Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2429

nivolumab 10mg/mL concentrate for solution for infusion (Opdivo®)

Bristol-Myers Squibb Pharmaceuticals Ltd

8 April 2022

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

nivolumab (Opdivo®) is accepted for use within NHSScotland.

Indication under review: as monotherapy for the adjuvant treatment of adult patients with completely resected oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.

In one randomised, double-blind, phase III study, nivolumab significantly improved disease-free survival compared with placebo in patients with oesophageal or gastro-oesophageal junction cancer who had complete resection and residual pathologic disease after neoadjuvant chemoradiotherapy.

This advice applies only in the context of approved NHSScotland Patient Access Scheme (PAS) arrangements delivering the cost-effectiveness results upon which the decision was based, or PAS/ list prices that are equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

As monotherapy for the adjuvant treatment of adult patients with completely resected oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.[1]

Dosing Information

As monotherapy, the recommended dose of nivolumab by intravenous infusion is either 240mg every 2 weeks or 480mg every 4 weeks for the first 16 weeks, followed by 480mg every 4 weeks. The maximum treatment duration for adjuvant therapy is 12 months.

Dosing delay or discontinuation may be required based on individual safety and tolerability. Refer to the summary of product characteristics (SPC) for details.

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.[1]

Product availability date

30 September 2021

Nivolumab meets SMC orphan equivalent and end of life criteria.

Summary of evidence on comparative efficacy

Nivolumab is a human monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with programmed death-ligand 1 (PD-L1) and PD-L2. This potentiates T-cell responses, including anti-tumour responses. [1,2]

The evidence for nivolumab in the adjuvant treatment of oesophageal or gastro-oesophageal junction cancer comes from one international, randomised, double-blind, placebo-controlled study, CheckMate 577. Eligible patients were aged ≥18 years with stage II or III carcinoma of the oesophagus or gastro-oesophageal junction (according to the American Joint Committee on Cancer 7th edition) which was histologically confirmed as predominantly adenocarcinoma or squamous cell carcinoma. They had completed neoadjuvant chemoradiotherapy (using platinum-based chemotherapy), followed by complete surgical resection but had residual pathologic disease on the pathology report of the resected specimens. They were disease-free within 4 weeks of randomisation and had Eastern Co-operative Oncology Group (ECOG) performance status score of 0 or 1.[2,3]

Four to 16 weeks after surgery, 794 patients were randomised to receive nivolumab or placebo in a 2:1 ratio. Nivolumab 240mg or placebo was administered intravenously over 30 minutes every 2 weeks for 16 weeks, followed by 480mg over 30 minutes every 4 weeks for up to one year or until recurrent disease, intolerable toxicity or withdrawal of consent. Randomisation was stratified according to histology (squamous cell carcinoma versus adenocarcinoma), pathologic lymph node

status (positive [≥ ypN1] versus negative [ypN0]) and tumour cell PD-L1 expression (≥1% versus <1% or indeterminate/non-evaluable). Dose reductions were not permitted to manage toxicity but treatment could be interrupted or delayed for up to 6 weeks during the first 16 weeks of the study or for up to 10 weeks during the rest of the study. [2,3]

The primary outcome was disease-free survival (DFS), defined as the time from randomisation to first recurrence or death, whichever occurred first before subsequent anti-cancer therapy. Recurrence was defined as the appearance of one or more new local, regional or distant lesions, as assessed by investigators. Efficacy analyses were performed in the intention to treat (ITT) population following a hierarchical statistical testing strategy, which included the primary outcome (DFS) and the secondary outcome (overall survival) at interim and final analyses. [2,3]

At the cut-off date in July 2020, after a median follow up of 24.4 months, median DFS was significantly improved in the nivolumab group compared with the placebo group. This was supported by results of an ad hoc updated analysis (cut-off date February 2021) after a median follow up of 32.2 months. At the first interim analysis for overall survival, only 228 of the total 460 deaths, planned for the final overall survival analysis, had occurred; the data were not mature and are not available. The study included exploratory outcomes of distant metastasis-free survival (DMFS: defined as the time between randomisation and date of first distant recurrence [determined by investigator and not including local or regional recurrences] or death from any cause) and investigator assessed progression-free survival after subsequent therapy (PFS2: defined as time between randomisation and date when patients progressed on subsequent therapy, started second subsequent therapy or died). These exploratory outcomes were not controlled for multiplicity and are descriptive only.[2,3] Details are presented in table 1.

