Protocol Contains CHECKPOINT INHIBITOR IMMUNOTHERAPY	
Indication	Treatment for non- metastatic, resectable, locally advanced, squamous cell carcinoma of the oral cavity, larynx, hypopharynx, or oropharynx in patients whose tumours express PD-L1 with a combined positive score of 1 or more who are naïve to SACT for H&N cancer. Disease must be staged as below: ○ **HPV-positive oropharyngeal:** Must be Stage III (T4, N0-2, M0). OR ○ **HPV-negative oropharyngeal, larynx, hypopharynx, or oral cavity:** Stage III or IVA
Treatment Intent	Neo-adjuvant pembrolizumab followed by adjuvant pembrolizumab with radiotherapy, with or without cisplatin.
Frequency and number of cycles	**Neo-adjuvant: Pembrolizumab 395mg subcutaneous** monotherapy repeated every 21 days for 2 cycles only. **Adjuvant with radiotherapy:** **Schedule 1 Pembrolizumab 790mg subcutaneous monotherapy*** every **42 days** for a maximum of 8 cycles, from the start of adjuvant treatment, in the absence of disease progression, unacceptable toxicity or withdrawal of patient consent whichever occurs first. **Schedule 2 Pembrolizumab 395mg subcutaneous** with **cisplatin 100mg/m^2** repeated every 21 days for 3 cycles, followed by **pembrolizumab 790mg subcutaneous monotherapy** every 42 days for a maximum of 6 cycles, in the absence of disease progression, unacceptable toxicity or withdrawal of patient consent whichever occurs first. *NB where the patient is unable to tolerate pembrolizumab 790mg SC every 42 days, patients can switch to pembrolizumab 395mg SC every 21 days, the 6-weekly schedule should be used as indicated in this protocol unless there are clear clinical reasons for preferring the 3-weekly schedule. Patients can switch to between SC and IV therapy (400mg iv every 6 weeks or 200mg iv every 3 weeks) if the clinical need arises, the switch takes place at the next scheduled dose.
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. **<u>Guidance for pembrolizumab monotherapy when used in the neo-adjuvant and adjuvant phase:</u>** • Monitor **FBC, U&Es, LFTs**, **LDH**, **Ca++** and **glucose** at each cycle. • If PLT <75 or neuts <1.0 d/w consultant. • During radiotherapy, if Hb <90g/l d/w consultant. • **Thyroid function** must be assessed at baseline then every 6-8 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 6-9 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.
- 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.
- **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.
- **Infusion / injection related reactions:**
    - Severe infusion / injection -related reactions have been reported in patients receiving pembrolizumab.
    - For severe infusion / injection reactions (grade 3-4), treatment should be stopped and pembrolizumab permanently discontinued.
    - Patients with mild or moderate infusion / injection 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 30minutes 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.
- 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.

- **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 6-week (or 3-week where appropriate) interval between doses.
- **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.
  - Vaccines should only be given where the benefit outweighs the risk and after discussion between consultant and patient.
- **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.

<u>Guidance for Pembrolizumab with Cisplatin in the adjuvant phase:</u>

- Consider **audiology** test for hearing impaired patients and monitor all patients for ototoxicity through-out treatment**.**
- C+G or EDTA can be used to measure renal function at clinicians' discretion. Must be >/= 40ml/min. If CrCl 40-60ml/min consider dose reduction of cisplatin.
- Monitor **FBC, U&Es, LFTs**, **LDH**, **Ca++** and **glucose** at each cycle.
- If neuts </=1.5 and/or PLT </=100 d/w consultant.
- During radiotherapy, if Hb <90g/l d/w consultant.
- **Thyroid function** must be assessed at baseline then every 6-8 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.
- **ECG baseline,** then every 6-9 weeks or as clinically indicated**.**
- **Hepatic impairment:**
  - **Cisplatin**- No dose adjustment required.
  - **Pembrolizumab-** see monotherapy section above.
- **Renal impairment:**
  - **Cisplatin** - If CrCl is <30ml/min, discontinue platinum agent.
  - **Pembrolizumab** see monotherapy section above.
- **Dose Modification:**
  - **Cisplatin** – Dose reduction should be considered if 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.
  - Cisplatin is known to induce neurotoxicity, neurologic examination at regular intervals is recommended.
  - In the event cisplatin is not tolerated by the patient it can be omitted or carboplatin prescribed as an alternative.
  - **Pembrolizumab –** dose reductions are not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.
- **Pembrolizumab Immune-related adverse reactions –** see monotherapy section above.
- **Pembrolizumab infusion related reactions –** see monotherapy section above

