NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer [ID1676]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer [ID1676]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

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2. **Clarification questions and company responses**
   a. Additional questions and responses

3. **Patient group, professional group and NHS organisation submissions** from:
   a. NCRI-ACP-RCP-RCR
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   a. Prof. Somnath Mukherjee, Consultant Clinical Oncologist – clinical expert, nominated by the Royal College of Physicians
   b. Prof. Anne Thomas, Professor of Cancer Therapeutics – clinical expert, nominated by Bristol-Myers Squibb
   c. Mr David Chuter – patient expert, nominated by Guts UK

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9. **Evidence Review Group critique of company response to technical engagement** prepared by ScHARR
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer

ID1676

Document B

Company evidence submission

March 2021

File name	Version	Contains confidential information	Date
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List of abbreviations

Abbreviation	Definition
5-FU	5-fluorouracil
AE	adverse events
AJCC	American Joint Committee on Cancer
CI	confidence interval
CRT	chemoradiotherapy
CSR	clinical study report
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTLA4	cytotoxic T-lymphocyte-associated protein 4
DBL	database lock
DFS	disease free survival
DMFS	distant metastasis free survival
ECOG PS	Eastern Cooperative Oncology Group Performance Score
eCRF	electronic case report form
ECS	Esophageal Cancer Subscale
eMIT	electronic market information tool
EQ-5D-3L	EuroQol questionnaire comprising 5 dimensions, with each dimension having 3 levels
ESMO	European Society for Medical Oncology
FACT-E	Functional Assessment of Cancer Therapy-Esophageal
FACT-G7	7-item version of FACT-General
GEJ	gastroesophageal junction
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IMAE	immune-mediated adverse event
IV	intravenous
ITT	intention-to-treat
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
OC	oesophageal cancer
OS	overall survival
OSCC	oesophageal squamous cell carcinoma
PAS	patient access scheme

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pathCR	pathologic complete response
PD-1	programmed cell death 1
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PFS2	progression-free survival after the next line of the subsequent therapy
PLD	patient-level data
QALY	quality-adjusted life-year
SAE	serious adverse event
SOC	standard of care
TNM	tumour, lymph node and metastasis
TRAE	treatment-related adverse event

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B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

Nivolumab (OPDIVO®) as monotherapy [redacted]. The decision problem is presented in Table 1.

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Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with resected oesophageal or gastro-oesophageal junction cancer.	[redacted]	The evidence presented in this submission is derived from the pivotal CheckMate 577 trial, which included patients with resected OC or GEJ cancer who have received chemoradiotherapy followed by complete resection.
Intervention	Nivolumab	Nivolumab	As per NICE scope
Comparator(s)	Routine surveillance	Routine surveillance	As per NICE scope
Outcomes	The outcome measures to be considered include: Overall survival Disease free survival Adverse effects of treatment Health-related quality of life	The outcome measures to be considered include: Disease free survival Adverse effects of treatment Health-related quality of life	Overall survival (OS) is a secondary endpoint in the pivotal trial, CheckMate 577, however OS data are not yet available at the time of submission as the data have not reached sufficient maturity.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the	Aligned with NICE reference case and NICE scope.	As per NICE scope

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	intervention, comparator and subsequent treatment technologies will be taken into account.		
Subgroups to be considered	None specified.	As per NICE scope	As per NICE scope
Special considerations including issues related to equity or equality	None specified.	As per NICE scope	As per NICE scope
GEJ, gastro-oesophageal junction; OC, oesophageal cancer			

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B.1.2 Description of the technology being appraised

Details of the technology being appraised in this submission are summarised in Table 2 and Section B.1.3.3. The Summary of Product Characteristics is attached as Appendix C. The European public assessment report describing nivolumab for the adjuvant treatment of patients with OC or GEJ cancer is not available at time of submission.

Table 2. Technology being appraised

UK approved name and brand name	Nivolumab (Opdivo®)
Mechanism of action	Programmed cell death 1 (PD-1) is an immune checkpoint protein receptor that is expressed on activated T cells.[1] Upregulation of PD-1 and its ligands is associated with poor prognosis in OC.[2] Exploitation of the PD-1 checkpoint pathway can facilitate evasion of immune surveillance by cancer cells.[2,3] Nivolumab is a fully human immunoglobulin G4 monoclonal antibody.[4] Nivolumab acts as a PD-1 immune checkpoint inhibitor which prevents the interaction of the PD-1 receptor with its tumour cell expressed ligands PD-L1 and PD-L2.[5-7] This inhibition prevents the evasion of tumour cells from destruction, and thus re-establishes T cell activity. Further details are provided in Section B.1.3.3
Marketing authorisation/ CE mark status	A regulatory submission was made to the EMA on [redacted]. The earliest point at which an opinion from CHMP could be anticipated would be [redacted] with a corresponding regulatory approval available in [redacted]. [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The proposed indication for nivolumab for the treatment of resected OC is as follows: [redacted]. Nivolumab monotherapy is licensed for the following indications: • Advanced (unresectable or metastatic) melanoma in adults, and in patients following who have had surgery for the removal of melanoma that has spread to the lymph nodes or elsewhere in the body. • Non-small cell lung cancer in patients previously treated with chemotherapy. • Advanced renal cell carcinoma in previously treated patients. • Classical Hodgkin lymphoma after an autologous stem cell transplant and treatment with brentuximab vedotin. • Metastatic squamous cell cancer of the head and neck following platinum-based therapy. • Advanced (unresectable or metastatic) urothelial cancer following platinum-based therapy. • Unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma in patients previously treated with fluoropyrimidine- and platinum-based chemotherapy.

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Method of administration and dosage	Nivolumab monotherapy at a dose of 240 mg administered intravenously (IV) over 30 minutes every two weeks for 16 weeks then at a dose of 480 mg administered IV over 30 minutes every four weeks, beginning at week 17, for a maximum total duration of one year.
Additional tests or investigations	No tests or investigations are required for the treatment with nivolumab beyond those routinely conducted in clinical practice
List price and average cost of a course of treatment	List price: Nivolumab: £3,159.60 per 240 mg (24 mL) vial; £1,316.40 per 100 mg (10 mL) vial; £526.80 per 40 mg (4 mL) vial. Cost per dose: £3,159.60 per 240 mg doseCost per dose: £6,319.20 per 480 mg dose. Patient Access Scheme price: Cost per dose: £[redacted] per 240 mg dose. Cost per dose: £[redacted] per 480 mg dose.
Patient access scheme (if applicable)	There is a confidential simple discount PAS for nivolumab which applies to all current and future indications.

CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; OC: oesophageal cancer; PAS: patient access scheme; PD-1: programmed cell death 1; PD-L1: programmed death ligand 1; PD-L2: programmed death ligand 2

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B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease background

Gastroesophageal cancers represent a significant health problem. There are over 9,000 reported cases of OC in the UK annually, which makes up around 3% of all new cancer cases in the UK.[8] Despite the comparatively low number of cases to some other cancers, OC is the seventh most common cause of cancer death in the UK overall, and the fourth most common for men. Five-year survival rates of OC are relatively poor, reported at around 16% in the UK.[9] Over 10,000 deaths due to OC were reported for the UK in 2019.[10] Globally, the average five-year survival for OC is reported to be around 25–45%,[11-14] and the global mortality to incidence ratio is 90%.[15] Patients with resected OC have limited treatment options available post-surgery to reduce the risk of recurrence and improve survival (Section B.1.3.2). Survival post-recurrence is particularly poor, with one population-based study from the Netherlands reporting median OS post-recurrence of 4.2 months in patients with OC or GEJ cancer who had received resection with or without [neo]adjuvant CRT.[16] This highlights the need for efficacious adjuvant therapies in this patient population.

The symptomatic burden of OC is high. Predominant symptoms of OC include difficulty swallowing, persistent indigestion or heartburn, unexplained weight lost and pain in throat or behind sternum. Dysphagia, is the most common symptom of OC.[17] Other symptoms include a cough which does not improve, a hoarse voice, feeling tired or having reduced energy.[18] Although many symptoms exist, they are often subtle and may not get picked up at an early stage of disease, hence, diagnosis of OC typically occurs at a late stage of the disease, with 70–80% of patients in England, Scotland and Northern Ireland (with known stage of diagnosis) diagnosed at stage III or IV.[8]

Gastroesophageal cancers can be categorised by location and histology. OC develops as a result of malignant cellular mutations in the inner lining of the upper, middle or lower parts of the oesophagus, whilst GEJ cancer develops at the lower portion of the oesophagus, at the point at which it joins the stomach (Figure 1).[19] GEJ either develops above or below the gastroesophageal junction and is subcategorised into three types, depending on the location. The two predominant histological subtypes are squamous cell carcinoma (SCC) and adenocarcinoma, originating from squamous and glandular cells, respectively.[20] Global variation exists in the incidence and prevalence of SCC versus adenocarcinoma.[21] SCC is the dominant histological type of OC globally, however, adenocarcinoma of the oesophagus forms the majority of cases in Western countries and is the most common type of OC in the UK,[20] with age-standardised estimated incidence in 2018 of 4.5 per 100,000 person years for adenocarcinoma compared with 2.1 for oesophageal squamous cell carcinoma (OSCC).[22]

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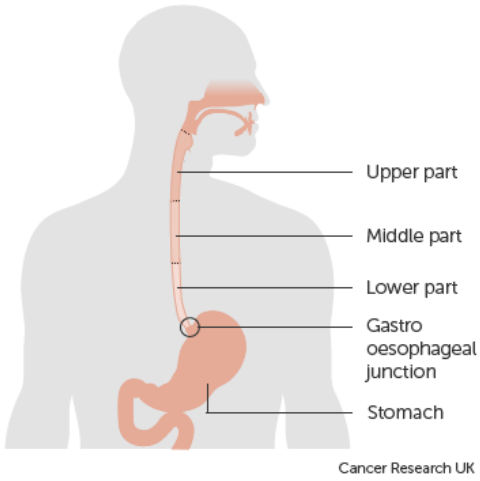

Figure 1. OC and GEJ cancer locations[19]

Staging of OC and GEJ cancer for UK patients is defined by the American Joint Committee on Cancer (AJCC) staging system.[23] Several staging systems exist, with post-neoadjuvant staging being pertinent for this indication, that is, for patients who have undergone neoadjuvant therapy and pathologic review of the resection sample.[24] This staging system utilises the tumour, lymph node and metastasis (TNM) staging categories (Figure 2) to define stages I–IV of OC (both SCC and adenocarcinoma) and is summarised in Table 3.[24]

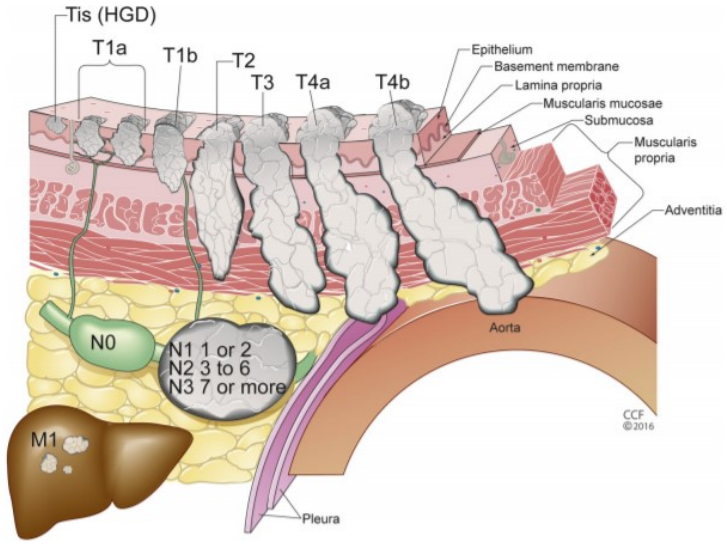

Figure 1. Eighth edition TNM categories. T is categorized as Tis: high-grade dysplasia (HGD). T1 is cancer that invades the lamina propria, muscularis mucosae, or submucosa and is subcategorized into T1a (cancer that invades the lamina propria or muscularis mucosae) and T1b (cancer that invades the submucosa); T2 is cancer that invades the muscularis propria; T3 is cancer that invades the adventitia; T4 is cancer that invades the local structures and is subcategorized as T4a (cancer that invades adjacent structures such as the pleura, pericardium, azygos vein, diaphragm, or peritoneum) and T4b (cancer that invades the major adjacent structures, such as the aorta, vertebral body, or trachea). N is categorized as N0 (no regional lymph node metastasis), N1 (regional lymph node metastases involving one to two nodes), N2 (regional lymph node metastases involving three to six nodes), and N3 (regional lymph node metastases involving seven or more nodes). M is categorized as M0 (no distant metastasis) and M1 (distant metastasis).

Figure 2. TNM categories for oesophageal cancer (reproduced from Figure 1 of Rice et al. 2017[25])

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Table 3. Post-neoadjuvant therapy staging (ypTNM staging) (adapted from Rice et al. 2017[24])

Stage	T category	N category	M category
I	T0-2: T0 – no evidence of primary tumour, T1 – tumour invades the lamina propria, muscularis mucosae or submucosa, T2 – tumour invades the muscularis propria	N0: no regional lymph node metastasis	M0: no distant metastasis
II	T3: tumour invades adventitia	N0: no regional lymph node metastasis	M0: no distant metastasis
IIIA	T0-2: T0 – no evidence of primary tumour, T1 – tumour invades the lamina propria, muscularis mucosae or submucosa, T2 – tumour invades the muscularis propria	N1: Metastasis in 1–2 regional lymph nodes	M0: no distant metastasis
IIIB	T4a: tumour invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum	N0: no regional lymph node metastasis	M0: no distant metastasis
	T3: tumour invades adventitia	N1-2: N1 – metastasis in 1-2 regional lymph nodes, N2 – metastasis in 3–6 regional lymph nodes	M0: no distant metastasis
	T0-3: T0 – no evidence of primary tumour, T1 – tumour invades the lamina propria, muscularis mucosae or submucosa, T2 – tumour invades the muscularis propria, T3 – tumour invades adventitia	N2: metastasis in 3–6 regional lymph nodes	M0: no distant metastasis
IVA	T4a: tumour invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum	N1-2, X: N1 – metastasis in 1-2 regional lymph nodes, N2 – metastasis in 3–6 regional lymph nodes, X – not defined.	M0: no distant metastasis
	T4b: tumour invades other adjacent structures, such as aorta, vertebral body, or trachea	N0-2: N0 – no regional lymph node metastasis, N1 – metastasis in 1-2 regional lymph nodes, N2 – metastasis in 3–6 regional lymph nodes, X – not defined.	M0: no distant metastasis
	T1-4: T0 – no evidence of primary tumour, T1 – tumour invades the lamina propria, muscularis mucosae or submucosa, T2 – tumour invades the muscularis propria, T3 – tumour invades adventitia, T4 – tumour invades adjacent structures	N3: metastasis in 7 or more regional lymph nodes	M0: no distant metastasis
IVB	T1-4: T0 – no evidence of primary tumour, T1 – tumour invades the lamina propria, muscularis mucosae or submucosa, T2 – tumour invades the muscularis propria, T3 – tumour invades adventitia, T4 – tumour invades adjacent structures	N0-3: N0 – no regional lymph node metastasis, N1 – metastasis in 1-2 regional lymph nodes, N2 – metastasis in 3–6 regional lymph nodes, N3 – metastasis in 7 or more regional lymph nodes	M1: distant metastasis

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As described above, the subtlety of the early symptoms means that diagnosis of OC typically occurs at stage III or IV, and survival outcomes for patients diagnosed at these late stages are particularly poor (Table 4). For patients diagnosed at stage III in England from 2013–2017, one-year survival was 54.8% and five-year survival was 16.3%. Patients diagnosed at stage IV had 20.8% one-year survival, and by 5 years, not enough patients were alive to enable survival estimates to be made.[26]

Table 4. One-year and five-year net survival for adults diagnosed with OC between 2013 and 2017 in England

Stage at diagnosis	Number of patients	One-year age-standardised survival (%)	Five-year age-standardised survival (%)
All stages	37,169	46.5	17.0
Stage I	3,651	84.5	52.8
Stage II	4,705	68.3	29.9
Stage III	10,952	54.8	16.3
Stage IV	11,093	20.8	NA

NA: not available, meaning there was not sufficient data available to make robust estimates of survival.
Table does not include the 92 patients with unstageable OC or the 6,676 patients with stage unknown/missing.
Adults: aged 15–99 years.
Source: Office for National Statistics[26]

Surgery for OC is associated with significant morbidity. In one study conducted in France comparing open surgery with hybrid minimally invasive surgery for OC, the overall rate of major complications at 30 days was 50%.[27] In the CROSS trial enrolling patients with OC or GEJ cancer, all health-related quality of life (HRQoL) endpoints declined significantly compared to baseline in the 3 months after surgical resection. This was observed in both treatment arms (neoadjuvant CRT followed by surgery or surgery alone).[28]

In addition to the direct impact of surgery, the presence of residual pathological disease strongly influences disease free survival (DFS) and OS post-resection for patients with locally advanced OC. The majority of patients (approximately 75%) have residual pathological disease following neoadjuvant CRT and resection.[12,14,16,29-32] The failure to achieve a pathologic complete response (pathCR) puts these patients at high risk of disease recurrence. Non-pathCR has been demonstrated to predict a significantly lower rate of both DFS and OS in patients treated with neoadjuvant CRT followed by surgical resection.[11,3334] In the CROSS trial, 42% patients without pathCR after CRT experienced a recurrence, compared to 17% patients with pathCR after CRT.[35] The high risk of recurrence is particularly significant in light of the very poor post recurrence survival, with only a short time from recurrence to death.[12,16] It should be noted that the primary endpoint in clinical trials of adjuvant therapies is typically DFS, which is used as a surrogate endpoint for OS as it displays a strong correlation with OS.[36-39]

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B.1.3.2 Current pathway of care

Treatment for OC depends on the size, type, location, and stage of the cancer.[23] Typically, guideline-recommended treatment comprises a combination of chemotherapy, radiotherapy and surgery, dependent on stage.[23,40] However, there are currently no adjuvant treatments commonly used in the post-surgery setting.

Clinical advice to the company suggests that treatment practice varies widely in the UK.[41] Patients diagnosed at an early stage of the disease are most commonly treated using surgery which may be curative, with other treatments used pre- or perioperatively, including chemotherapy and radiotherapy, depending on disease extent as well as patient's overall health and preference. In England, between 2013–2014, 19% of patients underwent surgery to remove the tumour either alone or in combination with other treatments including chemo- or radiotherapy, as part of their primary cancer treatment.[42]

Figure 3 depicts a summary of the treatment pathway adapted from that presented by Lordick et al 2016[23] as part of the ESMO clinical practice guidelines. A summary is provided below:

- CT and/or radiotherapy are commonly utilised prior to surgery for patients with OC/GEJC to reduce the risk of recurrence and increase survival. If chemo(radio)therapy is completed ahead of surgery, it is defined as preoperative (neoadjuvant) treatment. In some adenocarcinoma cases, perioperative therapy may be used, where some treatment cycles are completed before surgery, then surgery is performed, and the remaining therapy cycles are only completed following surgery.[23,40,43,44] Treatment with pre- or perioperative therapy is reported to convey a survival benefit compared to surgery alone.[44,45]
- Surgery is the primary treatment for limited, localised disease.[23,40] NICE guidance describes the aim of surgery to be the achievement of complete resection at all margins (R0) with the avoidance of microscopic (R1) or macroscopic (R2) residual disease.[43]
- Post-surgery, patients are usually monitored, often known as 'watchful waiting' or routine surveillance. There is no other adjuvant treatment (i.e. additional treatment after surgery) available in the UK that could reduce the risk of relapse and improve post-resection survival. Thus, there is an unmet need for an effective adjuvant therapy such as nivolumab.

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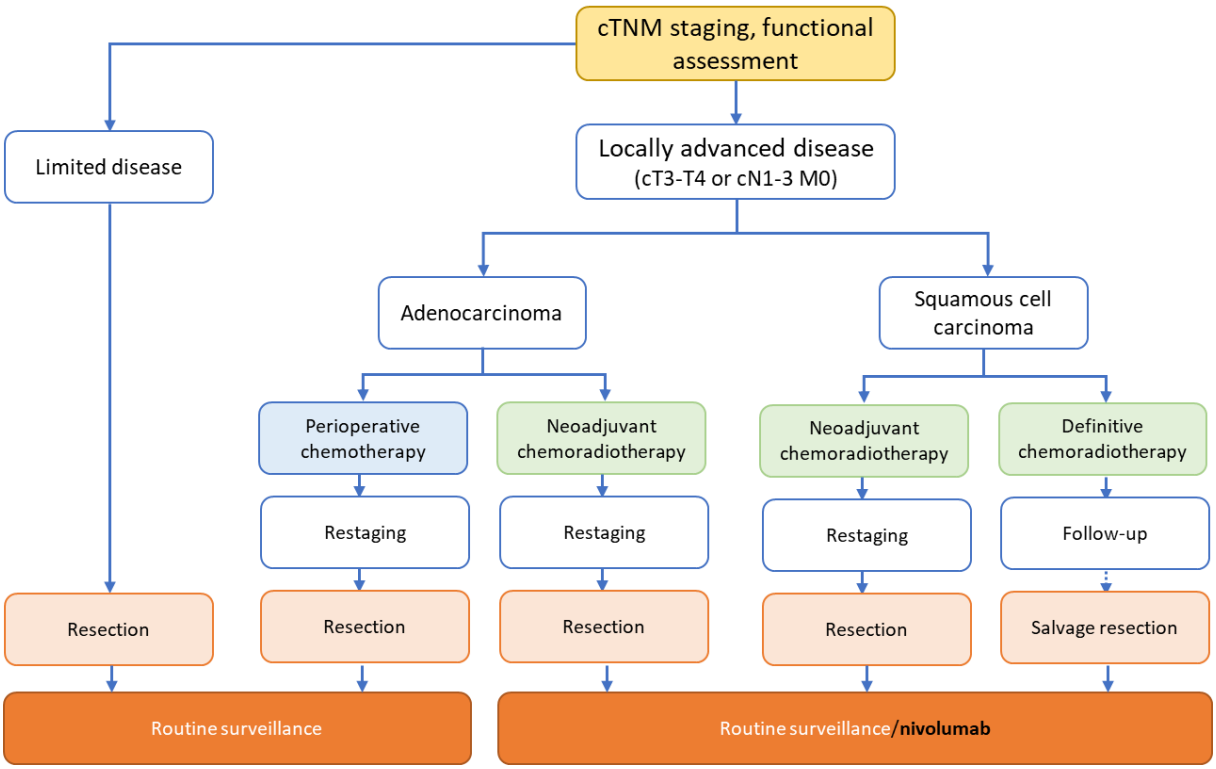

Figure 3. Treatment pathway for local/local regional resectable OC in UK (derived from Lordick et al. 2016[23])

Similar to ESMO[23] and NICE guidelines,[43] NCCN guidelines[40] recommend no treatment beyond routine surveillance for patients with OSCC who have received neoadjuvant chemoradiation and present with no cancer at resection margins (R0).[40] Adenocarcinoma patients may receive neoadjuvant CRT or neoadjuvant or perioperative CT ahead of surgery; although NCCN guidelines include post-operative C(R)T regimens as an option for some adenocarcinoma patients, UK clinicians have advised that this is not used in UK clinical practice.[41] Clinical advice to the company is that all patients post-resection are followed up every three months in year 1, every six months in years 2 and 3, annually in years 3 to 5 and are then discharged.[41] These follow-ups do not include any routine scans or endoscopies; such investigations are instigated if the patient presents with symptoms of recurrence.

In contrast to patients whose tumour is completely resected during surgery, patients with incomplete resection have markedly reduced survival.[24] Additional treatment or a switch to palliative approach is recommended for patients in whom tumour resection was unsuccessful.[40] However, no evidence on the use of nivolumab in the setting of incomplete resection is available at present, and the management of these patients will not be discussed further.

Importantly, there is no NICE-defined standard of care (SOC) for patients with OSCC or adenocarcinoma who have clear resection margins, but are found to have residual disease on pathology (i.e. do not achieve a pathCR), which is the population analogous to that enrolled in CheckMate 577. Approximately 75% patients with OC have residual pathological

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disease following neoadjuvant CRT and resection,[12,14,16,29-32] leaving them at high risk of disease recurrence,[11,33-35] and post-recurrence survival is very poor.[16] Hence, there is a significant unmet need for effective and well-tolerated adjuvant therapies to reduce the risk of recurrence and consequent death in this patient population.

B.1.3.2.1 Nivolumab within the current clinical pathway

Treatment of patients with resected OC is predominantly limited to routine surveillance, due to limited or no treatment options post-resection. Five-year survival after surgery is reported to be around 25–45%,[11-14] highlighting the poor outcomes in this patient population, so there is considerable room for improving outcomes of patients with OC/GEJ cancer, thus demonstrating an unmet treatment need in this area.

Nivolumab would represent a new immunotherapy treatment modality and has the potential to increase DFS and OS in patients who were previously treated with CRT followed by surgical resection. The introduction of nivolumab would change the treatment paradigm for these patients, for whom there is currently no routine SOC, and is therefore representative of a 'step-change' in the management of OC and GEJ cancer after being surgically rendered disease free.

B.1.3.3 Nivolumab mechanism of action

Immunotherapy involves the development and utilisation of treatments which are able to exploit the body's own immune system to destroy cancer cells.[46] T cells are a component of the human immune system that act to recognise antigens on the surface of diseased cells, including cancer cells. Normal cells evade this response via the stimulation of checkpoint proteins, using activating ligands. Cancer cells have adapted to exploit this same process to evade destruction by T cells. Recently, antibodies which are designed to block these checkpoint proteins, i.e. checkpoint-inhibitors, have been developed. Checkpoint inhibitors can prevent the cancer-driven T cell suppression and thus reactivate the immune response against cancer cells. Programmed cell death 1 (PD-1) is a potent T cell immune checkpoint protein which is expressed at high levels on activated T cells.[1] Two known ligands of PD-1 exist: PD-L1 and PD-L2.[47]

Nivolumab is a first-in-human immunoglobulin G4 PD-1 immune checkpoint inhibitor antibody that acts to prevent the interaction of PD-1 with its ligands (Figure 4).[4,7] As a result of blocking this interaction, T cell activity is restored as the patient's own immune system is activated to destroy the cancer cells. Clinical efficacy and a favourable safety profile of nivolumab have been demonstrated in multiple cancer types including melanoma, metastatic renal cell carcinoma, Hodgkin lymphoma, head and neck cancer, urothelial cancer, non-small cell lung cancer and unresectable advanced OSCC.[48]

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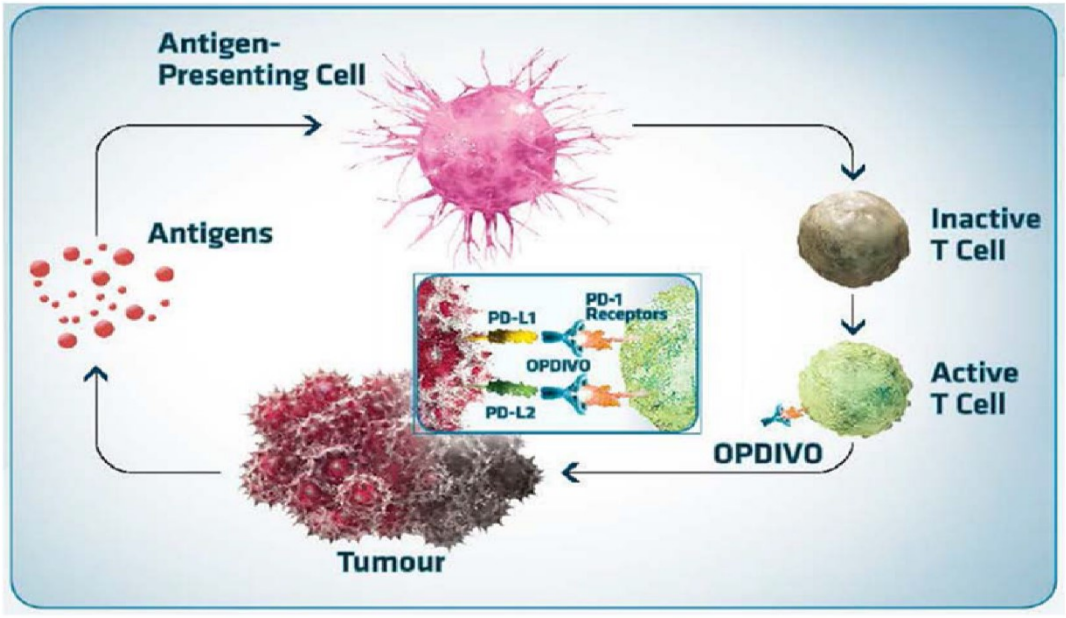

Figure 4. Nivolumab stimulation of immune-mediation destruction

B.1.3.3.1 Unique features of response to immunotherapy

Anti-cancer therapies are typically targeted to reduced tumour burden via directly disrupting tumour cell proliferation or by the induction of apoptosis. Nivolumab, like other immunotherapeutic agents, has a substantially different mechanism of action to conventional chemotherapy. As a result of this, varied patterns of response can be observed with this type of therapy in comparison to chemotherapy.

Immunotherapies initiate the recruitment of host immune cells to the tumour site, meaning that the initial response to therapy is generally delayed in comparison with traditional chemotherapies.[49] This leads to a pattern of response that is characteristic of immunotherapies, with a high initial hazard of events that then declines to a low, steady rate. The unique mechanisms of action of immunotherapies have also been associated with a prolonged survival benefit after treatment cessation in a proportion of patients. For example, nivolumab therapy was associated with 13.4% 5-year OS in patients with non-small cell lung cancer, versus 2.6% in patients treated with docetaxel.[50]

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B.2 Clinical effectiveness

Key points

- Treatment with nivolumab has significant benefits in terms of DFS, safety and patient reported outcomes.
- During CheckMate 577, nivolumab-treated patients achieved significantly improved DFS over patients treated with placebo (median DFS: 22.4 months versus 11.0 months).
- OS data from CheckMate 577 is not available at the time of submission, as the data have not reached sufficient maturity.
- Nivolumab was well tolerated and demonstrated an acceptable safety profile. Incidence of grade 3–4 adverse events (AEs) was similar for nivolumab and placebo (34% versus 32%), and most AEs experienced upon treatment with nivolumab were grade 1 or 2.
- Quality of life improved during the trial, as determined by EQ-5D, EQ-VAS and FACT-E in both treatment arms, suggesting that nivolumab has no detrimental effect on health-related quality of life.
- The results from CheckMate 577 represent the first advance in years for this patient group and could lead to the establishment of trimodality therapy followed by nivolumab as a new standard of care.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was undertaken to identify the clinical effectiveness evidence (efficacy and safety) of interventions for the treatment of resected OC or GEJ cancer. Full details of the methods and processes employed to identify and select the relevant clinical evidence are summarised in Appendix D.

The SLR identified 53 randomised controlled trials considering a population with resectable OC/GEJ cancer. Only 12 trials considered adjuvant therapy, and five compared adjuvant and neoadjuvant treatment. Adjuvant therapies evaluated in RCTs were chemotherapy, CRT, radiotherapy and nivolumab. Of these 17 RCTs, 11 had surgery alone as a comparator. No RCTs were identified that evaluated adjuvant CT in a European setting. The SLR also identified 92 non-randomised studies in the adjuvant setting, predominantly retrospective analyses. The results of this SLR indicate that there are limited active treatments available in the adjuvant setting, therefore watchful waiting is the best available comparator, in line with NICE clinical guidelines. Further details of the SLR are available in Appendix D.

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B.2.2 List of relevant clinical effectiveness evidence

Evidence to support the effectiveness of nivolumab for the treatment of resected OC or GEJ cancer is derived primarily from CheckMate 577 (NCT02743494), shown in Table 5.

Table 5. Clinical effectiveness evidence

Study	CheckMate 577				
Study design	Phase III, multicentre, randomised, double blind, placebo-controlled study				
Population	Adult patients with stage II or III carcinoma of the oesophagus or GEJ who have completed pre-operative chemo radiotherapy followed by surgery. Patients must have had a complete resection with negative margins and have residual pathologic disease post-surgery.				
Intervention(s)	Nivolumab monotherapy at a dose of 240 mg administered intravenously (IV) over 30 minutes every 2 weeks for 16 weeks, followed by 480 mg administered as an IV infusion over 30 minutes every 4 weeks beginning at week 17, for a total duration of one year				
Comparator(s)	Placebo monotherapy administered as an IV infusion over 30 minutes every 2 weeks for 16 weeks followed by IV placebo infusion over 30 minutes every 4 weeks beginning at week 17, for a total duration of one year.				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	Source of direct comparative evidence evaluating the efficacy of nivolumab versus placebo in the correct patient population				
Reported outcomes specified in the decision problem	Disease free survival (DFS) Adverse events (AEs) and safety outcomes Health-rated quality of life Note: Overall survival (OS) was assessed in CheckMate 577 but is not yet available at the time of submission as the data have not reached sufficient maturity.				
All other reported outcomes	Additional exploratory endpoints included: • DMFS • Overall PD-L1 status and impact as a predictive biomarker for DFS and OS • Additional potential biomarkers associated with DFS and OS and/or incidence of AEs of nivolumab on biomarker status • The effect of genetic variation in select genes including PD-1, PD-L1, PD-L2 and CTLA4 on clinical endpoints and/or incidence of AEs • Characterisation of the pharmacokinetics and exposure-response relationships • Immunogenicity of nivolumab • PFS2				

AE: adverse event; DFS: disease free survival; CTLA4: cytotoxic T-lymphocyte-associated protein 4; DMFS: distant metastasis-free survival; GEJ: gastroesophageal junction; IV: intravenous; OS: overall survival; PD-1: programmed death 1; PD-L1: programmed death ligand 1; PD-L2: programmed death ligand 2; PFS2: progression free survival after the next line of subsequent therapy

Source: CheckMate 577 protocol[51]

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B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

A summary of the methodology for CheckMate 577 is provided in Table 6, with further details provided in Sections B.2.3.1.1 to B.2.3.1.5.

Table 6. Summary of trial methodology

Trial number (acronym)	CheckMate 577
Location	Argentina, Australia, Belgium, Brazil, Canada, China, Czech Republic, Denmark, France, Germany, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Mexico, Netherlands, Poland, Republic of Korea, Romania, Russian Federation, Singapore, Spain, Switzerland, Taiwan, Turkey, **UK**, and USA
Trial design	Phase III, multicentre, randomised, double-blind, placebo-controlled
Eligibility criteria for participants	Adults (≥ 18 years) with stage II or III (per AJCC 7th edition) carcinoma of the oesophagus or GEJ and histologically confirmed predominant adenocarcinoma or squamous cell carcinoma.
Settings and locations where data were collected	The study was conducted in 170 sites across USA, Europe and Asia
Trial drugs	Intervention (n = 532): Nivolumab monotherapy at a dose of 240 mg administered intravenously (IV) over 30 minutes every 2 weeks for 16 weeks, followed by 480 mg administered as an IV infusion over 30 minutes every 4 weeks beginning at week 17, for a maximum total duration of one year
	Comparator (n = 262): Placebo monotherapy administered as an IV infusion over 30 minutes every 2 weeks for 16 weeks followed by IV placebo infusion over 30 minutes every 4 weeks beginning at week 17, for a maximum total duration of one year
Permitted and disallowed concomitant medications	Disallowed: The following medications were prohibited during the treatment and follow-up phases (before recurrence) of the study (unless used to treat a drug-related adverse event): • Immunosuppressive agents • Immunosuppressive doses of systemic corticosteroids (except as specified in permitted medications) • Any concurrent anti-neoplastic therapy (including, but not limited to chemotherapy, hormonal therapy, immunotherapy, radiation therapy, or standard or investigational agents for treatment of oesophageal or GEJ cancer. • Any live/attenuated vaccine during treatment and until 100 days post the last dose.
	Permitted: Patients are permitted the use of topical, ocular, intra-articular, intranasal and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement doses of systemic corticosteroids are permitted even if > 10 mg daily prednisone (or equivalent). A brief course (less than 3 weeks) of corticosteroids for prophylaxis (e.g., for contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
Primary outcomes	DFS (defined as the time between randomization date and date of recurrence or death, whichever occurs first)
Other outcomes used in the economic model/specified in the scope	OS (defined as the time between the date of randomisation and the date of death) – OS data is not available at the time of submission. Adverse events Patient-reported outcomes (EQ-5D-3L, FACT-E, ECS, FACT-G7)
Pre-planned subgroups	Age categorisation 1

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	< 65 ≥ 65 and < 75 ≥ 75 Age categorisation 2 < 65 ≥ 65 Sex Male Female Race White Black or African American Asian Other Region Asia ROW [Including US/Canada, Europe] Baseline ECOG PS 0 1 Disease at study entry (tumour location) Oesophageal cancer Lower third Middle third Upper third Gastroesophageal junction cancer Siewert-Stein Type I Siewert-Stein Type II Siewert-Stein Type III Not reported Disease stage at initial diagnosis Stage II Stage III Not reported Histology Adenocarcinoma Squamous cell carcinoma Other Histological grade G1/G2 G3/G4 GX Not reported Pathologic lymph node status ypN0 ≥ ypN1 Unknown Pathologic tumour status ypT0 ypT1/ypT2 ypT3/ypT4 Unknown Time from beginning of neoadjuvant chemoradiotherapy to complete resection < 6 weeks ≥ 6 weeks Not reported Time from complete resection to randomisation < 10 weeks ≥ 10 weeks HER2 status (CRF) Positive Negative Unknown

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	Not reported PD-L1 status at baseline (LAB) (1% cut-off) ≥ 1% < 1% Indeterminate/non-evaluable PD-L1 status at baseline (LAB) (5% cut-off) ≥ 5% < 5% Indeterminate/non-evaluable PD-L1 status at baseline (LAB) (10% cut-off) ≥ 10% < 10% Indeterminate/non-evaluable
Race "Other" category includes "American Indian or Alaska Native", "Native Hawaiian or Other Pacific Islander" and "Not Reported" patients. For the PD-L1 status at baseline categories, these values were based on central laboratory assessments and not the Interactive Response Technology. CRF: case report form; CRT: chemoradiotherapy; DFS: disease free survival; ECOG PS: Eastern Cooperative Oncology Group Performance Score; ECS: Esophageal Cancer Subscale; EQ-5D-3L: EuroQol questionnaire comprising 5 dimensions, with each dimension having 3 levels; FACT-E: Functional Assessment of Cancer Therapy-Esophageal; FACT-G7: 7-item version of FACT-General; GEJ: gastroesophageal junction; HER2: human epidermal growth factor receptor 2; LAB: laboratory value; OS: overall survival; PD-L1: programmed death ligand 1; PFS2: progression free survival after the next line of the subsequent therapy; ROW: rest of world; US: United States Source: CheckMate 577 protocol[51] and clinical study report (CSR)[52]	

B.2.3.1.1 Study design

CheckMate 577 is an ongoing Phase III randomised, multicentre, double blind, placebo-controlled study of adjuvant nivolumab or placebo (Clinical Trials identifier NCT02743494). The objective of the study was to evaluate the efficacy and safety of nivolumab in patients with resected OC or GEJ cancer. The trial was initiated in July 2016 and was conducted across multiple countries.

Patients were randomised in a 2:1 ratio to treatment with nivolumab (240 mg every two weeks IV for eight cycles followed by 480 mg every four weeks IV for eight cycles for a total of a year or until recurrent disease) or placebo. Randomisation was stratified by histology (squamous vs adenocarcinoma), pathologic lymph node status (positive [≥ ypN1] vs negative [ypN0]) and tumour cell PD-L1 status (≥ 1% vs < 1% or indeterminate/non-evaluable). The maximum duration of treatment was one year, after which patients entered the follow-up phase. The study design of CheckMate 577 is provided in Figure 5.

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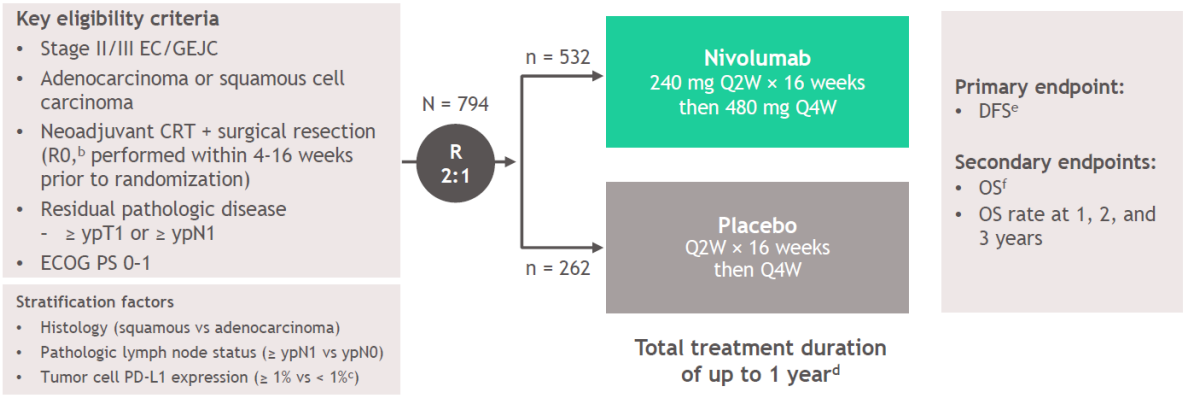

Figure 5. Study design of CheckMate 577[53]

[a]ClinicalTrials.gov number, NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumour present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumour cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a pre-specified interim analysis; [f]The study will continue as planned to allow for future analysis of OS.

Data presented in this submission are derived from published data based on a database lock (DBL) July 2020.[52]

B.2.3.1.2 Eligibility criteria

Patients with resected OC or GEJ cancer who have received CRT followed by surgery were enrolled and randomised post-resection. The main eligibility criteria are listed in Table 7; please see the trial protocol for a full list of inclusion and exclusion criteria.[51]

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Table 7. Inclusion and exclusion criteria for CheckMate 577

Key inclusion criteria	Key exclusion criteria
• Men or women of at least 18 years of age • Stage II or Stage III (per AJCC 7th edition) carcinoma of the oesophagus or GEJ and histologically confirmed predominant adenocarcinoma or squamous cell carcinoma • Completed pre-operative (neoadjuvant) chemoradiotherapy followed by surgery. Platinum based chemotherapy should be used. • Complete resection (R0) and surgically rendered free of disease with negative margins on resected specimens. • Residual pathologic disease i.e. non-pathCR of their cancer with at least ypN1 or ypT1 listed on the pathology report of the resected specimens. • ECOG PS score of 0 or 1 • All patients must have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomisation.	• Patients who do not receive concurrent chemoradiotherapy prior to surgery. • Patients who only receive chemotherapy or only radiation prior to surgery • Patients with cervical oesophageal carcinoma. • Patients with Stage IV resectable disease. • Patient who received treatment directed against the resected cancer after complete resection • Patients with previous malignancies unless a complete remission was achieved at least five years prior to study entry and no additional therapy is required or anticipated to be required during the study period (exceptions are noted in the protocol) • Patients with active, known or suspected autoimmune disease. • Patients with a condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration. • Patients with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity. • Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
CTLA: cytotoxic T-lymphocyte-associated protein 4; ECOG PS: Eastern Cooperative Oncology Group Performance Score; pathCR: pathological complete resection; PD-1: programmed cell death 1; PD-L1: programmed death ligand 1 Source: CheckMate 577 protocol[51]	

B.2.3.1.3 Study medications

Patients were randomised in a 2:1 ratio to the nivolumab or placebo groups. After randomisation, the nivolumab group received nivolumab treatment (240 mg IV 30 minutes infusion every two weeks for 16 weeks, followed by 480 mg nivolumab every four weeks beginning at week 17). Patients randomised to receive placebo received equivalent placebo infusions over 30 minutes with the same dosing schedule as nivolumab. Treatment was continued for a total of one year or until recurrent disease, unacceptable toxicity, or withdrawal of consent. Details of disallowed and permitted medications are detailed in Table 6, Section B.2.3.1.3.