Table 1: Efficacy results in all randomised patients of the CheckMate 577 study[2,3]

	Pre-specified interim analysis (July 2020)		Updated ad hoc analysis (February 2021)	
	Nivolumab (n=532)	**Placebo (n=262)**	**Nivolumab (n=532)**	**Placebo (n=262)**
Median duration of follow-up, months	24.4		32.2	
Primary outcome				
Patients with a DFS event, n (%)	241 (45%)	155 (59%)	268 (50%)	171 (65%)
Median DFS, months	22.4	11.0	22.4	10.4
HR (95% CI), p-value	0.69 (0.56 to 0.85), p<0.001		0.67 (0.55 to 0.81)	
DFS rate at 6 months	72%	63%	-	-
DFS rate at 12 months	-	-	62%	46%
DFS rate at 24 months	-	-	48%	36%
Exploratory outcomes				
Patients with DMFS event, n (%)	218 (41%)	134 (51%)	253 (48%)	154 (59%)
Median DMFS, months	28.3	17.6	29.4	16.6
HR (95% CI)	0.74 (0.60 to 0.92)		0.71 (0.58 to 0.87)	
Patients with PFS2 event, n (%)	163 (31%)	100 (38%)	203 (38%)	120 (46%)
Median PFS2, months	Not reached	32.1	Not reached	30.7
HR (95% CI)	0.77 (0.60 to 0.99)		0.77 (0.61 to 0.96)	

DFS=disease-free survival; HR=hazard ratio; CI=confidence interval; DMFS=distant metastasis-free survival; PFS2=progression-free survival after subsequent therapy

In CheckMate 577, quality of life was measured as an exploratory outcome using the Functional Assessment of Cancer Therapy-Esophageal (FACT-E) questionnaire, FACT-General (FACT-G), the abbreviated FACT-General (FACT-G7) questionnaire and EuroQoL 5 dimensional 3-level (EQ-5D-3L) utility index and visual analogue scale. Baseline scores were similar in nivolumab and placebo treated patients. Mean changes from baseline increased (indicating improvement) for both treatment groups at all timepoints, when results were available for ≥10 patients, with the exception of a decrease from baseline at follow-up visit 2 for FACT-G7 and for FACT-G and FACT-G7 follow-up visits 1 and 2 in the placebo group.[2,3]

At the cut-off date of July 2020, the median duration of treatment was 10.1 months (range <0.1 to 14.2) in the nivolumab group and 9.0 months (range <0.1 to 15.0) in the placebo group. In the nivolumab group, 30% (157/532) of patients had received any subsequent treatment compared with 42% (111/262) of placebo patients. The most frequently administered treatments in the respective groups were other systemic anticancer therapy/chemotherapy (23% and 32%), radiotherapy (8.1% and 16%) and surgery (0.9% and 7.6%). Of systemic therapy, the majority of

patients received various chemotherapy medicines. Targeted therapy was used in 2.4% and 4.2% of patients respectively and immunotherapy in 0.8% and 7.3%, respectively. [2,3]

Summary of evidence on comparative safety

At the July 2020 cut-off date of CheckMate 577, any treatment-emergent adverse event was reported by 96% (513/532) of nivolumab patients and 93% (243/260) of placebo patients and these were considered treatment-related in 71% and 46% respectively. In the nivolumab and placebo groups respectively, a grade 3 or higher treatment-emergent adverse event was reported in 34% versus 32% of patients and a serious adverse event in 30% of both groups. The proportions of patients with an adverse event that led to discontinuation were 13% of patients in the nivolumab group versus 7.7% of patients in the placebo group. [2,3]

