Indication	Pembrolizumab in combination with chemotherapy for previously untreated advanced oesophageal (squamous or adenocarcinoma) or HER-2 negative gastroesophageal adenocarcinoma either of which expresses PD-L1 with a combined positive score of >/=10. Chemotherapy options are: Capecitabine & Oxaliplatin Or alternatively if oxaliplatin is unsuitable or squamous carcinoma: Carbo X (UGI-007) CX (UGI-006) CF (UGI-005) CarboF (UGI-008) NB the patient must not have received prior treatment with any antibody which targets PD-1 or PD-L1 or PD-L2 or CD137 or OX40 or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4).
Treatment Intent	Palliative.
Frequency and number of cycles	There are 2 alternative dosing schedules for pembrolizumab, **200mg IV** every **3 weeks** or **400mg IV** every **6 weeks.** For chemotherapy frequency and number of cycles refer to the relevant KMCC protocol. NB: Pembrolizumab & chemotherapy will be built as 6 x 21-day cycles on Aria. Continue pembrolizumab until disease progression or unacceptable toxicity or patient choice or after 2 years of treatment (or after 35 x 3-weekly cycles or its equivalent if 6-weekly dosing is used).
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.
	• **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.
	  ○ 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.
	• *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	UGI-069 V1.1

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

In combination with chemotherapy, repeat every 21 day for 6 cycles: give pembrolizumab before chemotherapy

NB: an alternate schedule of pembrolizumab 400mg every 42 days may be used where appropriate

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.**	

<u>Monotherapy, repeat every 42 days. Where patient is unable to tolerate the 42-day schedule revert to the 21 day schedule.</u>
NB: this alternative dosing schedule may be used in combination with chemotherapy where appropriate (give pembrolizumab before chemotherapy).

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	**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. **Only dispense when pembrolizumab given as monotherapy. When given in conjunction with chemotherapy, give antiemetics as per chemotherapy protocol.**