B.2.3.1.4 Study endpoints and assessments

The primary, secondary and exploratory endpoints of CheckMate 577 are provided in Table 8.

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The primary endpoint was DFS, defined as the time from randomisation to first recurrence or death, whichever occurs first. This is the most appropriate primary endpoint in this indication because the goal of adjuvant therapy is to remain disease-free. DFS allows direct measurement of clinically confirmed disease recurrence and can therefore be used to evaluate whether adjuvant immunotherapy prevents or delays recurrence. Furthermore, DFS is expected to have a strong correlation with OS in this patient population,[36,37,39] therefore, although the OS data are currently immature, the anticipated DFS-OS correlation suggests that any DFS benefit seen will translate to an OS benefit (see section B.2.12.2.1.1).

Table 8. Study endpoints in CheckMate 577

CheckMate 577 study outcomes	
Primary endpoint	• Disease free survival (DFS) ○ Defined as the time from randomisation to first recurrence or death, whichever occurs first.

Secondary and exploratory endpoints	Secondary endpoints:
	• Overall survival (OS)
	  ○ Defined as the time from randomisation to death.
	• Overall survival rate
	  ○ The probability that a patient is alive at 1, 2 and 3 years, respectively, following randomisation.
	Key exploratory endpoints:
	• Safety and tolerability:
	  ○ Incidence of adverse events (AEs),
	  ○ Serious adverse events (SAEs),
	  ○ Deaths,
	  ○ Laboratory abnormalities
	• Distant-metastasis free survival (DMFS), defined as the time from randomisation to the first distant recurrence or death, whichever occurs first
	• PD-L1 status as predictive biomarker measured by the primary endpoint of DFS and the secondary endpoint of OS based on PD-L1 status level
	• PFS2, defined as the time from randomization to the date of investigator-defined documented objective disease progression on the subsequent next-line therapy or start of second subsequent next-line therapy or death due to any cause, whichever occurs first.
	• Quality of life, measured using the EQ-5D-3L and FACT-E
	• Please see the study protocol for further exploratory endpoints, including biomarker analysis, immunogenicity, and pharmacokinetics

AE: adverse event; DFS: disease free survival; ECOG PS: Eastern Cooperative Oncology Group Performance Score; ECS: Esophageal Cancer Subscale; EQ-5D-3L: EuroQol questionnaire comprising 5 dimensions, with each dimension having 3 levels; FACT-E: Functional Assessment of Cancer Therapy-Esophageal; FACT-G7: 7-item version of FACT-General; OS: overall survival; PD-L1: programmed death ligand 1; PFS2: progression free survival after the next line of the subsequent therapy; SAE: serious adverse event Source: CheckMate 577 protocol[51] and CSR[52]	

B.2.3.1.5 Baseline characteristics

The demographics and baseline characteristics of patients enrolled in CheckMate 577 are summarised in Table 9. A total of 794 patients were enrolled. At the data cut-off (July 2020), overall median follow-up was 24.4 months. The median age in the nivolumab and placebo group was 62.0 (range: 26–82) and 61.0 (range: 26–86), respectively. Most patients in both arms were < 65 years old, although a substantial proportion in the nivolumab arm (37.4%)

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and the placebo arm (33.6%) were aged 65 years or older. The majority of patients were white (81.6%), male (84.5%) and the predominant histological type was adenocarcinoma (70.9%). Geographically, the largest proportion of patients came from Europe, followed by US/Canada, the rest of the world and Asia. Most patients had PD-L1 expression of less than 1%. Patients randomised to the nivolumab arm were overall comparable to patients randomised to the placebo arm in terms of baseline characteristics. Disease stage at initial entry as well as disease location were also similar between the groups.

Table 9. Characteristics of participants in the studies across treatment groups

Baseline characteristic		Nivolumab	Placebo
Cohort size		532	262
Age	Median (range), years	62.0 (26-82)	61.0 (26-86)
	< 65 years, n (%)	333 (62.6)	174 (66.4)
Sex, n (%)	Female	83 (15.6)	40 (15.3)
	Male	449 (84.4)	222 (84.7)
Race, n (%)	White	432 (81.2)	216 (82.4)
	Asian	83 (15.6)	34 (13.0)
Geographic location, n (%)	US/Canada	167 (31.4)	88 (33.6)
	Europe	202 (38.0)	101 (38.5)
	Asia	77 (14.5)	29 (11.1)
	ROW	86 (16.2)	44 (16.8)
ECOG PS, n (%)	0	308 (57.9)	156 (59.5)
	1	224 (42.1)	106 (40.5)
Histological type, n (%)	Adenocarcinoma	376 (70.7)	187 (71.4)
	Squamous cell carcinoma	155 (29.1)	75 (28.6)
	Other	1 (0.2)	0
Baseline PD-L1 status, n (%)	≥ 1 %	89 (16.7)	40 (15.3)
	< 1 %	374 (70.3)	196 (74.8)
	Indeterminate/non-evaluable	69 (13.0)	26 (9.9)
Disease at initial diagnosis, n (%)	OC	320 (60.2)	155 (59.2)
	GEJ cancer	212 (39.8)	107 (40.8)
Disease stage at initial diagnosis, n (%)	Stage I	0	0
	Stage II	179 (33.6)	99 (37.8)
	Stage III	351 (66.0)	163 (62.2)
	Stage IV	0	0
	Not reported	2 (0.4)	0
Disease at study entry, n (%)	OC	311 (58.5)	151 (57.6)
	OC lower third	101 (38.0)	96 (36.6)
	OC middle third	82 (15.4)	46 (17.6)
	OC upper third	27 (5.1)	9 (3.4)
	GEJ	221 (41.5)	111 (42.4)
	GEJ type I	91 (17.1)	49 (18.7)
	GEJ type II	99 (18.6)	46 (17.6)
	GEJ type III	26 (4.9)	14 (5.3)
	GEJ not reported	5 (0.8)	2 (0.8)

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Pathologic TN classification at study entry: tumour, n (%)	ypT0	31 (5.8)	16 (6.1)
	ypT1	83 (15.6)	33 (12.6)
	ypT2	119 (22.4)	73 (27.9)
	ypT3	286 (53.8)	138 (52.7)
	ypT4	10 (1.9)	2 (0.8)
	Unknown	3 (0.6)	0
Pathologic TN classification at study entry: nodes, n (%)	ypN0	227 (42.7)	109 (41.6)
	≥ ypN1: ypN1	186 (35.0)	87 (33.2)
	≥ ypN1: ypN2	94 (17.7)	49 (18.7)
	≥ ypN1: ypN3	25 (4.7)	16 (6.1)
	Unknown	0	1 (0.4)
ECOG PS: Eastern Corporative Oncology Group Performance Score; GEJ: gastroesophageal junction; OC: oesophageal cancer; PD-L1: programmed death ligand 1; ROW: rest of world Source: CheckMate 577 CSR[52]			

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Statistical analyses

A summary of statistical methodology for CheckMate 577 is provided in Table 10.

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Table 10. Summary of statistical analyses for CheckMate 577

	CheckMate 577
Primary objective	To compare DFS of nivolumab versus placebo in patients with resected OC or GEJ cancer.
Analysis populations	Enrolled: all patients who signed the informed consent form, obtained a subject number and were registered in interactive response technology (IRT; used for pre-treatment disposition). **Randomised**: patients randomised to any treatment arm through the IRT (primary analysis population, used for demography, protocol deviations, baseline characteristics, and efficacy). Treated: all randomised patients who received at least one dose of any study treatment (used for drug exposure and safety) Immunogenicity patients: nivolumab treated patients with baseline and at least one post-baseline assessment for anti-drug antibody (used for immunogenicity).
Statistical analysis of primary endpoints	The primary analysis was based on the randomised population. DFS was compared between treatment arms using a 2-sided log rank test, stratified by the 3 randomisation stratification factors (tumour cell PD-L1 status: ≥ 1% vs < 1% or indeterminate/non-evaluable], pathologic lymph node status [positive (≥ ypN1) vs negative (ypN0)], and histology [squamous vs adenocarcinoma]). The HR for DFS with its corresponding alpha-adjusted 2-sided 96.4% confidence interval (CI) was estimated via a stratified Cox model with treatment arm as the only covariate in the model. Adjustment on the CI was based on the actual alpha level, which was based on actual DFS events observed. See section 7.5.2 of the statistical analysis plan (SAP) for further details of the primary analysis. Sensitivity analyses around the primary endpoint were also planned; these are described in the trial protocol[51] and section 7.5.2.1 of the SAP[54].
Statistical analysis of key secondary endpoints	OS is only to be tested after superiority has been demonstrated in DFS. OS will be compared between treatment arms using a 2-sided log rank test, stratified by the 3 randomisation stratification factors. Survival rate analysis will be carried out only for those time points which are mature enough by the time of the given database lock. Point estimates will be provided using K-M product-limit method. For each survival rate per treatment arm, two-sided 95% CIs using log-log transformation will be computed. No formal statistical comparison between the two arms will be performed on the survival rate. The final analysis of OS is planned to occur when 460 OS events would be observed and is not yet available at time of submission. See section 7.5.3 of the SAP for further details of the secondary analyses.[54]
Statistical analysis of safety endpoints	Safety analyses were performed for all treated patients. Descriptive statistics of safety were presented using MedDRA version 23.0 and National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 (v 4.0) by treatment arm. All on-study SAEs, drug-related SAEs, AEs, drug-related AEs, IMAEs, and select AEs were tabulated using worse grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. Frequency, management, and resolution of IMAEs and select AEs were analysed. See section 7.6 of the SAP for further details of the safety analyses.[54]
Statistical analysis of other relevant endpoints (biomarker analysis)	Analyses were based on all randomised patients if not otherwise specified. Evaluation whether tumour cell PD-L1 status is a predictive biomarker for DFS was an exploratory objective. Analyses for tumour cell PD-L1 were based on baseline PD-L1 positive status using 1%, 5%, and 10% cut-offs. For the association between tumour cell PD-L1 status and DFS, a curve was estimated using the K-M product-limit method for each treatment arm. Within each PD-L1 status subgroup, a HR (with corresponding 2-sided 95% CI) was estimated via an unstratified Cox model with treatment arm as the only covariate in the model. A Forest plot of HRs with 95% CIs was generated. See section 7.8 of the SAP for further details of the PD-L1 statistical analysis.[54]

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Statistical analysis of other relevant endpoints (patient-reported outcomes assessments)	The analysis of EQ-5D-3L and FACT-E were restricted to randomised patients who had an assessment at baseline and at least one post-baseline assessment. EQ-5D-3L descriptive analyses included: questionnaire completion rate; a by-patient listing of the level of problems in each dimension, corresponding to EQ-5D-3L health state, utility index score and visual analogue scale (VAS) score; proportion of patients reporting problems for the 5 EQ-5D-3L dimensions at each assessment time point; mean score and mean change from baseline at each assessment time point summarised by treatment group using descriptive statistics (N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum) and a line graph summarising the mean changes from baseline for EQ-5D-3L utility index and VAS scores. Esophageal Cancer Subscale, Functional Assessment of Cancer Therapy-General (FACT-G), FACT-G7 and Functional Assessment of Cancer Therapy-Esophageal total scores and changes from baseline were summarised at each assessment time point using descriptive statistics (N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum). See section 7.9 of the SAP for further details of the patient-reported outcomes statistical analysis.[54]
Sample size, power calculation	The sample size determination took into consideration the comparison of the primary endpoint of DFS and the first secondary endpoint of OS between the 2 treatment arms. The study required approximately 760 patients to be randomised (achieved > 760) at a 2:1 ratio to nivolumab and placebo and observations of at least 440 DFS events in order to achieve approximately 91% power to detect an average hazard ratio (HR) of 0.72 at a 2-sided alpha of 0.05. The sample size determination accounts for 1 DFS interim analysis. OS will be tested following the overall hierarchical testing procedure upon demonstration of superiority in DFS at either interim or final analyses for all randomised patients. With the sample size of 760, it is required to observe at least 460 OS events at the final OS analysis in order to achieve approximately 90% power to detect an average HR of 0.73 at a 2-sided alpha of 0.05. The power of the OS final analysis accounts for 2 OS interim analyses that occur at the same time as the DFS interim and DFS final analyses, respectively.
Data management, patient withdrawals	Protocol-required data were collected on eCRFs, which were completed by investigational site personnel and reviewed/approved by the investigator. Data on SAEs were submitted to BMS using electronic SAE reports.

AE: adverse event; CI: confidence interval; CRT: chemoradiotherapy; CTCAE: common terminology criteria for adverse events; DFS: disease free survival; eCRF: electronic case report form; GEJ: gastroesophageal junction; HR: hazard ratio; IHC: immunohistochemistry; IMAE: immune-mediated adverse event; IRT: interactive response technology; K-M: Kaplan-Meier; OC: oesophageal cancer; OS: overall survival; PD-L1: programmed death ligand 1; SAE: serious adverse event; SAP: statistical analysis plan; SD: standard deviation; VAS: visual analogue scale.
Source: CheckMate 577 CSR[52] and SAP[54]

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B.2.4.2 Sample size and power calculation

CheckMate 577 consisted of two arms, with 794 patients randomised in a 2:1 ratio to nivolumab or to placebo. This study was intended to verify the superiority of the nivolumab group over the placebo group in terms of DFS (the primary endpoint). The sample size determination considered the comparison of the primary endpoint of DFS between the two treatment arms and the first secondary endpoint of OS between the two treatment arms. Further details are provided in Table 10.[54]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Quality assessment of the pivotal CheckMate 577 trial was conducted using the University of York, Centre for Reviews and Dissemination (2008) checklist,[55] as shown in Table 11. There were no notable quality issues.

Table 11. Quality assessment of the relevant clinical effectiveness evidence

Study questions	Grade (yes/no/not clear/NA)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in dropouts between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination[55]) ITT: intention-to-treat; NA: not applicable.	

The complete quality assessment is available in Appendix D.

B.2.6 Clinical effectiveness results of the relevant trials

Evidence for the clinical efficacy of nivolumab is derived from the CheckMate 577 study, a Phase III placebo-controlled study. The design, methodology and results for CheckMate 577 are described in Section B.2.6.1.

B.2.6.1 CheckMate 577 - Patient disposition

A total of 1,085 patients were enrolled and 794 were randomised to receive either nivolumab (n = 532) or placebo (n = 262). Two patients randomised to placebo were not treated – one patient no longer met the entry criteria, and the other requested to discontinue study treatment. At the time of the DBL, 755 (95.3%) patients were continuing in the study, of

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whom 50 (31 in the nivolumab arm and 19 in the placebo arm) were still on treatment and the remaining 742 patients were in the post-treatment follow-up period. A summary of patient disposition is provided in Table 12.

Table 12. CheckMate 577: patient disposition

	Nivolumab	Placebo
Number of patients (randomised)	532	262
Number of treated patients	532	260
Continuation in the treatment period at database lock, n (%)		
Patients still on treatment	31 (5.8)	19 (7.3)
Patients no longer on treatment	501 (94.2)	241 (92.7)
Reasons for discontinuation of the treatment period, n (%)		
Completed treatment	229 (43.0)	99 (38.1)
Disease recurrence	149 (28.0)	113 (43.5)
Study drug toxicity	57 (10.7)	8 (3.1)
Death	1 (0.2)	0
Adverse event unrelated to study drug	15 (2.8)	9 (3.5)
Patient request to discontinue	30 (5.6)	5 (1.9)
Patient withdrew consent	12 (2.3)	4 (1.5)
Lost to follow-up	0	1 (0.4)
Poor/non-compliance	1 (0.2)	0
Other	7 (1.3)	2 (0.8)
Continuation in the study at end of treatment, n (%)		
Continuing in the study*	507 (95.3)	248 (95.4)
Not continuing in the study	25 (4.7)	12 (4.6)
Reasons for not continuing in the study follow-up period, n (%)		
Death	8 (1.5)	4 (1.5)
Patient withdrew consent	13 (2.4)	5 (1.9)
Lost to follow-up	3 (0.6)	2 (0.8)
Other	1 (0.2)	1 (0.4)

*Includes patients still on treatment and patients off treatment continuing in the follow-up period
Source: CheckMate 577 CSR[52]

B.2.6.2 CheckMate 577 - Baseline patient characteristics

Full details of the baseline characteristics are provided in Table 9, Section B.2.3.1.5.

B.2.6.3 CheckMate 577 - Results

At the data cut-off (July 2020), median follow up was 24.4 months. A summary of the key outcomes from CheckMate 577 is provided in Table 13.

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Table 13. CheckMate 577: nivolumab efficacy

Endpoint		Nivolumab	Placebo
Evaluable patients		532	262
DFS	Median DFS (95% CI), months	22.41 (16.62, 34.00)	11.04 (8.34, 14.32)
	6-month DFS rates (95% CI), %	72.3 (68.2, 76.0)	63.4 (57.2, 69.0)
	Events, n (%)	[redacted]	[redacted]
	Type of event: recurrence, n (%)	219 (41.2)	147 (56.1)
	Local recurrence, n (%)	33 (6.2)	20 (7.6)
	Regional recurrence, n (%)	32 (6.0)	24 (9.2)
	Distant recurrence, n (%)	154 (28.9)	103 (39.3)
	Type of event: death without recurrence, n (%)	[redacted]	[redacted]
DMFS	Median DMFS (95% CI), months	[redacted]	[redacted]
	6-month DMFS rates (95% CI), %	[redacted]	[redacted]
	Events, n (%)	[redacted]	[redacted]
PFS2	Median PFS2 (95% CI), months	[redacted]	[redacted]

CI: confidence internal; DFS: disease free survival; DMFS: distant metastasis-free survival; NA: not applicable; PFS2: progression free survival on subsequent systemic therapy
Source: CheckMate 577 CSR[52]

B.2.6.3.1 Disease free survival

Treatment with nivolumab monotherapy demonstrated a statistically significant and clinically relevant improvement in DFS in comparison to placebo (median DFS of 22.4 months vs 11.0 months, respectively; HR = 0.69 [96.4% CI: 0.56, 0.86], stratified log-rank test p-value = 0.0003). The corresponding Kaplan-Meier plots are presented in Figure 6. Fewer patients experienced DFS events in the nivolumab arm (45.3%) than the placebo arm (59.2%). Most DFS events were disease recurrences, affecting 219 patients in the nivolumab arm (41.2%) and 147 patients in the placebo arm (56.1%). The most common type of recurrence was distant recurrence (Table 14). Deaths without recurrence were [redacted] events recorded across both arms (Table 14).

Table 14. DFS events in all randomised patients

	Nivolumab	Placebo
Patients with a DFS event, n (%)	[redacted]	[redacted]
Recurrence, n (%)	219 (41.2)	147 (56.1)
Local, n (%)	33 (6.2)	20 (7.6)
Regional, n (%)	32 (6.0)	24 (9.2)
Distant, n (%)	154 (28.9)	103 (39.3)
Death without recurrence, n (%)	[redacted]	[redacted]

DFS: disease free survival.
Source: CheckMate 577 CSR[52]

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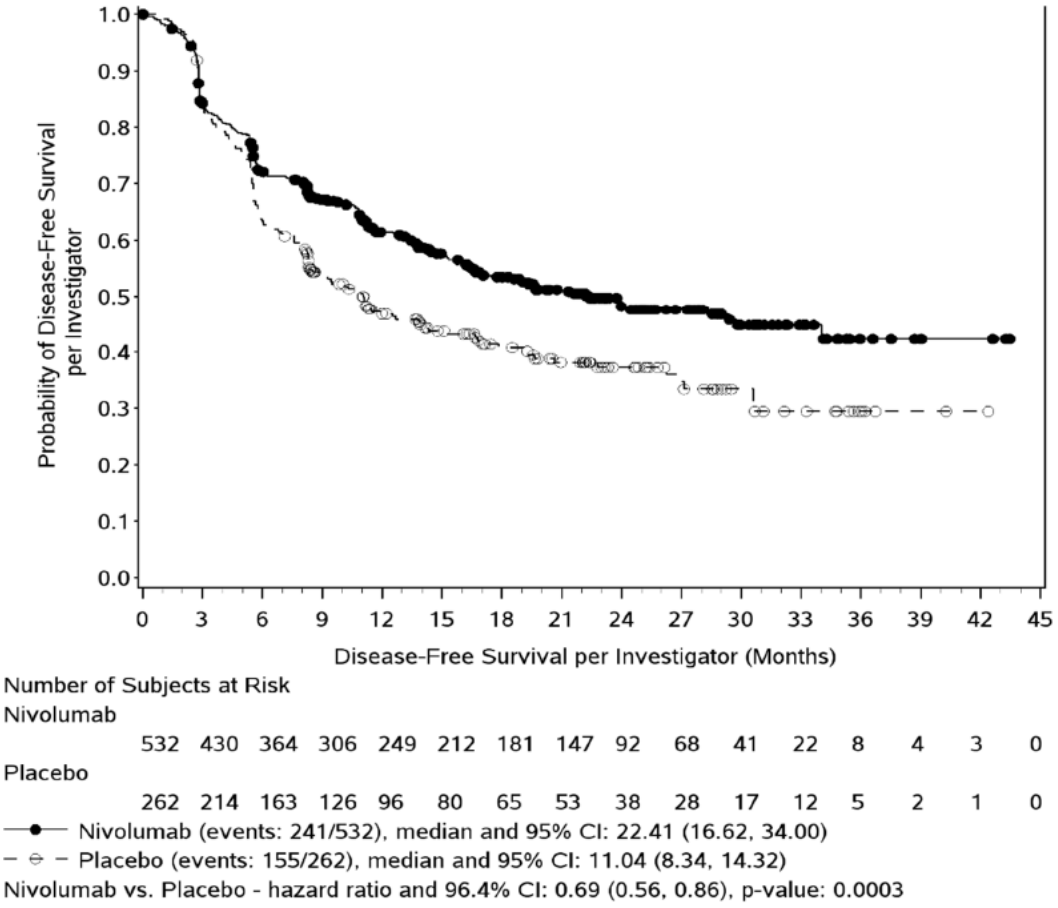

Figure 6. Kaplan-Meier plot of DFS in all randomised patients (source: CheckMate 577 CSR[52])

Statistical model for hazard ratio and p value: stratified Cox proportional hazard model and stratified log-rank test. Symbols represent censored observations.

B.2.6.3.2 Overall survival

OS was a secondary objective of CheckMate 577. At the time of this pre-specified interim analysis (DBL July 2020) OS data were not mature and the company remains blinded to OS analyses per treatment arm. OS data are therefore not presented as part of this submission. Limited OS data are common in an adjuvant treatment setting where survival is relatively long in comparison with the typical duration of a clinical trial, however, DFS is anticipated to be a strong surrogate for OS when assessing adjuvant OC and GEJ cancer therapy[39] (see section B.2.12.2.1.1).

B.2.6.3.3 Distant metastasis-free survival

Distant metastasis-free survival (DMFS) was defined as the time between the date of randomization and the date of first distant recurrence or death, whichever occurred first. Local or regional recurrence were not considered as an event for DMFS. Patients treated with nivolumab achieved longer median DMFS ([redacted] months) compared with those receiving placebo ([redacted] months) (HR = [redacted] [95% CI: [redacted]]). In total, [redacted] ([redacted]%) nivolumab-treated

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and [redacted] ([redacted]%) placebo-treated patients experienced DMFS events. The corresponding Kaplan-Meier plots are presented in Figure 7. [16]

[redacted]

Figure 7. Kaplan-Meier plot of DMFS in all randomised patients (source: CheckMate 577 CSR[52])
Statistical model for hazard ratio: stratified Cox proportional hazard model. Symbols represent censored observations.

Distant metastasis has been associated with poorer survival outcomes; for example, in a population-based study from the Netherlands, patients with distant recurrence had median post-recurrence OS of 4.0 months, compared to 7.4 months for patients with locoregional recurrence.[16] Therefore, the longer DMFS experienced by patients treated with nivolumab, compared to those receiving placebo, may translate into an improvement in OS and further demonstrates the benefit of nivolumab therapy.

B.2.6.3.4 Progression free survival on subsequent systemic therapy

A total of [redacted] patients did not receive subsequent systemic therapy, so that progression free survival on subsequent systemic therapy (PFS2) was measured as the time between the randomisation date and death date, or the last known alive date if the patient was alive. For the [redacted] patients who received subsequent systemic therapy, PFS2 was the time between the randomisation date and objectively documented progression per investigator assessment on the subsequent systemic therapy, second subsequent systemic therapy, or until death from any cause, whichever occurred first. Subsequent systemic therapies received by patients are detailed in Table 15.

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Table 15. Subsequent systemic therapies

	Nivolumab	Placebo
Number of patients (randomised), n	532	262
Number of patients who received subsequent systemic therapy, n (%)	[redacted]	[redacted]
Subsequent systemic therapies received, n (%)		
Immunotherapy	[redacted]	[redacted]
Anti-PD1	[redacted]	[redacted]
Investigational agent	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Anti-PDL1	[redacted]	[redacted]
Avelumab	[redacted]	[redacted]
Anti-CTLA4	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]
Other immunotherapy	[redacted]	[redacted]
Targeted therapy	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]
Investigational agent	[redacted]	[redacted]
Ramucirumab	[redacted]	[redacted]
Other systemic anticancer therapy – experimental	[redacted]	[redacted]
Chemotherapy[a]	[redacted]	[redacted]
Other[b]	[redacted]	[redacted]
Number of lines of subsequent therapy		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
≥ 4	[redacted]	[redacted]

Source: CheckMate 577 CSR[52]
[a] Most common chemotherapies were fluorouracil and oxaliplatin.
[b] Mostly supportive treatments, including primarily folinic acid, but also zoledronic acid, and denosumab.

PFS2 favoured nivolumab over placebo. Median PFS2 [redacted] and was [redacted] months (95% CI: [redacted]) in the placebo arm. HR favoured the nivolumab arm over the placebo arm: [redacted] (95% CI: [redacted]). Among the PFS2 events:

- [redacted] ([redacted]) in the nivolumab arm and [redacted] ([redacted]) events in the placebo arm were due to death,
- [redacted] ([redacted]) in the nivolumab arm and [redacted] ([redacted]%) in the placebo arm were due to progression on subsequent systemic therapy,
- [redacted] ([redacted]%) in the nivolumab arm and [redacted] ([redacted]%) in the placebo arm were due to start of second subsequent systemic therapy.

The corresponding Kaplan-Meier plots are presented in [redacted]Figure 8. These PFS2 data suggest that the clinical benefit of nivolumab may be seen even after the disease has

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recurred. This potential benefit of nivolumab post-recurrence in this setting will be confirmed once OS data become available.

Figure 8. Kaplan-Meier plot of PFS2 in all randomised patients (source: CheckMate 577 CSR[52])

Statistical model for hazard ratio: stratified Cox proportional hazard model. Symbols represent censored observations.

B.2.6.3.5 Patient-reported outcomes

CheckMate 577 collected patient reported outcomes through the EuroQol 5 dimensional 3-level (EQ-5D-3L) index and also the Functional Assessment of Cancer Therapy-Esophageal (FACT-E) questionnaire as well as selected components including the Esophageal Cancer Subscale (ECS), FACT-General (FACT-G) and 7-item version of the FACT-General (FACT-G7). Both nivolumab treated and placebo treated patients had improvements in HRQoL during the treatment period.

B.2.6.3.5.1 Functional Assessment of Cancer Therapy - Esophageal (FACT-E)

Response rates for the FACT-E questionnaire at baseline were > 96% in both arms (96.8% and 96.9% of nivolumab and placebo treated patients respectively), whilst completion rates were > 80% in both arms at all subsequent on treatment assessment points.

Mean FACT-E total scores at baseline were numerically similar between the nivolumab (n = 499, mean [SD]: 133.40 [20.97]) and placebo (n = 253, mean [SD]: 134.03 [20.40]) arms. Mean changes from baseline increased for both treatment arms at all timepoints that included at least 10 patients. By Week 53, which was the latest currently available timepoint with > 10 responses, the scores improved in both arms and remained numerically similar between the arms (n = 45, mean [SD]: 134.58 [22.20] in the nivolumab arm vs n = 20, mean [SD]: 144.03 [20.37] in the placebo arm) (Figure 9). Formal statistical testing of between-arm differences in QoL was not performed. The results were, in general, similar for the Esophageal Cancer Subscale (ECS) and FACT-G and FACT-G7.

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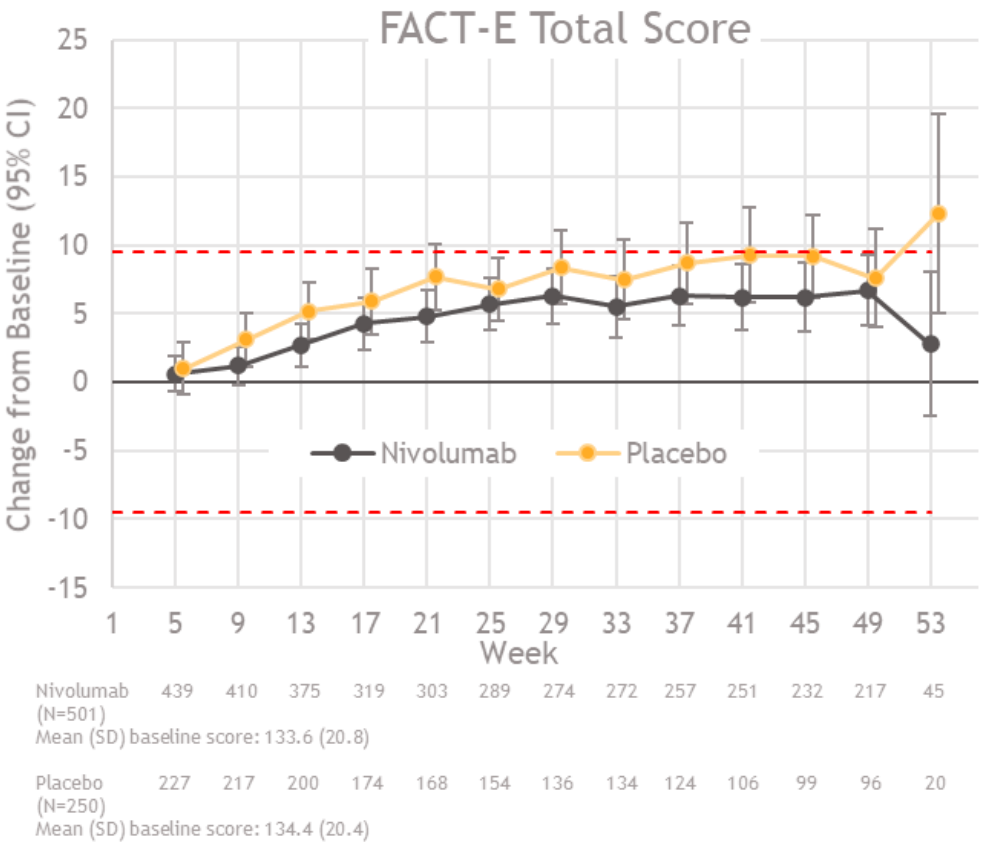

Figure 9. Overall self-rated health status FACT-E and change from baseline means and 95% CI over time in all randomised patients (source: ASCO-GI 2021 oral presentation[56])

B.2.6.3.5.2 EQ-5D-3L

Greater than 95% of patients completed the EQ-5D-3L visual analogue scale (VAS) at baseline (95.7% and 95.8% of nivolumab and placebo treated patients, respectively). Similar to FACT-E, completion rates were > 80% at all subsequent on treatment assessments.

Mean EQ-5D-VAS score at baseline was numerically similar between the nivolumab (n = 509, mean [SD]: 70.4 [22.3]) and placebo (n = 251, mean [SD]: 69.1 [24.1]) arms. By Week 53, which was the latest time point with > 10 responses, the scores improved in both arms and remained numerically similar between the arms (n = 48, mean [SD]: 83.1 [12.9] in the nivolumab arm vs n = 21, mean [SD]: 85.7 [20.0] in the placebo arm) (Figure 10). Formal statistical testing of between-arm differences in QoL was not performed.

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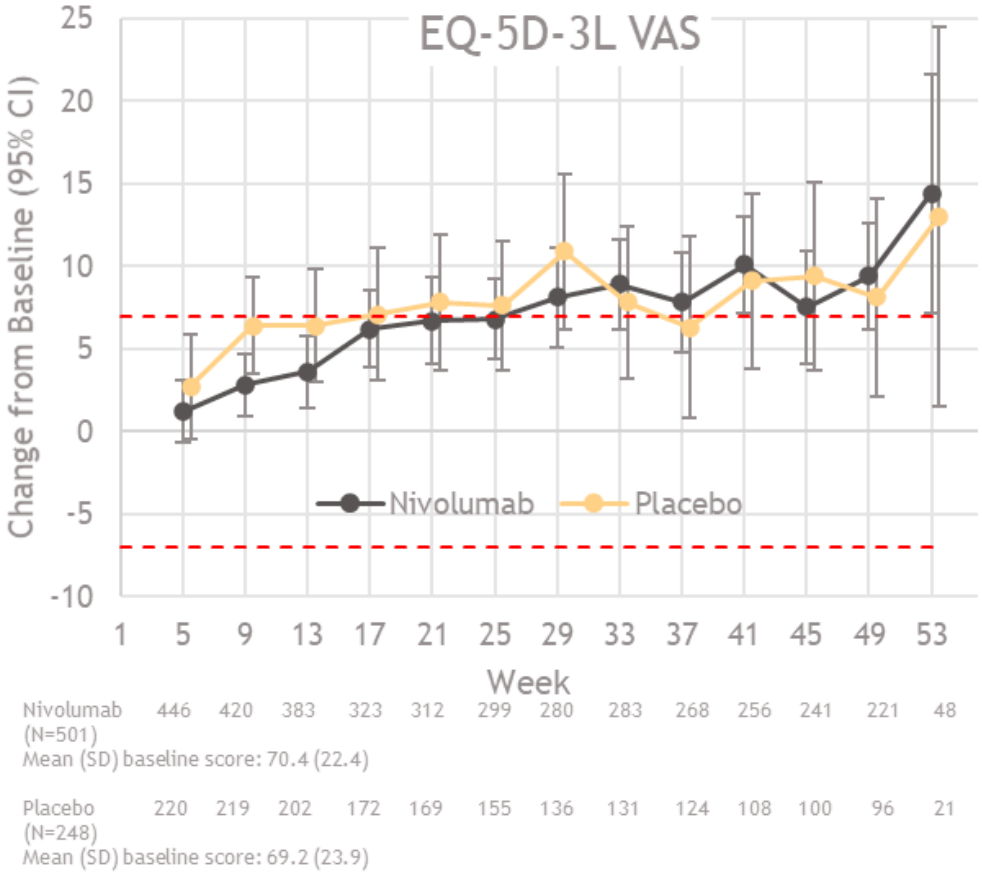

Figure 10. Overall self-rated health status EQ-5D VAS and change from baseline means and 95% CI over time in all randomised patients (source: ASCO-GI 2021 oral presentation[56])

The pattern of results for EQ-5D-3L utility index was similar to the EQ-5D VAS, with an increase in mean scores from baseline seen from week 9 in nivolumab treated patients and from week 13 in placebo treated patients (Figure 11). Mean EQ-5D-3L score at baseline was numerically similar between the nivolumab (n = 506, mean [SD]: 0.8203 [0.1790]) and placebo (n = 248, mean [SD]: 0.8310 [0.1629]) arms. At the latest timepoint with at least 10 responses, week 53, the scores improved in both arms and remained numerically similar between the arms (n = 48, mean [SD]: 0.8207 [0.2143] in the nivolumab arm vs n = 20, mean [SD]: 0.8349 [0.1983] in the placebo arm.

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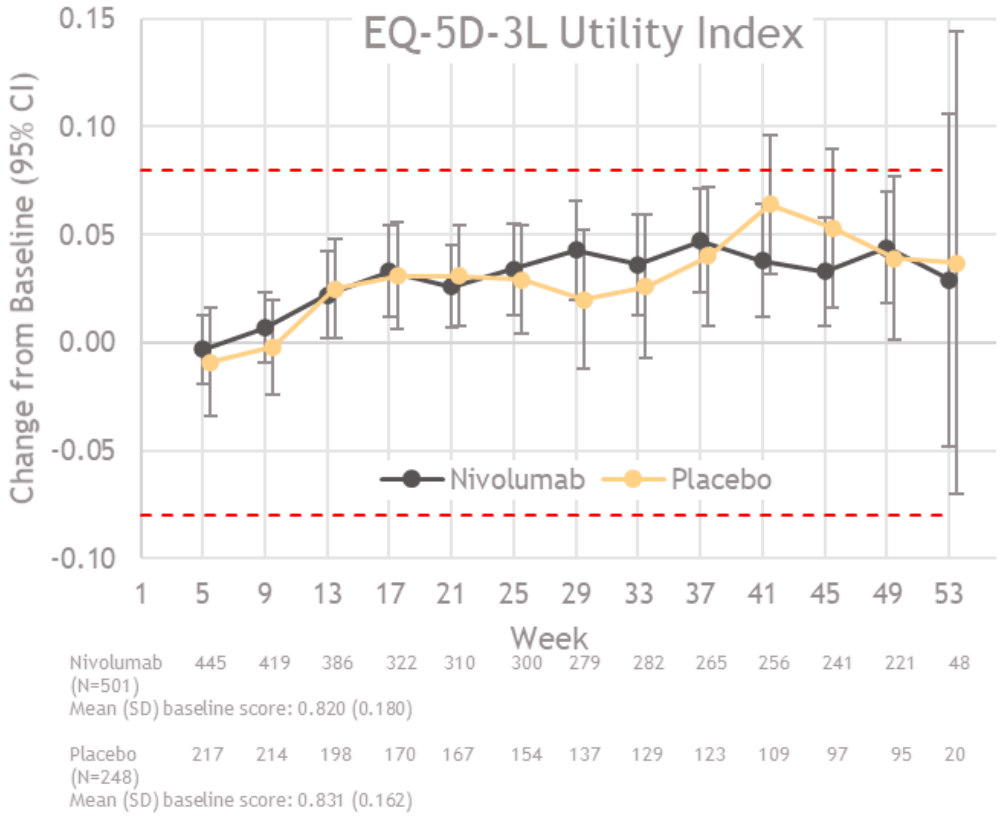

Figure 11. EQ-5D-3L utility index score and change from baseline means and 95% CI over time in all randomised patients (source: ASCO-GI 2021 oral presentation[56])

B.2.7 Subgroup analysis

DFS was analysed by a number of pre-planned subgroups, summarised in Table 6.[52]

The median DFS and hazard ratios (HRs) for key subgroup analyses are detailed in Figure 12, and a more detailed discussion of the PD-L1 subgroups can be found in Figure 13, section B.2.7.1. Overall, subgroup analyses of DFS favoured nivolumab over placebo with a HR of < 1 in nearly all of the pre-specified groups, including tumour histology (SCC and adenocarcinoma) and pathologic lymph node status (positive, ≥ ypN1 and negative, ypN0).

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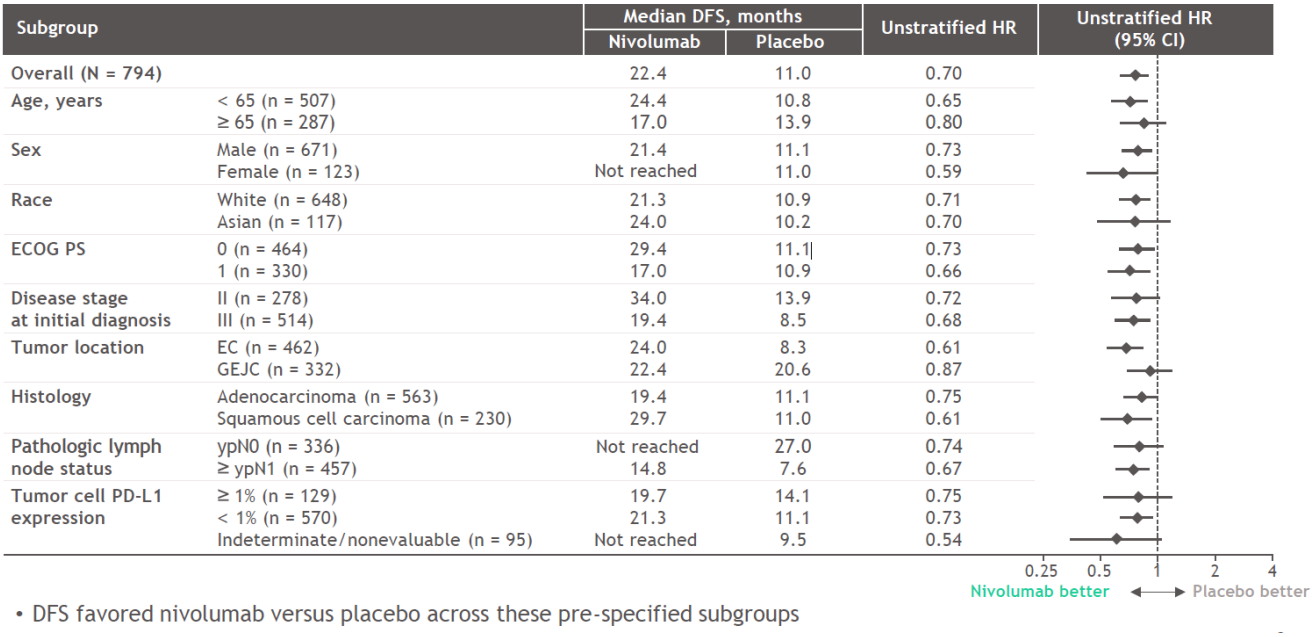

Figure 12. Forest plot of subgroup analysis on disease free survival[53]

AEs were also analysed by subgroups of age, sex and geographic region. Overall, the frequencies of all-cause and treatment-related AEs (TRAEs) in the nivolumab and placebo arms in these subgroups were similar to the overall study population by treatment (see B.2.9).[52] Subgroup analysis of AEs by race had limited interpretability as most patients were in one category (White).

In the Endocrine Disorder system organ class, more all-cause AEs and TRAEs were reported in women (all-cause 28.9%, treatment-related 24.1%) than men (all-cause 14.9%, treatment-related 13.8%). In the Metabolism and Nutrition Disorders system organ class, more all-cause AEs and TRAEs were reported in men (all-cause 28.7%, treatment-related 9.4%) than women (all-cause 22.9%, treatment-related 4.8%).

No overall differences in all-causality AEs and TRAEs were observed in older patients (≥ 65 and < 75, and ≥ 75 and <85 years old) compared with younger patients (< 65 years old).

B.2.7.1 DFS by PD-L1 expression levels

Importantly, nivolumab demonstrated superior efficacy versus placebo regardless of tumour cell PD-L1 status (Figure 13), which was a stratification factor applied during randomisation. At higher cut-offs of PD-L1 expression (≥ 5% and ≥ 10%), an improved HR for DFS was observed.