The most frequently reported (incidence ≥10%) treatment-emergent adverse events reported in the nivolumab and placebo groups were: diarrhoea (29% in both), fatigue (27% versus 24%), nausea (23% versus 21%), cough (18% in both), vomiting (15% versus 16%), decreased appetite (15% versus 10%), dysphagia (13% versus 17%), decreased weight (13% versus 8.8%), pruritus (13% versus 6.2%), rash (12% versus 6.5%) abdominal pain (12% versus 14%), constipation (11% versus 12%), hypothyroidism (11% versus 1.5%) and dyspnoea (10% in both groups). In the nivolumab group, the most commonly reported immune-mediated adverse events were hypothyroidism/thyroiditis (11%), rash (7.9%), hyperthyroidism (6.6%) and pneumonitis (4.5%). The incidences of adverse events were similar at the February 2021 cut-off date. [2]

The safety data from CheckMate 577 are consistent with the known safety profile for nivolumab and no new risks have been identified.[2]

Summary of clinical effectiveness issues

Oesophageal cancer is the seventh most common type of cancer and the sixth most common cause of deaths worldwide. There are two histological types: adenocarcinomas (which usually occurs in the lower oesophagus, including those in the gastro-oesophageal junction) that is more common in the UK and squamous cell carcinoma (which usually occurs in the upper or middle part of the oesophagus). At diagnosis, approximately 50% are locally or loco-regionally advanced and have the potential to be cured with loco-regional therapy. For patients with locally advanced adenocarcinoma, treatment options include neoadjuvant chemoradiotherapy or perioperative chemotherapy, both with surgery. For patients with locally advanced squamous cell carcinoma, treatment options include neoadjuvant chemoradiotherapy followed by curative surgery or definitive chemoradiotherapy with or without salvage surgery.[2,4,5] The combination of neoadjuvant chemoradiotherapy followed by surgery is generally more often considered for patients with squamous cell carcinoma but the risk of disease recurrence remains high and 70% to 75% of patients do not achieve a pathologic complete response after neoadjuvant chemoradiotherapy and prognosis is poorer than in patients who do. [2] Nivolumab is the first medicine to be licensed for the adjuvant treatment of patients who have received neoadjuvant chemoradiotherapy followed by complete resection but are found to have residual pathologic disease in the resected

tumour after their chemoradiotherapy.[1] There are currently no other treatments for these patients who undergo routine surveillance. Clinical experts consulted by SMC considered that nivolumab fills an unmet need in this therapeutic area, by providing a treatment option for these patients. Nivolumab meets SMC orphan equivalent and end of life criteria for this indication.

The CheckMate 577 study demonstrated that nivolumab significantly improved DFS, with a gain of 11.4 months over placebo at the pre-specified interim analysis, which was maintained at a later ad hoc analysis. This is an acceptable outcome in the adjuvant setting provided there is no detrimental effect on overall survival. There have been insufficient deaths to analyse overall survival and this is a limitation of the current evidence. The aim of adjuvant treatment is to increase the cure rate but DFS results after a follow-up of longer than 36 months would be needed to support this. However, the results were considered indicative of clinical benefit and a detrimental effect on overall survival was considered unlikely. The marketing authorisation holder should submit results from the second interim and final analyses of overall survival from CheckMate 577 to the EMA by 30 September 2024. Available results for the descriptive, exploratory outcomes, DMFS and PFS2, also favoured nivolumab over placebo. The safety data from CheckMate 577 are consistent with the known safety profile for nivolumab and there was no detrimental effect on quality of life. However, despite the known and relatively manageable safety profile of nivolumab, long-term safety data are awaited in this new indication where no other treatments are licensed.[2,3]

Study patients represent the full licensed indication under review and pre-specified subgroup analyses indicated that the treatment effect on DFS was generally consistent across subgroups according to histology, pathologic lymph node status and PD-L1 status. However, at the July 2020 cut-off date, there was a higher relative treatment effect in patients with squamous cell carcinoma (n=230, hazard ratio [HR] 0.61 [95% confidence interval [CI]: 0.42 to 0.88]) than with adenocarcinoma (n= 563, HR 0.75 [95% CI: 0.59 to 0.96]). A higher relative treatment effect was also observed in patients with positive lymph nodes (n=457, HR 0.67 [95% CI: 0.53 to 0.86]) compared with patients with negative lymph nodes (n=336, HR 0.74 [95% CI: 0.51 to 1.06]). There was a consistent DFS treatment effect by PD-L1 status (≥1% or <1%) but at higher levels of PD-L1 expression (for example ≥5% and ≥10%) improved DFS hazard ratios for nivolumab over placebo were observed. Post hoc analysis according to a PD-L1 combined positive score of ≥5 or <5 indicated a DFS treatment benefit for nivolumab in both subgroups. The study was not powered for subgroup analyses and these results should be treated with caution. [2,3]

