Indication	Monotherapy for unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 14 days. Continue until disease progression, unacceptable toxicity or patient choice. Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment with nivolumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.
Monitoring Parameters pre-treatment	• Monitor FBC, U&Es, LFTs, random blood glucose at each cycle • If PLT <75 or neuts <1.0 d/w consultant. • Thyroid function and 9am cortisol level must be assessed at baseline then every 8 weeks and as clinical indicated. • **Hepatic Impairment:** No dose adjustment in mild hepatic impairment. Use with caution in patients with moderate (total bilirubin > 1.5 x ULN to 3 x ULN and any AST) or severe (total bilirubin >3 x ULN and any AST) hepatic impairment, d/w consultant as data limited to advise guidance. • **Renal Impairment:** No specific dose adjustment is necessary in patients with mild to moderate renal impairment. Severe renal impairment d/w consultant data to limited to advise guidance. • Use with caution in patients with a baseline performance score >/=2, apparent tumour invasion on organs located adjacent to the oesophagus (e.g. the aorta or respiratory tract), active autoimmune disease, or medical conditions requiring systemic immunosuppression, after careful consideration of the potential risk-benefit. • The patient should have no symptomatically active brain metastases or leptomeningeal metastases. • The use of systemic corticosteroids and immunosuppressant before starting treatment should be avoided, however may be used after starting treatment to treat immune-related adverse reactions. • **Infusion related reaction:** Severe infusion reactions have been reported. In case of a severe or life-threatening infusion reaction, the nivolumab infusion must be discontinued and appropriate medical therapy administered. 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. • **Dose modification:** Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. For treatment modification see table 1 in EAMs protocol: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/890519/Nivolumab_TP_for_HCP.pdf • **Adverse reactions:** • **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 myositis have also been reported. ○ 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 EAMs protocol) 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. • Rare cases of Steven Johnsons syndrome (SJS) and Toxic epidermal necrolysis (TEN) have been observed. If symptoms or signs of SJS or TEN appear, treatment with nivolumab should be discontinued and the patient referred to a specialised unit for assessment and treatment. If the patient has developed SJS or TEN with the use of nivolumab, permanent discontinuation of treatment is recommended. • 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. • Treatment with nivolumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with nivolumab versus the risk of possible organ rejection should be considered in these patients. • Nivolumab can potentially cause fatigue in some patients and therefore use caution when driving or using machines. • 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. • The patient should be provided with the Patient Alert card with each prescription (to be carried until at least 5 months after the last dose of treatment).
Post treatment observation (if required)	• 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	EAMS document https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-nivolumab-for-treatment-of-adult-patients-with-unresectable-advanced-recurrent-or-metasta KMCC protocol MULTI-001 v6

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

Repeat every 14 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		
	NIVOLUMAB	**240mg**	IV	30 min	Can be given undiluted or diluted. If diluted, give in 100ml 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	up to 3 times a day for 3 days, then 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.	
	Loperamide	2mg-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if specified.	