Indication	**Nivolumab in combination with chemotherapy for untreated unresectable advanced or metastatic squamous cell or adenosquamous carcinoma of the oesophagus with a tumour cell PD-L1 expression of >/=1% and a PD-L1 combined positive score of <10** **Nivolumab in combination with platinum and fluoropyrimidine-based chemotherapy for previously untreated advanced or metastatic HER-2 negative adenocarcinomas of the stomach, gastro-oesophageal junction or oesophagus which express PD-L1 with a combined positive score (CPS) of 5 or more.** NB In **both indications** the patient cannot 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) unless the patient discontinued or completed checkpoint inhibitor immunotherapy as part of adjuvant therapy (NICE TA746) without disease progression and at least 6 months has elapsed between the date of the last immunotherapy treatment and the date of first diagnosis of relapse with recurrent or metastatic disease. Chemotherapy options are: Capecitabine & Oxaliplatin Carbo X (UGI-007) CX (UGI-006) CF (UGI-005) CarboF (UGI-008) NB: Oxaliplatin and Modified DeGramont may also be used as an alternative chemotherapy regimen with nivolumab given at a dose of 240mg every 14 days.
Treatment Intent	Palliative
Frequency and number of cycles	There are 3 schedules for nivolumab*, **360mg IV** every 3 weeks when administered with 3 weekly chemotherapy, **240mg IV** every 2 weeks administered with 2 weekly chemotherapy (Oxaliplatin and Modified DeGramont) and a **480mg IV** 4-weekly maintenance dose. *Some of the dosing schedules for nivolumab are outside the license for the particular indication (the 360mg dosing schedule for nivolumab is unlicensed for squamous cell carcinoma and the 480mg dosing schedule is unlicensed for adenocarcinoma). For full details please see SPC. Clinicians must be mindful of their individual responsibilities, and follow Trust procedures when prescribing unlicensed medicines. For chemotherapy frequency and number of cycles refer to the relevant KMCC protocol. NB: Nivolumab & combination 3 weekly chemotherapy will be built as 6 x 21-day cycles on the eprescribing system. Continue nivolumab until disease progression or unacceptable toxicity or patient choice or after 2 calendar years of treatment regardless of any treatment breaks. A formal medical review must be scheduled to take place by the end of the 2nd cycle of 3 weekly treatment (or equivalent) 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, random blood glucose at each cycle. • Refer to chemotherapy protocol for haematological parameters. Where these are not met, d/w consultant. For nivolumab monotherapy, if PLT <75 or neuts <1.0 d/w consultant. • **Nivolumab monitoring parameters (refer to chemotherapy protocol for chemotherapy monitoring)** • 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 24hours of the last steroid dose. • Confirm the patient has no symptomatically active brain metastases or leptomeningeal metastases. • **Renal impairment:** No specific dose adjustment is necessary in patients with mild to moderate renal impairment. Severe renal impairment d/w consultant. • **Hepatic impairment:** No dose adjustment in mild hepatic impairment. Use with caution in patients with moderate (total bilirubin > 1.5xULN to 3xULN and any AST) or severe (total bilirubin >3xULN and any AST) hepatic impairment. • **Infusion-related reactions**: In the event of severe infusion-related reactions, discontinue nivolumab and administer appropriate treatment. In the event of a mild or moderate reaction, treatment may be continued with close monitoring. Pre-medication with paracetamol and chlorphenamine should be considered for subsequent treatment. • The use of systemic corticosteroids and other immunosuppressants at baseline, before starting treatment, should be avoided, however, systemic corticosteroids and other immunosuppressants can be used after starting treatment to treat immune-related adverse reactions. • **Dose modification:** Dose escalation or reduction of nivolumab is not appropriate. Dosing delay or discontinuation may be required based on individual safety and tolerability. • **Cytomegalovirus (CMV)** infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Patients on nivolumab who present with diarrhoea or other symptoms of colitis, and those who do not respond to steroid treatment for immune-related colitis, should be fully investigated. For further guidance see https://www.gov.uk/drug-safety-update/nivolumab-opdivo-reports-of-cytomegalovirus-cmv-gastrointestinal-infection-or-reactivation. • **Immune- related reactions:** ○ Most common reactions are pneumonitis, colitis, nephritis, hepatitis, hyperthyroidism, hypothyroidism, hypophysitis, diabetes, diabetic ketoacidosis, immune-related rash, hypopituitarism, confusion, peripheral neuropathy, blurred vision, eye pain, hypotension, flushing, arthralgia, and myalgia. ○ 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, nivolumab should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, nivolumab should be permanently discontinued. ○ Cases of myocarditis have been reported, if a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a

	specialist for assessment. Once a diagnosis of myocarditis is established, nivolumab should be withheld or permanently discontinued. ○ Treatment must be permanently discontinued for any grade 4, recurrent grade 3 (or first occurrence of grade 3 if specified in guidance) or Grade 2 or 3 immune related adverse reactions that persist despite treatment modifications and any severe or life-threatening immune-related adverse reactions. Treatment must also be permanently discontinued if corticosteroid dosing cannot be reduced to < 10mg prednisolone or equivalent per day. ○ If corticosteroids are used to treat an immune related reaction they should be tapered over at least 1 month. Treatment should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy. ○ See guidelines for management of immune-related adverse reactions following immunotherapy: https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/ • **Haemophagocytic lymphohistiocytosis (HLH)** has been observed with nivolumab. If HLH is confirmed, administration of nivolumab should be discontinued and treatment for HLH initiated. • Each ml of nivolumab contains 0.1 mmol (or 2.5mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet. • **Driving:** Nivolumab can potentially cause fatigue in some patients and therefore use caution when driving or using machines. • The patient should be provided with the OPDIVO® Patient Alert card with each prescription (to be carried until at least 5 months after the last dose of treatment). • Patients must be advised to contact the oncology team or the 24-hour hot-line immediately 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 should be monitored (for at least up to 5 months after the last dose) for immune related adverse reactions as these can occur any time during or after stopping treatment.
References	KMCC protocol UGI-074 V2 CDF list accessed online 29.07.2024 V1.316

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

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

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	**Give antiemetics as per chemotherapy protocol**				
	NIVOLUMAB	**360mg**	IV	30 min	Can be given undiluted or diluted. If diluted, give in100ml Sodium Chloride 0.9% via in-line low- protein binding 0.2 micrometre filter. The diluted solution should have a final concentration ranging from 1 to 10mg/mL. **Flush the line with sodium chloride 0.9% for injection at the end of the infusion**
TTO	Drug	Dose	Route	Directions	
	Give antiemetics as per chemotherapy protocol.				

NB: Nivolumab may also be given at a dose of 240mg every 14 days if given with 2 weekly chemotherapy

Cycle 7 onwards: Monotherapy, repeat every 28 days.
Where a patient is unable to tolerate nivolumab every 4 weeks, 240mg nivolumab every 2 weeks may be given as an alternative

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	Metoclopramide	20mg	PO		STAT
	NIVOLUMAB	**480mg**	IV	30 min	Can be given undiluted or diluted. If diluted, give in100ml Sodium Chloride 0.9% via in-line low- protein binding 0.2 micrometre filter. The diluted solution should have a final concentration ranging from 1 to 10mg/mL. **Flush the line with sodium chloride 0.9% for injection at the end of the infusion**
TTO	Drug	Dose	Route	Directions	
	Metoclopramide	10mg	PO	10mg 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.	