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	N	Nivolumab N of Events (N of Subjects)	Nivolumab mDFS (95% CI)	Placebo N of Events (N of Subjects)	Placebo mDFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivolumab vs Placebo
>= 1% PD-L1 Expression	129	40 (89)	19.65 (11.33, N.A.)	24 (40)	14.13 (5.49, 22.80)	0.75 (0.45, 1.24)
< 1% PD-L1 Expression	570	175 (374)	21.26 (16.30, 34.00)	118 (196)	11.10 (8.25, 15.21)	0.73 (0.57, 0.92)
>= 5% PD-L1 Expression	88	26 (60)	28.32 (13.27, N.A.)	18 (28)	9.23 (3.25, 27.04)	0.60 (0.33, 1.10)
< 5% PD-L1 Expression	611	189 (403)	19.65 (15.93, 34.00)	124 (208)	11.14 (8.34, 16.66)	0.75 (0.60, 0.94)
>= 10% PD-L1 Expression	71	21 (47)	28.32 (13.27, N.A.)	16 (24)	8.31 (2.99, 22.80)	0.51 (0.27, 0.99)
< 10% PD-L1 Expression	628	194 (416)	19.65 (15.93, 34.00)	126 (212)	11.14 (8.34, 16.66)	0.76 (0.61, 0.95)
Indeterminate/Non-Evaluable	95	26 (69)	N.A. (13.31, N.A.)	13 (26)	9.49 (3.38, N.A.)	0.54 (0.27, 1.05)

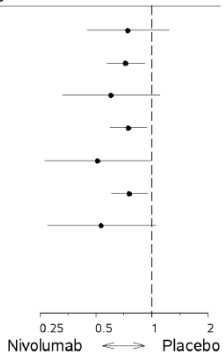

Figure 13. Forest plot of disease free survival by PD-L1 status (source: CheckMate 577 CSR[52])

B.2.8 Indirect and mixed treatment comparisons

Direct evidence on comparative efficacy of nivolumab versus routine surveillance was derived from a single clinical trial (CheckMate 577), so that no meta-analysis or indirect treatment comparison was required.

B.2.9 Adverse reactions

Key points

- In patients with OC and GEJ cancer who have undergone surgical resection following neoadjuvant CRT, nivolumab has a safety profile that is consistent with previous reports in other indications.
- AE rates were similar between the nivolumab and placebo arms.

Safety data for nivolumab for the adjuvant treatment of OC or GEJ cancer are available from CheckMate 577. In general, nivolumab presented with an acceptable safety profile, which is well characterised and in line with other indications. The safety profile of nivolumab among subgroups of age, sex, race, and geographical region was consistent with the overall study population (see B.2.7). No new safety concerns were identified with adjuvant nivolumab monotherapy. Overall, frequencies of drug-related AEs, serious adverse events (SAEs) and AEs leading to discontinuation were low in both the nivolumab and placebo arms.

B.2.9.1 Extent of exposure

At the time of the July 2020 DBL, 86.1% of patients treated with nivolumab received 90% to <110% of the planned dose intensity (Table 16). The median number of nivolumab doses received was [redacted], and the median number of placebo doses received was [redacted]. The median duration of study therapy was 10.14 and 8.99 months in the nivolumab and placebo arms, respectively.

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It should be noted that dose reductions or escalations were not allowed during the study.

Table 16. CheckMate 577: extent of exposure to study drug (July 2020 DBL)

	Nivolumab (N = 532)	Placebo (N = 260)
Number of doses received		
Mean (SD)	[redacted]	[redacted]
Median (min–max)	[redacted]	[redacted]
Cumulative dose (mg)		
Mean (SD)	4167.7 (2239.2)	N.A.
Median (min–max)	5280.0 (240–6240)	N.A.
Relative dose intensity (%)		
≤ 110%	1 (0.2)	N.A.
90% to < 110%	458 (86.1)	N.A.
70% to < 90%	67 (12.6)	N.A.
50% to < 70%	4 (0.8)	N.A.
< 50%	2 (0.4)	N.A.

max: maximum; min: minimum; N.A: not available; SD: standard deviation

Patient 110-910 was randomised to placebo and received placebo in Cycles 1, and 2, and Cycles 4 to 8, with the exception of Cycle 3 when the patient received a single dose of nivolumab. This nivolumab dose is not counted in dosing summary in either the placebo arm or in the nivolumab arm.

Source: CheckMate 577 CSR[52]

B.2.9.2 Overall adverse events

Similar frequencies of all-causality AEs occurred in the placebo (93.5%) and nivolumab (95.9%) arms (Table 17). The majority of AEs were grade 1 or 2. The most common AEs in both treatment arms were diarrhoea (29.1% for nivolumab, 29.2% for placebo), fatigue (27.1% for nivolumab, 24.2% for placebo) and nausea (22.7% for nivolumab, 21.2% for placebo). All-causality grade 3–4 AEs occurred in 34.4% and 32.3% patients in the nivolumab and placebo arms, respectively.

Table 17. Overall adverse events – safety population of CheckMate 577

Safety parameters	No. of patients (%)			
	Nivolumab (N = 532)		Placebo (N = 260)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
All-cause AEs				
Overall	510 (95.9)	183 (34.4)	243 (93.5)	84 (32.3)
Most frequent AEs (≥ 10 % of any grade in any treatment arm)				
Diarrhoea	155 (29.1)	5 (0.9)	76 (29.2)	2 (0.8)
Fatigue	144 (27.1)	7 (1.3)	63 (24.2)	3 (1.2)
Nausea	121 (22.7)	4 (0.8)	55 (21.2)	0
Cough	98 (18.4)	1 (0.2)	48 (18.5)	1 (0.4)

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Safety parameters	No. of patients (%)			
	Nivolumab (N = 532)		Placebo (N = 260)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Vomiting	80 (15.0)	3 (0.6)	42 (16.2)	3 (1.2)
Decreased appetite	79 (14.8)	5 (0.9)	26 (10.0)	2 (0.8)
Dysphagia	69 (13.0)	4 (0.8)	43 (16.5)	9 (3.5)
Weight decreased	69 (13.0)	2 (0.4)	23 (8.8)	0
Pruritis	68 (12.8)	2 (0.4)	16 (6.2)	0
Rash	63 (11.8)	4 (0.8)	17 (6.5)	1 (0.4)
Abdominal pain	62 (11.7)	3 (0.6)	37 (14.2)	3 (1.2)
Constipation	61 (11.5)	0	32 (12.3)	0
Hypothyroidism	56 (10.5)	0	4 (1.5)	0
Dyspnoea	54 (10.2)	3 (0.6)	27 (10.4)	1 (0.4)
Arthralgia	53 (10.0)	1 (0.2)	21 (8.1)	0
Gastroesophageal reflux disease	41 (7.7)	1 (0.2)	34 (13.1)	0
Headache	41 (7.7)	1 (0.2)	29 (11.2)	0
AE: adverse event. Source: CheckMate 577 CSR table 8.1-1[52]				

B.2.9.3 Treatment-related adverse events

TRAEs were experienced by 70.7% and 45.8% of nivolumab- and placebo-treated patients, respectively (Table 18). The most commonly experienced TRAE was fatigue (16.9% and 11.2% in the nivolumab and placebo arms, respectively). Diarrhoea was the second most common TRAE in the nivolumab arm and most common in the placebo arm, affecting 16.5% and 15.0% of patients in the nivolumab and placebo arms, respectively. All other TRAEs were experienced by ≤ 10% patients in either arm.

Of the most common TRAEs, the organ classes with the most notable difference between treatment groups were skin (24.4% nivolumab, 10.8% placebo) and endocrine (17.5% nivolumab, 2.3% placebo). Few of these were categorised as grade 3–4 (skin: 1.3% nivolumab, 0.4% placebo; endocrine: 0.9% nivolumab, 0.0% placebo).

Table 18. Treatment-related AEs reported in CheckMate 577

Safety parameters	No. of patients (%)			
	Nivolumab (N = 532)		Placebo (N = 260)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Treatment-related AEs				
Overall	376 (70.7)	71 (13.3)	119 (45.8)	15 (5.8)
Treatment-related AEs (≥ 5 % in any treatment arm)				
Fatigue	90 (16.9)	6 (1.1)	29 (11.2)	1 (0.4)
Diarrhoea	88 (16.5)	2 (0.4)	39 (15.0)	2 (0.8)

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Safety parameters	No. of patients (%)			
	Nivolumab (N = 532)		Placebo (N = 260)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Pruritus	53 (10.0)	2 (0.4)	9 (3.5)	0
Rash	52 (9.8)	4 (0.8)	10 (3.8)	1 (0.4)
Hypothyroidism	50 (9.4)	0	4 (1.5)	0
Nausea	47 (8.8)	0	13 (5.0)	0
Hyperthyroidism	35 (6.6)	0	1 (0.4)	0
Arthralgia	30 (5.6)	1 (0.2)	4 (1.5)	0
Aspartate aminotransferase increased	29 (5.5)	2 (0.4)	10 (3.8)	0
Asthenia	28 (5.3)	0	4 (1.5)	0

AE: adverse event
Source: CheckMate 577 CSR table 8.1-1[52]

B.2.9.4 Serious adverse events

A similar proportion of patients experienced at least one all-cause SAE in the nivolumab (29.7%) and placebo (30.0%) arms (Table 19). The most frequently reported any-grade all-cause SAEs for nivolumab were pneumonia (3.0%), malignant neoplasm progression (2.3%), pneumonia aspiration (1.3%), pneumonitis (1.1%), and dysphagia (1.1%). The most frequently reported any-grade all-cause SAEs for placebo were malignant neoplasm progression (3.1%), pneumonia (1.9%), dysphagia (1.9%), pleural effusion (1.5%), and pneumothorax, dyspnoea, diaphragmatic hernia, and oesophageal stenosis (each 1.2%).

The frequency of treatment-related SAEs was low in both the placebo and nivolumab arms. Treatment-related SAEs were reported in fewer than 8% of patients in both the nivolumab (7.5%) and placebo (2.7%) arms (Table 19). Grade 3–4 treatment-related SAEs were reported in 5.5% patients in the nivolumab arm and 1.2% patients in the placebo arm.

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Table 19. SAEs and treatment-related SAEs reported in ≥ 1% of all treated patients in CheckMate 577

Safety parameters		No. of patients (%)					
		Nivolumab (N = 532)			Placebo (N = 260)		
		Any grade	Grade 3–4	Grade 5	Any grade	Grade 3–4	Grade 5
Serious adverse events							
Total patients with an event		158 (29.7)	107 (20.1)	9 (1.7)	78 (30.0)	53 (20.4)	6 (2.3)
Gastrointestinal disorders	Total	43 (8.1)	34 (6.4)	0	26 (10.0)	21 (8.1)	0
	Dysphagia	6 (1.1)	4 (0.8)	0	5 (1.9)	4 (1.5)	0
	Diaphragmatic hernia	4 (0.8)	4 (0.8)	0	3 (1.2)	2 (0.8)	0
	Oesophageal stenosis	4 (0.8)	4 (0.8)	0	3 (1.2)	3 (1.2)	0
Infections and infestations	Total	31 (5.8)	26 (4.9)	0	10 (3.8)	5 (1.9)	1 (0.4)
	Pneumonia	16 (3.0)	13 (2.4)	0	5 (1.9)	3 (1.2)	0
Respiratory, thoracic and mediastinal disorders	Total	29 (5.5)	16 (3.0)	1 (0.2)	15 (5.8)	4 (1.5)	1 (0.4)
	Pneumonia aspiration	7 (1.3)	4 (0.8)	1 (0.2)	0	0	0
	Pneumonitis	6 (1.1)	3 (0.6)	0	2 (0.8)	1 (0.4)	0
	Pleural effusion	5 (0.9)	4 (0.8)	0	4 (1.5)	2 (0.8)	0
	Pneumothorax	3 (0.6)	3 (0.6)	0	3 (1.2)	1 (0.4)	1 (0.4)
	Dyspnoea	1 (0.2)	1 (0.2)	0	3 (1.2)	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Total	19 (3.6)	10 (1.9)	4 (0.8)	20 (7.7)	13 (5.0)	4 (1.5)
	Malignant neoplasm progression	12 (2.3)	8 (1.5)	3 (0.6)	8 (3.1)	4 (1.5)	4 (1.5)
Treatment-related serious adverse events							
Total patients with an event		40 (7.5)	29 (5.5)	1 (0.2)*	7 (2.7)	3 (1.2)	0
Respiratory, thoracic and mediastinal disorders	Total	11 (2.1)	6 (1.1)	0	3 (1.2)	1 (0.4)	0
	Pneumonitis	6 (1.1)	3 (0.6)	0	2 (0.8)	1 (0.4)	0

* this event was deemed not to be treatment-related by the investigator after the database lock based on further evaluation of the fatal event.

Source: CheckMate 577 CSR table 8.3-1 and table 8.3-2[52]

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B.2.9.5 Select AEs, immune-mediated AEs and other events of special interest

Select AEs, immune-mediated AEs (IMAEs) and other events of special interest (OESIs) occurred more frequently in the nivolumab arm than the placebo arm (Table 20), however, most select AEs and IMAEs were grade 1 or 2.

Most select AEs were considered drug-related by the investigator. The most frequently reported any grade drug-related select AEs by preferred term (PT) were as follows in each treatment arm: nivolumab: diarrhoea (16.5%), pruritus (10.0%), rash (9.8%), aspartate aminotransferase (AST) increased (5.5%), alanine aminotransferase (ALT) increased (4.7%); placebo: diarrhoea (15.0%), rash (3.8%), and AST increased (3.8%). Across the select AE categories, the majority of events in the nivolumab arm were manageable using the established algorithms, with resolution occurring when immune-modulating medications (mainly systemic corticosteroids) were administered. Except for endocrine events, most drug-related select AEs with nivolumab had resolved (ranging from 65.4% to 100% across categories) at the time of the DBL. Some endocrine select AEs were not considered resolved due to the continuing need for hormone replacement therapy.

Table 20. Select AEs, immune-mediated AEs and other events of special interest reported in CheckMate 577

Safety parameters	No. of patients (%)			
	Nivolumab (N = 532)		Placebo (N = 260)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
All-cause select AEs				
Skin	169 (31.8)	7 (1.3)	48 (18.5)	1 (0.4)
Gastrointestinal	157 (29.5)	6 (1.1)	77 (29.6)	3 (1.2)
Endocrine	101 (19.0)	5 (0.9)	8 (3.1)	0
Hepatic	79 (14.8)	14 (2.6)	31 (11.9)	6 (2.3)
Pulmonary	29 (5.5)	6 (1.1)	5 (1.9)	1 (0.4)
Hypersensitivity/Infusion Reactions	15 (2.8)	1 (0.2)	5 (1.9)	0
Renal	12 (2.3)	1 (0.2)	7 (2.7)	0
Treatment-related select AEs				
Skin	130 (24.4)	7 (1.3)	28 (10.8)	1 (0.4)
Endocrine	93 (17.5)	5 (0.9)	6 (2.3)	0
Gastrointestinal	91 (17.1)	4 (0.8)	40 (15.4)	3 (1.2)
Hepatic	49 (9.2)	6 (1.1)	18 (6.9)	4 (1.5)
Pulmonary	23 (4.3)	6 (1.1)	4 (1.5)	1 (0.4)
Hypersensitivity/Infusion Reactions	10 (1.9)	0	3 (1.2)	0
Renal	7 (1.3)	1 (0.2)	2 (0.8)	0
All-causality non-endocrine IMAEs within 100 days of last dose treated with immune modulating medication				
Rash	42 (7.9)	5 (0.9)	4 (1.5)	1 (0.4)

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Safety parameters	No. of patients (%)			
	Nivolumab (N = 532)		Placebo (N = 260)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Pneumonitis	24 (4.5)	9 (1.7)	4 (1.5)	1 (0.4)
Diarrhoea/Colitis	10 (1.9)	4 (0.8)	2 (0.8)	1 (0.4)
Hepatitis	6 (1.1)	4 (0.8)	3 (1.2)	3 (1.2)
Nephritis and Renal Dysfunction	2 (0.4)	1 (0.2)	1 (0.4)	0
Hypersensitivity	1 (0.2)	0	1 (0.4)	0
All-causality endocrine IMAEs within 100 days of last dose with or without immune modulating medication				
Hypothyroidism/Thyroiditis	59 (11.1)	2 (0.4)	3 (1.2)	0
Hyperthyroidism	35 (6.6)	0	1 (0.4)	0
Adrenal Insufficiency	5 (0.9)	2 (0.4)	1 (0.4)	0
Diabetes Mellitus	3 (0.6)	2 (0.4)	0	0
Hypophysitis	1 (0.2)	0	0	0
All-causality OESIs within 100 days of last dose with or without immune modulating medication				
Myocarditis	3 (0.6)	3 (0.6)	0	0
Pancreatitis	1 (0.2)	1 (0.2)	0	0
Guillain-Barré Syndrome	1 (0.2)	1 (0.2)	0	0

AE: adverse event; IMAE: immune mediated adverse event; OESI: other event of special interest; SAE: serious adverse event
Source: CheckMate 577 CSR table 8.1-1[52]

B.2.9.6 Deaths and discontinuations due to AEs

Any-grade all-causality AEs leading to discontinuation were reported in 12.8% patients in the nivolumab arm and 7.7% patients in the placebo arm. Grade 3–4 AEs leading to discontinuation were reported in 7.1% patients in the nivolumab arm and 6.2% patients in the placebo arm. Any-grade TRAEs leading to discontinuation were reported in 9.0% patients in the nivolumab arm and 3.1% patients in the placebo arm. Grade 3–4 TRAEs leading to discontinuation were reported in 4.9% patients in the nivolumab arm and 2.7% patients in the placebo arm.

At the time of the July 2020 DBL, OS data were not mature, therefore the Company has remained blinded to the death summary by treatment arm. One grade 5 drug-related SAE (cardiac arrest) was reported in one patient in the nivolumab arm (Table 19). This event was deemed not to be treatment-related by the investigator after the DBL

B.2.10 Ongoing studies

Checkmate 577 remains ongoing. Per protocol, the final OS analysis will be done when [redacted], which is expected approximately [redacted] months from the time of the first randomised patient.

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B.2.11 Innovation

Nivolumab represents a step-change for the adjuvant treatment of OC and GEJ cancer as it is the first and only active treatment approved in the UK in this indication. Nivolumab is a checkpoint inhibitor immunotherapy that acts via facilitating the body's own immune system to target and destroy cancer cells (Section B.1.3.2.1).

The introduction of nivolumab has the potential to alter the treatment pathway for patients with resected OC and GEJ cancer, who currently receive no active adjuvant treatment, and therefore represents a step-change in the management of these patients. The benefits of nivolumab include:

- **Improved DFS:** Treatment options for patients with OC/GEJ cancer who have had successful resection with pathologic residual disease is limited, with management of these patients restricted to routine surveillance despite the high risk of recurrence, and the risk of associated poor survival. Nivolumab demonstrated a significant extension in DFS versus placebo alone in patients with resected OC/GEJ, with a 31% reduction in the risk of recurrence or death and a doubling of median DFS. DFS benefit was also observed across multiple pre-specified subgroups. These benefits of nivolumab pertaining to DFS are likely to readily translate into an extension of OS, due to the close surrogate relationship between the two in this setting. Nivolumab is therefore a much-needed therapy that can reduce the risk of relapse and, likely, death.

- **No adverse impact on quality of life:** As detailed in Section B.2.6.3.5, patients treated with nivolumab reported no worsening in quality of life during the study when using disease-specific (FACT-E) or general (EQ-5D) measures. Across most time points analysed, quality of life was similar between nivolumab- and placebo-treated patients, with both arms showing either maintenance compared to baseline or a trend of improvement through week 53. Nivolumab was well tolerated, which is an important benefit in an adjuvant therapy for a group of patients who are at risk of suffering concurrent post-operative complications.

- **Facilitation of normal life:** Due to the improved quality of life and tolerability, treatment with nivolumab has the potential to facilitate patients to continue a normal life, spending less time in hospital and thus more time at home. Administration of nivolumab is a maximum of once every two weeks which enables patients to schedule outpatient appointments in a predictable manner.

In summary, the availability of nivolumab offers an opportunity to make a significant and substantial impact on health-related aspects and addresses a current unmet need, that is, a lack of SOC for the management of these patients. Adoption of nivolumab in this therapeutic indication in NHS England would represent a significant development in the management of this life-threatening condition.

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B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings from the clinical evidence

The clinical evidence supporting the use of nivolumab for resected OC or GEJ in patients who were previously treated with CRT was derived from the randomised controlled trial CheckMate 577.

CheckMate 577 was a Phase III, multicentre, randomised, double-blind, placebo-controlled study which demonstrates the benefits of nivolumab over placebo in terms of DFS and safety, as described in Section B.2. Based on the available data, benefits of nivolumab in terms of extending DFS were observed over the initial 40-month period, with a doubling of median DFS (22.4 months for nivolumab vs 11.0 months for placebo) and a reduction in the risk of recurrence or death by 31% versus placebo. DFS is anticipated to be predictive of OS in this patient population (see section B.2.12.2.1.1). Nivolumab showed either maintenance from baseline or trends of improvement in quality of life measures, similar to those observed for placebo, and was well-tolerated; its safety profile was acceptable and similar to that observed for placebo.

Overall, nivolumab offers a favourable benefit-risk profile for patients with resected OC and GEJ cancer, who currently have no SOC treatments available post-resection.

B.2.12.2 Strengths and limitations of the clinical evidence base

The main limitations of the clinical evidence base are presented in Section B.2.12.2.1 whilst strengths of the evidence are set out in Section B.2.12.2.2. These limitations should be viewed within the context of the study strengths and the high unmet need in this patient population.

B.2.12.2.1 Limitations of study evidence

Nivolumab clinical efficacy is informed using the pivotal trial, CheckMate 577. There are limitations within the study; however, these limitations should be considered within the context of the study strengths and the high unmet need in this patient population.

B.2.12.2.1.1 Overall survival

OS data were not mature and the company remains blinded to OS analyses per treatment arm. OS data are therefore not presented as part of this submission.

However, DFS is expected to have a strong correlation with OS in this patient population,[36,37,39] therefore, although the OS data are currently immature, the DFS-OS correlation suggests that any DFS benefit seen will translate to an OS benefit.

DFS has been demonstrated to be an acceptable surrogate endpoint for OS in the adjuvant treatment of gastric cancer,[36] in the neoadjuvant treatment of gastroesophageal adenocarcinoma,[37] [redacted].[39] In these studies,

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the surrogate threshold effect based on adjusted regression analysis was 0.92, 0.79 and [redacted], respectively, meaning that a future trial with a HR for DFS below these thresholds is likely to yield a HR below 1.0 for the treatment effect on OS, which would reflect an OS benefit of nivolumab.

B.2.12.2.2 Strengths of study evidence

CheckMate 577 is a well-designed, Phase III randomised controlled trial which provides evidence of the clinical efficacy of nivolumab versus placebo. The sizes of the patient cohorts were large (532 and 262 in the nivolumab and placebo arms, respectively). Patient-reported outcomes are available, whereby quality of life was assessed through collection of EQ-5D data, providing utility estimates which are directly attributable to treatment with nivolumab. CheckMate 577 compares nivolumab with placebo, representing routine surveillance, which is the current SOC in the adjuvant setting, as described in relevant clinical guidelines,[23,40] including those presented by NICE,[43] for the management of this patient group.

The most important treatment outcomes for most OC patients after tumour resection include long-term survival without disease recurrence (DFS), reduced side effects, and quality of life. Nivolumab provides significant benefits for each of these outcomes:

- Improved DFS
- Maintained quality of life
- Tolerability

The safety and efficacy of nivolumab are of particular importance in the setting of resected OC, where there is a lack of SOC for the maintenance of DFS and thus, the prevention of recurrence. In this setting, nivolumab offers a well-tolerated therapeutic option with the potential to offer significant survival benefit in this patient population. Many patients are medically fragile after surgery for OC or GEJ cancer, therefore the tolerability of nivolumab is a key benefit. The availability of nivolumab would provide an opportunity to make a significant and substantial impact on health-related benefits and address a current unmet need.

B.2.12.3 Relevance of the evidence base to the decision problem

The submission presents one study, CheckMate 577, in line with the decision problem. Outcomes considered in the submission closely mirror the decision problem set out by NICE. The evidence base presented within this submission represents the best available evidence and is directly relevant to the decision problem. OS, while evaluated in the trial and listed in the scope, could not be provided at the time of submission due to data immaturity.

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B.2.12.4 External validity of study results to patients in routine clinical practice

Patients enrolled in the available studies can be considered broadly representative of UK practice, in terms of baseline characteristics, with subgroups provided for analysis where possible.

B.2.12.4.1 Relevance to UK patient population

Whilst only 1% of the nivolumab treated patients were from the UK, 38% were from Europe, and 31% from US or Canada (Section B.2.3.1.5). Just under 15% of nivolumab treated patients were from Asia, with similar proportions observed in placebo treated patients. Given that Western patients are expected to have similar prognoses and treatment pathways, patients in CheckMate 577 are expected to be generally representative of a UK patient population.

B.2.12.4.2 UK standard of care

As outlined in Section B.1.3.2, UK guidelines recommend routine surveillance for patients who have had successful (R0) resection, and thus, no specific treatments are recommended currently for these patients. This is in line with recommendations from ESMO and NCCN.

CheckMate 577 compared nivolumab to a placebo arm, representing routine surveillance, as recommended by guidelines, hence, it is considered that the control arm is a relevant comparator to the UK setting for treatment of OC patients who have received surgical resection following neoadjuvant CRT. In the UK, neoadjuvant CRT is highly variable, thus whilst the placebo arm of CheckMate 577 reflects SOC in the treatment of OC/GEJ cancer, it may not entirely reflect the UK treatment paradigm. Reimbursement of nivolumab for this indication could therefore elicit a change in current UK practice and bring the UK treatment approach closer to the gold standard of trimodality treatment as established in the CROSS trial[14,57] and as recommended by several clinical guidelines.[23,40]

B.3 Cost effectiveness

Base case analysis

- In line with estimates of short life expectancy in patients, the base case analysis predicts [redacted] and [redacted] discounted LYs for routine surveillance and nivolumab respectively, informed by the randomised, placebo-controlled CheckMate 577 trial.
- Use of nivolumab is estimated to result in an increased mean post recurrence survival (PRS) of [redacted] years. Nivolumab is also associated with additional discounted quality-adjusted life-years (QALYs) and discounted life years of [redacted] and [redacted], respectively, when compared to routine surveillance.

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- Discounted incremental costs were estimated to be £[redacted] under base case assumptions and the resultant ICER was £21,047 per QALY, which is cost-effective at a willingness-to-pay threshold of £30,000 per QALY.

Sensitivity analysis

- In the deterministic and probabilistic sensitivity analyses, nivolumab was cost-effective in the vast majority of scenarios at a willingness-to-pay threshold of £30,000 per QALY.
- Extensive scenario analyses were undertaken, reflecting the assumptions required to undertake plausible, robust and transparent base case analysis.
- Within these scenario analyses, the large majority of ICERs remain below the £30,000 per QALY threshold.

B.3.1 Published cost-effectiveness studies

In line with the NICE Guide to the methods of technology appraisal 2013,[58] an SLR was conducted to identify cost-effectiveness studies for any adjuvant intervention for resected OC or GEJ cancer. In brief, electronic database searches (MEDLINE, Embase, the NHS EED and EconLit) were conducted on 15 August 2019 and updated on 30 November 2020. In total, 17 publications were identified, reporting on 16 RCTs, of which 10 considered adjuvant therapies. Details of the SLR can be found in Appendix G.

Table 21. Study characteristics of economic modelling studies of patients with resected OC or GEJ cancer

Study name	Model structure	Intervention(s)	Patient population
Caruso, 2020[59]	N/A (database analysis)	Robotic gastrectomy Open gastrectomy	Patients with preoperative diagnosis of gastric cancer.
Zhang 2019[60]	Markov model	Adjuvant chemoradiotherapy (CRT) Adjuvant chemotherapy (CT) Observation (OB)	Adult patients with histologically proven stage IB to IIIC gastric or gastroesophageal adenocarcinoma who had received D2 R0 gastrectomy.
Zhan, 2019[61]	Markov model	Neoadjuvant chemoradiotherapy (vinorelbine+cisplatin), (NCRT) Surgery alone	Histologically confirmed, potentially curable ESCC clinically staged as T1-4N1M0/T4N0M0 (stage IIB or III)
Nunez, 2019[62]	N/A (case matched analysis)	Robotic gastrectomy Open gastric resection	Patients who underwent robotic and open gastric resection

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Study name	Model structure	Intervention(s)	Patient population
Fong Soe Khioe, 2018[63]	Markov model	Statin + SoC (surgery ± perioperative chemotherapy) SoC (surgery ± perioperative chemotherapy)	Patients with oesophageal adenocarcinoma
Chu, 2018[64]	Markov model	Esophagectomy Endoscopic therapy (ET)	Patients with oesophageal adenocarcinoma with TNM stage T1aN0M0 or T1bN0M0
Lin, 2015[65]	N/A (case matched analysis)	Neoadjuvant concurrent chemoradiotherapy (NCCRT) Esophagectomy alone	Locally advanced stage oesophageal squamous cell carcinoma patients
Wu, 2014[66]	Markov model	S-1 chemotherapy, XELOX chemotherapy Surgery alone	Patients with gastric cancer and undergoing D2 gastrectomy in China.
Chongqing, 2014[67]	Markov model	Adjuvant chemotherapy (ACT) + surgery (capecitabine + oxaliplatin after D2 gastrectomy) Surgery alone (gastrectomy)	Confirmed stage II–IIIB gastric cancer without metastatic disease and they had adequate renal, hepatic, and haematological function.
Tan, 2013[68]	Markov model	Adjuvant capecitabine + oxaliplatin (XELOX) Adjuvant tegafur + fluorouracil + oteracil (S-1) Surgery alone	Patients with stage II-IIIB gastric cancer.
Hisashige, 2013[69]	N/A (trial analysis)	Adjuvant chemotherapy (S-1 therapy) Surgery alone	Patients with completely resected stage II/III gastric cancer, who underwent gastrectomy with extended lymph-node dissection.
Lee, 2013[70]	Decision tree	Minimally invasive esophagectomy (MIE) Open esophagectomy	Patients with resectable oesophageal cancer
Hultman, 2012[71]	N/A (case matched analysis)	Cytoreductive surgery (CRS) + Hyperthermic intraperitoneal chemotherapy (HIPEC) + Early postoperative intraperitoneal chemotherapy (EPIC) Palliative systemic chemotherapy alone	Patients with peritoneal metastasis from gastric cancer
Wang, 2012[72]	Decision tree	Short-Term administration of Single Prophylactic Antibiotic Long-Term administration of Single Prophylactic Antibiotic	Patients undergoing elective gastric tumour surgery, aged 18 to 70 years.

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Study name	Model structure	Intervention(s)	Patient population
Wang, 2008[73]	Assumed Markov model	Surgery + adjuvant chemoradiotherapy (5-FU + leucovorin) Surgery alone	Patients with resectable adenocarcinoma of the stomach or gastroesophageal junction. Patients with surgically resected stage IB to IV (M0) gastric adenocarcinoma
Farndon, 1998[74]	N/A (prospective and retrospective case-series analysis)	Resection External bean Radiotherapy Brachytherapy Laser Intubation No treatment	Primary oesophageal carcinoma
Davini, 1997[75]	N/A (survival curve fitting analysis)	Multimodal therapy: Neoadjuvant chemotherapy (2 courses) + radiotherapy (1 course) + surgery Surgery	Oesophageal adenocarcinoma

B.3.2 Economic analysis

The economic case presented in this submission is based on conventional cost-utility analysis, assessing the use of nivolumab versus routine surveillance for the adjuvant treatment of resected OC or GEJ cancer, taking into account a simple discount patient access scheme (PAS) for nivolumab.

Of the studies identified in the SLR, the majority were Markov models with three states; commonly these were disease- or recurrence-free health states, post recurrence health states and death. The other analysis types identified were decision tree and within-trial analysis. A targeted literature review (TLR) of models used for HTA in the adjuvant setting also revealed the majority used Markov models, with only two of the ten HTA submissions identified using a partitioned survival framework.[76]

Partitioned survival models, particularly those using the common oncology three state framework comprising disease event, post event and OS, require direct use of both progression free survival (PFS) or DFS, and OS curves to derive time with progressed or recurred disease. Without OS data, it is not possible to implement a partitioned survival model. Therefore, the predominance of Markov models used in the adjuvant setting identified by the SLR and TLR is expected, because where there is the potential for long-term survival (or a group with long-term survival), as with adjuvant therapies, OS data are commonly not available. This was noted in several of the documents reviewed during the TLR. The immaturity of OS data from CheckMate 577 prohibits the construction of a partitioned survival model for this submission.

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Compared to partitioned survival models, the main issues with time-invariant Markov models relate to underlying assumptions and the applicability of time invariance and marginal intensity of transition hazard. Articles evaluating the differences between partitioned survival and Markov models for oncology highlight that as long as the underlying assumptions about patient movement are similar and reasonable, the outcomes should not be too different.[77,78] However, given that it is unlikely that the incidence of disease recurrence or death is time invariant in patients who have undergone resection for OC or GEJ cancer, it was considered that the most appropriate method would be a semi-Markov structure, While time-invariant and partitioned survival models may be adequate, where data is available to inform transitions, alternative approaches can offer more granularity.

Given these factors, a semi-Markov model structure has been utilised in order to replicate survival outcomes with a higher degree of accuracy than either a standard partitioned survival model or time-invariant Markov model, although differences in outcomes should be minimal, particularly where appropriate transition rates have been derived and appropriate assumptions used.[79] The semi-Markov approach allows the dependence between events to be captured, and permits time-dependent transitions between health states, for example, the transition from recurred disease to death depends on how long a patient has spent in the recurred disease state. This removes the necessity for a priori assumptions that would be required for a traditional Markov model.

The model utilises three health states (disease free, recurred disease and death) to reflect disease trajectory and the cost and utility consequences of different health states. The model structure reflects the most important outcomes for post-resection OC and GEJ cancer patients: survival (disease free and post recurrence), side effects, symptom control and quality of life. Survival curves are used to estimate DFS and post recurrence survival (PRS) in each treatment arm. Health state utilities and costs have been applied to reflect the symptom control and quality of life experienced by patients receiving nivolumab or routine surveillance, and the associated economic burden. Treatment-specific AE probabilities and event-specific costs are used to estimate the incidence of and economic consequences associated with TRAEs (Section B.3.3.2.4).

The structure of the semi-Markov model accommodates treatment discontinuation modelled from PLD and stopped at a defined time point and a pooled subsequent line of therapy, with mortality modelled through a survival curve obtained from the literature.[80]

B.3.2.1 Description of analyses

Data from CheckMate 577 have been used to inform decision making and provide certainty around the beneficial clinical impact of nivolumab as adjuvant treatment of patients with resected OC or GEJ cancer in the UK. CheckMate 577 data have been used to inform comparative efficacy in the base case analysis, as this Phase III randomised controlled trial provides direct evidence for nivolumab versus a placebo treatment (assumed equivalent to routine surveillance), and so can be considered the best available evidence. All analyses within this submission have been conducted from the payer perspective, in this case the NHS.

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B.3.2.2 Patient population

This economic evaluation considers the use of nivolumab for adjuvant treatment of patients with OC or GEJ cancer who have received CRT followed by surgery, in line with the anticipated licensed indication.

In the base case analysis, baseline patient parameters are derived from the baseline characteristics of patients enrolled in CheckMate 577, as detailed in Table 22.

Table 22. Baseline parameters in base case

Parameter	Mean	SE	Source
Age (years)	60.5	0.337	CheckMate 577 patient-level data[52]
Proportion of cohort male	0.845	0.013	
SE: standard error			

B.3.2.3 Model structure

A de novo semi-Markov model was developed, applying health states representing disease free, recurred disease and death (Figure 14). These health states reflect disease severity and incorporate use of healthcare resources, HRQoL and mortality rates. The model estimates the proportion of the cohort in each state using spline fits in the disease free state and literature-derived survival in the recurred disease state (see B.3.2.3.1).

To reflect the nature of OC/GEJ cancer and available evidence, the model assumes that OC/GEJ cancer phases are consecutive, which means patients are not able to revert to disease free status once the disease has recurred. This assumption has been validated by clinical advice that patients in the UK who experience a local recurrence would not be likely to receive another surgical therapy, therefore further treatment options are expected to be similar for those who experience metastatic recurrence.[41] The recurred disease state attempts to capture any and all potential further line treatments for both local and metastatic recurrences.

Using a weekly cycle length, the model predicts the proportion of the population who experience a recurrence or death event. Weekly cycles were considered appropriate for this evaluation because it enables the model to reflect the varying timings of drug administrations associated with both nivolumab and subsequent therapies. Weekly cycles also capture a realistic time scale over which patients experience changes in their symptoms or response to treatment.

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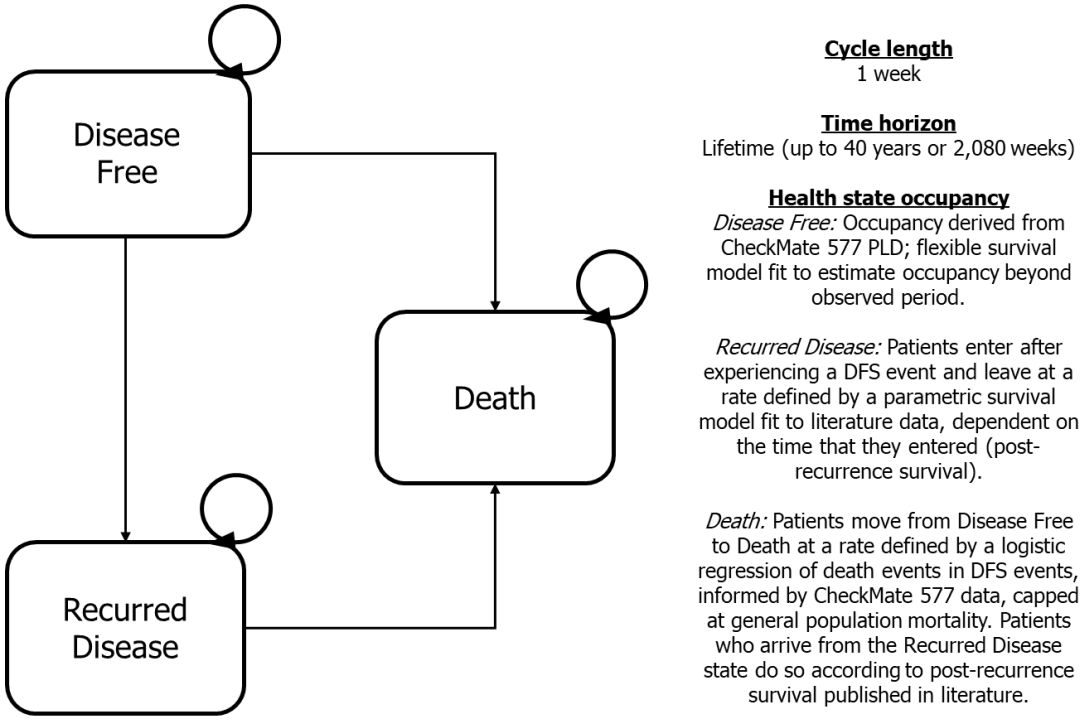

Figure 14. Model Schematic

DFS: disease free survival; PLD: patient-level data

Table 23. Definition and source of transitions

Transition	Description	Source
1	Disease free → Death	Background mortality (life tables) and logistic regression predicting DFS events that are death events
2	Disease free → Recurred disease	Pivotal study (DFS primary endpoint)
3	Recurred disease → Death	Lou et al, 2013[80]
DFS: disease free survival		

B.3.2.3.1 Derivation of health state occupancy estimates

Health state occupancy in the disease-free health state is defined by transitions from disease free to recurred disease and from disease free to death.

The transition from disease free to the recurred disease health state is informed by treatment-specific log-normal spline fits to DFS endpoints, derived from available patient-level data (PLD) from CheckMate 577 (described in Section B.3.3.2).

Pre-recurrence mortality (i.e. the transition directly from disease free to death) for the first three years in the disease free health state was modelled using a logistic regression of pre-recurrence death events in the CheckMate 577 PLD; specifically any events that were death without recurrence. This was done in order to predict the proportion of patients who leave

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the disease free health state and move straight to the death health state. After three years post-surgery without a recurrence, it is assumed that patients begin to experience mortality and recurrence events equivalent to the general population; this assumption has been validated by UK clinicians, who report that post-surgical patients are considered disease free and that their risk of recurred disease or mortality converges with that of the general population at around three years.[41]

Once patients experience a recurrence and move to the recurred disease state, they are assumed to experience death events conditional on having experienced a recurrence. Due to immaturity of the OS data, the PLD were not able to provide death events for modelling an OS curve to inform this transition. Therefore, the modelled death events post recurrence are informed by the literature (Lou et al, 2013[80]). An alternative literature source for post-recurrence survival was explored in scenario analysis (B.3.8.4.6) and model outcomes were validated against published outcomes (section B.3.9). This transition is derived by fitting curves to OS data from Lou et al.[80] Methods for deriving these curves and evidence for the suitability of this study to inform the model are provided in Section B.3.3.2.

B.3.2.3.2 Derivation of treatment line occupancy

Patients enter the model following neoadjuvant CRT and subsequent successful surgery can receive nivolumab or routine surveillance. In clinical practice, treatment cessation may be caused by loss of clinical benefit or may be related to other factors, such as AEs. Duration of time on study therapy is derived directly from the observed data in CheckMate 577 and incorporated into the cost-effectiveness model via a time on treatment curve. The base case analysis assumes that nivolumab treatment in the disease free health state is limited to a maximum of one year, in line with trial design[51,52] and with previous nivolumab indications (adjuvant treatment of non-small cell lung cancer).[48]

From the disease free state patients either remain without a recurrence, experience death without recurrence and move to the death health state or experience a recurrence and move to recurred disease state. Once in the recurred disease state they are assumed to receive subsequent treatment lines. For simplicity, it is assumed that patients do not discontinue this final line of therapy, and it is assumed to comprise all possible therapies that patients may subsequently receive, either sequentially or concurrently.

B.3.2.3.3 Outcome measures

The primary model output is the incremental cost-effectiveness ratio (ICER) expressed as incremental costs per quality-adjusted life-year (QALY) gained. The model provides an overview of other health economic outcomes, such as life years gained, and clinically relevant outcomes, such as predicted median DFS and PRS.

A TLR was undertaken to evaluate modelling approaches for adjuvant therapies in resectable cancers.[76] No previous NICE Technology Appraisals have been identified for adjuvant OC therapies. Table 24 provides a comparison versus a previous appraisal for adjuvant treatment of resected melanoma with an immunotherapy (TA553).[81]

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A similar approach to cost-effectiveness analysis was taken in TA553 as for this submission. A lifetime horizon was used to capture all potential costs and benefits and efficacy and utility data were derived from the key trial and sourced from the literature when trial data were not suitable. The most notable difference between the analyses is the use of a four-state model in TA553, as it was deemed necessary to separate recurrence types to ensure the model was clinically relevant. Clinical advice has indicated that after resection for OC or GEJ cancer, metastatic and local recurrences would be treated broadly similarly, with no additional surgery for local recurrence.[41] This negates the need for any additional health states in the cost-effectiveness model described in this submission. Indeed, the recurred disease health state is assumed to comprise a heterogenous group and all assumptions relating to the recurred disease health state are applied equally to both nivolumab and routine surveillance arms.

Table 24. Features of the economic analysis

Factor	Current appraisal		Previous appraisal (TA553)[81]
	Chosen values	Justification	Notes
Time horizon	Lifetime (up to 40 years or 2,080 weeks)	This ensures that all events have occurred, and all patients are accounted for. However, a shorter time horizon is assessed in sensitivity analysis.	Lifetime (~46 years)
Treatment stopping rule	One year	Treatment stopping was used in CheckMate 577 at one year. The efficacy data reflects this important treatment component	One year in line with KEYNOTE-054 trial protocol
Source of utilities	CheckMate 577 provides EQ-5D-3L data that can be used to derive utility inputs for use in nivolumab and routine surveillance arms. Previous submission data is used where PRS values are not available	CheckMate 577 collected utility data using the EQ-5D-3L. In line with the NICE reference case, trial utilities collected as part of CheckMate 577 (baseline and every 6 weeks until the end of the treatment phase and subsequently every 12 weeks during the follow-up phase) have been applied in the base case analysis for both treatments. Data from a NICE submission for 2L oesophageal cancer is used to estimate utility post recurrence due to large missing values in the post recurrence set from CheckMate 577.	KEYNOTE-054 and Literature
Source of costs	NHS reference costs, Healthcare costing standards for England, eMIT	As per NICE reference case	As per NICE reference case
2L: second line; eMIT: electronic market information tool; EQ-5D: EuroQol-5 dimension			

B.3.2.4 Intervention technology and comparators

As outlined in Section B.1.3.20, UK guidelines along with clinical expert opinion obtained during a clinical advisory board meeting supported evidence for a lack of adjuvant treatments that could reduce rates of recurrence for post-surgery OC patients. Therefore, the most appropriate comparator is routine surveillance.