	• **Common drug interactions (for comprehensive list refer to BNF/SPC):**
	  ○ **Cisplatin -** Caution when used concurrently with other nephrotoxic or ototoxic drugs. Caution in patients receiving phenytoin, levels may be affected.
	• **Pregnancy and contraception:**
	  ○ **Cisplatin:** Women of childbearing potential should use effective contraception and not consider pregnancy during treatment and men are advised to use effective contraception and not to conceive children during treatment see brand specific SPC for further information.
	  ○ **Pembrolizumab-** see monotherapy section above.
	• 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	KMCC protocol MULTI-003 V15 CDF list V1.391 accessed online 01.04.2026 SPC accessed online 03.03.2026 https://www.nejm.org/doi/full/10.1056/NEJMoa2415434 https://clinicaltrials.gov/study/NCT03765918 CDF list V1.402 accessed online 16.06.2026 V2 updated to include Hb guidance during radiotherapy as requested by consultant A. Zeniou

NB for funding information, refer to the CDF and NICE Drugs funding spread sheet

NEO-ADJUVANT:

Cycle 1 and 2 only: Repeat every 21 days

NB Pembrolizumab can be given at a dose of 200mg IV every 21 days if there is a clinical requirement.

Day	Drug	Dose	Route	Injection 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 WITH RADIOTHERAPY for the first 6 to 6.5 weeks: Schedule 1

Cycle 1 to 8 Pembrolizumab monotherapy: Repeat every 42 days

NB Pembrolizumab can be given at a dose of 400mg IV every 42 days if there is a clinical requirement.

Day	Drug	Dose	Route	Injection Duration	Administration
1	Metoclopramide	20mg	PO		stat
	PEMBROLIZUMAB	**790mg**	SC	2 mins	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.	

if the patient is unable to tolerate pembrolizumab 790mg SC every 42 days, patients can switch to pembrolizumab 395mg SC every 21 days.

ADJUVANT WITH RADIOTHERAPY for the first 6 to 6.5 weeks: Schedule 2 Part 1: 3 cycles only

Pembrolizumab with cisplatin: Repeat every 21 days

NB Pembrolizumab can be given at a dose of 200mg IV every 21 days if there is a clinical requirement.

Day	Drug	Dose	Route	Injection 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.
	Sodium Chloride 0.9%	1000ml	IV	2 hrs	+ 20mmol KCL+ 10mmol Mg^{2++}
	Sodium Chloride 0.9%	1000ml	IV	2 hrs	+ 20mmol KCL
	Aprepitant	125mg	PO		Take one 125mg capsule **one hour prior to chemo** on Day 1
	Mannitol 10%	200mls	IV	15 min	
	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 min	Sodium chloride 0.9% 50ml
	Dexamethasone	8mg	PO		
	CISPLATIN	**100mg/m²**	IV	2 hrs	In 1000ml Sodium chloride 0.9%
	Furosemide	40mg	IV/PO		If urine output <100ml/hr or weight gain>2kg
	Sodium chloride 0.9%	1000ml	IV	2 hrs	+ 20mmol KCL + 10mmol Mg^{2}+
	*Furosemide	40mg	IV/po	*** ONLY IF REQ'D**	If patient remains in a 2L positive balance
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.	
	Dexamethasone	6mg	PO	OM for 3 days starting on the day after cisplatin	
	Aprepitant	80mg	PO	80mg OM on day 2 and day 3 only.	
	Ondansetron	8mg	PO	BD for 5 days (start evening of day 1)	

ADJUVANT treatment to continue following completion of schedule 2 part 1

Schedule 2 part 2: pembrolizumab monotherapy for a maximum of 6 cycles: Repeat every 42 days

NB Pembrolizumab can be given at a dose of 395mg SC every 21 days if there is a clinical requirement.

Day	Drug	Dose	Route	Injection Duration	Administration
1	Metoclopramide	20mg	PO		stat
	PEMBROLIZUMAB	**790mg**	SC	2 mins	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.	