OSIMERTINIB (Tagrisso) PEMETREXED CARBOPLATIN

INDICATION (ICD10) C34

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (OSI4)

1. Osimertinib in combination with pemetrexed and platinum-based chemotherapy for the first line treatment of adult patients with 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, has had no prior treatment with an EGFR inhibitor unless osimertinib has been received as adjuvant treatment for resected stages IB to N2 only IIIB NSCLC with either an EGFR exon 19 deletion or exon 21 substitution mutation and the patient did not progress whilst still receiving adjuvant Osimertinib. If CNS spread is present is either asymptomatic and not requiring regular steroids or has a stable neurological status for at least 2 weeks after completion of definitive therapy. PS 0 or 1.

REGIMEN

Cycles 1 to 4

Carboplatin to start 30 minutes after completing pemetrexed

Day 1	Pre-medication: Dexamethasone 4mg bd for 3 days (starting the day before chemotherapy)	
	PEMETREXED	500mg/m^2 in #ml diluent IV infusion over 10 minutes
	CARBOPLATIN	AUC 5 in #ml glucose 5% IV infusion over 30 minutes
		Dose calculated by EDTA GFR or calculated CrCl + 25 x AUC. (Maximum dose when using CrCl 125+25 x AUC)
Days 1 to 21*	OSIMERTINIB 80mg tablet orally once daily continuously	

Cycle 5 onwards (if continuing beyond cycle 34 discontinue on Aria and restart at cycle 5)

Day 1	Pre-medication: Dexamethasone 4mg bd for 3 days (starting the day before chemotherapy)	
	PEMETREXED	500mg/m^2 in #ml diluent IV infusion over 10 minutes
Days 1 to 21	OSIMERTINIB 80mg tablet orally once daily continuously	

diluent volume for dose prescribed as per national standardised product specification or licensed dose

*If there is an urgent clinical need to commence osimertinib prior to the cytotoxic chemotherapy, it is permitted, but the maximum supply of osimertinib before chemotherapy commences is 30 days (1 original pack of osimertinib tablets) and there must be no undue delay in the commencement of cytotoxic chemotherapy.

CYCLE FREQUENCY AND NUMBER OF CYCLES

Combination treatment every 21 days for 4 cycles. A formal medical review as to how osimertinib plus chemotherapy is being tolerated and whether treatment with such treatment should continue or not will be scheduled to occur at least by the end of the second 3-weekly cycle of treatment. Osimertinib and pemetrexed every 21 days from cycle 5 until disease progression. Osimertinib should be stopped if there is disease progression in the CNS that cannot be treated with surgery or stereotactic radiotherapy.

ADMINISTRATION

Osimertinib
Available as 40mg and 80mg tablets.
Swallowed whole with water once daily With or without food.
If the patient is unable to swallow the tablet, the tablet may first be dispersed in 50ml of non-carbonated water. It should be dropped in the water, without crushing, stirred until dispersed and immediately swallowed. An additional half a glass of water should be added to ensure that no residue remains and then immediately swallowed. No other liquids should be added.

ANTI-EMETICS

Moderate risk day 1 cycles 1 to 4 (carboplatin containing cycles)
Low risk day 1 cycle 5 onwards

CONCURRENT MEDICATION REQUIRED

Carboplatin	Anaphylaxis treatment should be prescribed if the patient has had an anaphylactic episode previously. Dexamethasone 20mg IV bolus Chlorphenamine 10mg IV bolus Carboplatin should be given at a slower rate e.g. 2-4 hours.
Osimertinib	Some of the following may be required for treatment of the skin rash: E45 / Diprobase, Hydrocortisone 1%/2.5%, Clindamycin gel 1%, Oxytetracycline 500mg po bd (for 2 weeks) Prednisolone 25mg po od for 7 days then reducing by 5mg per day to stop. Diarrhoea – Loperamide may be required
Pemetrexed	Ensure premedication taken Dexamethasone 4mg bd for 3 days (starting the day before chemotherapy) Folic acid 400mcg/day orally starting 1 to 3 weeks before chemotherapy continuing until 21 days after the last dose of pemetrexed. Hydroxycobalamin 1000mcg IM every 9 weeks starting 1 to 3 weeks before chemotherapy (give with every 3rd cycle of chemotherapy)

