BC Cancer Protocol Summary for First-Line Treatment of Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Platinum, Pemetrexed and Osimertinib

Protocol Code	*LUAVPPOSI*
Tumour Group	*Lung*
Contact Physician	*LU Systemic Therapy*

ELIGIBILITY:
Patients must have:
- Previously untreated locally advanced, metastatic, or recurrent non-squamous NSCLC not amenable to curative surgery or radiation,
- EGFR mutation-positive tumour with exon 19 or L858R mutation, either alone or in combination with other EGFR mutations, and
- ECOG performance status of 0 or 1.

Patients should have:
- Adequate hematologic, hepatic and renal function, and
- Asymptomatic/stable brain metastases (if applicable)

Note:
- Patients may be started on osimertinib (LUAVOSIF) while waiting for chemotherapy to be scheduled for a maximum of 30 days

EXCLUSIONS:
Patients must not have:
- Progression on or within 6 months of completing adjuvant or neoadjuvant treatment,
- Had previous treatment in the advanced setting,
- ECOG greater than or equal to 2,
- Congenital long QT syndrome or a persistent corrected QT interval (QTc) of ≥ 470 msec, or
- History of interstitial lung disease (ILD)

TESTS:

- Baseline: CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, calcium, magnesium, ECG
- Baseline, if clinically indicated: MUGA scan or echocardiogram (monitoring of LVEF is recommended at baseline and at 12-week intervals)
- Before each treatment Cycles 1 to 4: CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, calcium, magnesium
- Before each treatment Cycles 5 onwards: CBC & Diff, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, calcium, magnesium
- If clinically indicated: ECG, chest x-ray or CT chest, MUGA scan or echocardiogram (monitoring of LVEF is recommended at baseline and at 12-week intervals)

PREMEDICATIONS:

- **Vitamin supplementation mandatory** starting at least 7 days prior to the first cycle, and to continue while on treatment, until 21 days after last pemetrexed dose:
  - folic acid 0.35 to 1 mg PO daily
  - vitamin B12 1000 mcg IM every 9 weeks
- **Cycles 1 to 4 only:** Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA).
  - **Prophylaxis for skin rash:** dexamethasone 8 to 12 mg PO prior to treatment, then 4 mg PO every 12 hours for 4 doses.
- **Cycle 5 onwards:** Antiemetics are not usually required.
  - **Prophylaxis for skin rash:** dexamethasone 4 mg PO BID for 3 days beginning the day before pemetrexed. (May proceed with treatment even if patient has not taken the pre-treatment dexamethasone doses. Instruct patient to begin immediately)

TREATMENT:
Cycles 1 to 4:

Drug	Dose	BC Cancer Administration Guideline
pemetrexed	500 mg/m^2	IV in 100 mL NS over 10 minutes*
CISplatin	75 mg/m^2	IV in 500 mL NS over 1 hour†
osimertinib	80 mg once daily	PO

* Pemetrexed may be given anytime during the pre-hydration period
† Pre- and post-hydration protocol for high-dose CISplatin required according to institutional guidelines (eg, prehydration with 1 L NS over 1 hour, CISplatin in 500 mL NS with potassium chloride 20 mEq, magnesium sulfate 1 g and mannitol 30 g)

- Repeat every 3 weeks for up to 4 cycles, then proceed to maintenance treatment

(cycle 5 onwards).

Cycle 5 onwards:

Drug	Dose	BC Cancer Administration Guideline
pemetrexed	500 mg/m^2	IV in 100 mL NS over 10 minutes
osimertinib	80 mg once daily	PO

- Repeat every 3 weeks until disease progression or unacceptable toxicity.
- If intolerant to maintenance pemetrexed, may continue maintenance therapy with single-agent osimertinib.

DOSE MODIFICATIONS:

1. HEMATOLOGY

***Based on day 1 counts*:**

ANC (x 10^9/L)		Platelets (x 10^9/L)	CISplatin and Pemetrexed Dose
greater than or equal to 1.5	and	greater than or equal to 100	100%
less than 1.5	or	less than 100	**Delay**

2. RENAL DYSFUNCTION

Calculated Cr Clearance (mL/min)	CISplatin Dose	Pemetrexed Dose
greater than or equal to 60	100%	100%
45 to less than 60	80% CISplatin or use CARBOplatin option	100%
less than 45	Hold regardless of type of platinum	Hold regardless of type of platinum

Alternatively, CARBOplatin may be used instead of CISplatin:

Drug	Dose	BC Cancer Administration Guideline
pemetrexed	500 mg/m^2	IV in 100 mL NS over 10 minutes
CARBOplatin	AUC 5 Dose = AUC x (GFR[††] +25)	IV in 250 mL NS over 30 minutes
osimertinib	80 mg once daily	PO

[††] GFR may be determined by nuclear renogram or estimated by the Cockcroft formula, at the discretion of the attending physician:

$$GFR = \frac{N \times (140\text{-age in years}) \times \text{wt (kg)}}{\text{Serum creatinine (micromol/L)}}$$

N = 1.04 (women) or 1.23 (men)

The estimated GFR should be capped at 125 mL/min when it is used to calculate the initial CARBOplatin dose. When a nuclear renogram is available, this clearance would take precedence.

