Indication	Untreated* PD-L1-positive or negative locally advanced or metastatic non-squamous non-small-cell lung cancer, with a histologically- or cytologically- confirmed diagnosis of stage IIIB, IIIC or IV non-squamous non-small cell lung cancer. NB: EGFR and ALK mutation testing must have been done and be negative. * Completion of treatment with chemotherapy or chemoradiotherapy or checkpoint inhibitor immunotherapy as part of neoadjuvant/adjuvant/maintenance therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of recurrent locally advanced or metastatic disease.
Treatment Intent	Palliative
Frequency and number of cycles	Every 3 weeks Maximum of 4 cycles of pembrolizumab, pemetrexed & carboplatin followed, in the absence of disease progression, with pembrolizumab & "maintenance" pemetrexed to continue for a total treatment duration **of 2 years (maximum of 35 cycles)** or until disease progression or unacceptable toxicity or withdrawal of patient consent, whichever occurs first. A formal medical review as to whether treatment with pembrolizumab in combination with pemetrexed plus carboplatin should continue or not will be scheduled to occur at least by the end of the first 6 weeks 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. • EDTA / DPTA or Est CrCl should be checked prior to cycle 1, 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, U&E's, LFT's, LDH, Ca++ and glucose at each cycle. • If WBC >3 and neuts 1.0-1.5 and PLT >/=100 proceed with treatment OR If neuts >1.5 and PLT >100 proceed with treatment. • If blood parameters not met defer treatment 1 week. • Delay of 2 weeks or 2 separate delays warrants dose reduction of 25% of cytotoxics. Do not reduce pembrolizumab. • Thyroid function must be assessed at baseline then every 6 weeks or as clinically indicated. To avoid delays, use previous results for prescribing purposes. • 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 24 hours of the last steroid dose. • **Hepatic impairment:** o Pemetrexed: 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. o Pembrolizumab: No dose adjustment is needed for patients with mild or moderate hepatic impairment. Pembrolizumab has not been studied in patients with severe hepatic impairment. • **Renal Impairment:** o If CrCl <45ml/min discontinue regimen.

- **Infusion related reactions to pembrolizumab**
  - For severe infusion reactions (grade 3-4), infusion should be stopped and pembrolizumab permanently discontinued.
  - Patients with mild or moderate infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.
- **Infusion-related reactions to carboplatin:**
  - 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.
- **Adverse events**
  - Neurotoxicity >/= grade 2 d/w consultant.
  - **Immune-related adverse reactions** may appear during or after treatment. The most common immune-related reactions are: pneumonitis, colitis, nephritis, hepatitis, symptomatic hypophysitis, hyperthyroidism, hypothyroidism and type 1 diabetes. The following additional, immune related adverse reactions have been reported in patients receiving pembrolizumab: uveitis, arthritis, myositis, pancreatitis, severe skin reactions, myasthenic syndrome, encephalitis, Guillain-Barre syndrome, optic neuritis, rhabdomyolysis, sarcoidosis, myocarditis, haemolytic anaemia and partial seizures arising in a patient with inflammatory foci in brain parenchyma.
  - See guidelines for management of immune-related adverse reactions following immunotherapy: https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/ available on KMCC website and the SPC.
  - 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, pembrolizumab should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, pembrolizumab should be permanently discontinued.
  - Pembrolizumab should be permanently discontinued for Grade 4 or recurrent Grade 3 adverse reactions, unless otherwise specified in the SPC.
  - For adverse events (other than neurotoxicity, immune-related adverse events, N&V and alopecia), 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.
  - Pembrolizumab may be continued if pemetrexed / carboplatin are discontinued and pemetrexed / carboplatin may be continued if pembrolizumab is discontinued.
- **Common Drug Interactions (for comprehensive list refer to BNF/SPC):**
  - **Carboplatin:** Concomitant nephrotoxic drugs, probenecid, penicillin, NSAIDs (see SPC).
  - **Pembrolizumab:** The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided; dexamethasone is permitted as

	prescribed within this protocol. Systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions Vaccines should only be given where the benefit outweighs the risk and after discussion between consultant and patient. • **Driving / using machinery:** Pembrolizumab can influence the ability to drive and use machines. Dizziness and fatigue have been reported following administration of pembrolizumab. • Each patient should be given a copy of the Keytruda ® patient alert card at each cycle. • 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. • Treatment breaks of up to 12 weeks beyond the expected 3-weekly cycle length are allowed but solely to allow any immune toxicities to settle. • **Notes on adjunctive medication.** • The first Vitamin B12 injection should be administered in the week preceding first cycle of pemetrexed, and once every 3 cycles thereafter. • 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-036 V4

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

Cycle 1 -4 Repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		
	PEMBROLIZUMAB	**200mg**	IV	30 min	in 100ml Sodium Chloride 0.9% via in-line low- protein binding 0.22 microns 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**
	PEMETREXED	**500mg/m²**	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	15min	Sodium chloride 0.9% 50ml
	CARBOPLATIN	**AUC 5 Dose = AUC X (GFR + 25) Max dose 700mg**	IV	30 mins	In Glucose 5% 500ml

TTO	Drug	Dose	Route	Directions
Day 1	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. 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) when required.
Dispense prior to cycle 1 and once every 3 cycles thereafter	Vitamin B_{12} injection	1000 micrograms	IM	First dose in the week preceding cycle 1 then a second dose at cycle 4. (PLT must be ≥50 for intramuscular injection). For maintenance treatment continue to dispense every 3 cycles thereafter.

Cycle 5 onwards: Repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		
	PEMBROLIZUMAB	**200mg**	IV	30 min	in 100ml Sodium Chloride 0.9% via in-line low- protein binding 0.22 microns 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**
	PEMETREXED	**500mg/m²**	IV	10min	100ml Sodium Chloride 0.9% or 5% glucose. (diluent dependent on brand)
TTO	Drug	Dose	Route	Directions	
Day 1	Dexamethasone	4mg	PO	BD for 3 days starting the day before chemotherapy (Do not dispense on cycle 35)	
	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 chemotherapy. Dispense original pack (90 tablets) when required.	
Dispense prior to cycle 1 and once every 3 cycles thereafter	Vitamin B_{12} injection	1000 micrograms	IM	First dose in the week preceding cycle 1 then a second dose at cycle 4. (PLT must be ≥50 for intramuscular injection) For maintenance treatment continue to dispense every 3 cycles thereafter.	