vomiting, diarrhoea, rash, dry skin, palmar-plantar erythrodysaesthesia syndrome, alopecia, fatigue and transaminases increased.

Interstitial lung disease (ILD)/Pneumonitis

ILD/pneumonitis adverse reactions were reported in 2.7% of patients receiving dacomitinib, and Grade ≥ 3 ILD/pneumonitis adverse reactions were reported in 0.8%, including a fatal event (0.4%). The median time to the first episode of any grade ILD/pneumonitis was 16 weeks and the median time to the worst episode of ILD/pneumonitis was 16 weeks in patients receiving dacomitinib. The median duration of any grade and Grade ≥ 3 ILD/pneumonitis was 13 weeks and 1.5 weeks, respectively. Patients with a history of ILD have not been studied.

Careful assessment of all patients with an acute onset or unexplained worsening of pulmonary symptoms (e.g., dyspnoea, cough, fever) should be performed to exclude ILD/pneumonitis. Treatment with dacomitinib should be withheld pending investigation of these symptoms. If ILD/pneumonitis is confirmed, dacomitinib should be permanently discontinued and appropriate treatment instituted as necessary.

Diarrhoea

Diarrhoea was the most frequently reported adverse reaction in patients receiving Dacomitinib (88.6%) and Grade ≥ 3 diarrhoea adverse reactions were reported in 9.4% of patients. In a clinical study, one patient (0.4%) had a fatal outcome.

The median time to the first episode of any grade diarrhoea was 1 week and the median time to the worst episode of diarrhoea was 2 weeks in patients receiving dacomitinib. The median duration of any grade and Grade ≥ 3 diarrhoea was 20 weeks and 1 week, respectively.

Diarrhoea may result in dehydration with or without renal impairment, which could be fatal if not adequately treated. Proactive management of diarrhoea should start at the first sign of diarrhoea especially within the first 2 weeks of starting dacomitinib, including adequate

hydration combined with anti-diarrhoeal medicinal products and continued until loose bowel movements cease for 12 hours. Loperamide should be used and, if necessary, escalated to the highest recommended approved dose. Patients may require dosing interruption and/or dose reduction of therapy with dacomitinib. Patients should maintain adequate oral hydration and patients who become dehydrated may require administration of intravenous fluids and electrolytes.

Skin-related adverse reactions

Rash, erythematous and exfoliative skin condition adverse reactions were reported in 79.2% and 5.5%, respectively, of patients receiving Dacomitinib. Skin-related adverse reactions were Grades 1 to 3. Grade 3 rash and erythematous skin condition adverse reactions were the most frequently reported Grade 3 adverse reactions (25.5%). Grade 3 exfoliative skin conditions were reported in 0.8% of patients.

The median time to the first episode of any grade rash and erythematous skin conditions was approximately 2 weeks and the median time to the worst episode of rash and erythematous skin conditions was 7 weeks in patients receiving dacomitinib. The median duration of any grade and Grade ≥ 3 rash and erythematous skin conditions was 53 weeks and 2 weeks, respectively. The median time to the first episode of any grade exfoliative skin conditions was 6 weeks and the median time to the worst episode of exfoliative skin conditions was 6 weeks. The median duration of any grade and Grade ≥ 3 exfoliative skin conditions was 10 weeks and approximately 2 weeks, respectively.

For prevention of dry skin, initiate treatment with moisturisers, and upon development of rash, initiate treatment with topical antibiotics, emollients, and topical steroids. Start oral antibiotics and topical steroids in patients who develop exfoliative skin conditions. Consider adding broad spectrum oral or intravenous antibiotics if any of these conditions worsen to greater than or equal to Grade 2 severity. Rash, erythematous and exfoliative skin conditions may occur or worsen in areas exposed to the sun. Advise patients to use protective clothing and sunscreen before exposure to the sun. Patients may require dosing interruption and/or dose reduction of therapy with dacomitinib.