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B.3.3 Clinical parameters and variables

B.3.3.1 Evidence synthesis

Evidence to describe the effectiveness of nivolumab for the adjuvant treatment of successfully resected OC or GEJ cancer is primarily derived from CheckMate 577, a randomised, placebo-controlled, Phase III study evaluating nivolumab as monotherapy for the treatment of resected OC or GEJ cancer. In the base case analysis, nivolumab efficacy has been derived from the nivolumab arm of CheckMate 577, while routine surveillance efficacy has been derived from the placebo arm. As such, there was no requirement to synthesise evidence.

B.3.3.2 Parameterisation of disease-free survival and post recurrence survival

B.3.3.2.1 Base case analysis: CheckMate 577

B.3.3.2.1.1 Survival analysis approach

Clinical data to inform the base case analysis have been derived from CheckMate 577. However, follow-up was substantially less than the 40-year time horizon of the model. Therefore, extrapolation of survival data from the study was required to inform long-term outcomes, undertaken with reference to the guidance from the NICE Decision Support Unit (DSU)[82,83] and Bagust and Beale (2014).[84]

A full description of methods is provided in Appendix M, sections 3.3–3.6. In brief, several parametric functions and hazard profiles that inform survival curves were explored using PLD from CheckMate 577 July 2020 DBL with log-normal spline fits assessed to be the best fitting for both arms.

B.3.3.2.1.2 Disease free survival

Recurrence events were based on investigator assessed DFS outcomes from CheckMate 577 and were defined as the time between the randomisation date and the first date of recurrence or death from all causes. Recurrence is specifically defined as the appearance of one or more new lesions which can be local, regional, or distant in location from the primary resected site. Parametric survival functions, including exponential, Weibull, log-logistic, lognormal, Gompertz and generalised-gamma survival distributions, were fitted to the extracted data using the R statistics environment. Also considered were spline models, mixture parametric, and semi-parametric models assessing the impact of different cut points and subsequent parametric functions, in line with the approach taken in recent appraisals of immunotherapies and suggested in TSD21.[85,86]

Goodness-of-fit was evaluated using the Akaike and Bayesian Information Criteria (AIC and BIC, respectively); minimisation of these measures is used to indicate goodness-of-fit whilst penalising overfitting, so that a smaller value demonstrates a more appropriate fit. In addition

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to assessment of goodness-of-fit statistics, the appropriateness of the parametric extrapolation was evaluated by visual inspection of the fit over the observed period and consideration of the log cumulative hazard plots. It is worth noting that while these methods for validating the extrapolation of recurrence events are appropriate, they are also necessarily constrained by derivation from observed data. Therefore, the plausibility of the extrapolation was assessed through consideration of the long-term hazard profile and the extrapolated mean survival estimates.

A more detailed description of survival extrapolation and outcomes is provided in Appendix M.3 and M.4. In brief, Kaplan-Meier plots describing DFS in the nivolumab and routine surveillance arms of CheckMate 577 demonstrated a high initial hazard during the initial study period, with a substantial number of events occurring immediately after study entry (Figure 15 (nivolumab) and Figure 16 (routine surveillance)). After approximately two years, the hazard in both arms became low and was similar between the arms (Figure 17).

Parametric and mixture parametric models were not considered to adequately reflect either this early change in hazard or the long-term outcomes for patients. Semi-parametric models with cut-points before approximately 15 months were also not able to fit the data well, as early cut points fall within the time when the hazard is changing too rapidly to provide a reliable fit. Semi-parametric models with later cut points fit the data better, but the extrapolation depended on a low number of events, which undermines the confidence in the shape of the curve. These semi-parametric models with later cut points were not considered to provide the most robust extrapolation and were therefore not considered for the base case, but as they fit the data adequately, they were explored in scenario analyses (section B.3.8.4.4).

Log-hazard, log-odds and log-normal spline models were evaluated; log-hazard splines did not fit the data well, however, log-odds and log-normal splines provided an improved fit. Overall, log-normal spline fits with one or two knots validated well to the observed data and to the expected disease trajectory for both the nivolumab and routine surveillance arms (Figure 18 and Figure 19 respectively). The log-normal spline fits with one knot were chosen to represent the base case, while fits with two knots were considered in scenario analysis (section B.3.8.4.4). It should be noted that all spline fits with zero knots were outside the CIs and were therefore discounted, and that curves with three knots did not represent the hazard in the nivolumab arm in the final months.

It is acknowledged that the spline models chosen have high predicted means, however, this was not considered a reason to disregard these models. All modelling methods produced models that predicted infinite means, which is usually indicative of a proportion of patients who continue to remain disease free throughout the remainder of their life. In the base case, it is assumed that all patients who remain disease free after three years would experience recurrence and death events at the rate of the general population; this assumption has been validated by UK clinicians (section B.3.2.3.1).[41] Therefore, the high means are constrained in the model by general population mortality. The most important factor in model choice therefore becomes the fit in the initial three years (or up to five years in the sensitivity

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analysis – see section B.3.8.4.1), and the flexibility of the log-normal spline models provided the most robust fit here.

Though every person in the disease-free health state is assumed to be free of disease clinically, it is acknowledged that there may be slightly higher mortality in the disease-free health state than general population initially, mostly due to post-surgical mortality. Time from complete resection to randomisation was > 4 weeks for [redacted] of patients and > 10 weeks for [redacted]% of patients. Therefore, for the majority of patients, this period of high mortality relating to surgery is assumed to have passed.

However, as a conservative assumption, the logistic regression predicting disease free events that were death events (i.e. deaths upon recurrence) is used for the first three years. This was used to model transitions from the disease-free health state to the death health state in each cycle. Briefly, upon recurrence, incident recurrence events need to be stratified into those characterised by disease recurrence and those characterised by death. The likelihood of death upon recurrence is time-dependent, with a very high initial hazard. Given this event likelihood profile, a number of logistic regression models fitting the DFS events from CheckMate 577 were considered. Multiple transformations for time were considered, both independently and within multivariable models, including log and square transformations. The final model selected was a logistic model with time as a single, linear covariate (Table 25).

After three years the mortality in the disease free health state is assumed as general population, and assumption which was validated by clinicians.[41] Outcomes from the model are validated against published studies (B.3.9).

Table 25: Probability of death on incidence of investigator assessed recurrence, model parameterisations

Arm	Intercept	Coefficient 1 (time)
Nivolumab	[redacted]	[redacted]
Routine surveillance	[redacted]	[redacted]

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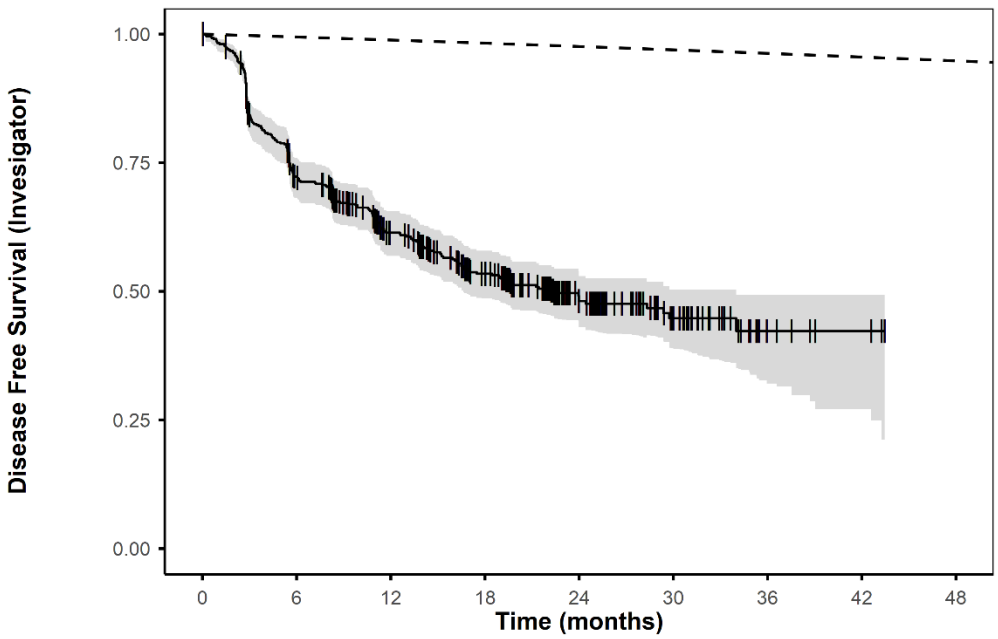

Cumulative Events	0	142	192	222	236	240	241	241	241
NAR	532	364	249	181	92	41	8	3	0

Figure 15: Disease free survival with UK general population mortality overlaid – nivolumab

Dotted line is age-adjusted UK general population mortality

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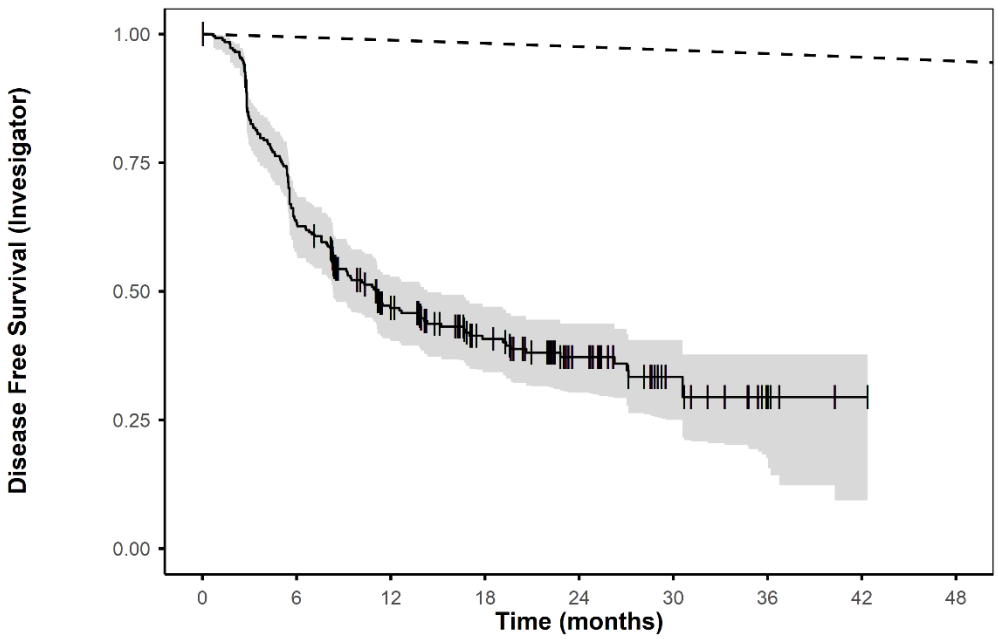

Cumulative Events	0	94	134	145	150	153	155	155	155
NAR	262	163	96	65	38	17	5	1	0

Figure 16: Disease free survival with UK general population mortality overlaid – routine surveillance

Dotted line is age-adjusted UK general population mortality

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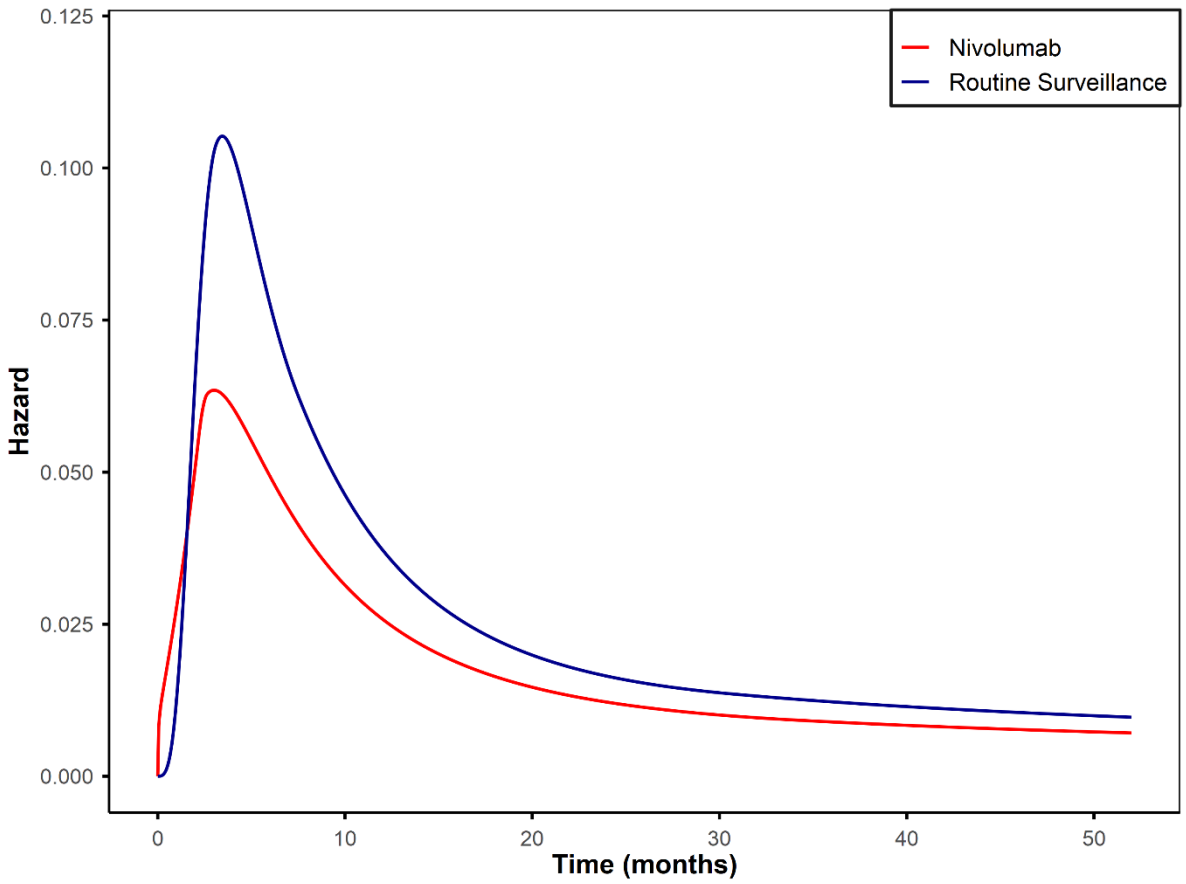

Figure 17: Royston Parmer spline of DFS hazard in CheckMate 577

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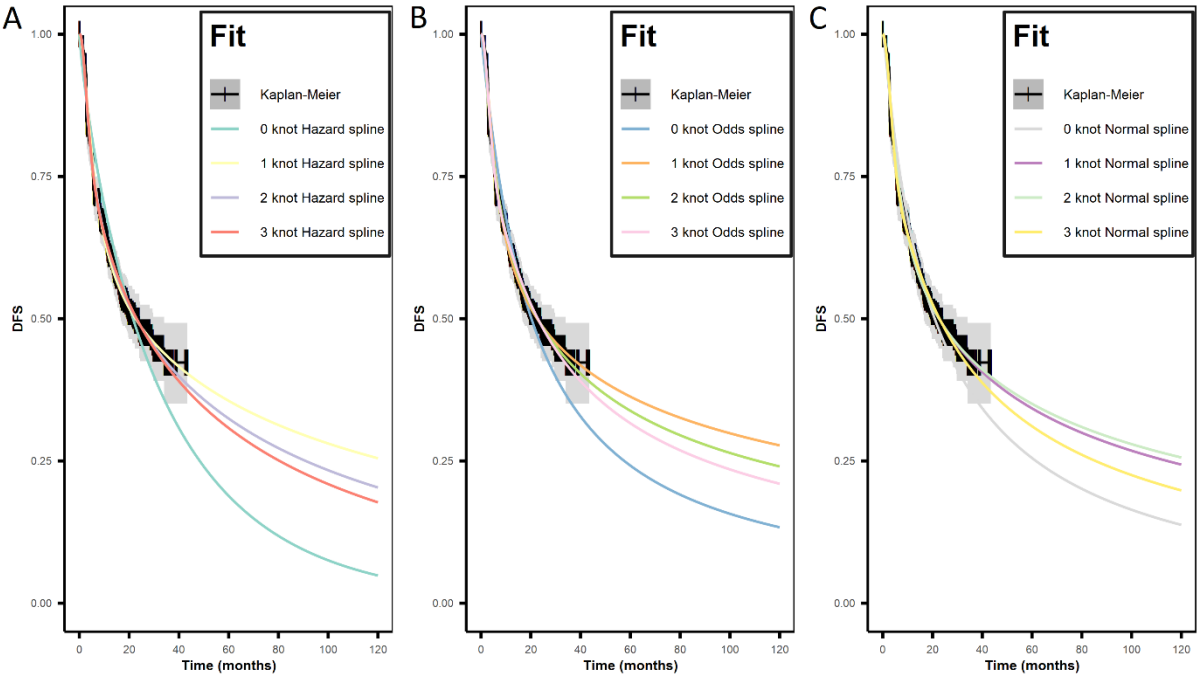

Fit Name	AIC	BIC	Median (Months)	Mean (Months)
0 knot Hazard spline	2121.69	2142.80	21.57 (18.47, 25.50)	35.75 (29.72, 43.58)
1 knot Hazard spline	2063.14	2094.80	22.55 (17.34, 32.27)	180.14 (75.82, 805.54)
2 knot Hazard spline	2060.54	2102.75	22.90 (18.14, 30.80)	95.02 (45.21, 329.63)
3 knot Hazard spline	2062.39	2115.16	23.04 (18.39, 30.56)	75.50 (41.60, 269.09)
0 knot Odds spline	2100.38	2121.48	20.24 (16.97, 24.54)	393.92 (131.47, 4188.36)
1 knot Odds spline	2062.09	2093.75	22.55 (17.22, 32.28)	N/A
2 knot Odds spline	2060.71	2102.93	22.78 (17.99, 30.89)	N/A (109.54, N/A)
3 knot Odds spline	2061.25	2114.02	22.81 (18.37, 30.25)	N/A (96.50, N/A)
0 knot Normal spline	2083.52	2104.63	20.90 (17.46, 25.49)	75.39 (53.56, 110.87)
1 knot Normal spline	2065.42	2097.08	22.74 (17.69, 30.94)	403.31 (134.01, 4067.82)
2 knot Normal spline	2067.75	2109.96	22.61 (17.66, 31.58)	588.18 (98.04, 9637.31)
3 knot Normal spline	2061.80	2114.57	22.83 (18.43, 30.01)	154.12 (60.17, 1356.29)

Figure 18: Spline curves fit to disease free survival – nivolumab

Panel A. log-hazard spline fits; Panel B. log-odds spline fits; Panel C. log-normal spline fits. N.B. log-normal spline fit with one knot used in the base case.

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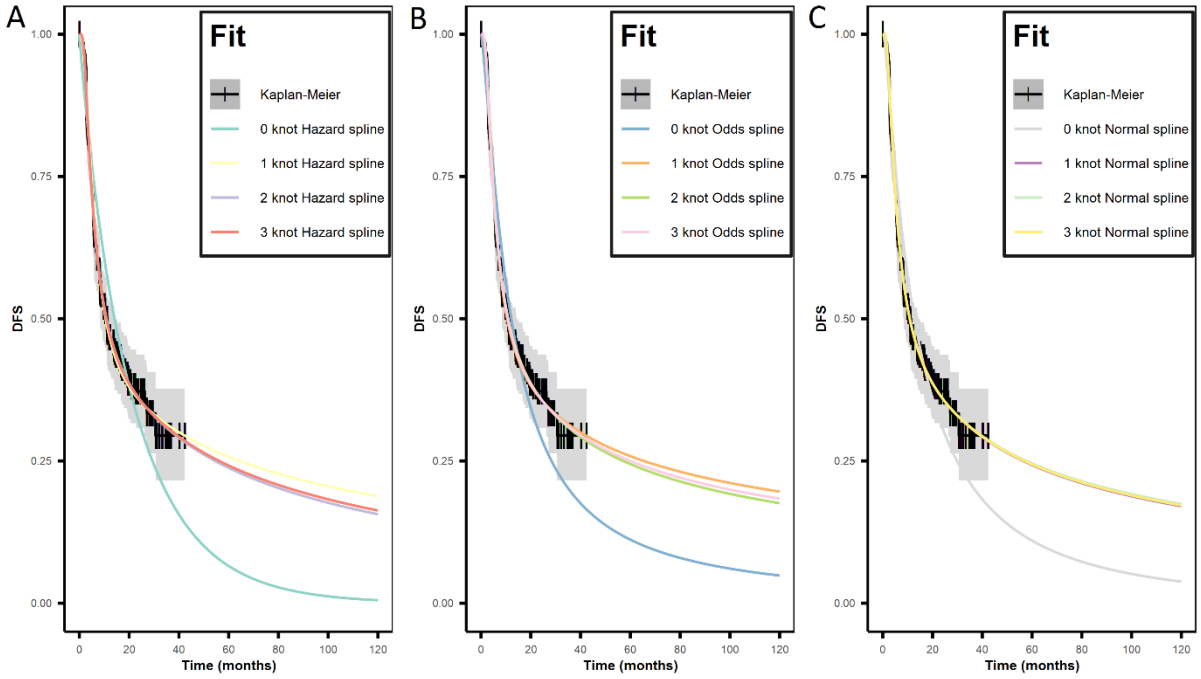

Fit Name	AIC	BIC	Median (Months)	Mean (Months)
0 knot Hazard spline	1249.88	1268.15	14.12 (11.87, 16.86)	21.31 (17.36, 26.50)
1 knot Hazard spline	1183.45	1210.86	10.57 (8.56, 13.66)	202.61 (49.13, 7100.08)
2 knot Hazard spline	1181.91	1218.45	10.92 (8.67, 14.47)	96.22 (33.50, 2566.38)
3 knot Hazard spline	1183.20	1228.88	10.90 (8.72, 14.44)	109.35 (33.64, 3947.44)
0 knot Odds spline	1223.05	1241.32	12.15 (10.01, 14.84)	44.42 (27.62, 85.06)
1 knot Odds spline	1181.74	1209.15	10.50 (8.36, 13.68)	N/A
2 knot Odds spline	1181.79	1218.34	10.90 (8.63, 14.43)	N/A (87.79, N/A)
3 knot Odds spline	1183.11	1228.79	10.83 (8.67, 14.41)	N/A (96.18, N/A)
0 knot Normal spline	1212.17	1230.44	12.75 (10.60, 15.45)	28.29 (20.94, 40.19)
1 knot Normal spline	1181.26	1208.67	10.92 (8.64, 14.28)	360.25 (64.17, 13344.54)
2 knot Normal spline	1183.22	1219.77	10.86 (8.62, 14.27)	430.29 (55.97, 19113.70)
3 knot Normal spline	1185.20	1230.89	10.87 (8.63, 14.46)	387.22 (50.01, 17272.59)

Figure 19: Spline curves fit to disease free survival – routine surveillance

Panel A. log-hazard spline fits; Panel B. log-odds spline fits; Panel C. log-normal spline fits. N.B. log-normal spline fit with one knot used in the base case

B.3.3.2.1.3 Post recurrence survival

As described in B.3.3.2.1 death events were not available from CheckMate 577 with which to model either OS or PRS.

Once patients experience recurrence, they are assumed to experience death events conditional on having experienced a recurrence. The hazard of experiencing a death event is therefore intrinsically related to the time since recurrence. The survival conditional on recurrence was sourced from Lou et al.,[80] which describes a patient population that had

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received an oesophagostomy for pathologic stage I to III oesophageal adenocarcinoma or squamous cell carcinoma and had experienced a recurrence following this treatment.[80] This is considered to directly reflect patients in CheckMate 577 who experience a recurrence, with the majority of patients from Lou et al[80] having undergone neoadjuvant chemo(radio)therapy. Importantly, the shape of the post recurrence curve shows a sharp decrease that flattens out, indicating a high rate of initial events that slows over time. This is as expected from a mixed group of patients with both adenocarcinoma and squamous cell carcinoma histologies, as a heterogeneous group of patients who have experienced recurrence, receiving any and all further lines, may progress and experience death at different times. These data were therefore considered representative of the CheckMate 577 study population and the likely survival trajectory after disease recurrence.

The Kaplan-Meier displayed in Figure S3 of Lou et al.[80] (Figure 20) were digitised using DigitizeIt™ and PLD recreated using the Guyot algorithm;[87] these demonstrated a constant hazard (Figure 21). Parametric models predicting survival were fitted to this data using the R statistics environment and the methodology as used for DFS (Figure 22). Of these, the best fitting model was selected (Gompertz), and this was used to estimate the conditional probability of experiencing a death event while patients were post recurrence, dependent on the time from recurrence (Figure 23). This survival extrapolation was used to derive transition matrices such that patients who enter the recurred disease state always experience post recurrence survival that is relative to their time of recurrence in the model. However, given the underlying uncertainty around the most relevant PRS, all models assessed have been run as scenarios in the cost-effectiveness model to determine the impact of model choice on the base case (B.3.8.4.5).

Progression post recurrence was not modelled as it was assumed that the treatment costs and the efficacy profile applied in the recurred disease health state were representative of any and all further lines that patients may receive.

The same post recurrence survival was applied to both arms, which is a conservative assumption that may underestimate the potential benefit of nivolumab.

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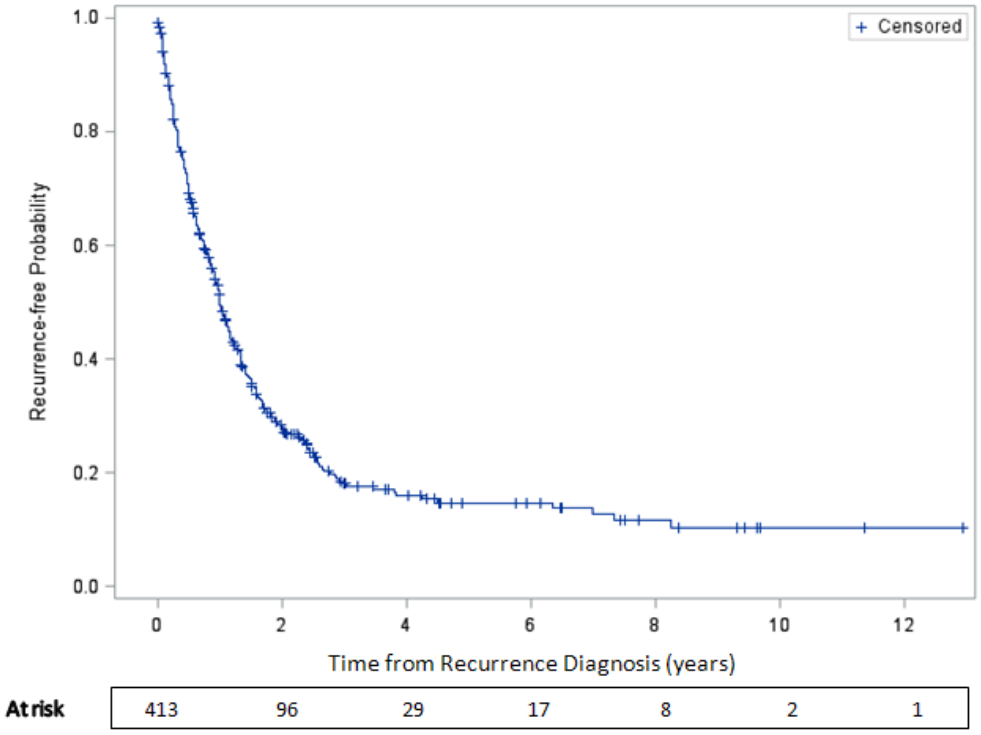

Figure 20: Kaplan-Meier curve for post recurrence survival from Lou et al (2013)[80]

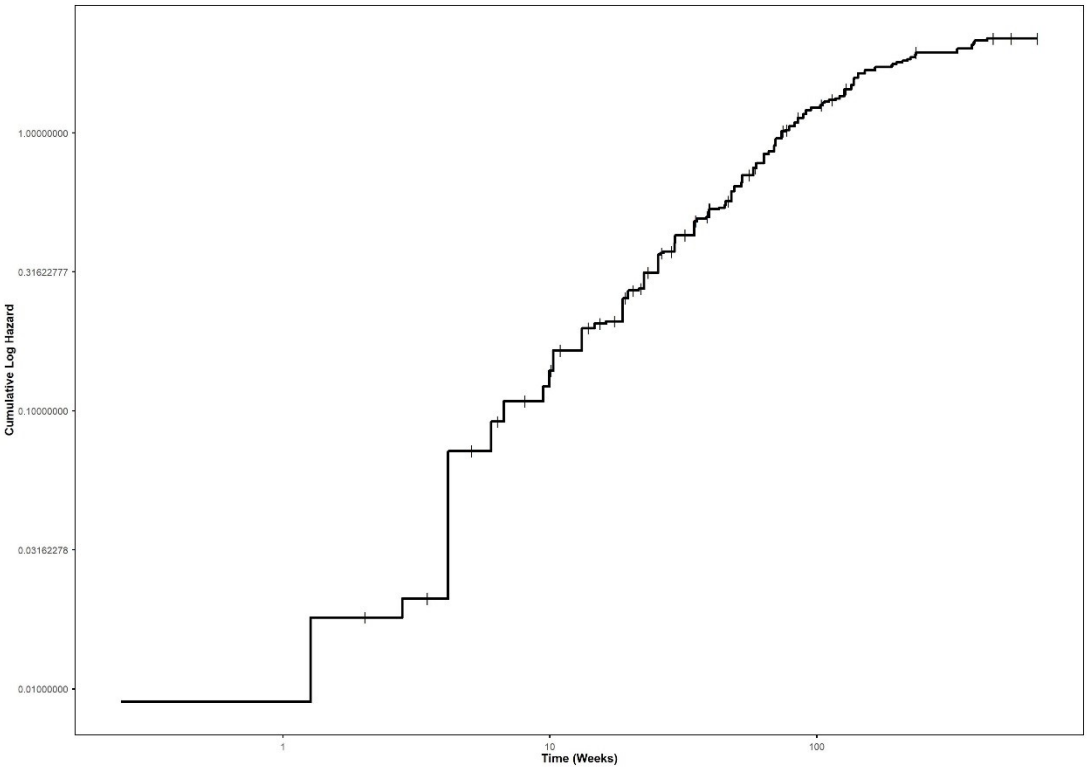

Figure 21: Recreated PLD post recurrence survival cumulative log hazard from Lou et al. (2013)[80]

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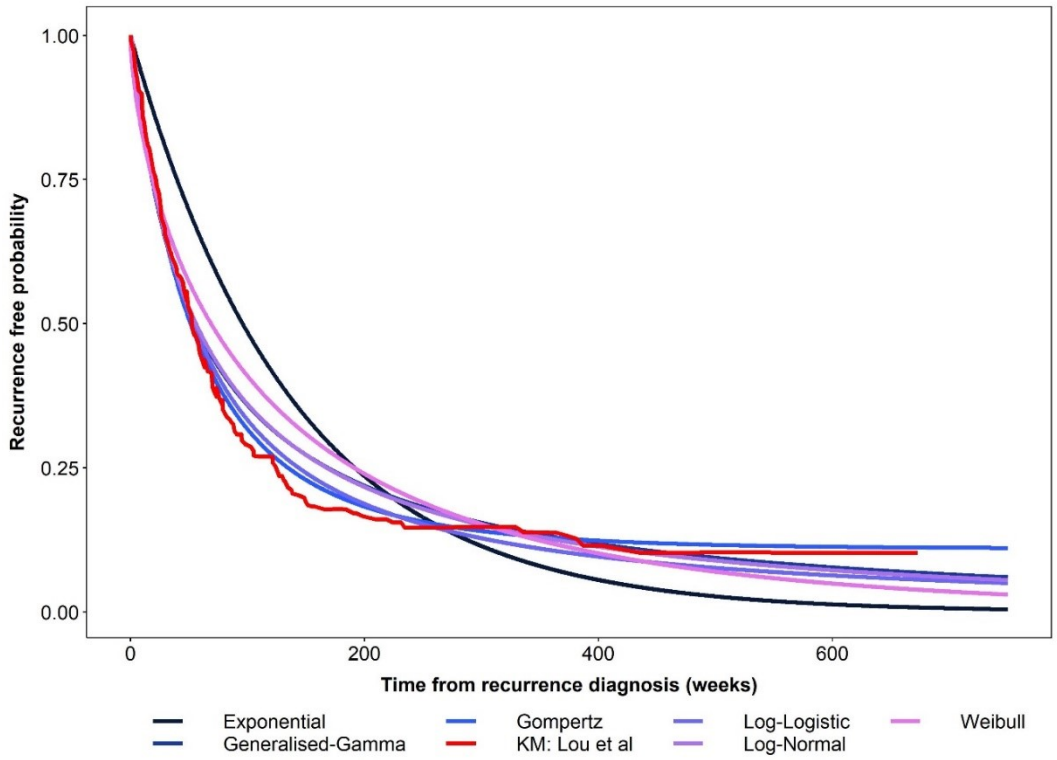

Figure 22: Parametric survival curves fitted to recreated post recurrence survival data from Lou et al. (2013)[80]

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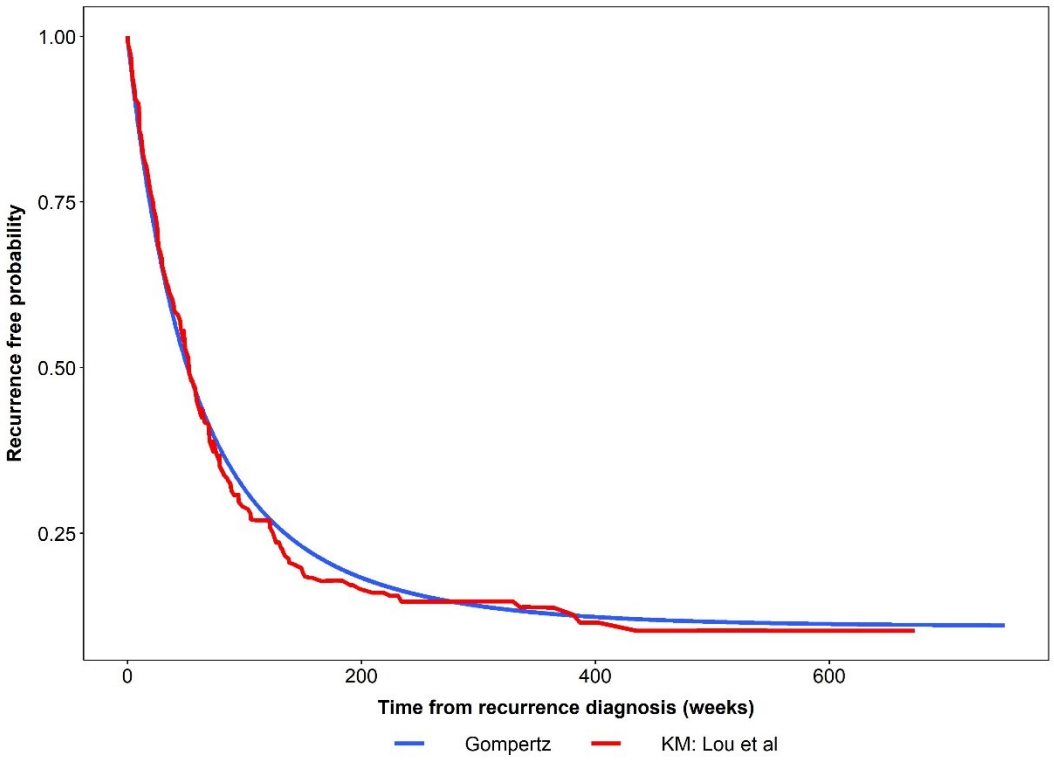

Figure 23: Gompertz survival model fitted to recreated post recurrence survival data from Lou et al. (2013)[80]

Table 26: Parameterisation for health states in the cost-effectiveness model

	Disease free survival	Post recurrence survival
Nivolumab		
Median (observed)	22.4	11
Extrapolation method	Log-normal spline curve with one internal knot	Gompertz parametric model
Median (from extrapolation)	22.74	11.84
Mean (from extrapolation)	403.31*	NA*
Routine surveillance		
Median (observed)	11.0	11
Extrapolation method	Log-normal spline curve with internal knots	Gompertz parametric model
Median (from extrapolation)	10.92	11.84
Mean (from extrapolation)	360.25*	NA*
* Constrained in the model by general population mortality to avoid infinite means.		

B.3.3.2.1.4 Time on treatment

It is clear that patients taking nivolumab were not on treatment for the entirety of their disease free time in CheckMate 577 (Figure 24), therefore time on treatment is modelled in the cost-effectiveness model directly from the observed data. As data were closed and nivolumab was taken for a maximum of one year, there was no requirement for

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extrapolation. The duration of study therapy curve is used to determine the proportion of patients who incur a cost of treatment and any treatment related disutility (if applicable).

There are a number of reasons why the DFS and duration of study therapy curves may deviate before one year. Patients may miss doses or cease treatment due to toxicity. Regardless, it is assumed that this is entirely reflective of what may happen in clinical practice and so appropriate to model in the base case.

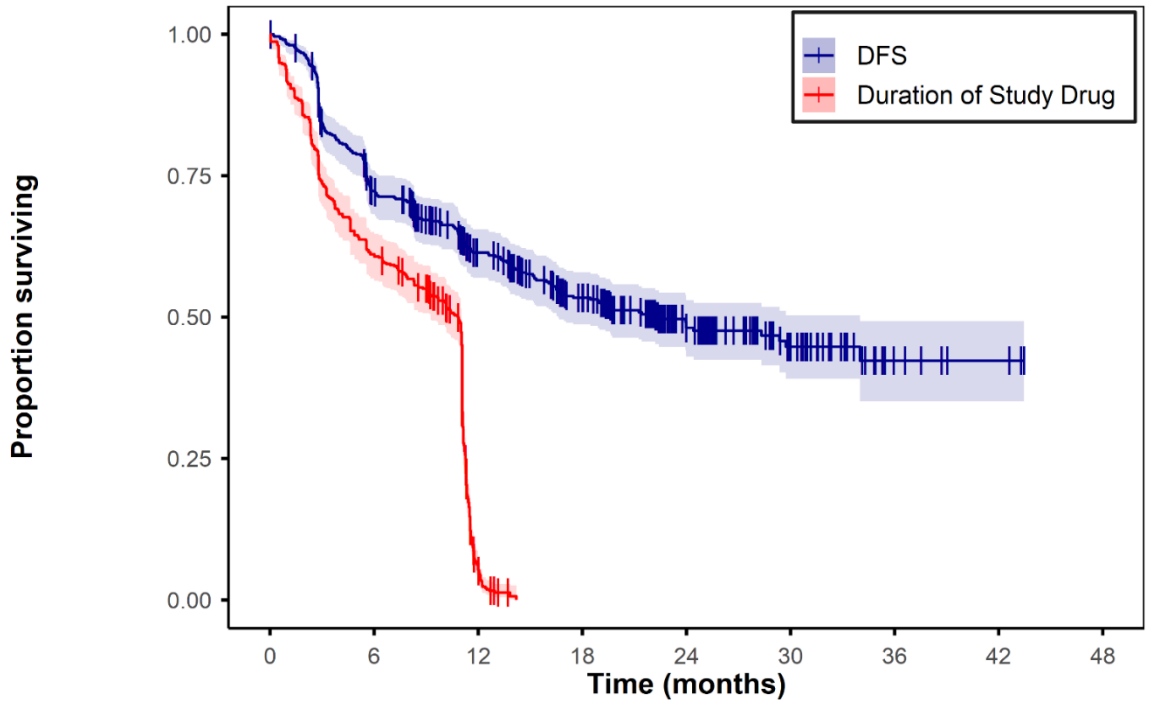

Figure 24: DFS and duration of study therapy – nivolumab

B.3.3.2.1.5 Validation of survival curves applied in the economic evaluation

There are no other studies with which to validate the results for extrapolation of the nivolumab arm other than the informing trial, CheckMate 577. The extrapolated curves and approaches were compared to the observed values as much as possible. This method informed selection of the most appropriate modelling approach and fit as a form of validation.

The log-normal spline models for routine surveillance and nivolumab were compared to the model outcomes and the observed values (Table 27 and Table 28) and show predictions very close to the observed values, substantially increasing confidence in the chosen fits.

Table 27: Log-normal spline model outcomes compared for nivolumab

	DFS at 6 months	DFS at 1 year	DFS at 2 years
Observed	72.2%	61.4%	48.1%
Log-normal 1 knot spline (curve model results)	73.5%	60.0%	47.8%

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	DFS at 6 months	DFS at 1 year	DFS at 2 years
Log-normal 1 knot spline (CEM results)	73.2%	59.5%	46.9%
CEM: cost-effectiveness model; DFS: disease free survival			

Table 28: Log-normal spline model outcomes compared for routine surveillance

	DFS at 6 months	DFS at 1 year	DFS at 2 years
Observed	63.4%	46.7%	37.2%
Log-normal 2 knot spline (curve model results)	64.0%	46.2%	35.0%
Log-normal 2 knot spline (CEM results)	63.7%	45.8%	34.4%
CEM: cost-effectiveness model; DFS: disease free survival			

The extrapolations from Lou et al. were validated against data available from a retrospective study conducted in the Netherlands which predicted similar median PRS; 11.4 and 11.2 months from the Lou et al. and Netherlands studies respectively.[88] The Netherlands study is used to inform scenario analysis (B.3.8.4.6).

B.3.3.2.2 All-cause mortality

The model includes age and sex-adjusted mortality based on information from UK life tables, described in Table 29.[89] These values are included in every cycle in addition to the disease-related mortality values and are applied multiplicatively. While some form of double counting occurs, this effect applies equally to all comparators and is likely to have a minimal impact on predicted survival (and hence cost-effectiveness).

Table 29. Excerpt from England and Wales life tables[90]

Age	Annual probability of mortality	
	Males	Females
50	0.0034	0.0022
51	0.0036	0.0024
52	0.0039	0.0026
53	0.0041	0.0027
54	0.0045	0.0029
55	0.0048	0.0032
-	-	-
95	0.2610	0.2282
96	0.2867	0.2508
97	0.3041	0.2671
98	0.3259	0.2913
99	0.3695	0.3095
100	0.3844	0.3434

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B.3.3.2.3 Treatment discontinuation

Disease free patients are expected to continue to receive nivolumab until recurrence or until one year, whichever occurs first. This is in line with the treatment protocol used in CheckMate 577.[51] The economic model uses the duration of study therapy recorded in CheckMate 577 to determine the exact proportion who are taking treatment before the one year cut off. It uses the DFS curve to determine the proportion who remain in the disease free health state.

Once a patient experiences recurrence they move to the recurred disease health state and are assumed to receive subsequent therapy. As outlined in Section B.1.3.20, UK guidelines along with clinical expert opinion obtained during a clinical advisory board meeting indicate a lack of adjuvant treatments able to reduce rates of recurrence for post-surgery OC and GEJ cancer patients.