As well as a lack of survival data, a number of limitations are associated with the CheckMate 577 study. The primary outcome of DFS was assessed by investigators, which may introduce assessment bias. Seventy-one percent of study patients had adenocarcinoma and although guidelines recommend chemotherapy or chemoradiotherapy with surgery, patients with adenocarcinoma are more likely to be treated with chemotherapy and surgery in clinical practice and would not then be eligible for adjuvant treatment with nivolumab. Study patients had a median age of 62 years and may be younger than patients with oesophageal cancer in clinical practice, where the peak incidence is in the seventh and eighth decades. In addition, study patients had an ECOG performance score of 0 or 1. However, patients eligible for adjuvant nivolumab in practice would need to be fit enough to have undergone chemoradiotherapy and

surgery. CheckMate 577 included a small number of patients aged ≥75 years (n=42) and in this subgroup the DFS HR was less clear and detrimental (HR 1.64 [95% CI: 0.68 to 3.91]). The SPC notes that data for adjuvant oesophageal or gastro-oesophageal junction cancer aged ≥75 years are too limited to draw conclusions. Study patients had stage II or III oesophageal or gastro-oesophageal junction cancer only and there is no evidence to support the adjuvant use of nivolumab in patients with stage IV resectable disease. Study patients had undergone major surgery within the previous 4 to 16 weeks and there is no evidence to support the use of adjuvant nivolumab starting more than 16 weeks after surgery.[1-5]

The introduction of nivolumab for this indication would offer patients with completely resected oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy, an active adjuvant treatment which may delay the time to disease recurrence. It is administered by intravenous infusion every 2 or 4 weeks for the first 16 weeks, and then every 4 weeks for up to one year. There are implications for patients and the service to administer treatment. Clinical experts consulted by SMC considered that nivolumab is a therapeutic advancement due to improvements in DFS and that the licensed indication would reflect the place in therapy in sufficiently fit patients.

Summary of comparative health economic evidence

To support their economic case, the company submitted a cost utility analysis covering nivolumab's full licensed indication. Within the model, nivolumab monotherapy was compared to routine surveillance. The model structure was a semi-Markov model containing three mutually exclusive health states of disease free, recurred disease and dead. The semi-Markov structure allowed the probabilities of moving from one state to another to change over time. A weekly cycle length was employed over a 40-year time horizon.

All patients started in the disease free state from which they could move into the recurred disease state or the dead state. The probability of continuing to be disease free was modelled separately between the first 5 years of occupancy and all subsequent periods. Within the first 5 years, remaining alive and in the disease free state was based on a survival function, derived from individual patient level data from the CheckMate 577 study.[3] The company assessed a variety of statistical forms for this survival function, before selecting the generalised F function. Over the first 5 years after surgery, mortality was assumed to be higher than subsequent years and so individuals' movement from the disease free to dead state was modelled by a logistic regression, which again used CheckMate 577 data. After 5 years, patients in the disease free state were assumed to be "cured", and so had no risk of recurrence and the same risk of death as the general population.

The recurred disease state represented all cases of recurrence and did not differentiate between cancer histology or location of recurrence. From there, it was assumed that patients could only transition to death. Insufficient data were available from the CheckMate 577 study to model post-regression survival. Instead, the submitting company used data from a retrospective follow-up study of patients with resected oesophageal cancer who had experience recurrence, Lou et al (2013).[6] A Gompertz survival function was applied to these data, and the same mortality rate was

used in each arm. This meant that nivolumab was assume to have no treatment effect after recurrence.

