Protocol Contains CHECKPOINT INHIBITOR IMMUNOTHERAPY	
Indication	Neo-adjuvant followed by adjuvant pembrolizumab for stage IIIB, C or D macroscopic resectable cutaneous, acral or mucosa melanoma. Patients should have had no prior treatment with any PD-1, PD-L1, PD-L2 or CTLA-4 therapy and have an ECOG PS of 0 or 1. Complete surgical resection of the tumour and therapeutic lymph node dissection should be scheduled to take place within 3 to 5 weeks of the last dose of neoadjuvant pembrolizumab and adjuvant pembrolizumab is expected to start within 3 months of surgery. NB patients with uveal melanoma, microscopic disease, unsuitable for surgical resection or have received any prior immunotherapy treatment for melanoma are not eligible for this treatment option. NB the use of neo-adjuvant followed by adjuvant pembrolizumab in this indication is off-label, therefore Trust policy regarding unlicensed medicines should apply.
Treatment Intent	Curative
Frequency and number of cycles	**Neo-adjuvant:** Pembrolizumab subcutaneous 395mg every 3 weeks for 3 cycles followed by surgery. **Adjuvant: (treatment to commence within 3 months of surgery, ideally as soon as possible)** Pembrolizumab subcutaneous 790mg every 6 weeks for a maximum of 7 cycles or alternatively, if there is a clinical requirement, pembrolizumab subcutaneous 395mg every 3 weeks for a maximum of 15 cycles. Continue until disease recurrence, unacceptable toxicity, loss of patient consent or up to the maximum duration of therapy whichever comes sooner. If a patient is unsuitable for sub cutaneous administration of pembrolizumab, the drug may be given intravenously at a dose of 400mg every 42 days or 200mg every 21 days. Patients can switch to between SC and IV therapy if the clinical need arises, the switch takes place at the next scheduled dose. A formal medical review by an oncologist to assess tolerability of treatment should be scheduled to take place by the start of the 3rd 3-weekly cycle of neoadjuvant treatment.

Monitoring Parameters	• **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.
	• 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.
	• **Pre-treatment cardiac assessment:**
	  ○ **ECG** baseline, then every 6 weeks or as clinically indicated.
	  ○ Check **BNP**, and **Troponin T** prior to treatment.
	• **Hepatic impairment:**
	  ○ **Prior to treatment:** No dose adjustment is needed for patients with for 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.
- **Infusion / injection related reactions:** Severe infusion / injection related reactions have been reported in patients receiving pembrolizumab. For severe infusion related reactions (grade 3-4), treatment should be stopped and pembrolizumab permanently discontinued.
  Patients with mild or moderate reactions may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.
- **Pembrolizumab Sub cutaneous administration:**
  - If SC Injection is being prepared on the ward Trust SOP should be followed.
  - Remove from fridge and allow to reach room temperature for at least 30 minutes before administration.
  - Withdraw the required volume either 2.4 mL (395 mg) or 4.8 mL (790 mg) using a sterile syringe and a transfer needle (18-21G recommended), according to the recommended dosage. To avoid needle clogging, change the needle to a 25-30G, 13 mm hypodermic injection needle immediately prior to subcutaneous injection.
  - Inject into the subcutaneous tissue of the thigh or abdomen, avoiding 5cm area around the navel.
  - Rotate injection sites for subsequent injection, selecting a site that is 2.5 cm from the previous injection site.
  - Do not inject into areas where the skin is damaged, sore, bruised, scarred, scaly, or has red patches.
  - During the treatment other medicinal products for subcutaneous administration should be injected at different sites.
- **Management of adverse reactions and dose adjustments:**
- **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.
- **Dose Modification:** dose reductions are not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.
- 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.
- **Common drug interactions (for comprehensive list refer to BNF/SPC):**
- 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.

	• **Missed dose:** If a planned dose is missed, the next dose should be administered as soon as possible. The administration schedule must be adjusted to maintain a 3-week (or 6-week where appropriate) interval between doses. • **Driving and Machinery:** Pembrolizumab may have a minor influence on the ability to drive and use machines. Fatigue has been reported following administration of pembrolizumab. • **Pregnancy and Contraception:** Women of childbearing potential should use effective contraception during treatment with pembrolizumab and for at least 4 months after the last dose of pembrolizumab. • Each patient should be given a copy of the relevant 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.
References	https://www.england.nhs.uk/wp-content/uploads/2026/04/2426-policy-proposition-neoadjuvant-pembrolizumab-v2.pdf SPC accessed online 12.05.2026 CDF list accessed online 12.05.2026 V1.396

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

Neo-adjuvant phase - Cycle 1 to 3: Repeat every 21 days.
Complete surgical resection of the tumour and therapeutic lymph node dissection should be scheduled to take place within 3 to 5 weeks of the last dose of neo-adjuvant pembrolizumab

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		stat
	PEMBROLIZUMAB	**395mg**	SC	1 min	Inject into the subcutaneous tissue of the left or right thigh or abdomen, avoiding 5cm area around the navel. Do not inject at other sites of the body. Injection sites should be rotated for successive injections.
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.	

Adjuvant phase - Cycle 4 to 10: Repeat every 42 days

Adjuvant pembrolizumab is expected to start within 3 months of surgery.

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		stat
	PEMBROLIZUMAB	**790mg***	SC	2 min	Inject into the subcutaneous tissue of the left or right thigh or abdomen, avoiding 5cm area around the navel. Do not inject at other sites of the body. Injection sites should be rotated for successive injections.
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.	

** Can be given at a dose of 395mg SC every 21 days, cycle 4 to 18, if the clinical need arises.*