Following recurrence, decisions about treatment options for local or metastatic recurred OC in terms of efficacy and toxicity were described as highly individual. Treatments such as oxaliplatin or cisplatin in combination with capecitabine or 5-fluororacil (5-FU) are usually the treatment of choice in this setting. Thus, the modelled subsequent line treatment after recurrence in both the routine surveillance and nivolumab arms is assumed to be the combination of these treatments. Subsequent therapy costs are a weighted average based on an assumed equal distribution between oxaliplatin + 5-FU, oxaliplatin + capecitabine, cisplatin + capecitabine and cisplatin + 5-FU. Progression events in this state are not modelled, but post recurrence survival is, as described in Section B.3.3.2.1.1.

B.3.3.2.4 Adverse events

AEs are an inevitable consequence of any intervention, and these events are applied in the model, affecting the costs accrued by patients on each intervention. To reflect the AEs that occurred in CheckMate 577, grade 3+ TRAEs that had more than three occurrences in any arm are modelled.

Data from CheckMate 577 were assumed to comprise all available evidence describing the safety profile of nivolumab and routine surveillance for the adjuvant treatment of OC or GEJ cancer. Grade 3+ TRAE rates were sourced from the DBL in July 2020. The event numbers are shown in Table 30 and resulting cyclical probabilities shown in Section B.3.4.2, Table 33.

Table 30. Adverse events derived from CheckMate 577

AEs leading to discontinuation	Number of Grade 3+ TRAE in nivolumab arm (n = 522)	Number of Grade 3+ TRAE in routine surveillance arm (n = 262)
Pneumonitis	8	1
Fatigue	5	1
Lymphocyte count decreased	5	1
Rash	4	1
Colitis	3	0
Interstitial lung disease	3	0

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AEs leading to discontinuation	Number of Grade 3+ TRAE in nivolumab arm (n = 522)	Number of Grade 3+ TRAE in routine surveillance arm (n = 262)
Myocarditis	3	0
AE: adverse event; TRAE: treatment-related adverse events		

Incidence probabilities were converted into monthly equivalents based on number of patients experiencing an event and follow-up time using standard formulae; inputs are summarised in Table 30. For entry into the model, these were converted to weekly probabilities and applied to all patients in the model in all cycles while receiving nivolumab. Thus, the model assumes that there is a constant rate of AEs during treatment. As most events are likely to occur in the initial trial period, this may overestimate the rate of AEs over long-term treatment and impacts the nivolumab arm disproportionately.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

An SLR was conducted to identify studies evaluating HRQoL for any adjuvant intervention for resected OC or GEJ cancer. Further details of the SLR can be found in Appendix G. The SLR found no studies that had specifically investigated the HRQoL of patients with OC or GEJ cancer in the adjuvant setting. However, the economic studies found in the economic SLR (Appendix G) were interrogated for relevant utility values. Most studies sourced were conducted in an Asian population, so relevance to the decision problem in this submission was difficult to quantify. In addition, not all studies were conducted in exactly the same indication. However, Zhang et al. 2019[60] and Chongqing et al. 2014[67] had health states and health state definitions that matched well to the present submission, and utility data from these studies were explored in scenario analysis (see B.3.4.1.3 and B.3.8.4.3).

Patient-reported outcomes were collected during CheckMate 577; specifically, EQ-5D-3L measures were available from patients throughout the trial. Patient baseline demographic and clinical characteristics were collected, and patient time of clinical recurrence and death were recorded if these events occurred within the follow-up period. This was used to calculate the utility values most appropriate to each health state and arm (sections B.3.4.1.1 and B.3.4.1.2). As the literature data are sparse, CheckMate 577 trial data were considered the most appropriate source of utilities to examine for the base case, where this was available (see discussion in B.3.4.1.3).

B.3.4.1.1 CheckMate 577 HRQoL data analysis methods

Individual patient questionnaires contain responses for the five reported EQ-5D-3L dimensions of health-related QoL, comprising mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and the Visual Analogue Scale (VAS).

The treatment and disease status of each patient at the time of each questionnaire was determined by the following:

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- If the questionnaire was completed before or on the day of discontinuation from treatment, the questionnaire was classed as being in the “on-treatment” dataset; otherwise “off treatment”.
- If the questionnaire was completed before or on the day of assessment of clinical disease identification per investigator, the questionnaire was classed as being in the “disease free per investigator” dataset; otherwise “recurred disease per investigator”.

Baseline values were taken preferentially at the baseline measure as defined in the dataset (Week 1).

Patient-assessed HRQoL data was collected with varying frequency through the trial, dependent upon recurrence status. Missingness was assessed according to whether patients had an observation within the expected period, for the trial phase that they were in, either treatment, follow-up or survival follow up. Full methods are described in Appendix N.

Assessments of EQ-5D-3L status in CheckMate 577 were carried out every four weeks during the treatment phase, followed by two assessments off-treatment at day 30 and 84 post treatment cessation, and measurements every three months thereafter of patient reported outcomes in survival follow-up.

Among the 794 patients enrolled in the population of interest, [redacted] patients died within the trial period and [redacted] patients were assessed as having disease recurrence. As of the July 2020 DBL, [redacted] completed or partially completed EQ-5D-3L questionnaires were available for analysis in the nivolumab arm and [redacted] in the placebo arm (which represents patients receiving routine surveillance).

B.3.4.1.2 CheckMate 577 HRQoL data analysis results

On-treatment missingness was considered to be low, typically with less than 20% at any observation period and typically ~10%. Off-treatment missingness was higher, but similar between arms. Results for this analysis can be seen in Figure 25 to Figure 28.

Data availability was high during the on-treatment period and showed no strong pattern of increasing or decreasing compliance over time. Missingness occurred mostly in non-monotonic patterns and was not obviously associated with proximity to death or recurrence. Therefore, there was no reason to reject an assumption of missing completely at random (MCAR) in the on-treatment trial phase.

However, data availability was poor in the off-treatment period, as the majority of patients who stopped treatment did not complete further questionnaires. This was considered likely to be associated with HRQoL, therefore missingness was very likely to be not at random, or if conditional upon observed covariates, there was unlikely to be sufficient data to inform an imputation model. Therefore, the on-treatment dataset was likely to be a good representation of the HRQoL in the on-treatment state, but the off-treatment dataset was unlikely to be a good representation of the HRQoL in the off-treatment state.

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The Dolan time trade-off (TTO) utility at baseline for the [redacted] and [redacted] patients in the nivolumab and placebo arms, respectively, are presented in Table 31. Baseline measurement across all 5 EQ-5D-3L dimensions provided a mean of [redacted] and [redacted], respectively. This was higher than that of an age- and sex-matched English cohort, which was expected to have a mean utility of 0.799, applying the tables reported by Szende et al (2004)[91] for the TTO measure to the intention-to-treat (ITT) CheckMate 577 population.

Table 31: Baseline HRQoL in CheckMate 577

Statistic	Nivolumab	Routine surveillance
Baseline responses (N)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
SD: standard deviation		

Simple mean values were calculated assuming a UK population for each arm (Table 32) and show that while on treatment, utility in the routine surveillance arm was marginally higher than in the nivolumab arm.

The on-treatment dataset in both arms was consistent over time, with little change from the baseline utility estimates. All long-term mean utilities based on the on-treatment dataset were comparable to matched general population norms, though a decrement associated with the use of an active treatment was clear. There was a consistent difference in utility between the nivolumab and placebo arms throughout the treatment period. This is expected, as nivolumab is an active treatment that has associated toxicity whereas placebo does not. This data set was therefore taken to be adequately representative of the utility experienced by patients while in the on-treatment period. It was determined that there was a utility decrement associated with nivolumab treatment, which was [redacted] over the treatment period (one year).

[redacted]

Figure 25. On treatment missing utility data - nivolumab

[redacted]

Figure 26. Off treatment missing utility data - nivolumab

[redacted]

Figure 27. On treatment missing utility data - routine surveillance

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Figure 28. Off treatment missing utility data - routine surveillance

Table 32. Mean utility by treatment status

	Nivolumab	Routine surveillance
On treatment disease free, mean (95% CI)	[redacted]	[redacted]
Off treatment disease free, mean (95% CI)	[redacted]	[redacted]
CI: confidence interval		

It was notable from this analysis that the utility values for both arms were higher than an age-matched UK population. There are several reasons why this may occur in the CheckMate 577 dataset:

- Patients in the CheckMate 577 trial are not exclusively from the UK and so the reported utility may be higher than would be expected in an entirely UK population. For example, 8% were from Japan, where people typically report higher age-matched utility than a comparable UK population.

- Patients enrolled in CheckMate 577 have previously had OC or GEJ cancer, received surgery and at treatment initiation are considered free from disease. Their comparable utility may, therefore, be higher than an age-matched general population and higher than patients with an active disease.

Given these factors, in the base case, the utility value used in the company cost-effectiveness model for the disease free health state was limited to an age-matched UK general population value for both arms. To acknowledge the treatment-related disutility observed in CheckMate 577, the disease free health state utility value for the nivolumab arm was as the routine surveillance arm with a utility decrement of [redacted]. This is also the justification for not assuming disutilities for AEs (Section B.3.4.2).

B.3.4.1.3 Recurred disease utility

As patients experience recurrence, they are assumed to move to a pooled subsequent treatment line representing all and any further lines and treatments, and associated outcomes. The simple means after recurrence for nivolumab and routine surveillance from CheckMate 577 outcomes data were 0.758 and 0.779, respectively. However, given the high amount of missingness in the follow-up outcome collection data set, it was considered that these post recurrence values were possibly too high to be plausible or reasonable. Instead utility values for the recurred disease health state were sourced from the literature.

To facilitate this, a pragmatic search was conducted of previous Technology Appraisals. The pre-progression health state utility values from ID1249[92] were deemed most appropriate. This describes patients in a second line setting with unresectable, advanced OC where standard chemotherapy has failed. The control arm value ([redacted]) was chosen, as this

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represented treatment with a taxane, as opposed to the treatment arm which represented patients who were taking nivolumab. Taxane therapy was considered to be more representative of the four treatment options that define the recurred disease health state.

It is acknowledged that this value is also high when compared to the general population and particularly given the heterogenous population represented in the recurred disease health state (this health state represents all lines and outcomes for patients post recurrence). Although the utility value of [redacted] was considered to be higher than might be expected in a UK-specific population, due to sparsity of data sources it was used in lieu of a more realistic figure. This is a conservative estimate in favour of the routine surveillance arm and scenario analysis demonstrates how alternative values might affect the base case (Section B.3.8.4.3).

Two studies identified in the economic SLR, Zhang et al. 2019[60] and Chongqing et al. 2014,[67] had health states and health state definitions that matched well to the present submission, and were interrogated for potential alternative utility values to explore in scenario analysis (see B.3.8.4.3). Both studies, which were conducted in patients with resectable gastric cancer, sourced utility values from a previously published cost-utility analysis.[66] The disease-free utilities used were high when compared to the UK general population. A similar finding was noted in the analysis from CheckMate 577 (see B.3.4.1.2 for further description). The post recurrence utility from Zhang 2019 and Chongquing 2014 was 0.42; this value is explored in scenario analysis, although caveats around its applicability are acknowledged and detailed (B.3.8.4.3).[60,67] Although the estimate provided in this study was considered unfeasibly low, the scenarios were run and presented to determine the impact of assuming alternative values for the recurred disease health state.

It is assumed that while a patient is in the recurred disease health state, there is no change in their utility. While in reality a patient may experience decreasing utility over time as they progress through treatment lines, the utility value chosen is assumed to be representative of the heterogeneous population.

B.3.4.2 Adverse reactions

All TRAEs that were grade 3+ and had more than 3 occurrences over the CheckMate 577 trial period were included in the model. These probabilities, derived from data found in the CSR,[52] are listed in Table 33. The model uses an annual probability input, but this input is adjusted to be applied weekly in the treatment trace. These are used to determine the cost of AEs.

Table 33. Base case analysis: annual adverse event probabilities for nivolumab and routine surveillance (CheckMate 577)

AEs leading to discontinuation	Annual probability of TRAE for nivolumab used in model	Annual probability of TRAE for routine surveillance used in model
Pneumonitis	0.0153	0.0038
Fatigue	0.0096	0.0038
Lymphocyte count decreased	0.0096	0.0038
Rash	0.0077	0.0038

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AEs leading to discontinuation	Annual probability of TRAE for nivolumab used in model	Annual probability of TRAE for routine surveillance used in model
Colitis	0.0057	0
Interstitial lung disease	0.0057	0
Myocarditis	0.0057	0
AE: adverse event; TRAE: treatment-related adverse event		

Disutility caused by AEs is not included in the model as it is assumed to be encompassed by the treatment specific utilities recorded in the trial. As described in Section B.3.4.1.2, the treatment-related utility decrement applied to the nivolumab arm is considered to be present in the CheckMate 577 data due to the AEs and toxicity related to active treatment compared to routine surveillance. As such, further application of AE specific disutilities is double counting and is therefore not applied in the cost-effectiveness model.

B.3.4.3 Health-related quality-of-life data used in the cost-effectiveness analysis

The primary source of HRQoL data used in the Company cost-effectiveness model was from the CheckMate 577 trial. Due to the unusually high utility of patients in the CheckMate 577 trial, general population mortality is used for disease free patients, with a treatment specific decrement applied to the nivolumab arm for the duration of treatment. Once patients have experienced a recurrence, a literature utility value is used, as reported in ID1249.[92] Summary details can be seen in Table 34.

Table 34. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (95% CI)	Reference in submission (section and page number)	Justification
Disease free (routine surveillance)	Age-dependent, general population utility (starting at 0.799 at age 60.5)	B.3.4.1.1	Trial utility was higher than general population, therefore it was thought appropriate to cap at general population
Disease free (nivolumab)	Age-dependent, general population utility (starting at 0.799 at age 60.5) with [redacted] annual decrement	B.3.4.1.1	Trial utility was higher than general population, therefore it was thought appropriate to cap at general population with a treatment-related decrement included for nivolumab, as seen in CheckMate 577
Recurred disease	0.747 (0.735, 0.823)	B.3.4.1.1	CheckMate 577 utility suffered high amounts of missingness and what was available was not considered representative of the modelled post recurrence population. Utility values were available from a 2L OC population that was deemed largely representative of the heterogenous second modelled line group in the CEM.
2L: second line; CEM: cost-effectiveness model; CI: confidence interval;			

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B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Nivolumab costs

The costs of nivolumab, including drug procurement and administration, are applied each cycle, based on acquisition and administration costs detailed in Table 35 and Table 36. The dosing frequency and routine was assumed as in CheckMate 577.

Table 35. Nivolumab dosing and acquisition

Dosing	240 mg IV infusion over 30 minutes Q2W for 16 weeks (Cycles 1–8) followed by nivolumab 480 mg IV infusion over 30 minutes Q4W beginning at Week 17 (2 weeks after the 8th dose) [Cycles 9–17] for a total duration of 1 year
Dose per cycle	120 mg
Cost (excluding PAS)	10 mg/mL concentration for solution for infusion in vial. 4 mL = £439.00; 10 mL = £1,097.00[93]; 24 mL = £2,633.00
Cost per dose (excluding PAS)	£2,633.00 (initial 16 weeks) and £5,266.00 (17th week onwards)
Administration costs	£252.73 (derived from costs detailed in Table 36)
Total (excluding PAS)	£2,885.73 (initial 16 weeks), £5,518.73
IV: intravenous; PAS: patient access scheme; Q2W: every two weeks; Q4W: every four weeks	

Table 36. Administration costs for nivolumab

Component	National cost collection for the NHS 2018/19[94]	Cost	Inflated cost (2020)
Deliver Simple Parenteral Chemotherapy at First Attendance	Weighted average of SB12Z codes (DCRDN: Daycase and Regular Day/Night; OP: Outpatient; Oth: Other)	£241.06	£252.73
Cost inflated to GBP2020			

B.3.5.1.2 Patient Access Scheme

A PAS has been applied, comprising a discount of [redacted] from the nivolumab list price. In order to best replicate the true economic impact of a positive recommendation for nivolumab, the economic evaluation presented in this submission applies the PAS in the base case analysis (Table 37).

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Table 37. Acquisition cost of nivolumab following application of PAS

	No PAS	PAS	Cost per cycles where cost accrued
4 mL vial	£439.00	[redacted]	-
10 mL vial	£1,097.00	[redacted]	-
24 mL vial	£2633.00	[redacted]	[redacted] 240 mg or [redacted] 480 mg
PAS: patient access scheme			

B.3.5.1.3 Comparators

The only comparator used in the model, routine surveillance, is assumed to have no acquisition costs.

B.3.5.1.4 Modelled subsequent lines of treatment cost

Upon recurrence, patients are assumed to receive the same modelled second line treatment in both lines. The treatment in this line is assumed to represent any and all further lines of treatment, from first line to palliative therapy. The chosen treatments are assumed to be used in any order and have been validated by clinicians.[41] This treatment is made up of four possible combinations of treatment; cisplatin + capecitabine, cisplatin + 5-FU, oxaliplatin + capecitabine, oxaliplatin + 5-FU. The model assumes patients are distributed evenly across these four treatment regimens with the costs, doses and assumed proportions of individual treatment components listed in Table 38.

All drug costs here are sourced from the electronic market information tool (eMIT). Appropriate dose sizes and frequencies were sourced from Cancer Therapy Advisor.[95] The dosage for cisplatin alone differs based on the treatment combination it is used with, as capecitabine + cisplatin (capecitabine has same dose) involves one IV administration of cisplatin 30 mg/m^2 every week whilst the 5-FU combination involves 75-100 mg/m^2 of cisplatin administered once every four weeks.

Table 38. Second line treatment cost and doses

Drug	Model cost (2020)	Source cost (2019)	Weeks between dose	Administration cost	Proportional weighting
Oxaliplatin	£19.21	£18.78	2	£252.73	50%
5-FU	£2.91	£2.84	1	£252.73	50%
Capecitabine	£79.03	£77.27	12	£0.00	50%
Cisplatin (with capecitabine)	£6.81	£6.66	1	£252.73	25%

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Cisplatin (with 5-FU)	£11.02	£10.78	4	£252.73	25%
5-FU: 5-fluorouracil NB: Capecitabine is dosed twice per day for 14 days, every 21 days. The average weeks between dose is shown in the table above.					

B.3.5.2 Health-state unit costs and resource use

B.3.5.2.1 Disease free

Following successful surgery, ESMO guidelines advise that follow-up visits focus on symptoms, nutrition and psychosocial support, involving the use of a multidisciplinary care team.[23] Aside from the cost of this team, the only other post-surgery cost included is scans and associated monitoring costs. This is a combination of reference costs for computed tomography (CT) and magnetic resonance imaging (MRI) scans on one area, using post-contrast, without contrast and pre- and post-contrast reference costs assumed evenly split. The frequency of resource use in the disease free health state is assumed to match the frequency of CT scans in the trial (performed every 12 weeks) for the first year, every six months in the second year, yearly from years three to five and then not at all. This resource use pattern was confirmed by clinical experts as the most appropriate and relevant to clinical practice. There was some discussion about whether six monthly visits would begin at nine months, however, a conservative approach was taken in the base case. This assumption that monitoring costs will decrease is due to patients not needing such substantial monitoring when they have gone long periods without recurrence. This aligns with the assumption of a general population risk of mortality and has been validated by clinical experts. A scenario in which monitoring used in trial (every three months throughout) is assumed has been explored (Section B.3.8.4.7).

Table 39. Disease free health state costs

AEs leading to discontinuation	Cost	Frequency weekly (initial period)	Source
Scans: CT/MRI	£132.85	0.083	NHS reference cost 2018/19
Oncologist	£280.00	0.083	Healthcare costing standards for England (2016)[96]
AE: adverse event; CT: computed tomography; MRI: magnetic resonance imaging			

B.3.5.2.2 Recurred disease

During a clinician survey conducted for a similar nivolumab indication (ID1249[92]), clinicians were asked to provide estimates of resource use associated with disease management. This survey was for unresectable advanced OC when standard chemotherapy has failed, but this model assumes recurrent cancer is equivalent to this in health state costs. The frequencies of resource use are described in Table 40 and the resource use estimates for the recurred disease health state are described in Table 41. It is assumed that, as with the utility

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application, patients in the recurred disease state will incur constant costs. Though there may be differences as patients move through treatment lines, the costs sourced are considered to represent most patients in the heterogenous post recurrence group.

Table 40. Disease management costs: frequency of resource use from clinician survey

		Consultations	Imaging scans	Blood tests	Liver function tests	Kidney function tests	Hospitalisations	Palliative care specialist nurse
Every 3 months	n	13	18	5	7	7	21	2
	%	33%	45%	13%	18%	18%	53%	5%
Monthly	n	17	8	16	20	20	9	10
	%	43%	20%	40%	50%	50%	23%	25%
Biweekly	n	8	4	4	3	3	3	14
	%	20%	10%	10%	8%	8%	8%	35%
Weekly	n	2	2	12	5	6	2	14
	%	0.050	5%	30%	13%	15%	5%	35%
Never	n	0	8	3	5	4	5	0
	%	0	20%	8%	13%	10%	13%	0
Mean frequency per week*		0.153	0.092	0.221	0.162	0.170	0.095	0.359

* The mean weekly frequency of each resource component was derived from the clinician survey and calculated in two steps:
1) Calculation of mean weekly frequency after removal of the 'Never' category^
2) Subsequent mean weekly frequency adjusted to account for the 'Never' component, where mean weekly frequency was multiplied by the total proportion of responses not in the 'Never' category
^ 'Never' category refers to the answer depicting that patients of the respective oncologist/nurse never used that particular resource for their patients on BSC
BSC: best supportive care

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Table 41. Cyclic (weekly) health state resource use and costs

Resource	Unit cost (£)	Source	Weekly cost	
			Use	Cost (£)
Clinician consultation	£187.36	National cost collection for the NHS 2018/19: Medical Oncology (weighted average of consultant led and non-consultant led; WF01A, WF01B, WF01C, WF01D, WF02A, WF02B, WF02C, WF02D)[94]	0.153	£28.67
CT scan	£97.15	National cost collection for the NHS 2018/19: Computerised Tomography (weighted average of direct access, outpatient and other costs; RD20A, RD21A, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z, RD27Z)[94]	0.092	£8.94
Full blood count	£2.79	National cost collection for the NHS 2019/19: Haematology; DAPS05[94]	0.221	£0.62
Renal function test	£1.10	National cost collection for the NHS 2019/19: Clinical Biochemistry; DAPS04[94]	0.162	£0.18
Hepatic function test	£1.10	National cost collection for the NHS 2019/19: Clinical Biochemistry; DAPS04[94]	0.170	£0.19
Hospitalisation	£534.07	National cost collection for the NHS 2018/19: Malignant Gastrointestinal Tract Disorders (weighted average of elective and non-elective long-stay FD11A, FD11B, FD11C, FD11D, FD11E, DF11F, F11G, FD11H, FD11J, FD11K[94]	0.095	£50.74
Palliative care specialist nurse	£76.74	National cost collection for the NHS 2018/19: Specialist Nursing, Palliative/Respite Care, Adult (weighed average of N21AF, N21AN)[94]	0.359	£27.55
Sum			**£116.87**	
Inflated sum			**£119.53**	
CT: computed tomography; NHS: national health service; SE: standard error SE assumed to be 20% of the mean value				

B.3.5.2.3 End of Life costs

End of life costs are detailed in Table 42, and were applied as a one-time cost in the cycle prior to death.

Table 42. End of life costs

	Costs	Inflated cost (2020)
	Mean	Mean (SE)
End-of-life costs	£7,287.00[97]	£8,364.08 (£1,672.82)
SE: standard error SE assumed to be 20% of the mean value		

B.3.5.3 Adverse reaction unit costs and resource use

Adverse reaction costs, adjusted for inflation, are listed in Table 43. Costs are taken from relevant technology appraisals or from literature where not otherwise available. Where neither literature nor previous TA costs are available, reasonable assumptions were made and are described below.

Table 43. Adverse event costs

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AEs leading to discontinuation	Mean cost used in the model	Source
Pneumonitis	£641.27	TA553[81]
Fatigue	£205.03	TA553[81]
Lymphocyte count decreased	£0.00	Assumed (TA553)[81]
Rash	£62.86	TA553[81]
Colitis	£3,193.34	Vouk et al 2015[98]
Interstitial lung disease	£641.27	Assumed same as pneumonitis
Myocarditis	£558.54	Assumed same as hyperthyroidism (TA553)[81]
AE: adverse event		

B.3.6 Summary of base-case analysis inputs and assumptions

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B.3.6.1 Summary of base-case analysis inputs

Table 44: Summary of cost-effectiveness model inputs

Variable			Value (SD)	Measurement of uncertainty and distribution	Section
Model settings	Annual cost discount rate		3.5%	-	B.3.2.1
	Annual benefit discount rate		3.5%	-	
	Willingness-to-pay threshold		£30,000	-	
	Time horizon		40	-	
Baseline parameters	Average baseline age of cohort (years)		60.5 (0.34)	Normal	B.3.2.2
	Percentage of cohort that are female (%)		0.85 (0.01)	Beta	
Efficacy	Disease free model - nivolumab		Log-normal spline, one internal knot	-	B.3.3.2.1.2
	Disease free model - routine surveillance		Log-normal spline, one internal knot	-	
	Death event logistic regression model constant		-3.107	-	B.3.3.2.1.2
	Death event logistic regression model time parameter		0.083	-	
	Post recurrence survival model		Gompertz	-	B.3.3.2.1.3
	Post recurrence survival model - shape		-0.007	-	
	Post recurrence survival model - rate		0.016	-	
	Duration of study therapy - nivolumab		Kaplan-Meier	-	B.3.3.2.3
	Duration of study therapy - routine surveillance		Kaplan-Meier	-	
	Adverse event rates (weekly)	***Nivolumab***			B.3.4.2
		Pneumonitis	0.024 (0.0005)	Beta	
		Fatigue	0.015 (0.0004)	Beta	
		Lymphocyte count decreased	0.015 (0.0004)	Beta	

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		Rash	0.012 (0.0003)	Beta	
		Colitis	0.009 (0.0003)	Beta	
		Interstitial lung disease	0.009 (0.0003)	Beta	
		Myocarditis	0.009 (0.0003)	Beta	
		Routine surveillance			
		Pneumonitis	0.006 (0.0005)	Beta	
		Rash	0.006 (0.0005)	Beta	
		Pruritus	0.006 (0.0005)	Beta	
		Psoriasis	0.006 (0.0005)	Beta	
Utilities	Age related	18–24	0.94	-	B.3.4.3
		25–34	0.927	-	
		35–44	0.911	-	
		45–54	0.847	-	
		55–64	0.799	-	
		65–74	0.779	-	
	Health State	Disease free	[redacted]	Beta	B.3.4.1.2
		Recurred disease	[redacted]	Beta	B.3.4.1.3
		Nivolumab treatment disutility	[redacted] (0.0014)	Beta	B.3.4.1.2
Costs	First modelled line treatment costs	Nivolumab drug cost - Week 1–16	£[redacted]	-	B.3.5.1.2
		Nivolumab drug cost - Week 17–52	£[redacted]	-	
		Routine surveillance drug cost	£0.00	-	B.3.5.1.3
		Administration cost	£252.73	-	B.3.5.1.2
	Modelled further lines treatment cost	Drug cost - oxaliplatin	£19.21	-	B.3.5.1.4
		Drug cost - 5FU	£2.91	-	
		Drug cost - capecitabine	£79.03	-	

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		Drug cost - cisplatin (with capecitabine)	£6.81	-	
		Drug cost - cisplatin (with 5FU)	£11.02	-	
		Administration cost	£252.73	-	
	Adverse event costs	Pneumonitis	£641.27 (128.25)	Gamma	B.3.5.3
		Fatigue	£205.03 (41.01)	Gamma	
		Lymphocyte count decreased	£0.00 (0)	Gamma	
		Rash	£62.86 (12.57)	Gamma	
		Colitis	£3,193.34 (638.67)	Gamma	
		Interstitial lung disease	£641.27 (128.25)	Gamma	
		Myocarditis	£558.54 (111.71)	Gamma	
	Health state costs	Disease free (initial period)	36.14 (7.23)	Gamma	B.3.5.2.1
		Disease free (second period)	£18.07 (3.61)	Gamma	
		Disease free (third period)	£9.04 (1.80)	Gamma	
		Recurred disease	119.53 (23.91)	Gamma	B.3.5.2.2
		Death event	8364.08 (1672.82)	Gamma	B.3.5.2.3

B.3.6.2 Assumptions

During the construction of economic models, it is necessary to make some assumptions, both input and structural. The assumptions are tested where possible in the sensitivity analysis conducted. These are detailed and justified in Table 45.

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Table 45. Modelling assumptions

Model input and section	Source/assumption	Justification
General modelling approach (B.3.2.3)	Patients are not modelled separately in terms of disease histology, location of recurrence or subsequent treatment line: • in the disease free health state, all patients are modelled as receiving the same monitoring; • local and metastatic recurrence are not modelled separately, therefore assume the same mortality and recurrence rate; • in the recurred disease state, patients are modelled as receiving the same pooled basket of subsequent lines of treatment regardless of region of recurrence (metastatic vs local).	There are no data currently available to inform post recurrence survival outcomes based on disease histology. The best available source for post-recurrence survival, Lou et al,[80] which aligns well to the CheckMate 577 population and the proposed indication, reports data for a mixed group of squamous cell carcinoma and adenocarcinoma patients. Therefore, in the absence of more granular data, the modelling approach is constrained to combining the two histologies. Clinical advice to the company stated that in the UK, treatment options are the same regardless of whether patients have experienced a local or metastatic recurrence (i.e. further surgery would not be offered to those with a local recurrence).[41] The use of a pooled basket of subsequent treatments, a literature utility value and not explicitly modelling progression after recurrence is supportive of a heterogenous recurred disease health state capturing all potential outcomes.
Time at which a general population risk is assumed in disease free health state (B.3.3.2.1.2)	It is assumed that at three years, patients in the disease free health state assume a general population risk of mortality and DFS events.	Trial evidence shows that after approximately two years the risk of DFS events becomes very low and comparable in both arms. Clinical advice to the company suggested that after resection, all patients would be considered disease free, but that the underlying hazard may not converge to the general population rate for approximately three to five years.[41]
Utilities in the disease free health state (B.3.4.1.2)	The utility value used for the disease free health state was limited to an age-matched UK general population value for both arms.	The utility value used for the disease free health state was derived from CheckMate 577 EQ-5D-3L data, however, the trial utility values for both arms were high compared to an age-matched UK population, therefore the utilities in the model were limited to an age-matched UK general population value.
Treatment specific utility, nivolumab arm, disease free health state (B.3.4.1.2, B.3.4.2)	AE disutility is assumed to be included within the health state utility recorded in the CheckMate 577 trial, which was employed in the model.	When an active treatment is compared to placebo it is expected that, during treatment, there may be decreased HRQoL in the active treatment arm due to treatment side-effects. The utility derived from trial HRQoL measurements is therefore considered to capture the disutility due to AEs and toxicity directly, as opposed to estimates from literature.
Resource use in disease free health state (B.3.5.2.1)	The multi-disciplinary teams are assumed to see patients at the same frequency as the patient receives scans.	This is a simplifying assumption, but given that scans are initially required once every 12 weeks, it is assumed reasonable that, during any given 12 week period, a patient would see members of the multidisciplinary team in that time. Once patients move to sparser visits the same assumption around the multi-disciplinary team is used for each time period.

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Recurred disease treatment options (B.3.3.2.3)	Modelled second line treatment is assumed to be equivalent across both arms.	There is currently no evidence to suggest that patients who experience a recurrence would be treated differently upon recurrence. It is acknowledged that this is largely because there are currently no treatment options post-surgery.
Time independence of costs and utilities in recurred disease health state (B.3.4.1.3 and B.3.5.2.2)	Those who remain in the recurred disease state long term are assumed to have equivalent utility and cost rates to those who are in for a short term.	As the recurred disease health state is considered to be a heterogenous group of any and all further lines of treatment, for simplicity it was assumed that the cyclical costs and utilities for these patients was representative of an average of their experience. These are applied continuously until a patient leaves the recurred disease state.
Recurred disease costs (B.3.5.1.4)	Modelled second line treatment is assumed to be an even distribution between four treatment combinations	Clinical advice to the company stated that the four subsequent line treatments identified are the most likely options for patients who have experienced a recurrence, regardless of whether it is local or metastatic.[41]
Transition from recurred disease to death (B.3.3.2.1.3)	Transition rates for estimating recurred disease to death movements were calculated from a parametric model fit to reconstructed PLD from published Kaplan-Meier data.[80] The same rates were applied to both arms.	As OS data from CheckMate 577 are immature, it was necessary to obtain post recurrence survival data from the literature to inform this model transition. The literature in this area is sparse, however one study was identified that describes a patient population that had received an oesophagostomy for pathologic stage I to III oesophageal adenocarcinoma or squamous cell carcinoma and had experienced a recurrence following this treatment.[80] The majority of patients in this study had also received neoadjuvant chemo(radio)therapy. Therefore, the patient population was considered to align well to CheckMate 577 and the proposed indication. The shape of the post-recurrence survival curve indicates a high initial rate of events that slows over time. This is as expected for a mixed group of patients with both adenocarcinoma and squamous cell carcinoma histologies, as this heterogeneous group of patients, receiving any and all further lines of therapy, may progress and experience death at different times. The application of the same post recurrence survival to both arms in the model is a conservative assumption that may underestimate the benefit of nivolumab.
AE: adverse event; DFS: disease free survival; HRQoL: health-related quality of life		

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B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The results of the base case analysis are summarised in Table 46.

For routine surveillance, the model predicted [redacted] discounted life years, with an accrual of [redacted] discounted QALYs over the modelled time horizon. Nivolumab use was estimated to result in an additional [redacted] discounted QALYs (total: [redacted] discounted QALYs) and an additional [redacted] discounted life years (total: [redacted] discounted life years). It was estimated that patients receiving nivolumab would spend [redacted] undiscounted years disease free (versus [redacted] undiscounted years for routine surveillance), with a subsequent [redacted] undiscounted years in the recurred disease health state (versus [redacted] undiscounted years for routine surveillance), indicating that nivolumab is associated with incremental benefit across all health states (Table 47). As patients who initiate on routine surveillance move to the post recurrence state faster, and a larger proportion of these patients experience recurrence, there are more gains (LY, QALY and costs) made in this health state for this arm than for nivolumab. The inverse is true for nivolumab.

Total discounted costs associated with nivolumab (with PAS), accrued over the modelled time horizon, were predicted to be £[redacted]. Incremental discounted costs were predicted to be £[redacted] over routine surveillance, under base case assumptions. The resulting ICER estimate for nivolumab versus routine surveillance was £21,047 per QALY gained. Therefore, the base case ICER is below a £30,000 per QALY willingness-to-pay threshold when the current nivolumab PAS discount is applied.

Table 46: Base case analysis results (with PAS, discounted)

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life Years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£21,047
ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life-year			

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Table 47: Base case disaggregated outcomes

	Component	Nivolumab	Routine surveillance	Incremental
Disaggregated costs (discounted)	Disease free	[redacted]	[redacted]	[redacted]
	Disease free (long term)	[redacted]	[redacted]	[redacted]
	Recurrence	[redacted]	[redacted]	[redacted]
	Death	[redacted]	[redacted]	[redacted]
	Treatment	[redacted]	[redacted]	[redacted]
	Modelled 2nd line	[redacted]	[redacted]	[redacted]
	AEs	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
Disaggregated QALYs (discounted)	Disease free	[redacted]	[redacted]	[redacted]
	Disease free (long term)	[redacted]	[redacted]	[redacted]
	Recurrence	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
Clinical outcomes (years, undiscounted)	Median DFS	[redacted]	[redacted]	[redacted]
	Mean DFS	[redacted]	[redacted]	[redacted]
	Median OS	[redacted]	[redacted]	[redacted]
	Mean OS	[redacted]	[redacted]	[redacted]
Time in health state (years, undiscounted)	Disease free	[redacted]	[redacted]	[redacted]
	Disease free (long term)	[redacted]	[redacted]	[redacted]
	Recurrence	[redacted]	[redacted]	[redacted]

AE: adverse event; DFS: disease free survival; OS: overall survival; QALY: quality-adjusted life-year

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B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Results from 1,000 iterations of the model using probabilistic values can be seen in Table 48 and show that results are in line with the deterministic analysis. Results converged after approximately 100 iterations and the chosen number is therefore considered appropriate for examination of parameter uncertainty in the model. The scatterplot shows that there is limited spread in the values from each iteration and these are predominantly contained in the north east quadrant under the willingness-to-pay threshold, demonstrating cost-effectiveness ([redacted]Figure 29). Out of the 1,000 iterations, approximately 71.6% estimated nivolumab to be cost effective (Figure 30) demonstrating a high certainty in the base case results.

Table 48: Probabilistic sensitivity analysis results

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life Years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)			**£21,328**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year			

[redacted]Figure 29. Scatterplot of probabilistic results

[redacted]

Figure 30. Cost-effectiveness acceptability curve

B.3.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) results indicate the parameters that influence the results and conclusions of the decision problem to the greatest degree (Table 49, Figure 31). Parameters with the greatest impact are baseline age, second modelled line treatment costs and benefits discounting. Baseline age is associated with the greatest influence because there is a short time, relative to lifetime, before patients start to experience age- and sex-adjusted general population mortality and utility. Therefore, adjusting the age at model initiation has a substantial effect on the output results.

The most notable cost difference between arms is that of active treatment in first line. However, it should be noted that in the base case the costs of second modelled line treatment are assumed to be the same in both arms once a patient experiences a recurrence. As the same treatment options are currently available to patients upon recurrence, there is no justification to change the second line costs for one arm and not the other.

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Table 49: Deterministic sensitivity analysis results

Scenario	Parameter variation	Incremental			ICER
		Costs	Life Years	QALYs	
Costs discounting	0%	[redacted]	[redacted]	[redacted]	£19,895
	6%	[redacted]	[redacted]	[redacted]	£21,508
Benefits discounting	0%	[redacted]	[redacted]	[redacted]	£13,828
	6%	[redacted]	[redacted]	[redacted]	£27,061
Age	80%	[redacted]	[redacted]	[redacted]	£14,717
	120%	[redacted]	[redacted]	[redacted]	£37,462
Proportion male	0%	[redacted]	[redacted]	[redacted]	£19,316
	100%	[redacted]	[redacted]	[redacted]	£21,359
Treatment costs (1L nivolumab arm)	80%	[redacted]	[redacted]	[redacted]	£15,611
	120%	[redacted]	[redacted]	[redacted]	£26,484
Treatment costs (1L routine surveillance arm)	80%	[redacted]	[redacted]	[redacted]	£21,047
	120%	[redacted]	[redacted]	[redacted]	£21,047
Treatment costs (modelled 2L nivolumab arm)	80%	[redacted]	[redacted]	[redacted]	£16,895
	120%	[redacted]	[redacted]	[redacted]	£25,200
Treatment costs (modelled 2L routine surveillance arm)	80%	[redacted]	[redacted]	[redacted]	£26,065
	120%	[redacted]	[redacted]	[redacted]	£16,030
Adverse event probabilities (nivolumab arm)	80%	[redacted]	[redacted]	[redacted]	£21,040
	120%	[redacted]	[redacted]	[redacted]	£21,054
Adverse event probabilities (routine surveillance arm)	80%	[redacted]	[redacted]	[redacted]	£21,048
	120%	[redacted]	[redacted]	[redacted]	£21,047
Health state costs	80%	[redacted]	[redacted]	[redacted]	£21,273
	120%	[redacted]	[redacted]	[redacted]	£20,857
Death cost	80%	[redacted]	[redacted]	[redacted]	£21,122
	120%	[redacted]	[redacted]	[redacted]	£20,973
Adverse event costs	80%	[redacted]	[redacted]	[redacted]	£21,041
	120%	[redacted]	[redacted]	[redacted]	£21,054
Health state utilities	80%	[redacted]	[redacted]	[redacted]	£23,325
	120%	[redacted]	[redacted]	[redacted]	£21,284
Nivolumab disutility	80%	[redacted]	[redacted]	[redacted]	£21,027
	120%	[redacted]	[redacted]	[redacted]	£21,068
Adverse event utility decrements	80%	[redacted]	[redacted]	[redacted]	£21,047
	120%	[redacted]	[redacted]	[redacted]	£21,047

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Figure 31. Tornado diagram

B.3.8.3 Summary of sensitivity analyses results

The sensitivity analyses show that the base case analysis is robust to the natural variation that may be seen in clinical practice. The PSA shows that in 71.6% of times, nivolumab would be considered cost-effective, which is within normal bounds. The most influential parameters on cost-effectiveness are the baseline age and, indirectly, the utility of patients who are disease free. Variation in these parameters is explored further in scenario analysis (Section B.3.8.4) and confirms that the base case is likely conservative and confidence in the estimate is high.

B.3.8.4 Scenario analysis

Scenario analysis was undertaken to examine the impact of structural and input assumptions that are necessary when building cost-effectiveness models. In all scenarios examined, nivolumab remained cost-effective at a £30,000 WTP threshold; results indicate that the base case is robust and there can be high certainty in the results.

B.3.8.4.1 Alternative time points at which general population risk is assumed

In the base case, it is assumed that after three years disease free, patients will start to assume a general population risk of disease and mortality, thus encountering lower health state costs. This assumption has been validated by clinical opinion, although it is important to consider that this time point may vary between patients in real-world practice. Clinicians advised that the time at which patients return to general population could be up to five years, therefore the impact of this was explored in scenario analysis. Where a patient assumes a general population risk at five years instead of three, the ICER is £25,141 and there would be no change in the decision regarding cost-effectiveness (Table 50). Importantly, in this scenario, the median and mean time in DFS are nearly identical to that of the base case.

Table 50: Scenario analysis results – general population risk at five years

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life Years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£25,141
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year			

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B.3.8.4.2 Alternative discounting

In anticipation of potential revisions to the reference case, the results where discounting for cost and benefits is 1.5% is also presented (Table 51).

Table 51. Discounting for costs and benefits at 1.5%

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life Years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£16,289
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year			

B.3.8.4.3 Variability in the post recurrence utility

As described in section B.3.4.1.3, there is reason to believe that the post recurrence utility value in the base case may be higher than patients may expect to experience. However, no alternative source has been found to inform this health state aside from a previous cost-effectiveness study in gastric cancer patients.[60,67] As described in B.3.4, this paper reported the post recurrence utility to be 0.42. In order to aid decision making, the post recurrence utility was arbitrarily varied from the study reported value to the base case value in order to understand the impact that this may have on the results of the cost-effectiveness model and therefore the decision that might be made should the true post recurrence value be different. In all scenarios examined, the decision would not change; nivolumab remains cost-effective (Table 52, Figure 32). Therefore, while knowing the true value may be difficult at this stage, the base case remains robust to changes. In addition, it is likely that the base case is overestimating the true ICER and should be considered conservative.

