Indication	Osimertinib in combination with pemetrexed and carboplatin for the first line treatment of recurrent or locally advanced or metastatic non-small cell lung cancer exhibiting epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution mutations. Patients must have had no prior treatment with an EGFR inhibitor unless previously treated with adjuvant osimertinib for resected stages IB to N2 only IIIB NSCLC and they did not progress whilst still receiving adjuvant osimertinib. NB the patients must have not received any previous cytotoxic chemotherapy or immunotherapy for recurrent/locally advanced/metastatic disease unless there was a clinically urgent need to give before the EGFR mutation status was known, in which case they may have received one cycle of cytotoxic chemotherapy.
Treatment Intent	Palliative
Frequency and number of cycles	Osimertinib and pemetrexed with carboplatin: Repeat every 21 days for a maximum of 4 cycles. Followed by Osimertinib and maintenance pemetrexed: Repeat every 21 days until disease progression or unacceptable toxicity or withdrawal of patient consent. Note: the use of osimertinib should be stopped if there is disease progression in the CNS that cannot be treated with surgery or stereotactic radiotherapy. A formal medical review as to how osimertinib plus chemotherapy is being tolerated and whether treatment should continue or not will be scheduled to occur at least by the end of the second 3-weekly cycle of treatment.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • **Haematological parameters:** • **Cycle 1 to 4:** • EDTA/DTPA should be used to measure GFR prior to cycle 1. C+G may be used to estimate CrCl if there is a delay in obtaining EDTA result, must be>/=45ml/min. • If EDTA unavailable carboplatin should be dosed on C&G at a dose of AUC 5. If, during treatment, GFR is reduced by >10% from baseline, discuss with clinician. • Monitor FBC, LFT's and U&E's at each cycle. • If WBC >3 and neuts 1.0-1.5 and PLT >/=100 proceed with chemo OR If neuts >1.5 and PLT >100 proceed with chemo. • If blood parameters not met interrupt treatment until recovery. • **Cycle 5 onwards:** • Monitor FBC, LFT's and U&E's at each cycle. • If WBC >3 and neuts 1.0-1.5 and PLT >/=100 proceed with chemo OR If neuts >1.5 and PLT >100 proceed with chemo. • If blood parameters not met interrupt treatment until recovery.

- **Osimertinib cardiac monitoring:**
  - For patients with CHF, electrolyte abnormalities or taking medication known to prolong QTc, monitor electrolytes and ECGs at baseline, after one month then as clinically indicated. Refer to Table 1 for dose modifications.
  - Cardiac monitoring including an assessment of LVEF at baseline and during treatment, should be considered in patients with cardiac risk factors, conditions that can affect LVEF, and in patients who develop relevant cardiac signs/symptoms during treatment.
- **Hepatic impairment:**
  - **Carboplatin:** No dose adjustment required.
  - **Pemetrexed:** d/w consultant in hepatic impairment (bilirubin >1.5 x ULN, AST / ALT > 3 x ULN, or AST/ ALT >5 x ULN if liver involvement), no data available.
  - **Osimertinib:** No dose adjustments recommended in mild or moderate (Child Pugh A or B) hepatic impairment. No dose adjustment is recommended if bilirubin ≤ 3 x ULN and any AST or total bilirubin </= ULN and AST >ULN. The safety and efficacy has not been established in severe hepatic impairment and is therefore not recommended.
- **Renal impairment:**
  - **Carboplatin:** stop if CrCl <30ml/min
  - **Pemetrexed:** If CrCl <45ml/min discontinue.
  - **Osimertinib:** No dose adjustment in mild, moderate or severe renal impairment. Limited data is available, and as such, caution is recommended in patients with end stage renal impairment (CrCl <15ml/min).
- **Carboplatin Infusion-related reactions:**
  - Mild/moderate reactions (grade 1-2): If symptoms resolve after treatment with hydrocortisone and chlorphenamine, the infusion may be restarted at 50% rate for 30 mins, then, if no further reaction, increase to 100% rate.
  - If symptoms do not resolve after treatment with hydrocortisone and chlorphenamine, do not restart the infusion. At consultant's discretion, patients may be rechallenged at a later date with additional prophylaxis. In the event of further reaction (grade 1-3), stop infusion and consider alternative treatment.
  - Severe (grade 3): Do not restart infusion. Consider alternative treatment.
  - Anaphylaxis (grade 4): Follow anaphylaxis protocol. Discontinue permanently and consider alternative treatment.
- **Management of adverse reactions and dose adjustments:**
- Osimertinib:
  - Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose should be reduced to 40 mg taken once daily.
  - If withheld for haematological toxicity and counts recover within 3 weeks of stopping osimertinib, re-start treatment either at 80mg od, or with a reduction to 40mg od. If blood counts do not recover after 3 weeks, permanently discontinue osimertinib.
  - Refer to Table 1 for dose modifications in the event of adverse reactions.
  - Assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude ILD. Treatment should be suspended whilst symptoms are investigated.
  - If ILD or pneumonitis is confirmed – permanently discontinue osimertinib
  - Steven Johnsons syndrome (SJS) and Toxic epidermal necrolysis (TEN): Cases of SJS and TEN have been observed. If symptoms or signs of SJS or TEN appear, treatment with osimertinib should be interrupted or discontinued and the patient referred to a specialised unit for assessment and treatment.
  - Routine use of skin moisturiser should be encouraged.
- **Pemetrexed and Carboplatin:**
  - Interruption of 2 weeks or 2 separate delays warrants DR of 25% of carboplatin/pemetrexed.