Hepatotoxicity and transaminases increased

Transaminases increased (alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased) were reported in 22.0% of patients receiving Dacomitinib and were Grades 1 to 3, with the majority Grade 1 (18.4%).

The median time to the first episode of any grade of transaminases increased was approximately 12 weeks and the median time to the worst episode of transaminases increased was 12 weeks in patients receiving dacomitinib. The median duration of any grade and Grade ≥ 3 transaminases increased was 11 weeks and 1 week, respectively.

Among NSCLC patients treated with dacomitinib 45 mg daily, there have been isolated reports of hepatotoxicity in 4 (1.6%) patients. Across the dacomitinib program, hepatic failure led to a fatal outcome in 1 patient. Therefore, periodic liver function testing is recommended. In patients who develop severe elevations in transaminases while taking dacomitinib, treatment should be interrupted.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	X				
Clinical Assessment	X		X		Every 3 cycles
SACT Assessment (to include PS and toxicities)	X	X	X	X	Every cycle
FBC	X	X	X	X	Every cycle
U&E & LFTs	X	X	X	X	Every cycle
LDH	X	X	X	X	Every cycle-for clinician to review if raised. To be assessed in combination with symptoms and radiological progression
CT scan	X				Every 3 months or as clinically indicated
Weight recorded	X	X	X	X	Every cycle. Height to be recorded on cycle 1 only
Height recorded	X				

Dose Modifications and Toxicity Management:

Recommended dose modifications for dacomitinib adverse reactions

Dose level	Dose (once daily)
Recommended starting dose	45 mg
First dose reduction	30 mg
Second dose reduction	15 mg

Management for Dacomitinib adverse reactions

Adverse reactions	Dose modification
Interstitial lung disease (ILD/Pneumonitis)	• Withhold dacomitinib during ILD/Pneumonitis diagnostic evaluation. • Permanently discontinue dacomitinib if ILD/Pneumonitis is confirmed.
Diarrhoea	• For Grade 1 diarrhoea, no dose modification is required. Initiate treatment with loperamide at first onset of diarrhoea. Encourage adequate oral fluid intake during diarrhoea. • For Grade 2 diarrhoea, if not improved to Grade ≤ 1 within 24 hours while using loperamide and adequate oral fluid intake, withhold dacomitinib. Upon recovery to Grade ≤ 1, resume dacomitinib at the same dose level or consider a reduction of 1 dose level. • For Grade ≥ 3 diarrhoea, withhold dacomitinib. Treat with loperamide and adequate oral fluid intake or intravenous fluids or electrolytes as appropriate. Upon recovery to Grade ≤ 1, resume dacomitinib with a reduction of 1 dose level.
Skin-related adverse reactions	• For Grade 1 rash or erythematous skin conditions, no dose modification is required. Initiate treatment (e.g., antibiotics, topical steroids, and emollients). • For Grade 1 exfoliative skin conditions, no dose modification is required. Initiate treatment (e.g. oral antibiotics and topical steroids). • For Grade 2 rash, erythematous or exfoliative skin conditions, no dose modification is required. Initiate treatment or provide additional treatment (e.g., oral antibiotics and topical steroids). • If Grade 2 rash, erythematous or exfoliative skin conditions persist for 72 hours despite treatment, withhold dacomitinib. Upon recovery to Grade ≤ 1, resume dacomitinib at the same dose level or consider a reduction of 1 dose level. • For Grade ≥ 3 rash, erythematous or exfoliative skin conditions, withhold dacomitinib. Initiate or continue treatment and/or provide additional treatment (e.g., broad spectrum oral or intravenous antibiotics and topical steroids). Upon recovery to Grade ≤ 1, resume dacomitinib with a reduction of 1 dose level.

Other	• For Grade 1 or 2 toxicity, no dose modification is required. • For Grade ≥ 3 toxicity, withhold dacomitinib until symptoms resolve to Grade ≤ 2. Upon recovery, resume dacomitinib with a reduction of 1 dose level.

References:

1. https://www.medicines.org.uk/emc/product/10356/smpc