Table 52: Scenario analysis results – variations in post recurrence utility

Post recurrence utility value	ICER	Decision
0.42	£19,210	Cost-effective
0.45	£19,367	Cost-effective
0.5	£19,634	Cost-effective
0.55	£19,909	Cost-effective
0.6	£20,191	Cost-effective
0.65	£20,481	Cost-effective
0.7	£20,780	Cost-effective
[redacted] (base case)	£21,047	Cost-effective
ICER: incremental cost-effectiveness ratio		

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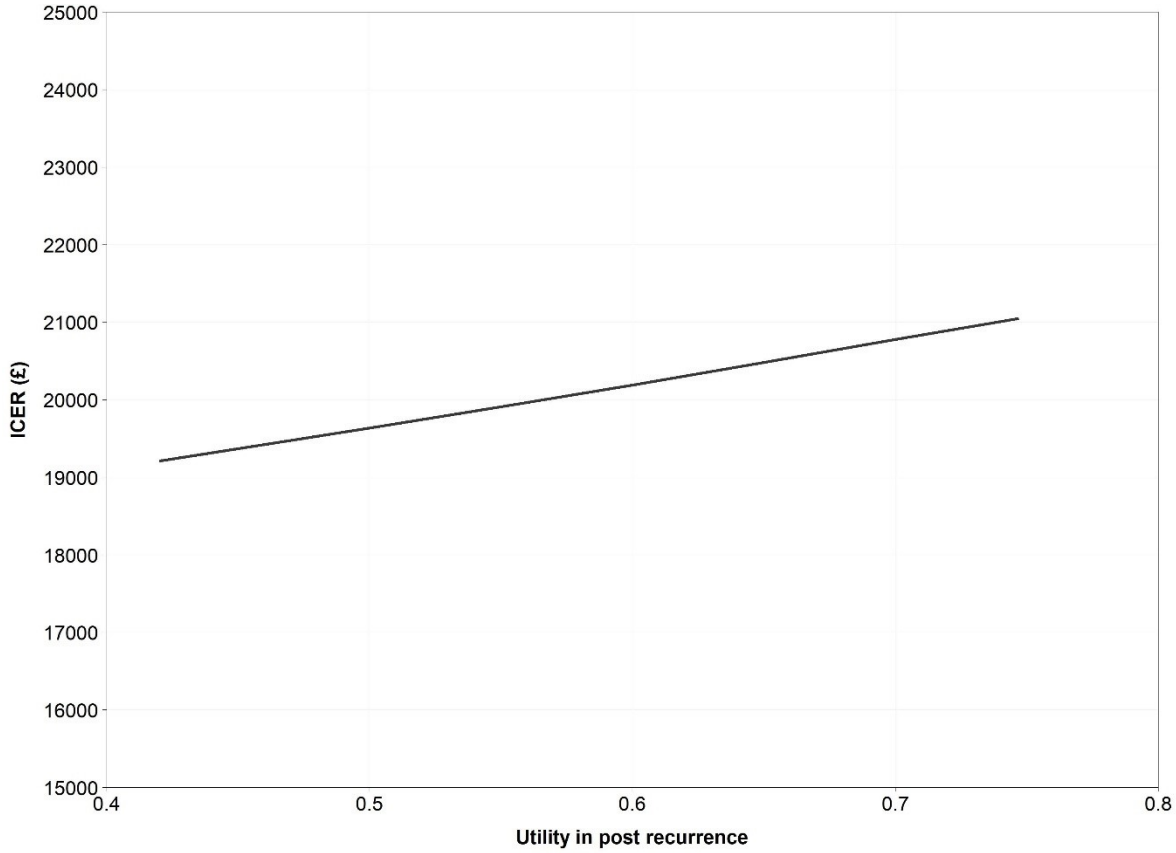

Figure 32: Change in ICER as post recurrence utility varies

B.3.8.4.4 Alternative DFS fits

As described in section B.3.3.2.1.2, the log-normal spline fits provided superior fitting to all other methods examined. There was little variation between the one and two knot log-normal splines although, on balance, one knot was considered the most appropriate for both nivolumab and routine surveillance arms.

Although semi-parametric curves did not fit the data well and lacked internal consistency, these issues were less apparent when the cut points were placed at later times. In particular once the initial period of high and varying hazard was over (greater than approximately 15 months), semi-parametric curves started to fit the observed data more accurately. These were not used in the base case because although they fit better than semi-parametric curves with earlier cut points, later cut points mean the extrapolated portions of the curves are informed by low numbers of patients and events, as many have already occurred. The positioning of the cut point is based on a judgement as to whether low patient numbers can accurately reflect the extrapolated period and could result in large uncertainty. Examining alternative fits as a scenario provides assurance that results were consistent between methods and therefore are likely to represent the likely trajectory of disease accurately.

In all scenarios examined, the decision regarding the cost-effectiveness of nivolumab would not change, demonstrating that the deterministic values are robust to the underlying assumptions and methods.

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Table 53: Scenario analysis results - alternative DFS fits

Nivolumab DFS model	Routine surveillance DFS model	ICER
Log-normal two knot spline	Log-normal two knot spline	£20,886
DFS SP Exponential cut 19.78	DFS SP Exponential cut 19.78	£18,880
DFS SP Gompertz cut 19.78	DFS SP Gompertz cut 19.78	£18,270
DFS SP L.logistic cut 19.78	DFS SP L.logistic cut 19.78	£18,682
DFS SP L.normal cut 19.78	DFS SP L.normal cut 19.78	£19,241
DFS SP Weibull cut 19.78	DFS SP Weibull cut 19.78	£18,720
DFS: disease free survival; ICER: incremental cost-effectiveness ratio		

B.3.8.4.5 Alternative post recurrence survival models

As described in Section B.3.3.2.1.3, a number of parametric models were fit to the recreated PLD presented in Lou et al.[80] to represent the PRS of patients in the cost-effectiveness model. It was judged that the Gompertz model fit to the data most accurately, however this is a subjective assessment, and it is important to quantify how the cost-effectiveness decision may change should an alternative model be considered appropriate. With all models run in scenario analysis, the decision would not change; the choice of PRS model has extremely limited impact on the results (Table 54).

Table 54: Scenario analysis results - alternative PRS models

Post recurrence survival (both arms)	ICER
Exponential	£21,271
Generalised gamma	£21,192
Gompertz (Base case)	£21,047
Log-logistic	£21,301
Log-normal	£21,213
Weibull	£21,244

B.3.8.4.6 Alternative post recurrence survival source

Data to inform the post recurrence survival trajectory of patients within this decision problem are particularly sparse. Data from a real world evidence study, Lou et al,[80] were used to inform the base case. This study analysed a patient population that matched well to the CheckMate 577 study population and intended indication, and the shape of the post recurrence survival curve was as expected for the patient group. However, it is important to consider that the results of the analysis may change should an alternative source be used. To evaluate the impact of this, an alternative source of post recurrence survival was considered as a scenario. This alternative real-world evidence study reported PRS of patients diagnosed with OC or GEJ cancer with disease recurrence, receiving either active systemic or other/no treatment after recurrence.[88]

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When this source was used to describe the PRS profile, the results show that there would be no change in the decision regarding cost-effectiveness. This is despite lower estimates of mean and median post-recurrence survival in the alternative source.

Table 55. Scenario analysis results – alternative post recurrence survival source

Post recurrence survival (both arms)	ICER
Exponential	£22,007
Generalised gamma	£21,943
Gompertz	£21,916
Log-logistic	£21,891
Log-normal	£21,941
Weibull	£21,996

B.3.8.4.7 Alternative monitoring frequency assumption

The assumption of monitoring frequency was based on clinical opinion although not aligned to the trial monitoring. During the trial, patients were monitored more frequently than they might be in clinical practice and this has been modelled to assess the impact should more frequent monitoring be adopted with the introduction of an active treatment. Where this approach is taken, nivolumab remains cost-effective when compared to routine surveillance.

Table 56: Alternative monitoring frequency assumption

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life Years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£23,676
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year			

B.3.9 Validation

B.3.9.1 Validation of cost-effectiveness analysis

Of the studies identified in the economic SLR, the majority predicted outcomes similar to those predicted by the Company CEM. It is important to note however, that populations included were varied and do not exactly match those enrolled in CheckMate 577. Due to the sparsity of available data this is to be expected and validation of results are therefore difficult. However, the literature identified by the SLR is useful in ensuring that there is some external validity in the results estimated by the Company CEM.

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Zhang et al. 2019[60] report total and incremental outcomes for adjuvant CRT, chemotherapy alone and observation only arms in patients who have undergone surgical resection for gastric cancer. It is important to keep in mind that patients with gastric cancer may be expected to have generally better prognosis, and therefore outcomes, than those with OC or GEJ cancer. However, these studies were used in lieu of literature specific to the population of interest because they can lend relevant information to the decision. Total QALYs were estimated between 3.59 months (observation alone) and 6.86 months (adjuvant CRT), which are similar to the estimates from the Company CEM (although slightly higher, as anticipated). Data informing the Zhang et al. model were derived from reconstructed PLD and used to inform a Markov model, so there are substantial differences between the implementations. Patients in the informing trial used for clinical inputs in the Zhang et al. study were similar to those in CheckMate 577 in their demographics and median treatment times.

Another study by Chongqing et al. (2014)[67] reported results for adjuvant chemotherapy versus surgery alone for gastric cancer, so the same caveats regarding the generalisability of these results apply. The surgery alone comparator is similar to the routine surveillance arm of CheckMate 577 and to the observation only arm reported in Zhang et al. This study estimated the total QALYs to be 6.46 and 5.45 for adjuvant chemotherapy and surgery alone, respectively. Both of these are higher than the total QALYs estimated by the Company CEM, though as discussed, this is to be expected. This study used a Markov model so, again, there were differences in the implementation although these did not result in clinical outcomes that were unable to validate to the literature.

Zhan et al. (2019) examined outcomes in a population that was similar to those enrolled in CheckMate 577 although only considered those with a squamous cell histology, rather than a mixed group. In this study, higher QALY gains were estimated than were seen in the Company CEM, however, these are not aligned to the other studies (i.e. gastric would be expected to have higher QALY gains again). In addition, the study publication did not provide any demographic information other than stage of disease at model initiation, with which to verify the comparability of this population with those patients in CheckMate 577.

Studies where a chemotherapy agent was compared to surgery alone are shown in Table 57, with the predicted total QALYs and LYs (if reported) alongside the Company CEM estimates. This demonstrate that there is substantial variation in the estimates between studies, although the estimates from the Company CEM is within these bounds and should be considered a robust representation of the likely outcomes for patients.

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Table 57. Comparison of economic outcomes from the Company CEM with published literature

Parameter	Company CEM	Wang et al 2008[73]	Hisashige et al 2013[69]	Chongqing et al 2014[67]	Wu et al 2014[66]	Zhan et al 2019[61]	Zhang et al 2019[60]
	Patients with resected OC or GEJ cancer	Patients with resectable adenocarcinoma of the stomach or GEJ	Patients with completely resected stage II or III gastric cancer	Confirmed stage II-IIIb gastric cancer	Gastric Cancer	ESCC stage IIb or III	Stage Ib – IIIC gastric or gastroesophageal adenocarcinoma
Country	Various	USA	Japan	China	China	China	China
Total QALYs	Nivolumab + surgery = [redacted] Routine surveillance + surgery= [redacted]	Surgery + adj CRT = 2.25 Surgery alone = 1.72	Adj CT (S1 therapy) + Surgery = 8.65 Surgery alone = 7.41	Adj CT + Surgery = 6.46 Surgery alone = 5.45	S1 CT + surgery = 10.8 XELOX CT + Surgery = 11.5 Surgery alone = 8.1	NCRT + surgery = 9.08 Surgery alone = 6.0	Adj CRT = 6.86 Adj CT = 5.05 Surgery alone = 3.59
Total LYs	Nivolumab + surgery = [redacted] Routine surveillance + surgery= [redacted]	Adj CRT + Surgery = 2.91(years additional survival) Surgery alone = 2.16 (years additional survival)		Adj CT + Surgery = 9.01 Surgery alone = 6.99			

Adj: adjuvant; CEM: cost-effectiveness model; CRT: chemoradiotherapy; CT: chemotherapy; ESCC: Oesophageal cancer, squamous cell histology; GEJ: gastroesophageal junction; LY: life year; NCRT: neoadjuvant CRT; OC: oesophageal cancer; QLAY: quality-adjusted life year

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B.3.10 Interpretation and conclusions of economic evidence

The cost-utility model presented set out to evaluate the cost-effectiveness of nivolumab compared to placebo for people with resected OC or GEJ cancer. This represents an innovative treatment that can offer a larger proportion of patients disease-free time.

The model sought to capture key clinical outcomes; the proportion who remain disease free, the time over which they remain disease free, the time to recurrence and death. The model design comprises a semi-Markov approach which is an important progression from traditional partitioned survival model designs commonly seen in oncology modelling. This is an important deviation because the inclusion of time dependency allows the benefit of delayed recurrence to be captured as well as the reduced proportion of patients who experience a recurrence to be captured.

Strengths in the modelling approach

The model design has been considered to reflect the key clinical events and the time patients spend each health state, as well as the proportions in each state over time. That is, time spent disease free and with recurrence are modelled with flexible methods and time dependency considered. The modelling method retains consistency with previous modelling approaches but has gone further in development to offer more granularity and accuracy.

Results have been validated where possible against relevant studies and outcomes. There is considerable variability in the data available due to numerous factors; limited publication in the specific indication under consideration, heterogenous populations and different pathways of care in different countries. However, the results estimated by the Company cost-effectiveness model are largely aligned to the reported literature.

Inputs have been validated against observed data where possible (e.g. survival analysis) although due to the sparsity of data this is challenging. All predicted survival data has validated well to that observed in the underlying trial, which increases confidence in the approach taken.

Treatment options can be quite personalised, particularly post recurrence, leading to a heterogenous post recurrence population. This requires simplifying assumptions to be made during the modelling process. Simplifying assumptions are present in all analyses and do not limit their usefulness; reflecting complex health situations through modelling is crucial to quantifying their cost and health outcomes. However, the evidence base must be considered alongside the results. The range of sensitivity analysis performed on the base case helps to qualify uncertainty, and a range of scenario analyses have been performed to address structural uncertainty introduced through model design and necessary assumptions. All scenarios point to the base case being conservative and robust to assumptions and natural variation in the underlying parameters.

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Limitations in the modelling approach

The most notable limitation that was encountered during the modelling process was the unavailability of OS data; greater maturity of data would allow for direct modelling of PRS or OS. This would lend greater confidence to the predicted OS benefit of nivolumab, which is currently supported by the impact of nivolumab on DFS. These data may also have enabled subsequent treatment lines to be specifically modelled, rather than combining all post recurrence lines to one health state.

As mentioned, the literature available to describe costs and outcomes in the relevant population is extremely limited. Therefore, some input data was not captured directly from the population of interest (cost and resource use in the recurred disease health state). This is not ideal, although reasonable efforts have been made to try and align as much as possible to suitable populations and evidence.

Finally, using literature data to recreate PLD is scientifically valid but it would always be preferable to work with and model PLD. Modelling with reconstructed PLD requires the assumption that the population that are reported are completely representative of the decision problem population. This in turn relies on accurate and thorough reporting. Where it is not possible to identify similarities and differences, the assumption has to be made that there is no difference. This does not limit the usefulness of the data but does require it to be evaluated with some caution.

Conclusions

Through all clinically plausible scenarios, nivolumab remains cost effective compared to routine surveillance. This is key because there is limited evidence with which to validate all inputs and outcomes, as is common for novel therapeutics within an indication. It is therefore important to frame the base case with the scenarios and sensitivity analysis; while the exact ICER for each patient may not be known, all scenarios and analysis explored remain cost effective, increasing the confidence that this would therefore be the case in clinical use, allowing for natural variation in the patient population. Importantly, the base case can be considered conservative, as the potential long term benefit of nivolumab cannot be captured post recurrence due to immaturity of OS data from CheckMate 577, despite this hazard reduction clearly being present after active treatment ceases.

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Appendices

In line with the user guide for company evidence submission template, appendices start at C, because document A is the submission summary and document B is the main submission.

Appendix number	Appendix Title	Location
C	Nivolumab SmPC NB: A version of the European public assessment report or scientific discussion is not yet available	Provided as a separate document
D	D1: Identification, selection and synthesis of clinical evidence: systematic literature review report	Provided as a separate document
E	Subgroup analysis	Provided in the main body of the report
	E1: CheckMate 577 Clinical Study Report	Provided as a separate document
F	Adverse reactions	Provided in the main body of the report
G	G1: Published cost-effectiveness studies: systematic literature review	Provided as a separate document
H	Health-related quality-of-life studies: systematic literature review	Captured within Appendix G
I	Cost and healthcare resource identification:	Captured within Appendix G
J	Clinical outcomes and disaggregated results from the model	Provided in the main body of the report
K	Checklist of confidential information	Provided as a separate document
L	Cost-effectiveness model user guide	Provided as a separate document
M	Survival analysis report	Provided as a separate document
N	Utility analysis report	Provided as a separate document

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer [ID1676]

Clarification questions

March 2021

File name	Version	Contains confidential information	Date
		Yes	

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

A1. Company submission (CS), Section B2.7: The ERG acknowledges that the study was not powered to test for an interaction between treatment and subgroups, and notes that the assessment of subgroups was done unadjusted for the stratification factors.

a) Please assess the interaction between treatment and patient characteristics in one or more multivariable models and include the stratification factors in each case.

As acknowledged by the ERG, the study was not powered to test for an interaction between treatment and subgroups. Formally testing heterogeneity the treatment effect via interaction tests for multiple subgroup analyses is subject to considerable limitations that are well characterized and consistent across all clinical trials, as the probability of a false positive finding will increase substantially.[1] For example, if the null hypothesis is true for each of 10 independent tests for interaction at the 0.05 significance level, the chance of at least one false positive result exceeds 40%. Thus, one must be cautious in the interpretation of such results.

In addition, in this setting, the sole p value from an interaction test is an inadequate basis for decision making. It is important to assess the estimated treatment effects in subgroups and to discuss the clinical relevance of observed differences.

Moreover, for subgroup analyses, unstratified analyses are usually performed as there is a risk of over-stratification. However as requested, stratified Cox proportional hazard (PH) models with treatment, subgroup and treatment*subgroup interaction were implemented for each demographic and baseline disease characteristic identified as pre-defined subset in CA209-577 to assess the interaction between treatment and subgroup (Appendix A).

For the purposes of displaying baseline characteristics, subgroups were retrieved from the Case Report Form (CRF) as this reflected the true patient population. For stratified analyses, stratification factors were based on data from Interactive Response Technology (IRT) collected at the time of the randomisation. The stratification factors were:
PD-L1 Status (>=1% vs. <1%/indeterminate/non-evaluable),
Pathologic Lymph Node Status (positive >=ypN1 vs. negative ypN0),
Histology (squamous vs adenocarcinoma).

The median disease-free survival (DFS) based on Kaplan-Meier (KM) product-limit method along with two-sided 95% CIs were produced for the following subgroups:

- Age category (< 65, ≥ 65 and < 75, ≥ 75; < 65 and ≥ 65)
- Sex (male, female)
- Race (White, Black or African American, Asian, Other)
- Region (Asia, RoW [including US/Canada, Europe])
- ECOG PS at baseline (0, 1)
- Disease at study entry (Esophageal cancer [EC], Gastroesophageal junction cancer [GEJ])
- EC: Lower third, middle third, upper third
- GEJ cancer: Siewert-Stein Type I vs. Type II vs. Type II
- Disease stage at initial diagnosis (Stage I-II, Stage III-IV) [No patients with disease Stage I or Stage IV at initial diagnosis, so the categories considered for Disease stage at initial diagnosis are rather Stage II vs Stage III]
- Histology (squamous, adenocarcinoma) (CRF info)
- Histological grade (G1/G2, G3/G4, GX)
- Pathologic lymph node status (ypN0, ≥ ypN1) (CRF info)
- Pathologic tumor status (ypT0, ypT1/ypT2, ypT3/ypT4, unknown)
- Time from beginning of neoadjuvant CRT to complete resection (< 6 weeks, ≥ 6 weeks)
- Time from complete resection to randomisation (< 10 weeks, ≥ 10 weeks)
- HER-2 status at study entry (negative, positive, unknown)
- Baseline PD-L1+ status based on a 1% cut off (≥ 1%, < 1%, indeterminate/non-evaluable) (CRF info)
- Baseline PD-L1+ status based on a 5% cut off (≥ 5%, < 5%, indeterminate/non-evaluable)

- Baseline PD-L1+ status based on a 10% cut off (≥ 10%, < 10%, indeterminate/non-evaluable)

The hazard ratio [HR] (95% CI) of nivolumab over placebo was calculated using the stratified Cox method with treatment, subgroup, and treatment*subgroup interaction. Note that the study was not powered for statistical comparison between nivolumab and placebo in subgroup analyses.

The KM median and the HR were presented only if there are at least 10 events in a respective subgroup category across the two treatment arms. The category NOT REPORTED and the subgroup categories with fewer than 10 events among the two treatment arms were not considered in the Cox PH models.

Overall, subgroup analyses of DFS favored nivolumab over placebo with a HR of < 1 in nearly all the pre-specified groups. DFS benefit with nivolumab over placebo was observed regardless of histology, pathologic lymph node status, and PD-L1 status.

- Histology:
    - squamous cell carcinoma: HR = [redacted]
    - adenocarcinoma: HR = [redacted]
- Pathologic lymph node status:
    - positive (≥ ypN1): HR = [redacted]
    - negative (ypN0): HR = [redacted]
- PD-L1 status:
    - PD-L1 ≥ 1%: HR = [redacted]
    - PD-L1 < 1%: HR = [redacted]
    - Indeterminate/non-evaluable: HR = [redacted]
    - For additional results by PD-L1 expression, see Appendix A.

Given some subgroups had small sample size, caution should be exercised when interpreting these subgroup results as it is not possible to extract any valid conclusion from these figures. Due to the small size of some subgroups, wide CIs for HR were observed.

b) The ERG prefers continuous baseline characteristics to not be dichotomised as this loses information and implies that there is a change in treatment effect at the cut-off. Please provide an analysis of

the effect of age as a continuous variable in a model allowing for non-linearity e.g. a spline model.

In addition to the dichotomised subgroups for age, these baseline characteristics were also considered as continuous variable, in a model assuming a linear relationship (Appendix A). It was not possible to produce a non-linear model in the time frame.

For age as a continuous variable, the p-value for the test of interaction of age and treatment was [redacted]. Overall, the p-values for the test of interaction between treatment and age based on the different cutoffs or as a continuous variable for DFS were consistent, suggesting similar nivolumab treatment effect between these subgroups, independently of age.

c) The ERG interprets the evidence in Figure 12 of the CS to suggest that the effect of treatment in patients whose tumour location is oesophageal cancer (OC) may be greater than in patients whose tumour location is gastroesophageal junction cancer (GEJC).

i) Please comment on this observation and the possible impact on the assessment of cost-effectiveness.

The CheckMate 577 trial was not powered to detect differences in subgroups by tumour location; nevertheless, in CheckMate 577, with a median follow-up of 24.4 months (range, 6.2–44.9), a DFS benefit with nivolumab over placebo was reported regardless of tumour location (HR, [redacted], [95% CI, [redacted]] and [redacted][95% CI, [redacted]]) for oesophageal cancer (OC) and gastroesophageal junction (GEJ) cancer, respectively).[2] In addition, a statistically significant disease-free survival (DFS) benefit of nivolumab was seen for the whole patient population, of whom 42% were GEJ cancer patients. Furthermore, the majority (~90%) of GEJ cancers are adenocarcinomas, with Siewert type I and II GEJ cancer considered biologically similar to oesophageal adenocarcinomas,[3,4] and the hazard ratio for DFS favoured adjuvant nivolumab in patients with adenocarcinoma (hazard ratio [HR] [redacted], 95% confidence intervals [CI] [redacted]).[5]

ii) Please comment on any difference in the distribution of tumour location between the Lou et al and CheckMate 577 studies.

The patient population included in Lou et al were “patients who had undergone esophagectomy for pathologic stage I to III esophageal adenocarcinoma or squamous cell carcinoma” but the Company is not aware of details as to whether GEJ cancer patients were

included or excluded, therefore is not able to comment on any differences with the CheckMate 577 population.

However, the Company notes that Figure 12 of the Company submission describes DFS, whereas the data from Lou et al were used to inform post-recurrence survival (PRS), because OS data from the CheckMate 577 trial are immature. There is no evidence supporting a differential effect of nivolumab on PRS by tumour location, therefore the Company does not consider this relevant to the use of Lou et al as a source of PRS data.

Nevertheless, as discussed in the Company submission B.3.8.4.6 and detailed in depth in our answers to B20 and B23, the population described in Lou et al provide a good match to the CheckMate 577 population and to the UK patient population, particularly considering the sparsity of published data for this indication. Furthermore, we apply the same PRS (derived from Lou et al) to both the nivolumab and routine surveillance arms, therefore any potential differential treatment effect of nivolumab post-recurrence is explicitly not modelled, which is a conservative assumption.

d) The ERG interprets the evidence to suggest that the effect of treatment in patients whose histology is squamous may be greater than in patients whose histology is adenocarcinoma.

iii) Please comment on this observation and the possible impact on the assessment of cost-effectiveness.

Though the point estimate between histology's may be different, the confidence intervals overlap and CheckMate 577 showed a statistically significant DFS benefit for nivolumab over placebo regardless of disease histology (squamous cell carcinoma: HR = [redacted](95% CI: [redacted]), adenocarcinoma: HR = [redacted](95% CI: [redacted])).[2] In addition, the multivariate model shows a p value of [redacted]for histology, suggesting that the impact of histology on treatment effect is not significantly different.

A2. CS, Figure 13. The ERG suggests that the hazard ratios by subgroup reflect the impact of arbitrarily defining different cut-offs for a continuous predictive variable. Please assess the interaction between treatment and PD-

L1 expression in a multivariable model with PD-L1 fitted as a continuous variable e.g. a spline model.

In addition to the dichotomized subgroups for PD-L1 status, these baseline characteristics were also considered as continuous variable, in a model assuming a linear relationship. The p-values for the test of interaction of PD-L1 status and treatment in addition to treatment and PD-L1 status in the stratified Cox PH model were [redacted], [redacted] and [redacted] based on the 1%, 5% and 10% cutoffs respectively. For PD-L1 as a continuous variable, the p-value for the test of interaction of PD-L1 status and treatment was [redacted].

Overall, the p-values for the test of interaction between treatment and PD-L1 status based on 1%, 5%, 10% or as a continuous variable for DFS are consistent, suggesting similar nivolumab treatment effect between these subgroups, independently of baseline PD-L1 status.

A3. Please clarify the definition of "serious" adverse events in the CheckMate577 trial?

In accordance with the CheckMate 577 study protocol, a Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

i. results in death
ii. is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
iii. requires inpatient hospitalisation or causes prolongation of existing hospitalisation (see **NOTE** below)
iv. results in persistent or significant disability/incapacity
v. is a congenital anomaly/birth defect
vi. is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalisation but, based upon appropriate medical and scientific judgment, may jeopardise the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation.) Potential drug induced

liver injury (DILI) is also considered an important medical event (see below for the definition of potential DILI).

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE as described in the CheckMate 577 study protocol. Although pregnancy, overdose, cancer, and potential DILI are not always serious by regulatory definition, these events were handled as SAEs. Any component of a study endpoint that is considered related to study therapy (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) was reported as SAE.

Potential DILI is defined as events meeting each of the following criteria:

1. Aminotransaminases (alanine aminotransferase or aspartate aminotransferase) elevation > 3 times upper limit of normal (ULN).
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase).
3. No other immediately apparent possible causes of aminotransaminase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

NOTE: The following hospitalisations are not considered SAEs in Company clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs

A4. Please clarify when CheckMate577 final analysis for disease free survival (DFS) / IA 2 for overall survival (OS) is expected? Please also clarify when the final analysis for OS is expected?

The DFS IA (July 2020 DBL) met its pre-specified statistical significance criteria; therefore, it is considered the final DFS analysis. The OS IA2 is planned when 80% of OS events are observed, projected for [redacted]. The final OS analysis is planned when 460 OS events are observed, projected for [redacted].

A5. Please clarify if the PRISMA Chart (CS Appendix D, p4) is for the economic review (appendix G) rather than the clinical systematic literature review (SLR)? Please provide the correct PRISMA chart for appendix D.

The PRISMA chart in Appendix D, p4 was for the economic review. The correct PRISMA is presented in Figure 1. Appendix D has been revised to correct this error and is attached to this response.

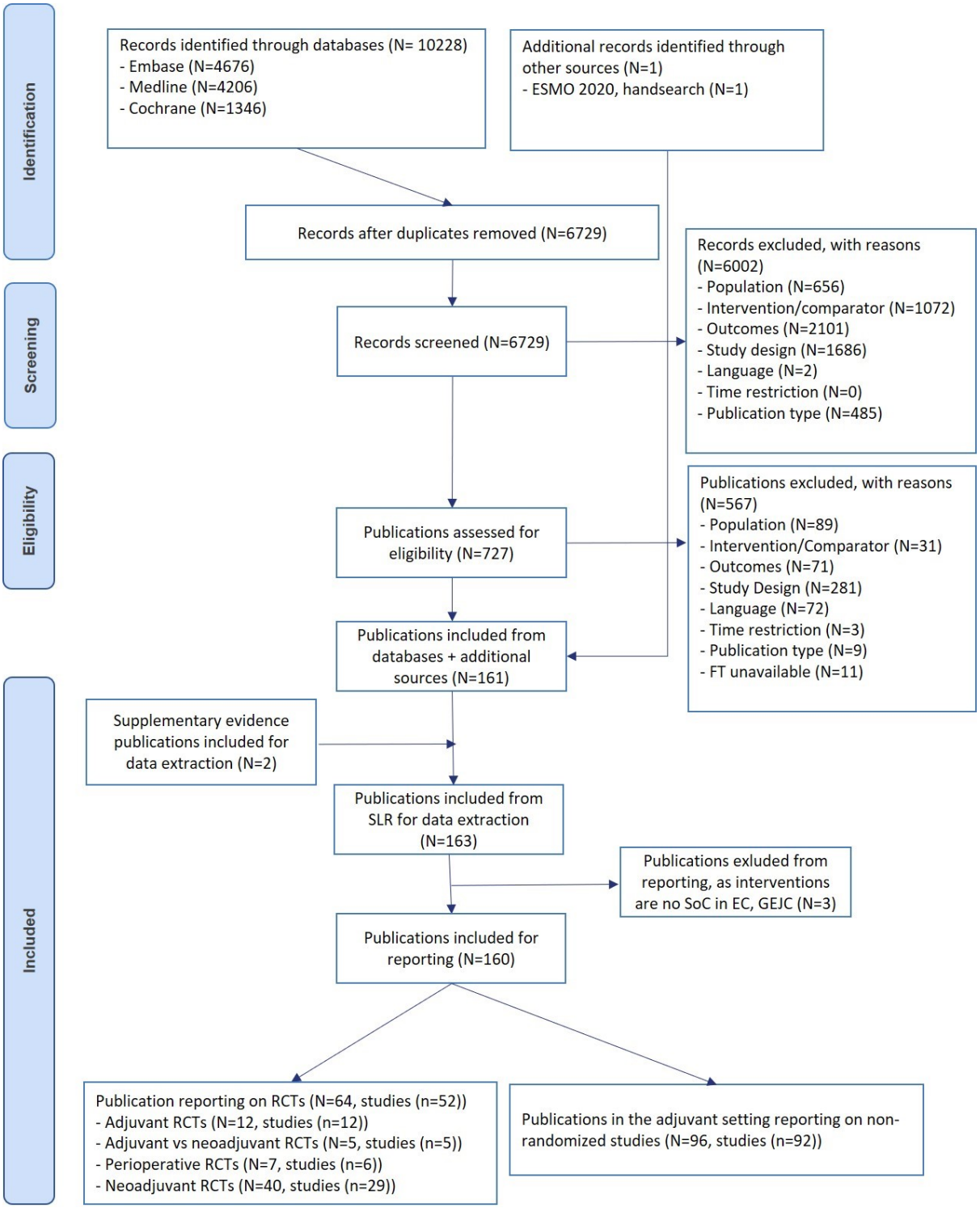


Figure 1. Clinical PRISMA flow chart

A6. Please clarify why conference proceedings were excluded from the clinical SLR.

Conference proceedings were included in the clinical SLR. The clinical SLR was conducted in two phases. In phase I (13 August 2019) only peer-reviewed publication databases were

searched (i.e., Medline, Embase, CENTRAL). In phase II (30 November 2020) the original SLR search was updated, and a search for conference proceedings (2018 onwards) was added to the SLR. As the original SLR was replicated, the main search strategy indeed includes a limitation to exclude conference proceedings. Therefore, a separate search strategy was added in phase II to identify relevant conference proceedings in Embase. Conferences that were not indexed in Embase were "hand-searched" using OC and GEJC search terms in whichever format was provided by the conference (e.g., PDF booklet, online search portal). The following conference proceedings were included:

- American Society of Clinical Oncology (ASCO) Annual Meeting
- ASCO Gastrointestinal Cancers (GI) Meeting
- European Society for Medical Oncology (ESMO) Annual Meeting
- American Association for Cancer Research (AACR) Annual Meeting

A7. Please clarify whether searches of trial registers other than CENTRAL were undertaken, for example in ClinicalTrials.gov or ICTRP.

No searches were undertaken in trial registries other than the CENTRAL database.

A8. Please clarify whether reference lists were checked for additional studies not identified in the SLR.

In phase I, bibliographies for the most recent/relevant SLR/meta-analyses (n = 5 studies) were screened to identify additional studies. In phase II, only bibliographies for included publications were checked for eligible studies. No additional studies in the adjuvant setting were identified.

A9 Please clarify whether CheckMate577 was identified by the SLR.

Yes, the CheckMate577 was identified by the SLR, as a conference proceeding.

Citation details: Kelly, R. J. et al. LBA9_PR Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study. Annals of Oncology 31, S1193-S1194, doi:https://doi.org/10.1016/j.annonc.2020.08.2299 (2020).

A10. Please provide details of ongoing studies (other than CheckMate577) of nivolumab in OC or GEJC, and their expected primary completion dates.

- ATTRACTION-5 (ONO-38, NCT03006705):71 a phase 3, randomised, multicentre, double-blind, placebo-controlled study of nivolumab in combination with adjuvant chemotherapy in gastric/GEJ cancer (expected primary completion date: June 2021)
- CA224-060 (NCT03662659):72 a randomised, open-label study of relatlimab (Anti-LAG-3) and nivolumab with chemotherapy versus nivolumab with chemotherapy as first-line treatment in patients with gastric/GEJ adenocarcinoma (expected primary completion date: December 2021)
- ATTRACTION-4 (ONO-37, NCT02746796):73 a randomised, multicentre study of nivolumab plus chemotherapy in patients with previously untreated advanced or recurrent gastric/GEJ cancer (primary completion date: January 2020)[6]
- CheckMate 648 (CA209-648, NCT03143153):74 a phase 3, open-label study of nivolumab + ipilimumab OR nivolumab + fluorouracil + cisplatin versus fluorouracil + cisplatin in subjects with unresectable advanced, recurrent, or metastatic previously untreated oesophageal squamous cell carcinoma (expected primary completion date: August 2021)
- FRACTION-GC (CA018-003, NCT02935634):75 a phase 2, fast real-time assessment of combination therapies in immuno-oncology study in participants with advanced gastric cancer (expected primary completion date: November 2021)
- CheckMate 649 (CA209-649, NCT02872116): a phase 3, open-label, randomised, multi-centre study of nivolumab in combination with chemotherapy in patients with untreated advanced and metastatic gastric/GEJ/EAC cancer (expected primary completion date: May 2021).

Section B: Clarification on cost-effectiveness data

B1. Priority: Please provide an updated base case (deterministic and probabilistic) that incorporates all changes that are made following the clarification process. Provide supplementary analyses as you see fit.

Upon review of the clarification questions, specifically B7, the Company has identified that an error was included inadvertently in the submitted model and have since corrected this. The Company thanks the ERG for their diligence and has provided details of the changes below, and an updated base case. All scenarios requested have also been incorporated into the model, and a summary of these scenarios can be found in Appendix B.

Change after review of question B7: In 'Treatment Trace' and 'Control Trace' cells L8:BU8 were altered to make sure the calculation included the first row (row 0), as identified by the ERG.

The 'Offset' function is structured as follows: Offset(reference, rows, cols, [height], [width]) The error was incurred as the 'rows' argument was set to 1 in the cells across the range L8:BU8. This has since been corrected to 0 and the resulting formulae now include cycle 0.

For example, cell L8 in "Treatment Trace" was changed (change in bold typeface) from:
=(SUM(OFFSET(L11,**1**,0,CEILING.MATH(intHorizon*(365.25/7)),1))/(365.25/7))/intCohort
to:
=(SUM(OFFSET(L11,**0**,0,CEILING.MATH(intHorizon*(365.25/7)),1))/(365.25/7))/intCohort
47 cells were changed in 'Treatment Trace' and 47 cells were changed in 'Control Trace'.

This change results in the total costs, QALYs and LYs changing from the submitted base case (presented in Table 1 and in Document B, Table 46). The updated base case is presented in Table 2, with a new ICER of £22,785.

Table 1: Submitted base case analysis results (with PAS, discounted)

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£21,047
ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life-year			

Table 2: Updated base case analysis results (corrected model with PAS, discounted)

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£22,766
ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life-year			

All clarification questions that relate to scenarios were run in the corrected model. The corrected version of the model has been supplied to the ERG with responses to the clarification questions for review and validation.

A number of additional changes were made in the CEM that is provided alongside the responses to the clarification questions although these do not affect the results of the analyses. These are detailed below:

In response to B29: The model that was initially submitted inadvertently varied two parameters at the same time. The correction is described in the response to B29. With this correction and that in response to B7, the updated deterministic sensitivity analysis (DSA) results can be seen in Figure 2.

Figure 2: DSA ICER Tornado diagram

In response to B33: In response to B33 the Company has made changes to the model such that it will report parameter inputs that result in a negative QALY gain for nivolumab during conduct of the probabilistic sensitivity analysis (PSA). This does not otherwise change the settings of the PSA that was submitted in the original Company CEM, however the results of the PSA have been updated in response to B7. Updated results are presented in Table 3, Figure 3 and Figure 4.

Table 3: Updated probabilistic sensitivity analysis results

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£22,822
ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life-year			

Figure 3: PSA scatterplot

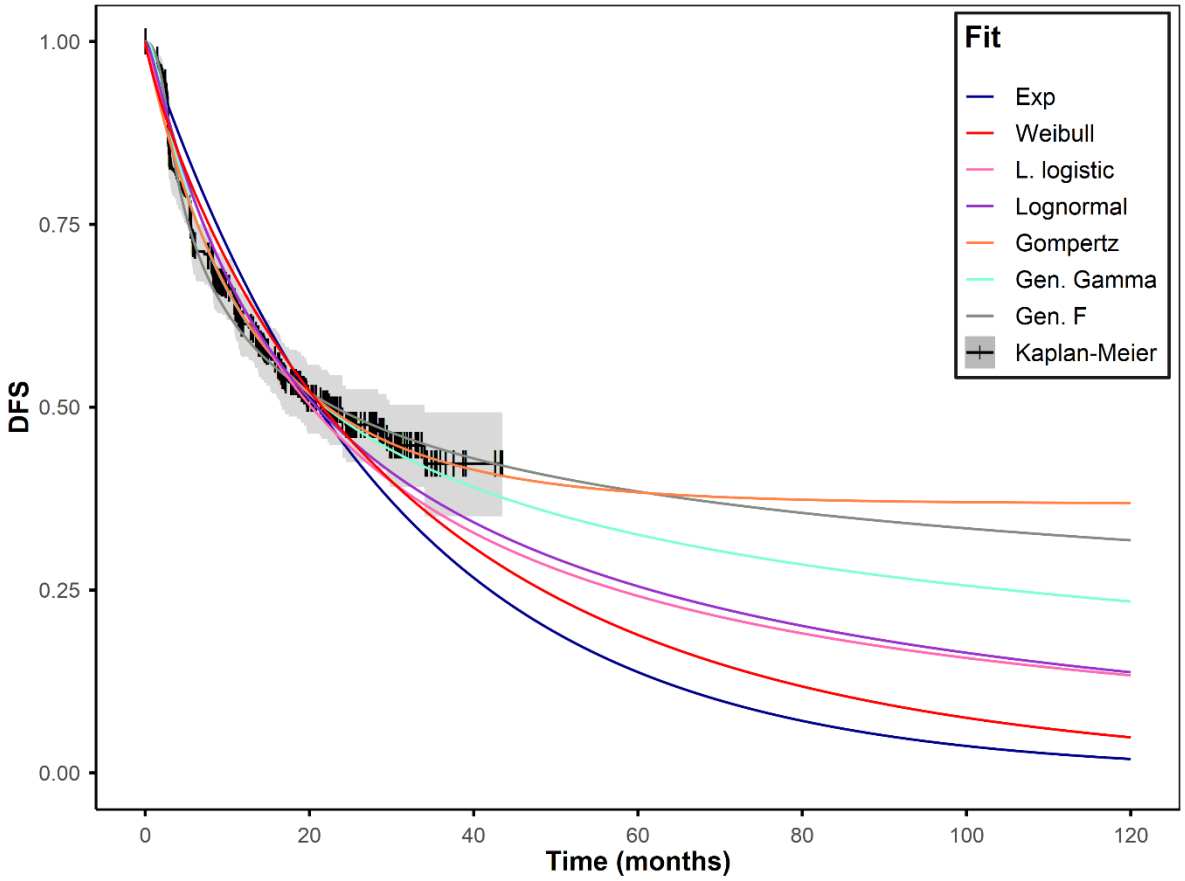
Figure 4: PSA cost effectiveness acceptability curve

B2. Priority: The model base case assumes that for people in the disease-free health state at three years there is no risk of disease progression beyond this time point and that all-cause mortality rates are applicable. As such, the projections of DFS beyond 3 years are irrelevant. As standard parametric models fit the data well for the first three years please clarify why parametric models were not used for DFS. Please provide ICERs for each parametric model explored.

As demonstrated in Figure 5 and Figure 6 (also shown in Appendix M 4.1.3, Figures 6 and 7), it is not correct to say that parametric models fit well to the observed CheckMate 577 data for the first three years. Of the available parameterisations, only Gompertz, generalised gamma and generalised F provide fits that are potentially viable, although all still provide a poor fit to the initial hazard profile and fail to capture the hazard in the tail of the data. While the impact of the data tail is limited, given the use of the general population mortality from three years, it remains best practice to review this fit as part of curve selection.

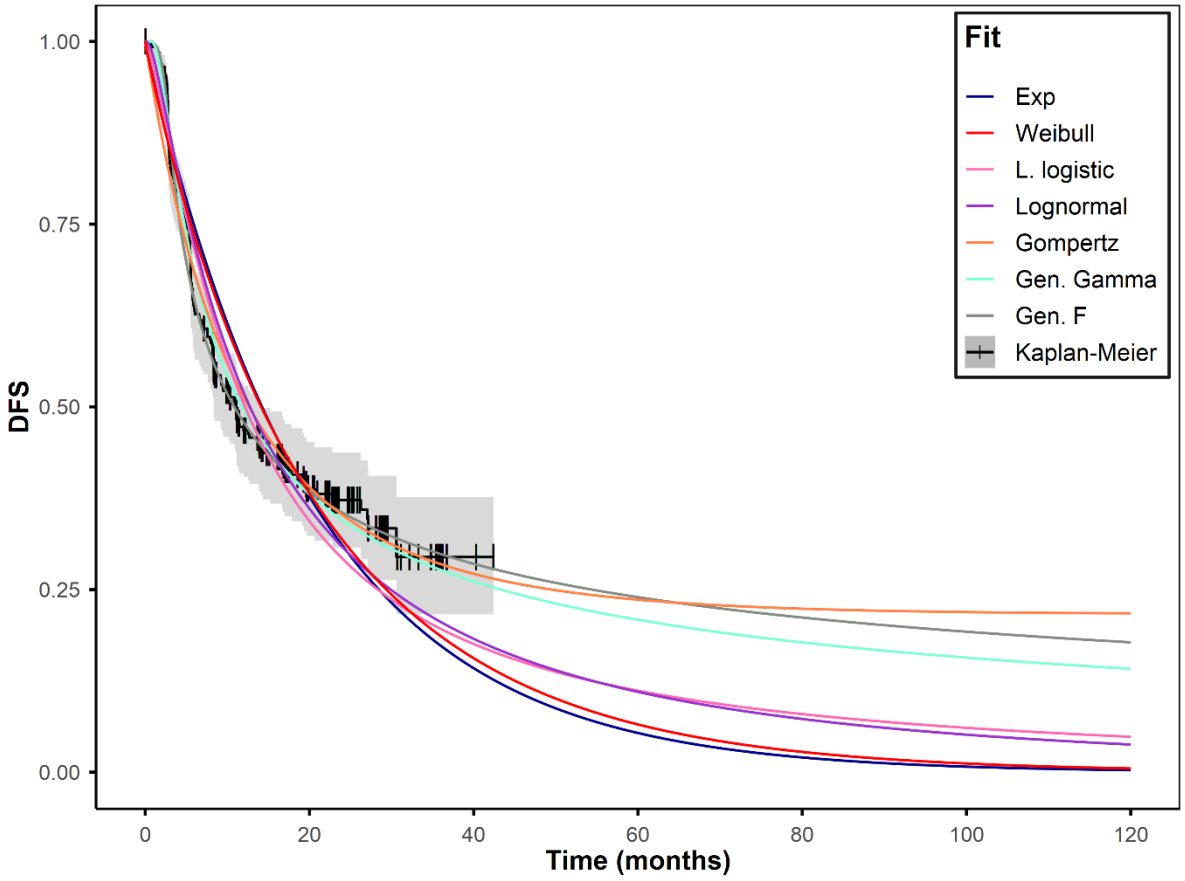
Despite these limitations, all fits have been assessed in scenario analysis through replacement of the relevant base case analysis curve, with results provided in Table 4.

