Indication	First line treatment of locally advanced or metastatic squamous non-small cell lung cancer with a PD-L1 tumour proportion score of 0-100% NB: Use only in patients with PD-L1 TPS of 50-100% if they require an urgent clinical response (e.g. impending major airway obstruction). NB: The patient must have not received any prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-CTLA-4 NB: 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	Repeat every 21 days for 4 cycles then repeat every 21 or 42 days depending on cycle choice. Maximum of **4 cycles** of pembrolizumab, carboplatin & paclitaxel followed by, in the absence of disease progression, continued treatment with pembrolizumab monotherapy* to continue for a total treatment duration of 2 years (maximum of 35 cycles including the initial 4 induction cycles of treatment or its equivalent if 6-weekly pembrolizumab monotherapy dosing is used from cycle 5) or until disease progression or unacceptable toxicity or withdrawal of patient consent, whichever occurs first. *There are 2 alternative dosing schedules for pembrolizumab monotherapy, **200mg IV** every **3 weeks** or 400**mg IV** every **6 weeks**. A formal medical review **MUST** occur by the end of the first 6 weeks of treatment to establish whether treatment should continue.
Monitoring Parameters pre-treatment	• **Monitoring parameters for induction phase (cycle 1 -4), for maintenance treatment (from cycle 5) follow KMCC SACT protocol MULTI-003 Pembrolizumab protocol.** • **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 should be used to measure GFR prior to cycle 1, must be >/= 30ml/min. C+G to estimate CrCl may only be used before CYCLE 1 when there is a delay in obtaining EDTA/DTPA result. • Discuss with consultant if creatinine clearance drops by 25%. • Monitor FBC, U&Es, LFTs LDH, Ca++ and glucose at each cycle. • If neuts <1.5 and/or PLT <100 defer treatment by one week and consider dose reduction of paclitaxel and carboplatin on subsequent cycles. Do not reduce pembrolizumab. • Thyroid function must be assessed at baseline then at least every 6 weeks. 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.

- **Renal Impairment:**
  - Carboplatin: stop if CrCl<30ml/min
  - Paclitaxel: no dose reduction necessary.
  - Pembrolizumab: No specific dose adjustment is necessary in patients with mild to moderate renal impairment. Severe renal impairment (CrCl<30ml/min) d/w consultant.
- **Hepatic impairment:** (prior to treatment, for immune related hepatitis see below)
  - Paclitaxel: If bilirubin < 1.25 x ULN and transaminase < 10 x ULN, dose at full dose. Otherwise consider dose reduction, not recommended in severe hepatic impairment.
  - 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.
- **Dose reductions:**
  - Paclitaxel: Dose reduce by 20% in the event of grade >/= 2 neuropathy and consider delay until recovery to </= grade 1. Consider omitting Paclitaxel in event of recurrent grade >/=3 neuropathy OR recurrent or persistent >/=grade 2 neuropathy following a dose reduction.
  - Dose reduction of carboplatin and paclitaxel should be considered if any other grade 3 or 4 non-haematological toxicity or repeat appearance of grade 2 (except N&V and alopecia). Delay until resolution of toxicity to </= grade 1.
  - Pembrolizumab: 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/ 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.
- **Infusion related reactions:**
  If the infusion related reaction can be attributed to a particular agent, treat as follows:
  - **Pembrolizumab:** Severe infusion-related reactions have been reported in patients receiving 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.
  - **Paclitaxel:** Patients developing hypersensitivity reactions may be re-challenged with full dose Paclitaxel following prophylactic medication (e.g. famotidine 40mg po given 4 hours prior to treatment plus hydrocortisone 100mg iv and chlorphenamine 10mg iv 30 minutes prior to treatment), then give paclitaxel over 3-6 hours (i.e. starting at over 6 hours and gradually increase rate if possible).

	○ **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 re-challenged at a later date with additional prophylaxis. In the event of further reaction (grade 1-3), stop infusion and consider desensitisation regimen. Severe (grade 3): Do not restart infusion. Consider re-challenge with carboplatin desensitisation regimen. Anaphylaxis (grade 4): Follow anaphylaxis protocol. Discontinue permanently and consider alternative treatment. • Pembrolizumab may be restarted within 12 weeks after last dose, if an adverse reaction remains at Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day. • **Common Drug Interactions (for comprehensive list refer to BNF/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. ○ **Carboplatin:** Caution with other nephrotoxic drugs. • **Driving/using machinery:** Pembrolizumab may have a minor influence on the ability to drive and use machines. Fatigue has been reported following administration of pembrolizumab. • **Missed dose:** If a planned dose of pembrolizumab is missed, it should be administered as soon as possible. The schedule of administration must be adjusted to maintain the appropriate interval between doses. • 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. • Patients must not have symptomatically active brain metastases or leptomeningeal metastases.
References	KMCC protocol LUN-043 v3

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

Cycles 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. **Flush the line with sodium chloride 0.9% for injection at the end of the infusion**
Give pre-meds 30 minutes prior to paclitaxel					
	Dexamethasone	16mg*	IV	bolus	
	Chlorphenamine	10mg	IV	bolus	
	Ondansetron	< 75yrs 16mg >/=75yrs 8mg	IV	15 min	In 50ml sodium chloride 0.9% 30 minutes prior to paclitaxel
	PACLITAXEL	**200mg/m²**	IV	Over 3 hours	Diluted in 500ml sodium chloride 0.9% (non PVC) Via in-line 0.22micron filter Doses <150mg in 250ml 0.9% sodium chloride
	CARBOPLATIN	**(AUC 6)** **Dose = AUC X (GFR + 25)** **(max 700mg)**	IV	30min	500ml glucose 5%
	***From 3rd infusion dexamethasone maybe reduced to 12mg IV**				

TTO	Drug	Dose	Route	Directions
Day 1	Dexamethasone	6mg	PO	OD for 3 days starting on day 2.
	Metoclopramide	10mg	PO	Up to 3 times a day as required. (max. 30mg per day including 20mg pre-chemo dose) Do not take for more than 5 days continuously.

MAINTENANCE: to continue in the absence of disease progression
Cycle 5 onwards: Repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		stat
	PEMBROLIZUMAB	**200mg**	IV	30min	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 3 times a day as required. (max. 30mg per day including 20mg pre-chemo dose) Do not take for more than 5 days continuously.	

Repeat every 42 days (alternative dosing schedule):

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		stat
	PEMBROLIZUMAB	**400mg**	IV	30min	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 3 times a day as required (max. 30mg per day including 20mg pre-chemo dose) Do not take for more than 5 days continuously.	