Quality of life data was collected within the CheckMate 577 study, but because of reliability and face validity issues, it was used in a way that made minimal impact upon the economic results. The utility value in the disease free state was capped at that for the general population, which started at 0.821, matched with the cohort starting age applied in the model. Because the estimates from the CheckMate 577 study sat above the general population, the age adjusted general population utility held throughout the model. The difference in utility values between the two arms of the study, while patients were on treatment, was used as a measure of adverse event related disutility of nivolumab treatment. Finally, utility values for the post-recurrence state were taken from the literature because of face validity issues with those collected as part of the study.

The model included acquisition and administration costs for nivolumab treatment and second line chemotherapy treatment. Routine surveillance was assumed to have no treatment costs. For wider costs, people in the disease free state were assumed to utilize CT scans with decreasing frequency the longer they remained disease free. Each CT scan was accompanied by some oncologists time. Those in the post-recurrence state were assumed to use consultations, imaging scans, blood tests, liver function tests, kidney function tests, hospitalisations and palliative case specialist nurse time. In addition, there was an end of life cost applied at the point of death.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

The base case economic analysis resulted in an incremental cost-effectiveness ratio of £17,043 per quality-adjusted life year.

As part of its submission, the company provided a range of additional scenarios, a selection of which are shown below:

Table 3: Scenario analysis results (using PAS price)

#	Base case description	Scenario analysis description	ICER
1	Patients in the disease free state are assumed to no longer be at risk of recurrence or have elevated mortality risk at 5 years	Patients in the disease free state are assumed to no longer be at risk of recurrence or have elevated mortality risk at 3 years	£17,100
2	Cohort starting age	Cohort starting age =	
		Minus 20%	£10,907
		Plus 20%	£36,648
3	Disease free survival curve - Generalised F	Disease free survival curve -	
		Log-normal two knot spline	£24,278
		Exponential	£24,389
		Gompertz	£18,866
		Log-logistic	£18,183
		Log-normal	£17,132
		Weibull	£18,709

4	Post regression survival curve - Gompertz	Post regression survival curve - Exponential Generalised gamma Log-logistic Log-normal Weibull	£17,380 £17,253 £17,465 £17,292 £17,332
5	Medicine administration costs based on the SB12Z HRG (£252.73) and second line medicine costs from eMIT	Medicine administration cost weighted average of SB14Z and SB15Z (£369.84) and second line medicine costs from BNF	£12,688

The strengths of the analysis were:

- The modelling approach was appropriate and was supported by a literature review of previous evaluations.
- The data used to model the disease free state came from a large, well conducted RCT.
- The ICER demonstrated reasonable stability across numerous factors.

The limitations of the analysis were:

- Experts consulted by SMC highlighted that use of nivolumab may result in patients switching from chemotherapy to chemoradiotherapy to meet nivolumab's licence. The cost implications of this in Scottish practice are unknown and it was not featured in the economic modelling.
- There was some uncertainty on the extrapolation of the disease free survival. The use of alternative survival functions with very similar fit over the study period, but with differing levels of projected survival at the 5-year mark (e.g. the log-normal two knot spline, see Scenario 5 in the table above) result in large differences in the ICER.
- The submission underestimated administration costs and second line treatment costs. Adopting alternative costs lowers the ICER (see Scenario 5).
- There was some uncertainty on the duration and make-up of second line treatment. The model assumes that patients in the recurred disease state receive second line treatment for the remainders of their lives, which may be inappropriate. Additionally, it may be that nivolumab is used in second line treatment across both arms. Neither of these options were explored in scenario analysis, but the implications were expected to be small.

Despite these limitations, the economic case for nivolumab was demonstrated.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from OCHRE and Guts UK Charity, which are both registered charities.

- OCHRE has not received any pharmaceutical company funding in the past two years. Guts UK Charity has received 1.2% pharmaceutical company funding in the past two years, with none from the submitting company.

- Oesophageal cancer is recognised as a hard-to-treat cancer. It is one of Scotland's least survivable cancers and is the fifth most common cause of cancer death in Scotland despite being only the eleventh most common cancer. The symptoms and the poor likelihood of recovery mean that the burden and impact of OC/GEJ cancer on patients and their families are high.

