Indication	Pembrolizumab in combination with chemotherapy for neoadjuvant treatment and then continued as adjuvant monotherapy* for 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. NB: The patient either has been documented as NOT having a NSCLC which harbours an EGFR 19 or 21 mutation or an ALK gene fusion or the patient has a squamous cell carcinoma and a decision to not test for an EGFR 19 or 21 mutation or an ALK gene fusion and proceed with pembrolizumab has been discussed with the patient during the consenting process, i.e. the patient has consented to be treated with an unknown EGFR/ ALK status. Chemotherapy options for neoadjuvant component with pembrolizumab are: A 2-drug combination of Cisplatin or Carboplatin AUC 5 with either pemetrexed or paclitaxel or gemcitabine or vinorelbine. *if the patient does not have surgery or radiotherapy or chemoradiotherapy, no adjuvant pembrolizumab can be given. i) if the patient has a resection, then post-operative radiotherapy or chemoradiotherapy can be given if indicated and in the absence of any progressive disease, the patient can proceed to adjuvant pembrolizumab. ii) if the patient does not have a resection, then post-operative radiotherapy or chemoradiotherapy can be given if indicated and in the absence of any progressive disease, the patient can proceed to adjuvant pembrolizumab. iii) if the patient does not have surgery or radiotherapy or chemoradiotherapy, no adjuvant pembrolizumab can be given. iv) if there is disease progression during neoadjuvant or adjuvant pembrolizumab, no further anti-PD1 or anti-PDL1 immunotherapy is funded in any indication.
Treatment Intent	Neo-adjuvant followed by Adjuvant monotherapy which is intended to commence no later than 12 weeks after surgery. NB for any patient requiring any form of post-operative radiotherapy this is to start no later than 8 weeks after surgery and adjuvant pembrolizumab to commence no later than 4 weeks after completion of radiotherapy.
Frequency and number of cycles	Neoadjuvant pembrolizumab 200mg with chemotherapy repeated every 21 days for a maximum of 4 cycles. (Alternatively, pembrolizumab 400mg iv every 42 days for 2 doses with chemotherapy). Adjuvant pembrolizumab 400mg monotherapy repeat every 42 days for a maximum of 7 cycles (where the patient is unable to tolerate the 400mg 42 day schedule revert to the 200mg 21 day schedule up to a maximum of 13 cycles). Continue pembrolizumab until any local or distant disease progression at any time in the neoadjuvant, peri-operative and adjuvant phases of treatment or unacceptable toxicity or patient choice or until completion of the maximum permitted cycles of adjuvant treatment (7 x 400mg 6-weekly doses or 13 x 200mg 3-weekly doses). A formal medical review must be scheduled to take place by the end of the second 3-weekly cycle to review tolerance and whether to continue 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. • Monitor FBC, U&Es, LFTs, LDH, Ca++ and glucose at each cycle. In addition, for 6 weekly pembrolizumab, monitor FBC, U&Es, LFTs, LDH, Ca++ and glucose 3 weeks after first dose at nurse review. • Refer to chemotherapy protocol for haematological parameters. Where these are not met, d/w consultant. For pembrolizumab monotherapy, if PLT <75 or neuts <1.0 d/w consultant. • 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 24 hours of the last steroid dose. • Confirm the patient has no symptomatically active brain metastases or leptomeningeal metastases. • Data from patients >/= 75 years are limited. For patients ≥ 75 years, pembrolizumab combination therapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis. • **Hepatic impairment:** Prior to treatment: No dose adjustment is needed for patients with mild or moderate hepatic impairment. Pembrolizumab has not been studied in patients with severe hepatic impairment (bilirubin > 1.5 x ULN, ALT, AST > 2.5 x ULN in the absence of liver metastases at baseline). During treatment: For immune related hepatitis see immune related toxicity guidance below. • **Renal impairment:** No specific dose adjustment is necessary in patients with mild to moderate renal impairment. Severe renal impairment d/w consultant, Pembrolizumab has not been studied in patients with CrCl < 30ml/min. • The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided. Systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions. Dexamethasone is permitted as prescribed within cytotoxic chemotherapy protocol. • **Dose reductions:** dose reductions are not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. • **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, Guillian-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/ • 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 may have a minor influence on the ability to drive and use machines. Fatigue has 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.
	• **Infusion related reactions**: Severe infusion-related reactions have been reported in patients receiving pembrolizumab.
	  o For severe infusion reactions (grade 3-4), infusion should be stopped and pembrolizumab permanently discontinued.
	  o Patients with mild or moderate infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.
	• *Pembrolizumab may be restarted within 12 weeks beyond the expected cycle length if an adverse reaction remains at Grade </= 1 and corticosteroid dose has been reduced to </= 10 mg prednisone or equivalent per day.

References	CDF list V1.328 KMCC protocol UGI-069 V3 Pembrolizumab SPC accessed online 24.10.2024

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

NEO-ADJUVANT: In combination with chemotherapy, repeat every 21 day for 4 cycles: give pembrolizumab before chemotherapy (pembrolizumab can be given at 400mg every 42 days if required for 2 doses).

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		Stat **Only dispense when pembrolizumab given as monotherapy. When given in conjunction with chemotherapy, give antiemetics as per chemotherapy protocol.**
	PEMBROLIZUMAB	**200mg**	IV	30 min	In 100ml Sodium Chloride 0.9% via in-line low- protein binding 0.22 microns filter. Flush the line with sodium chloride 0.9% for injection at the end of the infusion
TTO	Drug	Dose	Route	Directions	
Day 1	Metoclopramide	10mg	PO	Up to TDS PRN (max. 30mg per day including 20mg pre-chemo dose) Do not take for more than 5 days continuously. **Only dispense when pembrolizumab given as monotherapy. When given in conjunction with chemotherapy, give antiemetics as per chemotherapy protocol.**	

ADJUVANT: Monotherapy, repeat every 42 days to a maximum of 7 cycles.
Where the patient is unable to tolerate the 400mg 42-day schedule revert to the 200mg 21 day schedule up to a maximum of 13 cycles.

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		Stat
	PEMBROLIZUMAB	**400mg**	IV	30 min	In 100ml Sodium Chloride 0.9% via in-line low- protein binding 0.22 microns filter. Flush the line with sodium chloride 0.9% for injection at the end of the infusion
TTO	Drug	Dose	Route	Directions	
Day 1	Metoclopramide	10mg	PO	Up to TDS PRN (max. 30mg per day including 20mg pre-chemo dose) Do not take for more than 5 days continuously.	