Additionally, a scenario is provided where the best standard parametric fit for both arms is assessed, presented in Table 5; nivolumab remains cost-effective in this scenario.



Fit Name	AIC	BIC	Parameters	Median (Months)	Mean (Months)
Exp.	2127.62	2131.89	lambda: 0.0330	20.98 (18.30, 24.28)	30.27 (26.40, 35.03)
Weibull	2121.69	2130.25	shape: 0.8584; scale: 33.0558	21.57 (18.47, 25.50)	35.75 (29.73, 43.58)
Gompertz	2094.14	2102.70	shape: -0.0535; rate: 0.0534	22.16 (17.77, 30.76)	N/A
L. logistic	2100.38	2108.93	shape: 1.0516; scale: 20.2428	20.24 (16.99, 24.54)	393.92 (131.47, 4188.4
ognormal	2083.52	2092.08	mu: 3.0395; sigma: 1.6020	20.90 (17.46, 25.49)	75.39 (53.56, 110.87)
en. Gamma	2071.69	2084.52	mu: 2.4381; sigma: 1.7821; Q: -0.9972	21.96 (17.60, 28.84)	N/A (108.77, N/A)
Gen. F	2046.64	2063.75	mu: 1.1323; sigma: 0.4760; Q: -6.7388; P: 14.0601	23.07 (17.01, 33.37)	N/A (38.41, N/A)

Figure 5: Parametric distributions fitted to DFS data – nivolumab arm



Fit Name	AIC	BIC	Parameters	Median (Months)	Mean (Months)
Exp.	1248.56	1252.13	lambda: 0.0487	14.22 (12.02, 16.88)	20.52 (17.35, 24.35)
Weibull	1249.88	1257.02	shape: 0.9468; scale: 20.7897	14.12 (11.87, 16.86)	21.31 (17.36, 26.50)
Gompertz	1232.17	1239.31	shape: -0.0477; rate: 0.0730	12.64 (10.33, 15.76)	N/A
L. logistic	1223.05	1230.19	shape: 1.2989; scale: 12.1505	12.15 (10.01, 14.84)	44.41 (27.59, 85.13)
Lognormal	1212.17	1219.31	mu: 2.5453; sigma: 1.2628	12.75 (10.60, 15.45)	28.29 (20.94, 40.18)
Gen. Gamma	1187.64	1198.34	mu: 1.7564; sigma: 1.1688; Q: -1.5152	11.78 (9.54, 14.89)	N/A (71.40, N/A)
Gen. F	1174.52	1188.79	mu: 1.0854; sigma: 0.2823; Q: -7.2939; P: 15.5229	10.85 (8.77, 14.63)	N/A (101.87, N/A)

Figure 6: Parametric distributions fitted to DFS data - routine surveillance arm

Table 4. Scenario analysis results: use of standard parametric fits

Parameterisation	Visual assessment of fit	ICER (£/QALY)
Nivolumab standard parametric fits (holding routine surveillance at generalised gamma)		
Exponential	Poor fit – extreme under and over estimation at all time points	£67,846
Gen Gamma	Poor fit – under and overestimation, poor representation of long-term trajectory	£19,570
Log logistic	Poor fit – extreme under and over estimation at all time points	£34,498
Log-Normal	Poor fit – extreme under and over estimation at all time points	£29,021
Weibull	Poor fit – extreme under and over estimation at all time points	£38,464
Routine surveillance parametric fits (holding nivolumab at Gompertz)		
Exponential	Poor fit – extreme under and over estimation at all time points	£8,268

Parameterisation	Visual assessment of fit	ICER (£/QALY)
Gompertz	Adequate fit – some under and overestimation, though reasonable representation of long-term trajectory	£18,144
Log logistic	Poor fit – extreme under and over estimation at all time points	£9,281
Log-Normal	Poor fit – extreme under and over estimation at all time points	£10,077
Weibull	Poor fit – extreme under and over estimation at all time points	£9,003

Table 5: Scenario analysis results: parametric Gompertz (nivolumab) and parametric generalised gamma (routine surveillance), (with PAS, discounted)

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£17,005
ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life-year			

For the nivolumab arm (Figure 5), there is clear and substantial under- and overestimation by all models in the first 36 months, with all curves falling outside the confidence intervals at numerous points. The only exception was the Gompertz model, which provides a good visual fit to the middle part of the data and predicts a median DFS closest to the observed median. However, the fit to the hazard in the initial six months is poor and the parameterisation does not capture the hazard in the tail of the data. The Company notes that the Gompertz model fitted to the nivolumab arm estimates parameters that are negative. The Company does not agree that this alone should disqualify a model from selection (see response to B20).

Similarly, the standard parametric models fitted to the routine surveillance arm were not considered to be a good fit due to substantial over- and underestimation by each model in the first 36 months and appearance of the curves outside the CIs (Figure 6). The best fitting parameterisations appear to be the generalised F and generalised gamma models. As the generalised gamma model predicts improved outcomes for routine surveillance in the first three years and the generalised F model is not explicitly recommended by TSD14, the scenario analysis results consider the generalised gamma model (Table 5).

Although it is agreed that visual assessment of parametric fit after three years is not strictly relevant to the base case analysis, this remains best practice when considering plausibility of

models. Further, it should be emphasised that assessing long-term extrapolations allowed evaluation of modelling assumptions in order to aid decision making. In this sense, the use of parametric models was considered in the context of other necessary base case modelling assumptions.

B3. Priority: Please provide an ICER using the kaplan meier (KM) data for DFS up until the period at which the long-term disease free is assumed to start (3 years).

Analysis where Kaplan-Meier data are used for the first 3 years shows that nivolumab is still cost-effective (Table 6).

Table 6: Scenario analysis results: Kaplan-Meier DFS up to 3 years (with PAS, discounted)

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£20,248
ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life-year			

Please note that updated DFS data (February 2021 DBL) became available to the Company after the date of the original submission, including DFS events up to month 51. The plateau seen in the Kaplan-Meier DFS data from the July 2020 DBL is sustained in the more recent DBL.

[redacted]

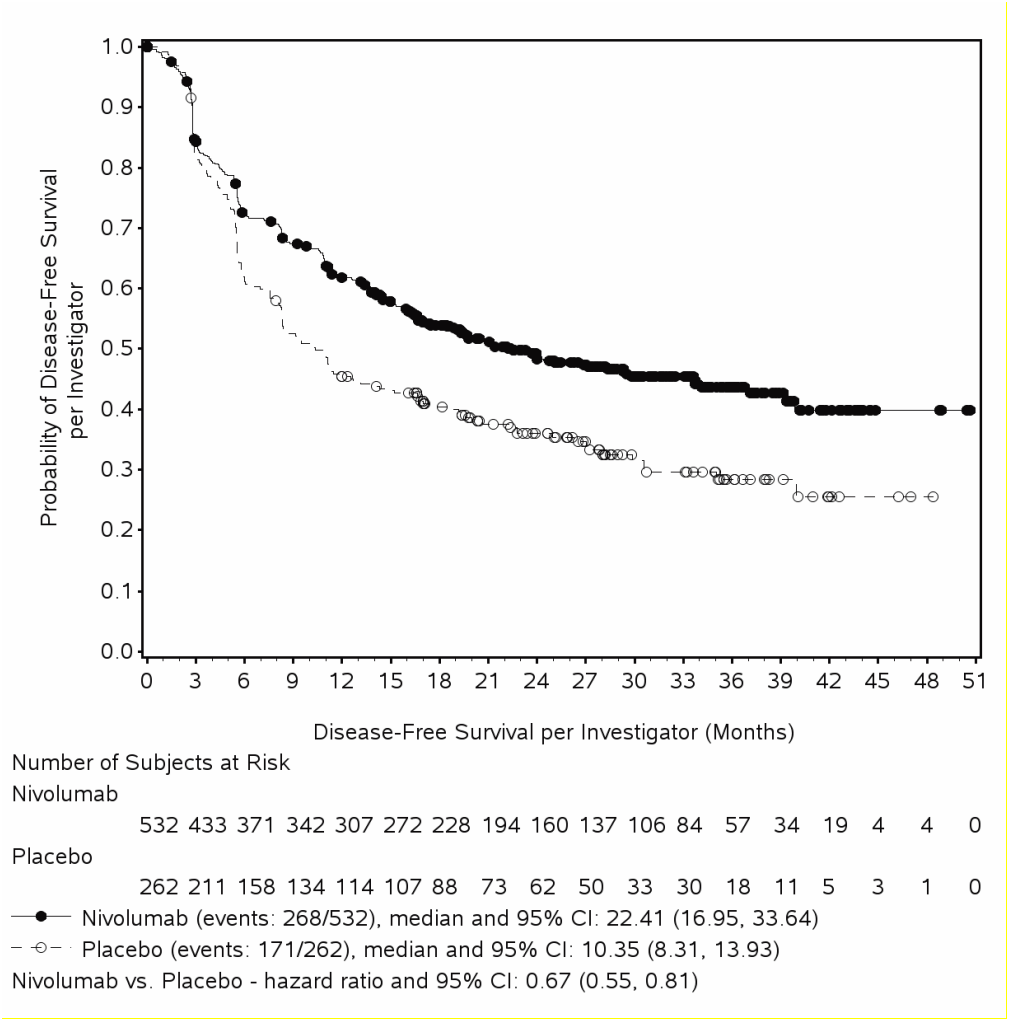


Figure 7. CheckMate 577 additional database lock (February 2021)

B4. Priority: Please clarify if it was only the company that was blinded to OS data and not the analysts. Furthermore, clarify how it is known the timing and number of deaths on each treatment arm with respect to progression free survival (PFS), (progression free survival on next line of therapy) PFS2 and the logistic regression.

Availability of OS data

According to the testing strategy presented in the CA209577 Statistical Analysis Plan (SAP), the DFS interim analysis (IA) was planned when at least [redacted] of all [redacted] DFS events ([redacted] DFS events) had been observed. OS IA1 was planned to occur the same time and it was projected that approximately [redacted] of OS events ([redacted] OS events) would be observed under protocol assumptions.

[redacted]

[redacted]

[redacted]

Availability of limited information on deaths as part of DFS and PFS2 endpoint

[redacted]

- Definition of DFS: DFS (per investigator assessment) was defined as the time between randomisation date and first date of recurrence or death, whichever occurs first.
- Definition of PFS2: For patients who did not receive subsequent systemic therapy, PFS2 was the time between the randomisation date and death date, or the last known alive date if the patient was alive. For patients who received subsequent systemic therapy, PFS2 was the time between the randomisation date and 1) objectively documented progression per investigator assessment on the subsequent systemic therapy, 2) second subsequent systemic therapy, or 3) until death from any cause, whichever occurred first. Patients without PFS2 events were censored on their last known alive date.

The logistic regression described in the Company submission section B.3.3.2.1.2 was used to model transitions from the disease free health state to the death health state in the first three years, for those patients that experienced pre-recurrence death events. This allowed for the prediction of the proportion of DFS events that are death events and accurate modelling of this transition.

B5. Priority: Please clarify if patients who died without receiving a subsequent treatment are counted as PFS2 events. Please also clarify if patients who have received a subsequent treatment and die are counted as PFS2 events, as are those who receive a second subsequent treatment. Please explain why the proportion of PFS2 events are similar between the two arms (the ERG has

noted the additional number of PFS2 events that were due to a second subsequent treatment in the control arm) yet the model predicts a noticeable difference in the proportions alive between the two arms at 36 months ([redacted]% in the nivolumab arm and [redacted]% in the control arm). That is, clarify why the model appears to not be predicting what was observed in the trial.

A full definition of PFS2 is provided in response to question B4. The Company confirms that patients who died without receiving a subsequent treatment were counted as PFS2 events.

If a patient received a subsequent systemic therapy, this patient would be considered as having a PFS2 event if the patient had 1) objectively documented progression per investigator assessment on the subsequent systemic therapy, 2) second subsequent systemic therapy, or 3) death.

At the July 2020 DBL, the median for PFS2 in the nivolumab arm [redacted], supporting benefit for nivolumab over control, as seen in Figure 1. Further, the Company would like to clarify that the modelled values for proportion alive quoted in the ERG question actually reflect those that have died at 36 months, not those that remain alive. Modelled proportion of patients remaining alive can be seen in Column O of the treatment and control traces in the CEM. Based on visual inspection of the Kaplan-Meier, the modelled proportion of people dead at 36 months (per the question: [redacted] in the nivolumab arm and [redacted] in the control arm) appears approximately in line with trial outcomes. This indicates that patients in the routine surveillance arm had either died more quickly than the nivolumab arm, or had progressed on treatment more so than those in the nivolumab, which is supported by the breakdown of PFS2 events (Company submission B.2.6.3.4).

Figure 8. CheckMate 577 Kaplan-Meier plot of PFS2 per investigator - all randomised patients

B6. Priority: Please clarify whether after the age of 75 years the utility for people alive in the model are the same regardless of whether someone is in disease-free survival, or has previously progressed and that these values are assumed to equal that of an age and sex-matched population. If this is correct, please clarify why it is assumed that having had oesophageal or gastro-oesphageal junction cancer is not associated with a reduction in utility, particularly when there has been progression, including on adjuvant nivolumab therapy. Please explore the impact of the ICER of assuming that people in disease-free survival have a lower utility than an age- and sex-matched population, and that those who have progressed have a lower utility than those in the disease-free state.

As discussed in Company submission B.3.4.1, there is a marked sparsity of utility data with which to populate the CEM. Analysis of the trial utilities were the best available evidence but estimated pre-recurrence utility values higher than an age- and sex-matched population. Though these values could be plausible, given that 577 patients are disease free at the start of treatment after having recovered from surgery and neo-adjuvant CRT, all patients in the model (regardless of health state) were limited to that of an age-matched population to ensure validity to the population concerned.

As detailed in B.3.4.1.3, trial data for patients with recurred disease had a high degree of missingness and was therefore was not used in the model; instead, the best available evidence was used to describe this patient group. The Company acknowledged and discussed that this value is also likely to be higher than an age- and sex-matched group and identify this as a weakness on page 85 of Document B and test this assumption in scenario analysis (B.3.8.4.3).

It is acknowledged that these assumptions result in the same utility applied in both the disease free and recurred disease health states, equivalent to an age- and sex-matched population after the age of 75 years. The Company recognises that this situation may be unlikely but highlight that it has not been possible to identify alternative utility values.

If a modelled patient is disease free and has reached the age of 75 years, it is assumed that the patients has been disease free for approximately 15 years, based on baseline characteristics. It seems reasonable to assume that, as such, their utility would not be greatly different from that of the general population. This is especially true at the age of 75 years, as it is important to consider that general population measures, such as utility or mortality, are not solely comprised of “healthy” individuals, rather all individuals. Therefore, the use of general population utility does not indicate that patients are without comorbidity, only that it is within the realms of that experienced by others of the same age.

It is acknowledged that patients who have experienced disease recurrence may have a utility lower than that of a general population group. This is particularly relevant for the recurred disease health state in the Company CEM because this represents a heterogeneous group of people who may be on any line of further treatment for OC/GEJ cancer. To address this uncertainty, the Company provided seven alternative scenarios where the health state utility for the recurred disease group was lower than the base case in B.3.8.4.3, Table 52. All scenarios resulted in a reduction of the ICER when compared to the base case ICER.

The assumptions around the utility value for the post recurrence and its impact on the decision problem were fully assessed in the original submission and a conservative approach was taken in the base case. In addition, where the post recurrence health state utility is lower in than that of the base case, the ICER will always be reduced when compared to the base case.

B7. Priority: In the Trace worksheets, the summary values calculated in row 8 appear to miss out the first cycle (row 11). Please clarify whether this represents an error in the model.

The Company has identified that this was an error and the Company CEM with the updated base case, submitted in response to clarification questions, includes the row identified by the ERG in the totals. This is detailed in response to question B1.

B8. Priority: Please provide an excel worksheet showing how the survival probabilities were calculated for each distribution used in the model, including life table data. For example, how are the probabilities contained in the "dblManualSurvMean3" range of the model calculated. Additionally, please provide the data used to fit the survival models

The process used to calculate the probabilities calculated in the model ranges such as "dblManualSurvMean3" are detailed broadly in Appendix M of the original submission, although the Company accepts that it would be helpful for the ERG to review the methods fully. As such, the R scripts used to generate these responses is included with example outputs (Appendix E: Code Appendices_B8). The input patient level data cannot be supplied but the methods can be followed. The code has been fully commented to facilitate thorough and swift review by the ERG. In addition, a summary has been provided below.

Spline Models

The code provided begins by creating an empty data frame to hold the output data. After this, the code sequences through the list of spline models that should be fitted, for example, a log hazard model with zero knots, and creates a survival model and outputs the results into the data frame.

The package performing this analysis is "survivalfitting", which is a bespoke package acting as an extension to "flexsurv" for obtaining survival extrapolations, calculating means and bootstrapping fits.

When the distribution type passed to the univarsuvfit() function is, for example, "log.hazard.0.spline", it is parsed using an internal function to determine [time.transform].[spline.type].[internal.knot]. These arguments are in turn, passed to "flexsurvspline".

The data contained in the univarsurvfit object are then extracted and placed in the data frame that was created initially. This data frame contains the probabilities that can be seen in the ranges “dblManualSurvMean#” in the Company CEM.

Semi-parametric models

Semi-parametric models are fitted in a similar way. The function make.semiparametric.fits.at.cut() requires arguments relating to the distribution fit and cut times that the analyst wishes to examine. In a similar way to the spline models, the function begins by creating an empty data frame that can be populated with the results from the model fit.

The univarsurvfit() function is again used to determine the parametric model, but from the cut point specified. This is then scaled to the Kaplan-Meier data as would normally happen for semi-parametric modelling, although this is done inside the function. Kaplan-Meier data are followed until the defined cut point, after which the parametric model is scaled dependent on the time from time zero to the cut point time; the parametric survival function evaluated at time minus time cut is multiplied by the survival at that time cut.

B9. Priority: The ERG has noticed that the final absorbing state is defined as the complement of the remaining health states. This is not considered to be good modelling practice as it could mask errors in the calculation of the remaining components within the model. Please add an explicitly calculated health state for death, and then show that the sum of all of the calculated health states equals the assumed number of patients at model entry.

The Company accepts that this is not optimal modelling practice but was provided as a model simplification. As the post recurrence health state assigns hazard of death to patients who enter dependent on when they enter, calculating death explicitly would require substantial additional complexity and space. Aligned to this request, the Company CEM with the updated base case, submitted in response to clarification questions, uses calculations to determine the health state occupancy of the final absorbing state. The complete responses will be provided by Friday 30th April.

B10. Priority: Please provide additional details on how time-dependency is incorporated in the model for the post recurrence OS states when distinguishing between patients who have had a recurrence in month 5 and patients who had a recurrence in month 25.

In the Company submission section B.3.2 it is stated that “The semi-Markov approach allows the dependence between events to be captured, and permits time-dependent transitions between health states, for example, the transition from recurred disease to death depends on how long a patient has spent in the recurred disease state.”

It is acknowledged that this paragraph was unintentionally ambiguous. To clarify, each patient who experiences a recurrence starts at the beginning of the PRS curve, irrespective of when the recurrence occurs. For the given example of patient A experiencing recurrence at month 5 and patient B experiencing recurrence at month 25, the probabilities are derived as follows. At month 5, patient A experiences a recurrence and has the time zero probability of death post-recurrence. At month 25, patient A will now be experiencing the probability of death post-recurrence at time 25 months, while patient B has the time zero probability of death post-recurrence.

B11 Priority: Appendix M, Section 4.1.1: Please provide smoothed plots of the empirical DFS hazard function

Smoothed plots of the DFS hazard can be seen in Figure 9 for nivolumab and Figure 10 for routine surveillance; the Royston-Parmer splines displayed in Document B are shown here alongside B-spline and Kernel smoothed hazards.

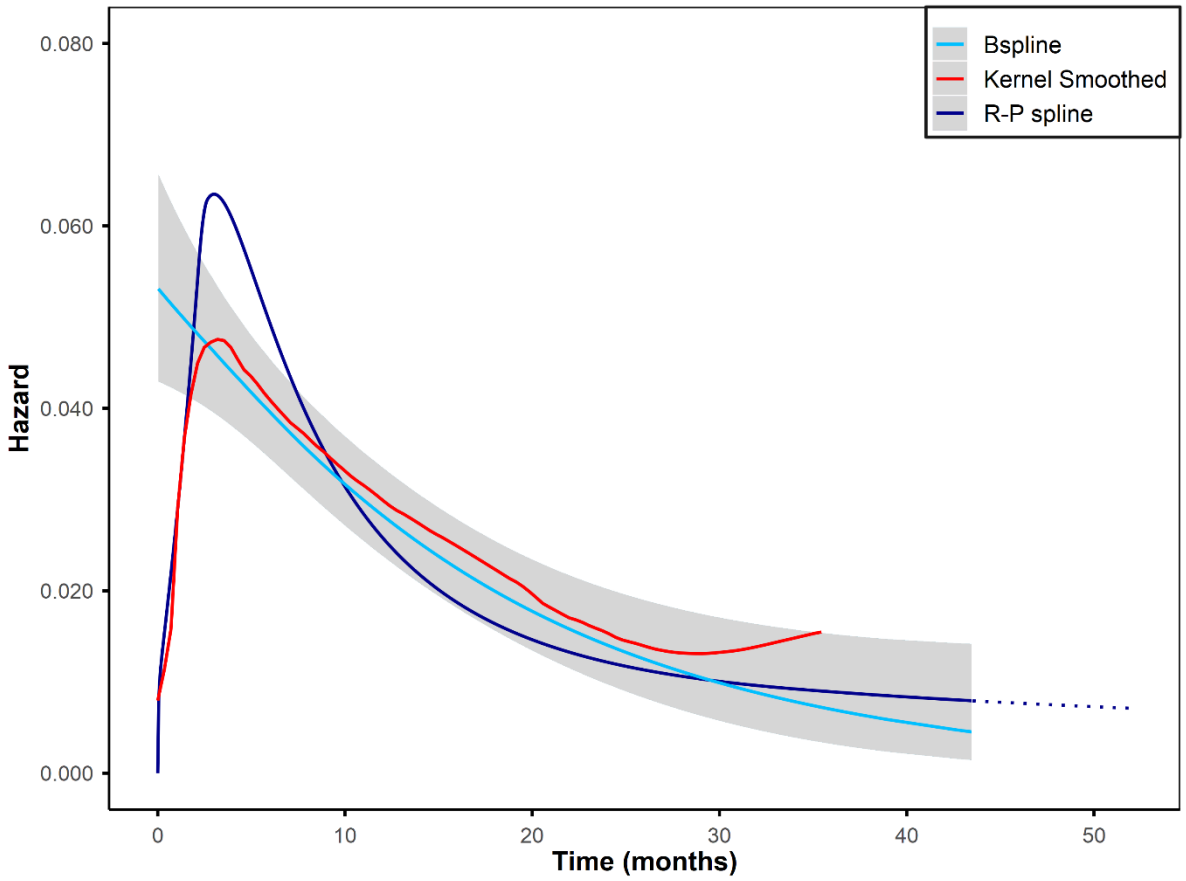


Figure 9. CheckMate 577 nivolumab arm smoothed hazard function

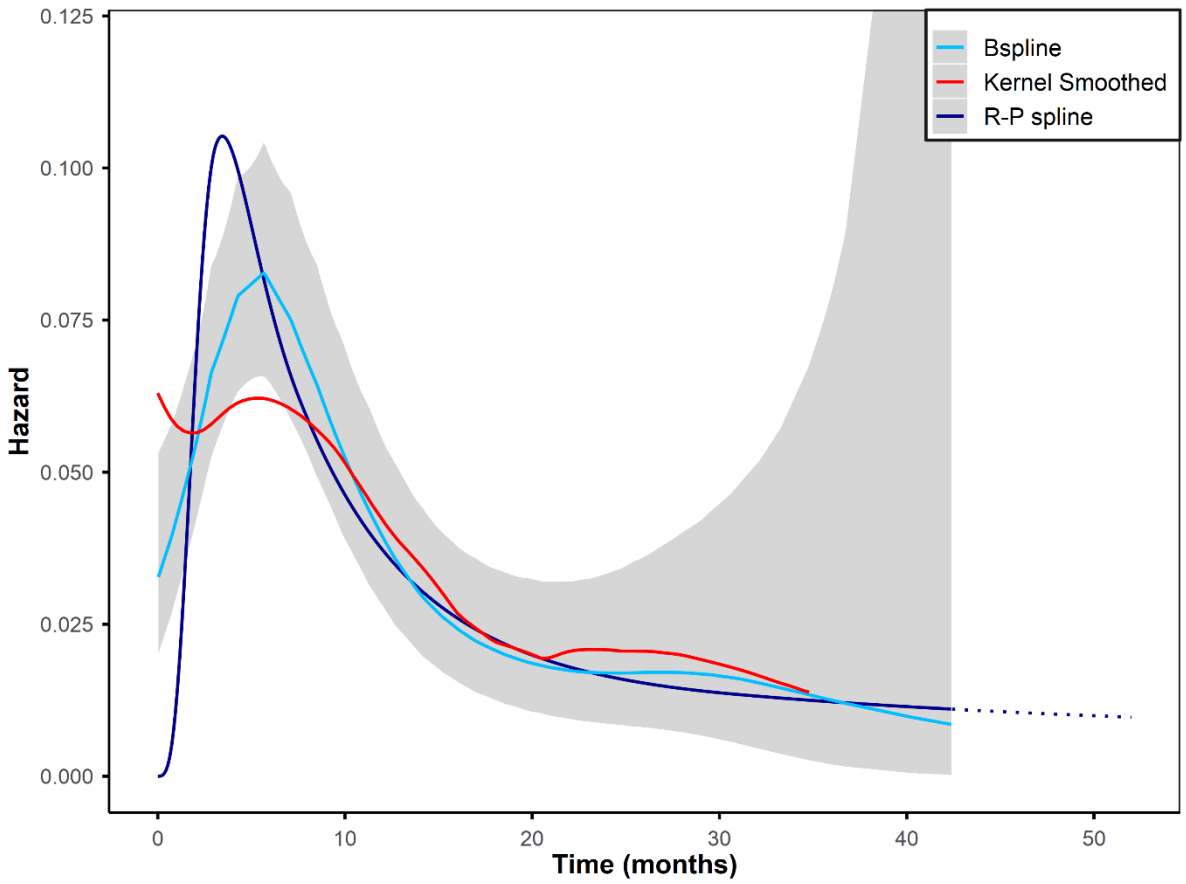


Figure 10. CheckMate 577 routine surveillance arm smoothed hazard function

B12 Clinical advice to the ERG has suggested that the standard of care for patients with recurrent OC/GEJ cancer has improved noticeably since the data reported in the Lou *et al*. paper, which were collected between 1996 and 2010. Please comment on this, and conduct additional sensitivity analysis on this, considering both improved survival and additional costs if appropriate.

The Company is not able to comment on clinical advice received by the ERG, however, our review of more recent analyses than Lou et al in comparable populations, including UK-specific publications for advanced oesophagogastric adenocarcinoma patients, suggests that any improvements in the standard of care have not translated to better post-recurrence survival outcomes (Table 7).

We note that although these two more recent publications were identified prior to submission, they were deemed less suitable to inform post-recurrence survival than Lou et al. Ford 2014[7] and Davidson 2018[8] both include gastric cancer patients, therefore the population included in Lou et al was considered more relevant to the decision problem. Data from the IKNL (Integraal Kankercentrum Nederland) study were used in scenario analyses

(Company submission B.3.8.4.6), in order to address any uncertainty pertaining to the relevance of the population described in Lou et al; the projected ICERs remained cost-effective at a WTP threshold of £30,000 (range £21,891 (log-logistic model) – £22,007 (exponential model)). The Company was not able to identify any data that would allow for further scenario analysis.

Furthermore, due to our assumption of equal post-recurrence survival in both the nivolumab and routine surveillance arms, any changes to standard of care will not impact the incremental results for cost effectiveness. Finally, clinical advice received by the Company stated that patients often decline further treatment post-recurrence, and therefore do not experience any treatment-derived improvement in survival.

Table 7. Comparison of survival outcomes from Lou et al with other sources

Study	Dates	Population	Treatment	Median OS, months (95% CI)	Median PRS, months (95% CI)
Lou 2013	1996–2010	Stage I to III OC (adenocarcinoma or SCC) who had undergone resection	Resection; 63% had received neoadjuvant CT or CRT	NR	11
Ford 2014[7]	2008–2010	Advanced oesophagogastric adenocarcinoma (OC, GEJC or GC); UK population	Had progressed on or within 6 months of 1L CT	5.2 (4.1–5.9) [docetaxel]; 3.6 (3.3–4.4) [control]	NA
Davidson 2018[8]	2009–2015	Advanced oesophagogastric adenocarcinoma (OC, GEJC or GC); UK population	≥ 1 cycle CT	11.5 (10.5–12.5)*	NA
IKNL study (data on file)[9]	2015–2016	Resected OC (adenocarcinoma or SCC) or GEJC	Resection; majority had neoadjuvant CRT	-	[redacted]
		Recurrent unresectable advanced/metastatic OC (adenocarcinoma or SCC) or GEJC	Active systemic therapy	[redacted]	NA

* from date of diagnosis of advanced disease
† OS for all patients who underwent resection i.e. includes disease free patients
§ irrespective of post-recurrence therapy
1L: first-line; CI: confidence interval; CRT: chemoradiotherapy; CT: chemotherapy; DFS: disease-free survival; GC: gastric cancer; GEJC: gastroesophageal junction cancer; IKNL: Integraal Kankercentrum Nederland; NA: not applicable; NR: not reported; OC: oesophageal cancer; OS: overall survival; PRS: post-recurrence survival; RFS: recurrence-free survival; SCC: squamous cell carcinoma

B13 CS, Section B2.12.4.2 states, "*In the UK, neoadjuvant CRT is highly variable, thus whilst the placebo arm of CheckMate 577 reflects SOC in the treatment of OC/GEJ cancer, it may not entirely reflect the UK treatment paradigm*." Appendix M, Section 3.1.1 states, "*the placebo arm is considered to represent the routine surveillance comparator in the cost-effectiveness mode*l." Please present SOC Kaplan-Meier survival functions of DFS for the UK patients alone and for the non-UK patients, comment on any difference

between them, and the impact on cost-effectiveness if they are materially different.

The Company is unable to provide the requested Kaplan-Meier survival functions, as there were [redacted] UK patients in CheckMate 577 and all were assigned to the nivolumab arm. However, we are confident that baseline characteristics of the CheckMate 577 population are generally representative of the UK OC/GEJ cancer population. Unlike many trials in the gastroesophageal cancer setting, the majority of patients were located in Europe (38%) or the US/Canada (32%), and patients of Asian ethnicity were in the minority (15% patients). In line with this demographic data, 71% patients enrolled had adenocarcinoma, which is reflective of the type of OC most common in the UK (age-standardised estimated incidence in 2018 of 4.5 per 100,000 person years for adenocarcinoma compared with 2.1 for squamous cell carcinoma[10]). Neoadjuvant CRT prior to resection is a current treatment option in the UK, and although not all UK patients are currently receiving neoadjuvant CRT, the survival outcomes from the trial are generalisable to a UK population and we do not anticipate any impact on cost-effectiveness.

B14. Appendix M, Page 5, Paragraph 3 states, "*splines with one or two knots provided the most accurate predictions for the extrapolated period*." Accuracy is a measure of the extent to which an estimate of a response is equivalent to the true value. The true survival function is not known after recurrence of disease in this patient population. Please clarify in what sense the models provide the most accurate predictions during the extrapolation period.

The use of the word "accurate" by the Company in this context related to the adherence of the model to the survival predicted by clinical opinion. The Company are happy that the sentence cited by the ERG could be rewritten to read, "*splines with one or two knots provided the most* ***likely clinical*** *predictions for the extrapolated period"* and this would not change the intended meaning.

B15. Appendix M, Section 4.1: The discussion on spline models in Section 4.1.6 states that, "*The high means can be constrained by general population mortality within a cost-effectiveness model and so are not reason to disregard models alone and would not result in infinite survival*."

Please clarify the relevance of assessing the clinical plausibility of the extrapolations from *any* of the survival models other than mixture models given that they too could be constrained by general population mortality.

As described in the answers to questions B2 and B3, the Company did not feel that it was helpful to disregard any fits to either observed or predicted disease trajectory immediately after 3 years, as this would not allow for proper evaluation of whether this modelling assumption would impact upon results. With particular relevance to this section in Appendix M and the discussion of spline models, generation of infinite means often raises concerns about the plausibility of the model. The Company chose to include detail on the general population constraints that are implemented in the model to clarify that using this model would not result in unrealistic predictions of disease trajectory. The Company is aware that while the appendices are predominantly reviewed by the ERG, these are also available upon request by any members of the public and so included this clarification to help avoid unnecessary confusion.

B16. Appendix M, Section 4.1.1: Please provide results of a re-analysis of DFS allowing for interval censored data

As requested, the Company performed post hoc sensitivity analyses regarding the comparison of DFS between nivolumab and placebo arm.

A sensitivity analysis of DFS using interval censoring approach was performed. The time period between time1 and time2 is the interval during which the DFS event (primary definition) occurred. Time1 and time2 of interval censoring are defined as:

- For patients who had DFS event per DFS primary definition (n = 396), time1 is the time from randomisation date to the last tumour assessment date prior to DFS event date, and time2 is time from randomisation date to the DFS event date.
- For patients who were censored for DFS per DFS primary definition (n = 398), time1 is time from randomisation date to the DFS censoring date, and time2 is infinite.

This was used to fit the proportional hazards regression models using interval censoring approach. The treatment arm is the only covariate in the model. The use of interval censoring made minimal difference to the HR of DFS comparing nivolumab and placebo ([redacted] with chi square p value = [redacted]).

B17. Appendix M, Section 4.1.5: Please clarify the inputs to the mixture models defined as “distribution/distribution” and how these relate to the survival function associated with the excess disease-related risk.

The inputs for the mixture models described in Appendix M, Section 4.1.5 are detailed in Table 8 and Table 9 for nivolumab and routine surveillance respectively.

Both components relate to the excess risk in all cases, but these are for unidentified subpopulations within the overall cohort and are then collated as follows:

$$S(t) = S\_LT(t) * (pi * S\_1(t) + (1-pi)*S\_2(t))$$

Where;

- S_LT is survival per lifetable
- S_1 is survival function due to excess hazard of one part of the mixture
- S_2 is survival function due to excess hazard of other part of the mixture
- pi is mixture fraction

Table 8: Mixture parametric parameters for DFS in the nivolumab arm

Distributions	**Additional distribution**		**Weibull distribution**		**Rho**
	Rate, Shape	**Scale, Rate**	**Shape**	**Scale**	
Exponential/Weibull	0.091015		1.224728	461.9204	0.44706
Weibull/Weibull	2.60152	3.892255	1.070792	48.70246	0.804817
Gamma/Weibull	7.567947	2.209581	1.019632	48.06159	0.821881
Gompertz/Weibull	0.079672	0.112646	1.178412	74.5509	0.657056
Loglogistic/Weibull	105.5157	2.795753	0.914416	39.65798	0.921687

Table 9: Mixture parametric parameters for DFS in the routine surveillance arm

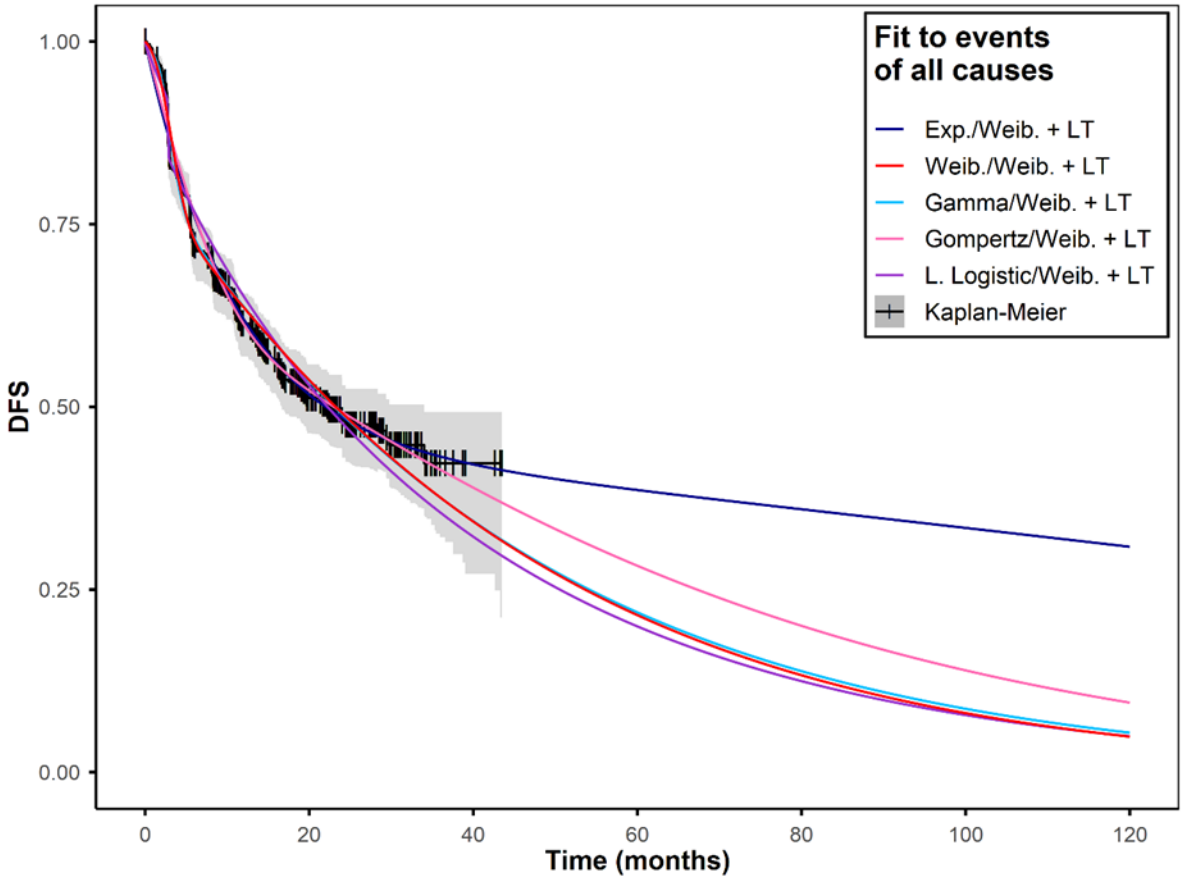
Distributions	**Additional distribution**		**Weibull distribution**		**Rho**
	Rate, Shape, Log mean	**Scale, Rate, Log SD**	**Shape**	**Scale**	
Exponential/Weibull	0.102799		4.718945	71.4204	0.306203
Weibull/ Weibull	2.011805	5.939125	1.399596	52.45932	0.534559
Gamma/ Weibull	3.316545	0.607779	1.446116	55.47437	0.514925
Gompertz/ Weibull	0.687996	0.027738	1.092274	33.97714	0.722587
Loglogistic/ Weibull	2.636424	5.053802	1.544671	63.03224	0.465039
Log-normal/Weibull	1.610034	0.624278	1.33922	65.79263	0.486349

B18. Appendix M, Section 4.1.5: It is stated that, "*none of the mixture parametric models provide a good fit to the data*". In fact, based on BIC, the log-logistic/Weibull model provides a better fit to the observed nivolumab data than any of the other models considered. Please clarify why the log-

logistic/Weibull mixture model is said to not provide a good fit to the observed data and why the predictions are considered not to be clinically valid.

The log-logistic/Weibull mixture model can be seen in Appendix M, Section 4.1.5 and in Figure 11. While the BIC does indicate that this model fits the best of the available models, it clearly does not visually adhere to the observed data at any point, appearing outside the CI of the Kaplan-Meier data multiple times. TSD14 recommends that model selection should comprise visual inspection, assessment of the log-cumulative hazard plots, as well as using the AIC/BIC tests. They also note that, *"An important limitation that is applicable to…AIC/BIC tests is that each are based only upon the relative fit of parametric models to the observed data"*. It also states that the AIC/BIC should not be the sole basis for any parametric model selection and throughout warns against relying on these statistics for model selection alone.

In addition, the log-logistic/Weibull model predicts that the mean DFS is 36.15 months and, visually, the model indicates that by 60 months, less than 25% of patients would still be disease free and that this would continue over 10 years until this proportion is near zero. This is at odds with what would be expected without active treatment (i.e. routine surveillance); for example, Kukar et al report a ~30% recurrence-free survival, with an extended plateau up to 84 months, in patients with oesophageal adenocarcinoma who had incomplete pathological response following neoadjuvant CRT and resection.[11] Similarly, the CheckMate 577 routine surveillance arm also displays a plateau. The existence of a proportion of patients who enter long-term remission was confirmed by clinical advice received by the Company. Therefore, aside from the extremely poor visual adherence to the observed data, selection of the log-logistic/Weibull model would imply that treatment with nivolumab resulted in substantially worse outcomes than for patients who did not receive any active treatment, which does not correspond to the data available and is unlikely to be clinically plausible.



Fit Name	AIC	BIC	Parameters for excess hazard	All-cause mean (Months)
Exp./Weib. + LT	2095.18	2175.05	rho: 0.447	95.77 (28.14, 127.06)
Weib./Weib. + LT	2063.23	2147.38	rho: 0.805	36.75 (29.96, 119.58)
Gamma/Weib. + LT	2056.45	2140.59	rho: 0.822	37.48 (31.04, 123.48)
Gompertz/Weib. + LT	2094.33	2178.48	rho: 0.657	44.54 (30.14, 128.80)
L. Logistic/Weib. + LT	1972.00	2056.15	rho: 0.922	36.15 (30.32, 65.21)
L. Norm./Weib. + LT	N/A	N/A	-	N/A

Figure 11: Mixture parametric models fit to nivolumab DFS

B19. Appendix M, Section 4.1.7 and 4.1.8: The algorithm states that "KM data applied to initial portion of curve with pooled hazard defining DFS outcomes thereafter chosen as the base case" while the next section states that "log-normal splines with one or two knots as the base case was considered the most appropriate approach". Please clarify which is the base case.

This was an editing error in section 4.1.7 Figure 18. We confirm that the base case analysis uses log-normal splines with one knot.

B20. Appendix M, Section 4.2:

a) Please provide evidence from CheckMate 577 to support the modelling assumption that post recurrence survival is the same for patients treated with nivolumab and routine surveillance.