- New medicines recently approved are only suitable for a very small number of patients which greatly adds to the psychological burden of diagnosis. This is the fourth new medicine submission that the oesophageal cancer charity has been invited to make in the twenty years of its existence. This is a clear and disheartening demonstration of how few options exist for these patients and how little progress has been made in improving treatment.

- Patients who are well enough to receive oesophageal re-sectioning face not only a long period of recovery but also life altering side effects permanently affecting their ability to eat, drink and sleep. The risk of recurrence after chemoradiotherapy and surgery is high, particularly for the approximately 75% patients where some of the cancer remains after treatment.

- This medicine could improve outcomes for suitable patients and clinical trials indicate the potential for another year of life after post-operative relapse. Patient informed choice in palliative treatment is very important to ensure that treatment is focused on the wishes of the person and their family. The importance of a treatment option that can reduce tumour growth and may provide improvement in quality of life should not be underestimated.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published national guideline 83 "Oesophago-gastric cancer: assessment and management in adults" in January 2018.[4] For patients with localised oesophageal and gastro-oesophageal junction adenocarcinoma who are going to have surgical resection, the guideline recommends a choice of chemotherapy, before or before

and after surgery, or chemoradiotherapy before surgery. The choice should be made after discussing the benefits, risks and consequences of each option with patient and those important to them. If available, patients should also be encouraged to join relevant clinical trials.

For patients with resectable, non-metastatic squamous cell carcinoma of the oesophagus, the guideline recommends a choice of radical chemoradiotherapy alone or chemoradiotherapy before surgery. The benefits, risks and consequences of each option should be discussed with the patient and those important to them. For patients who have no symptoms or evidence of residual disease after treatment for oesophago-gastric cancer with curative intent should be provided information about symptoms of recurrence and offered rapid access to the oesophago-gastric multi-disciplinary team if they develop and routine follow-up or surveillance is not recommended to detect recurrent disease.

The European Society for Medical Oncology (ESMO) published "Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up" in August 2016.[5] The guideline states that the main factors for selecting primary therapy are tumour stage and location, histology and patient's performance status and co-morbidities. For patient with locally advanced adenocarcinoma, the guideline recommends either neoadjuvant chemoradiotherapy or perioperative chemotherapy with surgery. For patients with locally advanced squamous cell carcinoma, the guideline recommends either neoadjuvant chemoradiotherapy followed by surgery or definitive chemotherapy followed by 3-monthly follow-up and salvage surgery on as an option for incomplete response or relapse.

These guidelines predate the availability of nivolumab for this indication.

Additional information: comparators

Routine surveillance.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
nivolumab	**By intravenous infusion, 240mg every 2 weeks or 480mg every 4 weeks for the first 16 weeks, followed by 480mg every 4 weeks. Maximum adjuvant treatment duration is 12 months**	**Up to 68,458**

Costs from BNF online on 31 January 2022. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 22 patients eligible for treatment with nivolumab in each year.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

References

1. Bristol-Myers Squibb Pharmaceuticals Limited. Nivolumab 10mg/mL concentrate for solution for infusion (Opdivo®), summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 16 January 2022
2. European Medicines Agency (EMA) European Public Assessment Report. Nivolumab (Opdivo®). 24 June 2021, EMEA/H/C/003985/II/0095. www.ema.europa.eu
3. Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E et al. Adjuvant nivolumab in resected esophageal or gastro-esophageal junction cancer. N Engl J Med 2021; 384: 1191-203.
4. National Institute for Health and Care Excellence (NICE). NICE Guideline 83. Oesophago-gastric cancer: assessment and management in adults. Published 24 January 2018 www.nice.org.uk
5. Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D et al. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016; 27 (Suppl 5): v50-v57.
6. Lou F, Sima CS, Adusumilli PS, Bains MS, Sarkaria IS et al. Esophageal cancer recurrence patterns and implications for surveillance. J Thorac Oncol. 2013; 8 (12): 1558-62.

This assessment is based on data submitted by the applicant company up to and including 11 March 2022.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.