	○ Neurotoxicity >/= grade 2 d/w consultant. ○ For other adverse effects, dose reduction should be considered if grade 3 or 4 non-haematological toxicity or repeat appearance of grade 2 (except N&V and alopecia). Delay until resolution of toxicity to < grade1. ○ Discontinue if a patient experiences any grade 3 or 4 toxicity after 2 dose reductions. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** • **Osimertinib:** Concomitant use of strong CYP3A inducers (e.g. rifampicin, carbamazepine, phenytoin) should be avoided. Concomitant use of St John's wort is contraindicated. Moderate CYP3A4 inducers should be used with caution. • **Pemetrexed:** Concomitant nephrotoxic drugs, probenecid, penicillin, NSAIDs use with caution (see SPC). • **Carboplatin:** Caution with other nephrotoxic drugs. • **Missed dose:** If a dose of osimertinib is missed, then it should be taken as soon as the patient remembers unless it is less than 12 hours before the next dose, in which case the patient should not take the missed dose. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet. • **Driving:** May cause fatigue in some patients and therefore use caution when driving or using machines. • **Notes on adjunctive medication** ○ The first Vitamin B12 (hydroxocobalamin) injection should be administered in the week preceding first cycle of chemotherapy and once every 3 cycles thereafter (can be given on the same day as pemetrexed). ○ Folic acid 400 micrograms PO OD should be started 7 days prior to the first dose of pemetrexed and continued until 21 days after last cycle of chemotherapy. ○ Ensure dexamethasone pre-medication has been taken prior to administering pemetrexed.
References	CDF list V1. 359 accessed online 15.04.2025 pemetrexed (Sandoz limited) SPC accessed online 30.04.2025 Tagrisso SPC accessed online 30.04.2025 KMCC protocol LUN-031 V5

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1: Recommended dose modifications for adverse reactions for osimertinib

Target organ	**Adverse reaction**[a]	**Dose modification**
Pulmonary	ILD/Pneumonitis	Permanently discontinue
Cardiac	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold 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
Other, including: • Primary rash • Diarrhoea • Mucositis	Grade 3 or higher adverse reaction	Withhold osimertinib for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding for up to 3 weeks	Osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue.
[a]The intensity of clinical adverse events graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.		

Cycle 1 to 4: repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	**PEMETREXED**	**500mg/m^2**	IV	10min	100ml Sodium Chloride 0.9% or 5% glucose. (diluent dependent on brand)
	Please ensure 30-minute break between pemetrexed and carboplatin administration				
	Ondansetron	<75yrs=16mg >/=75yrs= 8mg	IV	15 min	Sodium chloride 0.9% 50ml
	CARBOPLATIN	**AUC 5 Dose = AUC X (GFR + 25)** Maximum dose 700mg	IV	30 mins	In Glucose 5% 500ml
TTO	Drug	Dose	Route	Directions	
Day 1	**OSIMERTINIB**	**80mg**	PO	OD. Available as 40mg and 80mg tablets. Swallow whole at the same time each day. Tablets should not be chewed or crushed. For patients who cannot swallow tablets, the dose may be dispersed in approx 50ml of noncarbonated drinking water. The tablet should be dropped into the water without crushing it, and stirred until dispersed. The dispersion should be swallowed immediately. The glass should then be rinsed with further water which should also be swallowed. Pack size 30 tablets Check supply before dispensing	
	Dexamethasone	4mg	PO	BD for 5 days starting the day before chemotherapy	
	Metoclopramide	10mg	PO	3 times a day for 3 days then 10mg up to 3 times a day when required. Do not take for more than 5 days continuously.	
	Folic acid	400 micrograms	PO	OD starting 7 days prior to first dose of pemetrexed and continue until 21 days after last cycle of chemo-therapy. Dispense original pack (90 tablets) when required.	
	Loperamide	2mg-4mg	PO	Take 4mg initially then 2mg after each loose stool when required (max 16mg a day) (dispense 1 x OP on cycle 1, then only when required)	
Dispense prior to cycle 1 and every 3 cycles thereafter	Vitamin B_{12} injection	1000 micrograms	Intramuscular	First dose in the week preceding cycle 1, then every 3rd cycle for the duration of treatment (PLT must be ≥50 for intramuscular injection). Dispense prior to cycle 1 for first dose.	

Cycle 5 onwards: repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	**PEMETREXED**	**500mg/m^2**	IV	10min	100ml Sodium Chloride 0.9% or 5% glucose. (diluent dependent on brand)
TTO	Drug	Dose	Route	Directions	
Day 1	**OSIMERTINIB**	**80mg**	PO	OD. Available as 40mg and 80mg tablets. Swallow whole at the same time each day. Tablets should not be chewed or crushed. For patients who cannot swallow tablets, the dose may be dispersed in approx 50ml of noncarbonated drinking water. The tablet should be dropped into the water without crushing it, and stirred until dispersed. The dispersion should be swallowed immediately. The glass should then be rinsed with further water which should also be swallowed. Pack size 30 tablets Check supply before dispensing	
	Dexamethasone	4mg	PO	BD for 3 days starting the day before chemotherapy	
	Metoclopramide	10mg	PO	3 times a day for 3 days then 10mg up to 3 times a day when required. Do not take for more than 5 days continuously.	
	Folic acid	400 micrograms	PO	OD starting 7 days prior to first dose of pemetrexed and continue until 21 days after last cycle of chemotherapy. Dispense original pack (90 tablets) when required.	
	Loperamide	2mg-4mg	PO	Take 4mg initially then 2mg after each loose stool when required (max 16mg a day) (dispense 1 x OP on cycle 1, then only when required)	
Dispense prior to cycle 1 and every 3 cycles thereafter	Vitamin B_{12} injection	1000 micrograms	Intramuscular	First dose in the week preceding cycle 1, then every 3rd cycle for the duration of treatment (PLT must be ≥50 for intramuscular injection). Dispense prior to cycle 1 for first dose.	