EXTRAVASATION AND TYPE OF LINE / FILTERS

Carboplatin – irritant
Pemetrexed - inflammatory

Peripheral line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs every cycle
Mg^{++} baseline and then as clinically indicated
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
GFR assessed using EDTA result or calculated creatinine clearance at the Consultant's discretion.
Patients with hydronephrosis or serum creatinine ≥100micromol/L need a serum creatinine checked every cycle.
ECG at baseline, after 2 weeks of treatment and for patients with ongoing risk of other QT prolonging medication or cardiac failure
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Carboplatin	Ototoxicity - monitor Neurotoxicity – monitor.
Osimertinib	Skin rash – initial rash may be severe. If infected may require oral antibiotics Diarrhoea - dose reduction may be required. Moderate or severe diarrhoea may require loperamide Interstitial lung disease/pneumonitis Cardiomyopathy QTc interval prolongation
Pemetrexed	Skin reactions Pneumonitis

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Carboplatin	Aminoglycosides increased risk of nephrotoxicity and ototoxicity. Renal function should be well monitored and audiometric tests as required. Carboplatin can cause a decrease in phenytoin serum levels. This may lead to reappearance of seizures and may require an increase of phenytoin dosages.
Osimertinib	Strong CYP3A inducers eg rifampicin and clarithromycin should be avoided
Pemetrexed	Aminogycosides – increased risk of nephrotoxicity and ototoxicity NSAIDs Avoid for at least 5 days prior to and 2 days after pemetrexed dose.

DOSE MODIFICATIONS

Haematological

Osimertinib

If neutrophils <1.0x10^9/l or platelets <50x10^9/l, osimertinib should be interrupted until blood counts have recovered.

If 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.

Aplastic anaemia - discontinue permanently.

Pemetrexed

Delay treatment until resolution then treat with appropriate dose modification.

Nadir neutrophils <0.5 and nadir platelets >50	75% of previous dose
Nadir platelets ≤50 regardless of nadir neutrophils	50% of previous dose

Treatment with pemetrexed should be discontinued if a patient experiences any haematologic or non-haematologic grade 3 or 4 toxicity after 2 dose reductions.

Non-haematological

Osimertinib

Cardiac

QTc interval >500msec on at least 2 separate occasions	Withold until interval <481 or recovery to baseline if baseline >481msec then resume at 40mg

QTC prolongation with signs/symptoms of life threatening arrhythmia	Discontinue permanently

Cutaneous
Stevens-Johnson syndrome - discontinue permanently

Other
Grade 3 or higher adverse reaction – withhold for up to 3 weeks
If improvement to grade 0-2 within 3 weeks - resume at 80mg or 40mg daily
If no improvement within 3 weeks - discontinue permanently

Pulmonary
Interstitial lung disease /pneumonitis - discontinue permanently

Pemetrexed

Any grade 3 or 4 non-haematological toxicities except mucositis	Give 75% of previous dose
Any diarrhoea requiring hospitalisation (irrespective of grade) or grade 3 or 4 diarrhoea	Give 75% of previous dose
Grade 3 or 4 mucositis	Give 50% of previous dose
Neurotoxicity grade 3 or 4	Discontinue therapy
If a patient experiences any haematological or non-haematological grade 3 or 4 toxicity after 2 dose reductions or immediately if grade 3 or 4 neurotoxicity is observed.	Discontinue therapy

Hepatic impairment
Osimertinib
No dose adjustments are necessary in patients with mild hepatic impairment (Child Pugh A) or moderate hepatic impairment (Child Pugh B).
No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1.0-1.5xULN and any AST) or moderate hepatic impairment (total bilirubin 1.5-3xULN and any AST).
Use in patients with severe hepatic impairment is not recommended

Pemetrexed
Total bilirubin should be ≤1.5xULN.
Alk phos, AST and ALT ≤3xULN. (Alk phos, AST, and ALT ≤5x normal is acceptable if liver has tumour involvement). Clinical decision

Renal impairment
Carboplatin

GFR / calculated CrCl ≤20ml/min or ≤30ml/min with pre-existing severe renal impairment	contraindicated

Osimertinib
Caution in severe renal impairment (CrCl <15ml/min) or end stage renal impairment.

Pemetrexed

CrCl ≤45ml/min	Not recommended

REFERENCES

1. CDF