Indication	Neoadjuvant treatment of previously untreated stage IIA or IIB or IIIA or N2 only IIIB non-small cell lung cancer and who are candidates for potentially curative surgery. Patients must not have an EGFR 19 or 21 mutation or an ALK gene fusion.
Treatment Intent	Neo-adjuvant
Frequency and number of cycles	Every 3 weeks for 3 cycles or until disease progression or unacceptable toxicity or withdrawal of patient consent. Formal medical review should take place before the end of the 2nd cycle of treatment. NB: • If the patient has a resection, adjuvant immunotherapy is not allowed in patients treated with neoadjuvant nivolumab plus chemotherapy. • If there is disease progression during neoadjuvant nivolumab plus chemotherapy, no further anti-PD1 or anti-PDL1 immunotherapy is funded in any indication. • Where patients do not go on to have a resection, see Blueteq form for eligibility for subsequent 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. • EDTA / DTPA or Est CrCl should be checked prior to cycle 1, must be >/= 45ml/min. If, during treatment, GFR is reduced by >10% from baseline, discuss with clinician. • Monitor FBC, U&E's, LFT's, and random glucose at each cycle. • If neuts >/=1.5 and PLT >/=100 proceed with treatment. • If blood parameters not met defer treatment 1 week and see dose reductions below. • Thyroid function must be assessed at baseline then every 6 weeks or as clinically indicated. • Cortisol monitoring should be undertaken in line with ESMO immunotherapy toxicity guidance available on KMCC website (see link below). Cortisol level should not be taken within 24hours of the last steroid dose. • **Hepatic impairment:** • d/w consultant if bilirubin >1.5 x ULN and AST / ALT > 3 x ULN, or AST/ ALT >5 x ULN and liver involvement. No data available for pemetrexed. • Nivolumab: No dose adjustment in mild hepatic impairment. Use with caution in patients with moderate (total bilirubin > 1.5xULN to 3xULN and any AST) or severe (total bilirubin >3xULN and any AST) hepatic impairment. • **Renal Impairment:** • If CrCl <45ml/min discontinue regimen. • Nivolumab: No specific dose adjustment is necessary in patients with mild to moderate renal impairment. Severe renal impairment d/w consultant. • **Adverse events and dose reductions** • 1st dose reduction: pemetrexed 25% DR, Carboplatin AUC 4. • 2nd dose reduction: pemetrexed 50% DR, Carboplatin AUC 3. • Do not dose reduce (or dose escalate) nivolumab. • If neuts <0.5 and/or PLT<50 dose reduce pemetrexed and carboplatin.

	• Febrile neutropenia >/= grade 3 (Neuts <1 and temp >38.3^{0}C or a sustained temperature of >/=38^{0}C for more than one hour) reduce pemetrexed and carboplatin. • Neurotoxicity >/= grade 2 d/w consultant. Discontinue pemetrexed and carboplatin if grade >/=3 neuropathy. • Diarrhoea >/= grade 3 reduce pemetrexed. • For adverse events (other than immune-related adverse events, N&V and alopecia, and those stated above), dose reduction of pemetrexed and/or carboplatin should be considered if grade 3 or 4 non-haematological toxicity or repeat appearance of grade 2. Delay until resolution of toxicity to </= grade 1. Discontinue pemetrexed and/or carboplatin if a patient experiences any grade 3 or 4 toxicity after 2 dose reductions. • **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. • **Nivolumab Infusion-related reactions**: In the event of severe infusion-related reactions, discontinue nivolumab and administer appropriate treatment. In the event of a mild or moderate reaction, treatment may be continued with close monitoring. Pre-medication with paracetamol and chlorphenamine should be considered for subsequent treatment. • Use with caution in patients with any history of active autoimmune disease, or medical conditions requiring systemic immunosuppression, after careful consideration of the potential risk-benefit. • **Immune- related reactions:** • Most common reactions are pneumonitis, colitis, nephritis, hepatitis, hyperthyroidism, hypothyroidism, hypophysitis, diabetes, diabetic ketoacidosis, immune-related rash, hypopituitarism, confusion, peripheral neuropathy, blurred vision, eye pain, hypotension, flushing, arthralgia, and myalgia. • Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported. For signs or symptoms of SJS or TEN, nivolumab should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, nivolumab should be permanently discontinued. • Cases of myocarditis have been reported, if a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment. Once a diagnosis of myocarditis is established, nivolumab should be withheld or permanently discontinued. • Treatment must be permanently discontinued for any grade 4, recurrent grade 3 (or first occurrence of grade 3 if specified in guidance) or Grade 2 or 3 immune related adverse reactions that persist despite treatment modifications and any severe or life-threatening immune-related adverse reactions. Treatment must also be permanently discontinued if corticosteroid dosing cannot be reduced to < 10mg prednisolone or equivalent per day. • If corticosteroids are used to treat an immune related reaction they should be tapered over at least 1 month. Treatment should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy.

	Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.
	• For guidance on managing immune-related adverse reactions, refer to SPC and guidelines available on KMCC website: https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/
	• Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Patients on nivolumab who present with diarrhoea or other symptoms of colitis, and those who do not respond to steroid treatment for immune-related colitis, should be fully investigated. For further guidance see https://www.gov.uk/drug-safety-update/nivolumab-opdivo-reports-of-cytomegalovirus-cmv-gastrointestinal-infection-or-reactivation.
	• Haemophagocytic lymphohistiocytosis (HLH) has been observed with nivolumab. Caution should be taken when nivolumab is administered as monotherapy or in combination with ipilimumab. If HLH is confirmed, administration of nivolumab should be discontinued and treatment for HLH initiated.
	• Each ml of nivolumab contains 0.1 mmol (or 2.5mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet.
	• **Driving / using machinery:** May cause fatigue in some patients and therefore use caution when driving or using machines.
	• The patient should be provided with the OPDIVO® Patient Alert card with each prescription (to be carried until at least 5 months after the last dose of treatment).
	• Patients must be advised to contact the oncology team or the 24-hour hot-line immediately if they experience any side effect, as some side effects worsen rapidly. Prompt management of side effects can ensure that the patient continues with treatment.
	• Patients should be monitored (for at least up to 5 months after the last dose) for immune related adverse reactions as these can occur any time during or after stopping treatment.
	• **Drug Interactions**
	• Concomitant nephrotoxic drugs, probenecid, penicillin, NSAIDs (see SPC)
	• The use of systemic corticosteroids and other immunosuppressants at baseline, before starting treatment, should be avoided, however, systemic corticosteroids and other immunosuppressants can be used after starting treatment to treat immune-related adverse reactions.
	• **Notes on adjunctive medication**
	  • The first Vitamin B12 injection should be administered in the week preceding first cycle of pemetrexed, and at the end of the 3rd cycle.
	  • 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 pemetrexed.
	  • Ensure dexamethasone pre-medication has been taken prior to administering pemetrexed.

References	KMCC protocol LUN-050 V1 SPC accessed online 27.11.2023

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

Cycle 1 -3 Repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		
	NIVOLUMAB	**360mg**	IV	30mins	Can be given undiluted or diluted. If diluted, give in100ml Sodium Chloride 0.9% via in-line low- protein binding 0.2 micrometre filter. The diluted solution should have a final concentration ranging from 1 to 10mg/mL. Flush the line with sodium chloride 0.9% for injection at the end of the infusion.
	Ensure dexamethasone pre-medication has been taken prior to administering pemetrexed.				
	Ondansetron	<75yrs =16mg ≥75yrs =8mg	IV	15min	Sodium chloride 0.9% 50ml
	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				
	CARBOPLATIN	**AUC 5** **Dose = AUC X (GFR + 25)** **Maximum dose 700mg**	IV	30mins	In Glucose 5% 500ml

TTO Cycles 1-3

TTO	Drug	Dose	Route	Directions
Day 1	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Do not take for longer than 3 days without contacting the oncology team. Dispense 30 capsules on cycle 1 then only if specified.
	Filgrastim	300 micrograms or consider dose of 480 micrograms if patient > 80kg	Sub cut	OD for 5 days starting on day 5
	Dexamethasone	4mg	PO	BD for 3 days starting the day before chemotherapy. (Do not dispense on cycle 3)
	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. Maximum 30mg per day including pre-med dose.
	Folic acid	400 micrograms	PO	OD starting 7 days prior to first dose of pemetrexed and continue until 21 days after last cycle of pemetrexed. Dispense original pack (90 tablets).
Dispense prior to cycle 1 and at the end of cycle 3	Vitamin B_{12} injection	1000 micrograms	IM	First dose in the week preceding cycle 1 then a second dose at the end of the 3rd cycle. (PLT must be ≥50 for intramuscular injection).