- Repeat every 3 weeks for up to 4 cycles, then proceed to maintenance treatment (cycle 5 onwards).

3. MUCOSITIS

For next cycle:

Mucositis Grade	CISplatin dose	Pemetrexed dose
0-2	100%	100%
3-4	100%	50% previous dose*
***Discontinue treatment after two dose reductions**		

4. OTHER TOXICITIES:

- For any other grade 3 or higher toxicity, delay CISplatin and pemetrexed treatment until toxicity resolves, then resume with 25% dose decrease if considered appropriate to resume by attending oncologist

5. OSIMERTINIB DOSE MODIFICATIONS:

Dose level -1: osimertinib 40 mg PO once daily

1. **Renal Impairment:** dose modification is not required in patients with mild or moderate renal impairment. Safety and efficacy has not been established in patients with end-stage renal disease (CrCl < 15 mL/min) or on dialysis.
2. **Hepatic Impairment:** dose modification is not required in patients with mild hepatic impairment. Safety and efficacy has not been established in patients with moderate or severe hepatic impairment.
3. **Interstitial Lung Disease (ILD):** permanently discontinue osimertinib for development of any grade of treatment-related ILD/pneumonitis.
4. **QT Prolongation:** treatment interruption and subsequent dose reduction is required for development of QTc prolongation (QTc > 500 msec on at least two 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). If QTc interval prolongation with signs/symptoms of serious arrhythmia, permanently discontinue osimertinib.
5. **Left Ventricular Dysfunction/Cardiomyopathy:** treatment interruption is recommended for asymptomatic, absolute decreases in LVEF of 10% from baseline and LVEF below 50%. If *symptomatic* congestive heart failure occurs at any time, treatment should be permanently discontinued.

PRECAUTIONS:

1. **Vitamin supplements**: appropriate prescription of folic acid and vitamin B12 is essential. The incidence of adverse events such as febrile neutropenia related to pemetrexed is higher without vitamin supplementation.
2. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
3. **NSAIDs**: Concurrent nonsteroidal anti-inflammatory agents should be avoided as they may decrease the renal clearance of pemetrexed.
4. **Renal Toxicity**: nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Use caution with pre-existing renal dysfunction.
5. **Neurotoxicity**: CISplatin is neurotoxic and may have to be discontinued if functionally important neuropathy develops. Particular caution must be used in individuals with existing neuropathy.
6. **Ototoxicity**: CISplatin is ototoxic and its use must be cautioned in individuals with existing hearing loss.
7. **Cardiomyopathy**: congestive heart failure, pulmonary edema, and decreased ejection fraction have been observed in patients treated with osimertinib. Fatal cardiomyopathy has been reported. LVEF should be assessed regularly during treatment, particularly in patients with known cardiac risk factors, and in patients who develop treatment-related cardiac symptoms.

8. **QT Interval Prolongation**: osimertinib is associated with concentration-dependent QT interval prolongation. Monitor ECG at baseline and correct electrolyte abnormalities prior to treatment. Continued monitoring of ECG and electrolytes is recommended during treatment, particularly in patients with predisposing conditions, and in those receiving concomitant drugs known to prolong the QT interval.
9. **Respiratory**: osimertinib has been associated with severe, life-threatening or fatal treatment-related interstitial lung disease/pneumonitis. Patients should be regularly monitored for pulmonary symptoms indicative of pneumonitis.
10. **Ocular Disorders:** osimertinib has been associated with keratitis, conjunctivitis, blepharitis, and dry eye. Ophthalmologic consultation should be considered for associated symptoms. Contact lens use is known to be an independent risk factor for ocular toxicity, including keratitis. Caution should be exercised when driving or operating machinery.
11. **Drug interactions**: concurrent use of strong CYP3A inducers should be avoided with osimertinib. If possible, concurrent therapy with drugs that prolong the QTc interval or disrupt electrolyte levels should also be avoided.
12. **Skin toxicity**: rash, including dermatitis acneiform, drug eruption, folliculitis, rash erythematous and maculopapular are common with osimertinib use. They appear on the face, scalp, “v”-shaped area of the chest, upper trunk and less frequently on the extremities, lower back, abdomen and buttocks. Severe rashes may require dose interruption and modification.
13. **Paronychia**: osimertinib is associated with paronychia, which typically occurs later in treatment (e.g., 4-8 weeks) and can cause severe pain. Preventative measures and good skin care may help to reduce the frequency and severity of symptoms.

Contact the LU Systemic Therapy physician at your regional cancer centre or LU Systemic Therapy Chair with any problems or questions regarding this treatment program.

REFERENCES:

1. Planchard D, Jänne PA, Cheng Y, et al; FLAURA2 Investigators. Osimertinib with or without Chemotherapy in *EGFR*-Mutated Advanced NSCLC. N Engl J Med. 2023 Nov 23;389(21):1935-1948.
2. Osimertinib (Tagrisso) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies, October 2024; 4(10): 1-26.