At present, we are unable to provide evidence from CheckMate 577 to support this assumption, as OS data are only available to a small group of the BMS project team working on the Type II procedure for OPDIVO as treatment adjuvant for Oesophageal or Gastro-oesophageal Junction Cancer (supported by Study CA209577). However, we consider the assumption that post recurrence survival is the same for patients treated with nivolumab and routine surveillance to be conservative, as it does not reflect any potential residual post-recurrence survival benefit of nivolumab. This is indirectly supported by two observations from the CheckMate 577 data currently available. Firstly, the DFS hazard for nivolumab is consistently lower than the hazard for routine surveillance, even after treatment cessation. Secondly, the PFS2 data favoured nivolumab over placebo, indicating that patients may receive a clinical benefit from nivolumab after recurrence.

b) Please clarify the impact of patient characteristics on post recurrence survival and whether the joint distribution of patient characteristics in Lou *et al.* is comparable to the joint distribution of the same patient characteristics in the UK population

The baseline characteristics relevant to the decision problem reported by Lou et al are age, sex, histology, pathologic stage and location of recurrence; however, the information provided by Lou et al is not sufficient to assess the joint distribution. A naïve comparison of each characteristic alone suggests that the population considered in Lou et al is comparable to the UK population for sex and age, but fewer stage III patients were included (Table 10); furthermore, as discussed in Company submission B.3.8.4.6, we would like to emphasise the sparsity of available alternative data relevant to this indication.

Table 10. Comparison of baseline characteristics in Lou et al to UK OC population

Characteristic	Lou et al	UK OC population	UK data source
Sex	77.4% male 22.6% female	Of those patients who receive RCT and surgical resection, 68.6% of patients are male	National Cancer Registration & Analysis Service and Cancer Research UK 2017[12]

Characteristic	Lou et al	UK OC population	UK data source
Age, mean (SD)	63 (10.7)	Of those patients who receive RCT and surgical resection, 42.9% of patients are aged 60-69 years and 73.9% are aged <70 years	National Cancer Registration & Analysis Service and Cancer Research UK 2017[12]
Histologic type	17.9% SCC, 82.1% AC	Age-standardised estimated incidence in 2018 of 4.5 per 100,000 person years for adenocarcinoma compared with 2.1 for SCC.	Arnold et al 2020[13]*
Pathologic stage	13.4% 0 31.9% I 29.9% II 24.8% III	 9.4% I 29.9% II 60.7% III†	National Cancer Registration & Analysis Service and Cancer Research UK 2017[12]
Recurrence	55.4% distant 27.8% locoregional 16.8% both	44% distant 23% locoregional 33% both	Knight et al 2017[14]
*Available data are for all OC † Calculated as % of patients diagnosed at stages I–III i.e. those relevant to the decision problem			

c) Please provide a plot of the smoothed empirical hazard function corresponding to the Lou et al data

The smoothed empirical hazard function corresponding to the Lou et al data is presented in Figure 12. The smoothed hazard shows a broadly monotonically decreasing hazard.

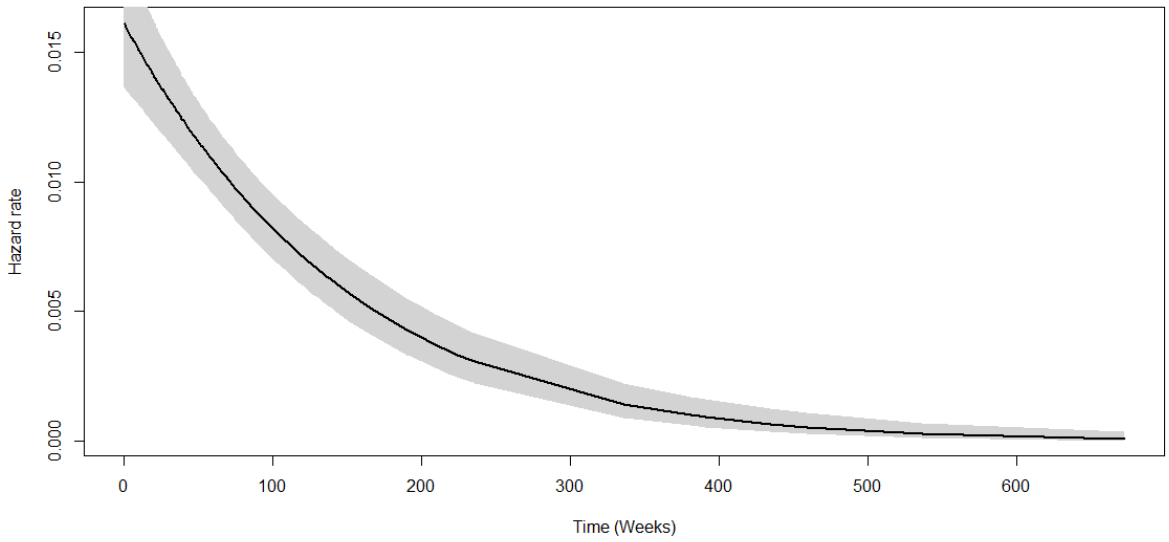


Figure 12. Smoothed empirical hazard function for post recurrence survival data from Lou et al

d) For a Gompertz distribution to provide a valid survival function the shape and scale parameters must both be positive; the resulting hazard function is monotonically increasing. Post-hoc constraints are possible, although this means that the models presented in Figure 21 do not represent the survival function used in the economic model

Please see our response to question B21 regarding the Company position on models with negative parameters.

B21. Please provide results of valid survival models that are representative of the empirical hazard function, adjusted for general population mortality if appropriate, and include 95% confidence intervals for the base case model.

A “proper” Gompertz model would be where the CDF covers a range 0-1, but a negative parameter does not render the model “invalid” as negative parameter Gompertz models are recognised. Having a “non-proper” survival distribution indicates that not all of the population is at risk of the event in question at all times, which is appropriate given that death could occur in this population from other means than disease; it does not indicate immortality.

If the process itself does not conform to a proper distribution, as the hazard disappears as time increases, then other processes must be considered to cause mortality among the survivors. The other distribution may not be identifiable in the original data, because it is left-

skewed and does not contribute much to the observed period. It may also result in a bimodal distribution, which none of the basic distributions allow.

The Company notes that of all parametric models fitted to this data set, the Gompertz model was considered to be the best fitting model after following advice in TSD14 relating to all the considerations and judgements required for model selection. However, all other models fit are provided in the CEM and are examined in survival analysis in Section B3.8.4.5.

B22. Appendix M, Section 3.4: Please provide a reference to support the assertion that information criterion cannot be used to compare non-nested models

Both the BIC and AIC are defined requiring that the true model be among the set. Burnham and Anderson[15] make clear that the TIC, which does not require this to be true, validates that the AIC can distinguish “good” models that do not contain the true model asymptotically; however, both techniques do require the candidates to be of good quality and require scrutiny in candidate selection.

This criterion is not necessarily met; whilst comparison of non-nested models is possible, it is at assumed that the model forms allow for nesting. An example is the Weibull distribution where the exponential and Raleigh are special cases with a fixed shape parameter. These happen to be two named distributions, but it is conceivable to nominate a large but finite set of distributions across the domain of the Weibull shape parameter and include all these distributions as candidate models. Should all these candidates be proposed, one has in effect reduced the degrees of freedom penalty in the AIC and BIC for the Weibull to 1 by introducing a large number of non-nested candidate parameters (each model has a different scale parameter, conditional upon shape “a”). In some cases, this would be sufficient to result in selection of one of these candidates over a two-parameter candidate of a more appropriate model type. Thus, it can be seen that the specification of non-nested models introduces an analyst degree of freedom which is not accounted for in information criteria.

B23. Appendix M, Section 3.2: Randomisation was stratified by histology (squamous vs adenocarcinoma), pathologic lymph node status (positive [≥

ypN1] vs negative [ypN0]) and tumour cell PD-L1 status (≥ 1% vs < 1% or indeterminate/non-evaluable). These are presumed to be prognostic factors.

a) Please confirm why the distributions of pathologic lymph node status and tumour cell PD-L status were not compared between Lou et al and CheckMate 577 in addition to sex, age and histology.

It is not possible to provide a comparison between pathologic lymph node status and tumour cell PD-L1 status in CheckMate 577 and Lou et al, as Lou et al did not report these factors. However, we would note that we are not aware of any evidence that they are predictive of PRS. Our review of the published literature (see also our response to B23b) identified one prospective database study of 379 patients from the Netherlands who had undergone resection with curative intent for OC, which found that characteristics of the primary tumour, including histological type and pTN stage, did not independently influence post-recurrence survival.[16]

b) Please confirm that there are no other baseline characteristics that are known to, or may affect, post-recurrence survival.

A review of the literature regarding baseline characteristics that may affect post-recurrence survival has been undertaken. No studies were found that identified any baseline characteristic as an independent predictor of post-recurrence survival. We would further note that in the studies detailed in our response to question B12, the 95% CIs around the median PRS are small, suggesting that heterogeneity within those populations is not reflected in the PRS outcome.

B24. The ERG presume half-cycle correction was not applied within the model due to the weekly time cycle. Please confirm if this is correct

This is correct; a half cycle correction was deemed unnecessary with such a short cycle length. This is also likely to be a conservative assumption, as such a correction would lead to patients entering the recurred state sooner and dying post recurrence more quickly, which would have a greater impact on decreasing the efficacy in the routine surveillance arm. Treatment costs would remain relatively unaffected as the majority of these are accrued in the first year. It is not anticipated that important clinical events, and associated cost and utility implications, would not be represented and captured with a cycle length of one week and therefore there is no reason to implement a half cycle correction.

B25. Please provide further details relating to the time dependent model and the static model used to estimate the probability that a disease-free survival event was death. Please provide the R script used to calculate the probabilities entered into the model.

The probability that a DFS event was death was estimated using simple logistic models; numerous models were evaluated. Specifically, the covariates that were evaluated are as follows:

- DFS time
- Square root, square, cube and log of DFS time
- DFS time + square root, square, cube and log of DFS time
- DFS time + square root of DFS time + square of DFS time
- DFS time + log of DFS time + square of DFS time
- DFS time + square root of DFS time + log of DFS time

where the DFS time is of only those who had DFS events that were death.
This assessment was done with the base stats package in R (generalised linear model), The script used to calculate these probabilities has been included alongside responses to the clarification questions (Appendix F: Code Appendices_B25).

B26. Please clarify why the utility from Szende *et al*. were deemed preferable to those from Ara and Brazier (Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010;13:509-18), particularly when the age bands are coarse, as noted in utilities remaining constant between the ages of 55 and 74 years. Please provide ICERs using the Ara and Brazier estimates.

Szende et al was chosen as it is more recent than the Ara and Brazier publication, although the Company would consider them comparable. The utilities reported between age 55 and 74 years were sourced from Szende et al, and the Company is confident that they were entered into the CEM correctly, as follows:

- Age 55-64: 0.799
- Ages 65-74: 0.779

A scenario was examined using the formula reported by Ara and Brazier:

*GP EQ-5D = 0.9508566 + 0.0212126*male - 0.0002587*age - 0.0000332*age^2*

The results are shown in Table 11: Scenario analysis results: Ara and Brazier utility (with PAS, discounted) and remain consistent with the base case.

Table 11: Scenario analysis results: Ara and Brazier utility (with PAS, discounted)

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life Years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£22,280
ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life-year			

B27. The ERG notes that when a parametric distribution is used for DFS it appears that the start of the long-term disease-free state is fixed at 3 years regardless of the values entered into 'intRemCycleTrt' and 'intRemCycleCtrl'. Please clarify whether this represents an error in the implementation of the model. Please amend the model to allow different values for transition to the long-term disease-free state.

The submitted model included parametric models that were inadvertently scaled such that the time component of the models was in months rather than in weeks (as the overall model is). As such, all parametric models assumed that the input time parameter was a month rather than week and so these models gave the same result regardless of where the start of the long-term disease-free state was stipulated.

The corrected model submitted with the responses to these questions contains the same parametric models but with appropriate scaling. In addition, scenarios showing the impact of parametric model selection are shown in the response to question B2 for clarity.

B28. Figure 24 appears to indicate that a small proportion of patients received nivolumab treatment for longer than 12 months. It is anticipated that the additional treatment would be associated with improved outcomes. Please clarify why these additional costs incurred after 12 months were omitted from the model and perform a sensitivity analysis with these costs included.

The Company chose to apply a 12-month limit in the model to those receiving treatment as this is in line with the treatment licence indication. However, as highlighted in the question, there were a small number of patients who stayed on treatment past the 12-month limit. Specifically, the Kaplan-Meier time on treatment curve plateaus at 61 weeks, where the

proportion remaining on treatment is 0.0065. A scenario analysis has been performed (Table 12) where the limit has been changed to 63 weeks. Nivolumab remains cost-effective and the decision is not changed from the base case analysis.

Table 12: Scenario analysis results: nivolumab treatment costs up to 63 weeks for those on treatment (with PAS, discounted)

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£23,052
ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life-year			

B29. Please confirm whether the deterministic sensitivity analyses in the company submission related to varying health state costs have reported the correct results. The ERG produced different results for this scenario, but matched the remainder.

During construction of the DSA, two parameters were inadvertently linked (including the health state costs), which is why these analyses were not able to be replicated by the ERG. This has now been corrected in the updated CEM and the results of the DSA can be seen in the response to B1 (Figure 2)

B30. Please clarify whether there were observed treatment-related adverse events that were of high costs or were debilitating to a patient that were omitted from the model due to having fewer than 3 occurrences in CheckMate 577

Table 13 shows the treatment-related adverse events (TRAEs), grade 3 and above, that occurred in both arms of the CheckMate 577 trial. Those currently included in the model are **emboldened** in the table and represent those occurring in three or more patients in either arm. There are two TRAEs in the table that meet this criteria but were excluded from the model; these are indicated in *italics* in the table. These two TRAEs – increased amylase and lipase – were excluded because they do not indicate or necessarily require any treatment that could be costed for.

There are a number of TRAEs that were omitted from the model due to having fewer than three occurrences in both arms; this was a simplifying assumption to avoid adding

unnecessary complexity to the CEM that would not aid decision making. In addition, treatment related toxicity was addressed in the model with the addition of a treatment related disutility applied only to the nivolumab arm. Therefore, inclusion of any further disutility relating to TRAEs would be considered double counting. Costs attributed to such small proportions of each arm would be expected to be negligible, even if individually high, and so would not be expected to impact cost-effectiveness greatly or change the direction of the decision.

Table 13: Treatment-related adverse events grade 3 and above in CheckMate 577

Treatment-related adverse events grade 3+ (excl. events > 100 days after treatment cessation)	Number of patients who experienced the adverse event							
	Nivolumab				Routine surveillance			
	Grade 3	Grade 4	Grade 5	Total	Grade 3	Grade 4	Grade 5	Total
Acoustic neuritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Amylase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Autoimmune arthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Autoimmune hepatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Autoimmune thyroiditis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood bilirubin increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cholangitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disseminated intravascular coagulation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diverticulitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment-related adverse events grade 3+ (excl. events > 100 days after treatment cessation)	Number of patients who experienced the adverse event							
	Nivolumab				Routine surveillance			
	Grade 3	Grade 4	Grade 5	Total	Grade 3	Grade 4	Grade 5	Total
Dyspnoea	[redacted]							
Dyspnoea exertional	[redacted]							
Encephalopathy	[redacted]							
Enterocutaneous fistula	[redacted]							
Fatigue	[redacted]							
Febrile neutropenia	[redacted]							
Guillain-Barre syndrome	[redacted]							
Hepatic function abnormal	[redacted]							
Hepatitis	[redacted]							
Herpes zoster	[redacted]							
Hyperglycaemia	[redacted]							
Hyperkalaemia	[redacted]							
Hypertension	[redacted]							
Hypokalaemia	[redacted]							
Hyponatraemia	[redacted]							
Immune-mediated enterocolitis	[redacted]							
Immune-mediated hepatitis	[redacted]							
Immune-mediated pneumonitis	[redacted]							
Influenza like illness	[redacted]							
Interstitial lung disease	[redacted]							
Lipase increased	[redacted]							
Liver disorder	[redacted]							
Lymphocyte count decreased	[redacted]							
Lymphopenia	[redacted]							
Mucosal inflammation	[redacted]							

Treatment-related adverse events grade 3+ (excl. events > 100 days after treatment cessation)	Number of patients who experienced the adverse event							
	Nivolumab				Routine surveillance			
	Grade 3	Grade 4	Grade 5	Total	Grade 3	Grade 4	Grade 5	Total
Muscle necrosis	[redacted]							
Musculoskeletal stiffness	[redacted]							
Myocarditis	[redacted]							
Neuropathy peripheral	[redacted]							
Pancreatitis	[redacted]							
Platelet count decreased	[redacted]							
Pneumonia	[redacted]							
Pneumonitis	[redacted]							
Pneumothorax	[redacted]							
Presyncope	[redacted]							
Pruritus	[redacted]							
Psoriasis	[redacted]							
Rash	[redacted]							
Rash macular	[redacted]							
Respiratory failure	[redacted]							
Seizure	[redacted]							
Sepsis	[redacted]							
Syncope	[redacted]							
Thyroiditis	[redacted]							
Type 1 diabetes mellitus	[redacted]							
Venous thrombosis	[redacted]							
Vomiting	[redacted]							
White blood cell count decreased	[redacted]							

B31. Please clarify whether the utility decrement of 0.007 associated with nivolumab treatment has been calculated as the difference in the on-treatment means provided in Table 32. Clarify why, using similar logic, it was assumed that there was no difference in off-treatment utility. Please also clarify whether all of the adverse events contained in Table 33 are likely to be prevalent when the EQ-5D questionnaire was completed. If some have resolved between questionnaire please clarify whether the 0.007 value underestimates the utility decrement associated with nivolumab treatment

The utility decrement of 0.007 associated with nivolumab treatment is the difference between the on treatment means in Table 32. No data from the off-treatment period was used because of the high amounts of missing data, as described in Section B 3.4.1.2 and shown in Figures 26 and 28 of the Company submission. As the rates of missingness were so high, any data from the off-treatment period was not considered to be useful. Means constructed from this data could have been used but would have been subject to substantial uncertainty given that at numerous time points, the proportion of missing entries is almost the same as those present. This evidence was not considered to be robust and as missingness was similar between arms, it was not thought to be related to treatment within one arm or another. In addition, there was no reason to anticipate that off-treatment utility would be different between arms.

B32. Please clarify why in Table 38 the proportional weighting adds up to 200%

Treatments are administered in pairs simultaneously, therefore 100% cost was assigned to each part of the treatment within the relevant pair. The possible combinations are:

- Cisplatin + 5-FU
- Oxaliplatin + 5-FU
- Cisplatin + capecitabine
- Oxaliplatin + capecitabine

B33. In Figure 29 the PSA indicates that nivolumab treatment could be associated with less QALYs than the control arm. Please explicitly clarify with what combinations of parameters negative QALYs are observed.

To facilitate examination of the parameters that lead to negative QALYs, the PSA has been adjusted such that if the ICER is negative, the model prints out efficacy and QALY inputs as they are being used. This change has been made in the updated model so that the ERG can

evaluate the outcomes. The output can be found in the 'PSA Output' sheet, columns EU upwards.

In all iterations of the PSA where there is a negative QALY gain associated with nivolumab, the cumulative hazard of a DFS event in the nivolumab arm is higher than that of the base case; in all of these iterations, the cumulative hazard of a DFS event in the routine surveillance arm was lower than the base case assumption. In one of the six iterations that resulted in a negative QALY gain (out of 500 iterations run) the cumulative hazard of PRS was lower than in the base case (for both arms). In addition, the cyclic probability of death on recurrence was lower than in the base for both arms in three of the six iterations; this indicates that patients were not recurring, rather than that they were experiencing death events.

Negative QALYs occur largely from the variation in the parameter inputs, whereby the hazard of a DFS event in the nivolumab arm is not just higher than in the base case, but at points higher than in the routine surveillance arm, particularly in the first few months. While this reflects potential variation in the inputs, and should be examined, it is important to frame this with respect to the likely clinical outcomes for patients and the observed evidence. The observed evidence indicates that patients who are taking nivolumab would have a lower risk of recurrence than those in the routine surveillance arm.

B34. Please clarify the HRG codes used to estimate the cost of MRI and CT imaging.

The NHS reference cost codes used were:

- MRI: RD01A-MRI without contrast+RD02A-MRI with contrast+RD03Z-MRI with pre and post contrast
- CT: RD20A-CT without contrast+ RD21A with contrast+ RD22Z-CT pre and post contrast

B35. Please comment and on and justify why the economic reviews reported in Appendices G-I all apply a cut-off date of 2019? Were these purely for the update searches? If so, please provide the eligibility criteria for the original economic, cost and utility reviews.

The economic reviews were conducted in two phases. In phase I (September 2019) the first literature search was done, in which peer-reviewed publications for OC and GEJC studies were searched in literature databases. In phase II (November 2020), an update of this

literature search was conducted. Therefore, a cut-off date of 2019 was added to the search. This phase was further extended with an additional database search to identify economic models in gastric cancer (GC), a search for conference proceedings and a search for HTA submissions to identify any additional economic evidence for the populations of interest. The original eligibility criteria of the economic reviews are presented in Table 1.

Table 14. Eligibility criteria original economic SLRs

Patient population	• Patients with local/locoregional resectable EC or GEJC • Patients who have had surgery or radiotherapy to remove or shrink tumor and are eligible to receive any adjuvant (post-operative) therapy • Adults (≥18 years of age)		
Interventions	N/A		
Comparators	N/A		
Topic	**Economic models**	**Resource use and costs**	**Utilities/ HRQoL**
Outcomes	• (Incremental) QALYs • (Incremental) LY • Cost/QALY • Cost/LY • Cost-benefit • Net present benefit	• Frequency of resource use ○ Hospitalization/ Inpatient days ○ ER visits ○ Outpatient visits • Medication use • Cost per visits • Cost per treatment • Indirect costs • Societal costs	• Utilities • QoL questionnaire results that can be mapped to utilities (e.g. EQ-5D, SF-36, SF-6D)
Study design	• Cost-effectiveness models • Cost-utility models • Cost-benefit models • HTA reports	<u>Economic models</u> • Cost-effectiveness models • Cost-utility models • Cost-benefit models • Budget impact models <u>Observational studies</u> • Non-randomized study • Single arm study • Follow-up study • Disease registry • Patient chart analysis • Database analysis	<u>Economic models</u> • Cost-effectiveness models • Cost-utility models • Cost-benefit models • Budget impact models <u>Observational studies</u> • Non-randomized study • Single arm study • Follow-up study • Disease registry • Patient chart analysis • Database analysis
Date	• No restriction		
Language	• English language		

B36. The ERG notes that the SLR of HRQoL (Appendix H) did not identify any studies containing utility data. However, the database searches to inform this review (reported in Appendix G) were designed around the facets of oesophageal cancer AND adjuvant therapy AND HRQoL. In the absence of any studies containing utility data for this narrowly-defined population, please clarify if the company considered searching for studies containing utility data about HRQoL in the broader population of oesophageal cancer?

It was decided to not search for studies containing utility data about HRQoL in the broader oesophageal population. As the population in the economic model concerned patients with resectable OC or GEJC, it was decided to use terms for oesophageal AND type of therapies OR condition of patients (i.e., resectable, operable) to identify HRQoL/utility data, as this would best reflect the population in the economic model population. It was believed that expanding the search to a broader population would result in HRQoL/utility data that would not match with the state of wellbeing of the population of interest and therefore could not support any decisions for selecting utility inputs for the economic model.

B37. Please provide further details on the selection process for choosing the utility source for recurred disease

As noted in the response to question B6, the availability of utility sources for both health states was extremely limited. As the recurred disease health state represented all further lines of treatment for OC/GEJ cancer, it was considered that this would broadly represent first line (1L), second line (2L) and third line (3L). As such, utility data was sought for these lines of treatment in OC/GEJ cancer. The Company has access to trial data (CheckMate 473) where utility was collected in patients with OC who had failed previous treatment (1L) and were being treated with taxane agents at 2L. This was considered the most appropriate and reliable source of evidence given that it was collected as part of a randomised controlled trial in the appropriate population who were being treated with a comparable treatment, and represents an appropriate average of all further lines of therapy.

As with the trial utility from CheckMate 577, the utility was higher than expected when compared to an age- and sex-matched population. The Company recognised that this may present problems relating to generalisability and also identified an alternative source from literature that reported the health state utility as 0.42, albeit in a gastric cancer population. To assess the impact of the assumption that the CheckMate 473 population utility represents that of the modelled recurred disease population in CheckMate 577, scenario analysis was presented in the submission (B.3.8.4.3), where the recurred disease health state utility was

varied from that reported in CheckMate 473 as the upper limit, to 0.42 as a lower limit. Given that all scenarios resulted in a reduced ICER compared to the base case, the Company is confident that the most conservative option was chosen in the base case, and in all scenarios nivolumab remains cost-effective.

B38. Please clarify whether in Figure 22 and 23 the y axis should read 'survival probability' rather than 'recurrence free probability'. If it is 'recurrence free probability' then please clarify why recurrence has been assumed to be equivalent to death. Please also supply the supplementary tables for Lou *et al*, in particular S3.

The Company has identified this as a labelling error and the ERG are correct in the assumption that the y axis should actually be labelled "Survival Probability".

The supplementary data from Lou et al consists of four figures only. These can be seen in Figure 13 to Figure 16, which are unchanged from the publication.

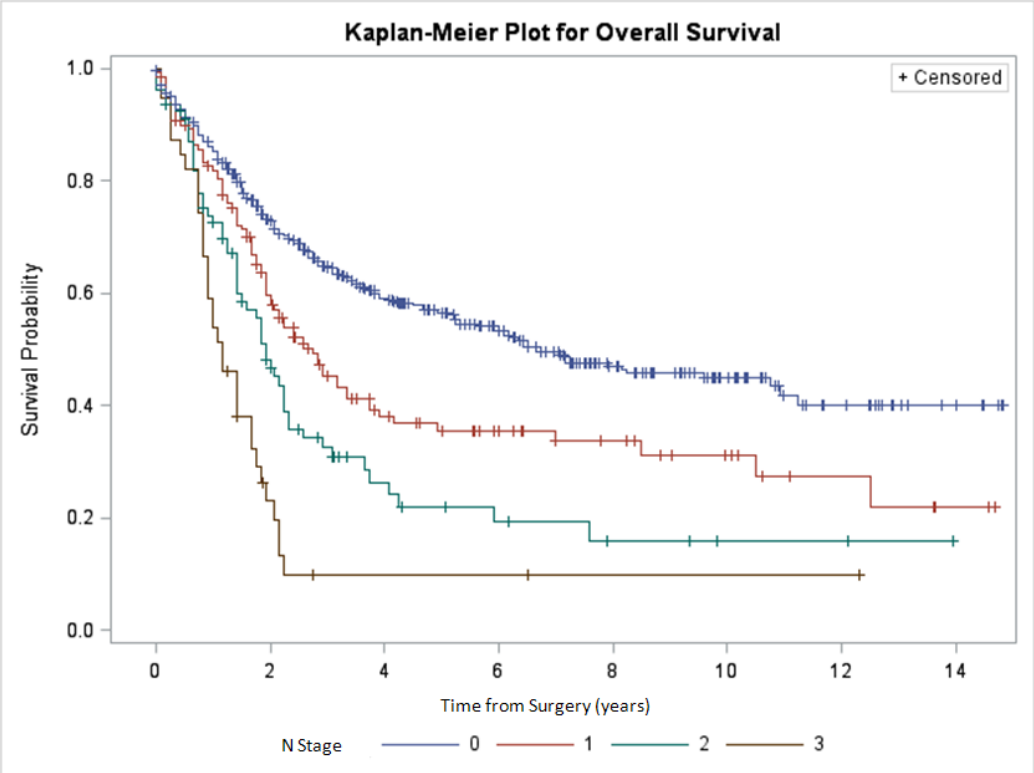


Figure S1

Figure 13: Figure S1 from Lou et al. Overall survival in patients with neoadjuvant treatment, by nodal stage (p<0.001)

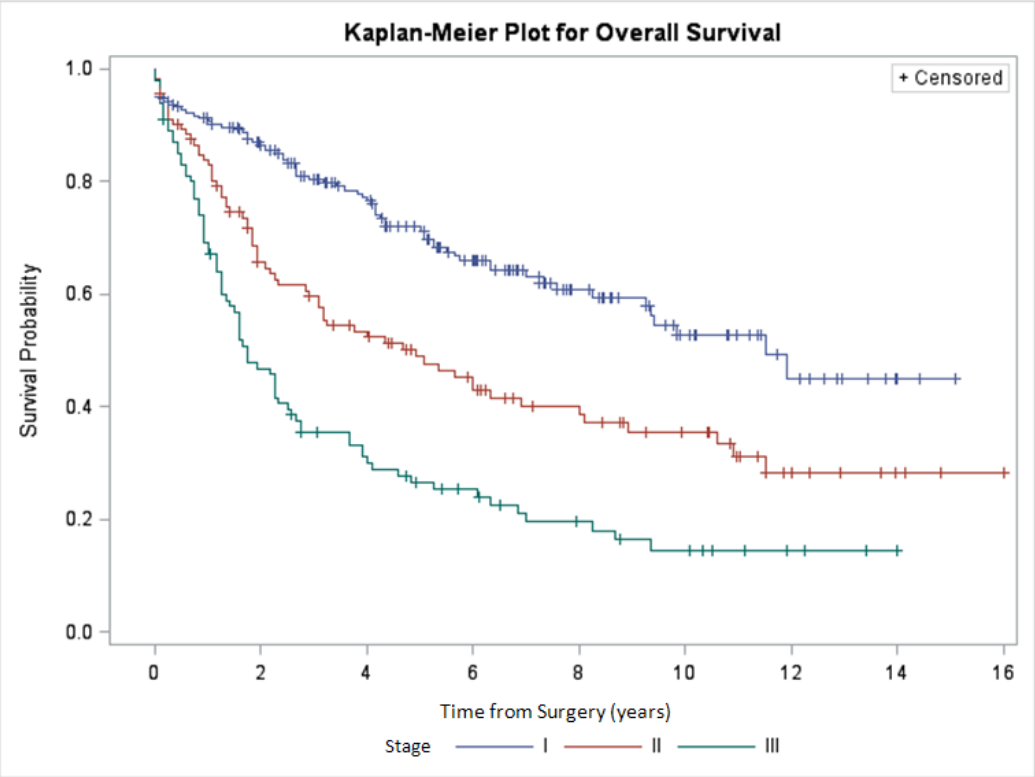


Figure S2

Figure 14: Figure S2 from Lou et al. Overall survival in patients without neoadjuvant therapy, by pathologic stage (p<0.001)

Figure S3

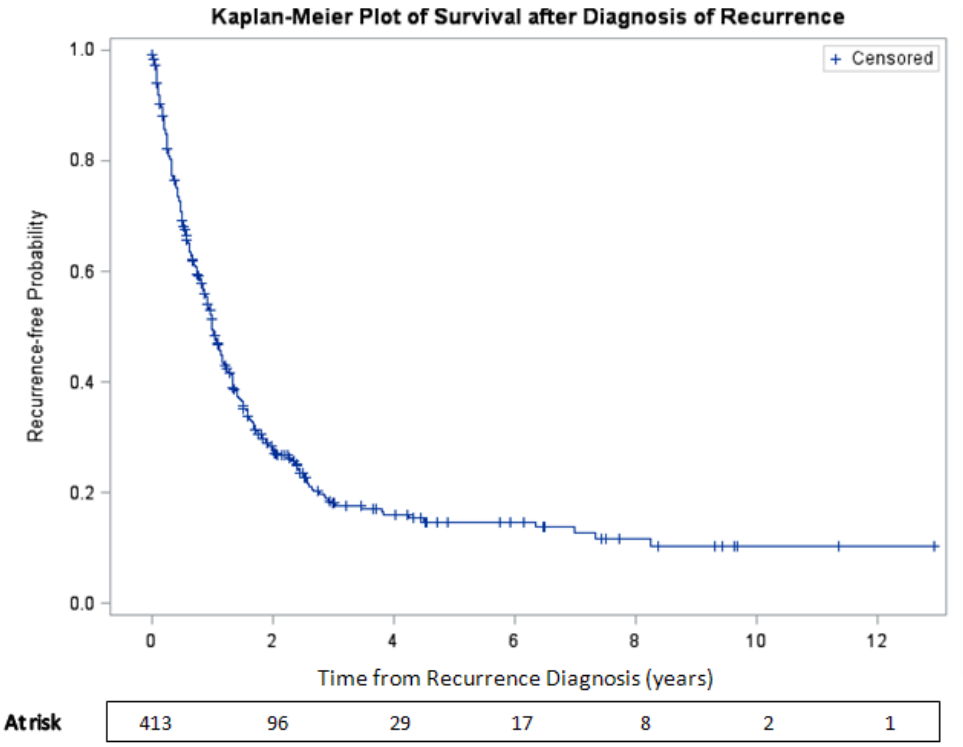


Figure 15: Figure S3 from Lou et al. Post recurrence survival (median 11 months [95% confidence interval, 11-14 months])

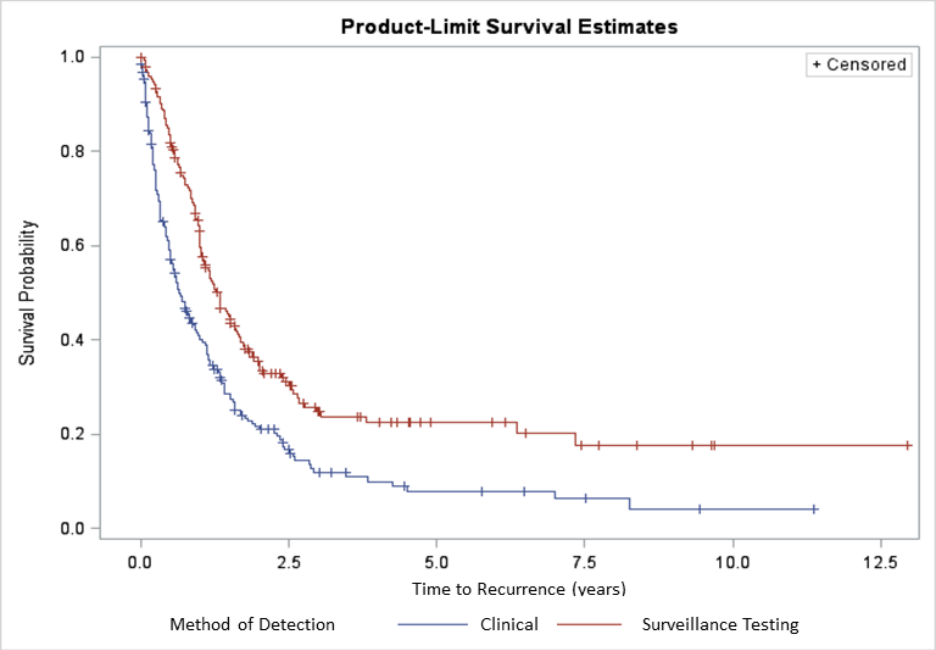


Figure 16: Figure S4 from Lou et al. Post recurrence survival by method of detection of recurrence (p<0.001)

Section C: Textual clarification and additional points

C1. Please clarify whether QALYs is the correct word in the following sentence on p 109 "Total QALYs were estimated between 3.59 months (observation alone) and 6.86 months (adjuvant CRT), which are similar to the estimates from the Company CEM (although slightly higher, as anticipated)"

QALYs is correct, but the text should have read: "Total QALYs were estimated as between 3.59 (observation alone) and 6.86 (adjuvant CRT), which are similar to the estimates from the Company CEM (although slightly higher, as anticipated)" i.e. the use of 'months' was an editing error.

<u>Additional Question from the ERG clarification call:</u>

1) **The age-dependent utility decrements tab in the economic model seems to be applying it the wrong way (either not apply when you say yes, or they are labelled wrong). Could the company please check?**

If Age Decrements is set to ‘No’, as is the current base case position, the lower value for either the age related utility or the health state utility is used; the assumption being that patients cannot have utility higher than the average for their age. If ‘Yes’ is selected, the health state utility is applied and the age-dependent utility decrement (calculated in column BI of the Treatment Trace and Control Trace worksheets) is subtracted.

The age-based utility works as intended but in the course of investigating this an error was identified in the treatment related utility calculation; instead of linking nivolumab disutility to time on treatment, it was linked to the DFS health state and a 52 week cut-off was applied. This has now been corrected to link nivolumab disutility to time on treatment. This change has been incorporated in the updated base case presented in the response to question B1.

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Appendices

Appendix name	Question(s)
ID1676 Appendix A_stratified analysis	A1, A2
ID1676 Appendix B_summary of scenarios	B1
ID1676 Appendix C_CE model	B1
ID1676 Appendix D_clinical SLR_revised	A5
ID1676 Appendix E_Code Appendices_B8	B8
ID1676 Appendix F_Code Appendices_B25	B25

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer [ID1676]

Additional clarification questions

March 2021

1. **Figure 5 and 6 show that the best fitting curve (AIC and BIC) is the Gen F curve, but this is not included in the model structure. Please could you adapt the model so that it can produce results (ICERs) with the Gen F curve?**

The adaptation has been included in the model version sent on 30.04.2021 (labelled H424 BMS Adj OC CEM 20210430 GenF). As can be seen in Table 1, inclusion of the gen F function improved the ICER versus the revised base case analysis, decreasing it from £22,766 to £17,729.

Table 1: Scenario analysis results: parametric Gen F (nivolumab and routine surveillance), (with PAS, discounted)

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£17,729
ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life-year			

2. **Please could you indicate how the response to B10 is included in the VBA code?**

In the module mod05Engine, beginning at Ln244Col8 the model calculates incident recurrences only for the intervention and then control arm. At Ln273Col9, the calculations loop through the incident recurrences for the remainder of the time horizon and calculates the survival. As such, the incident group are calculated separately to the prevalent recurred patients each cycle to allow for those occurring in the current cycle to begin at time 0 of the post recurrence survival curve.

For clarity, no model adaptation was undertaken in response to B10; this approach describes the original and current version of the model.

3. **Please could you revise Figure 9 so that the confidence intervals are fitted around the empirical hazard?**

Please see the revised figures below.

Figure 9. CheckMate 577 nivolumab arm

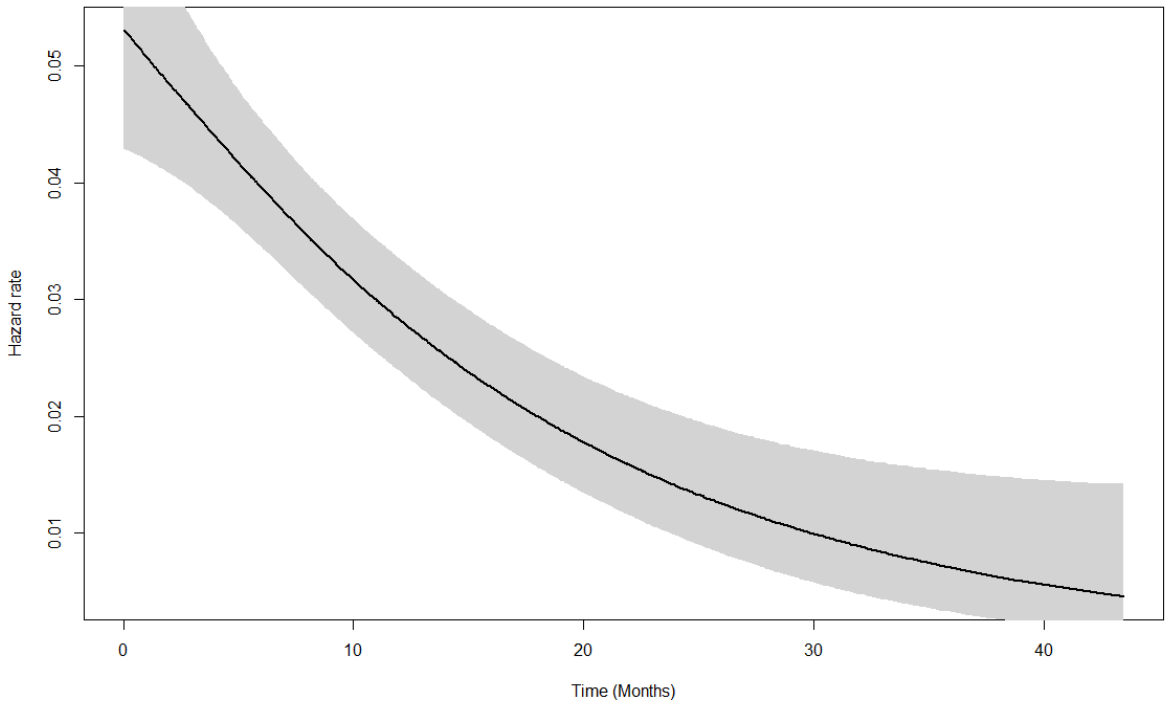
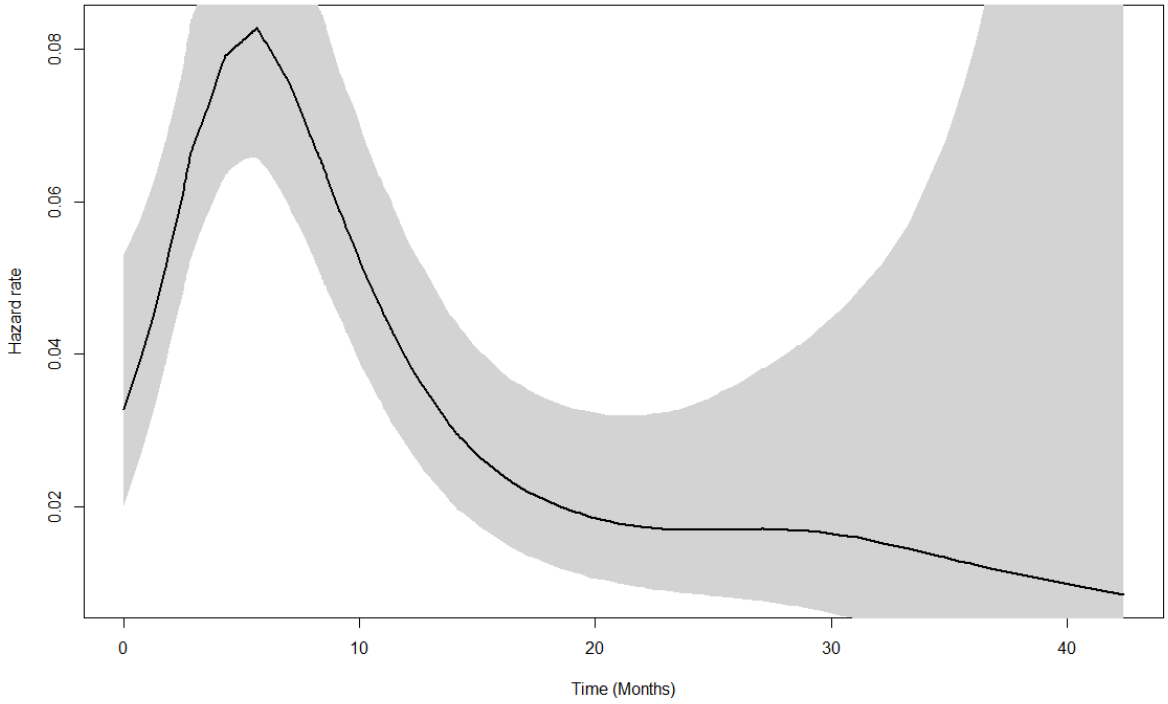


Figure 10 CheckMate 577 routine surveillance arm


Hazard rate
0.02
0.04
0.06
0.08
0
10
20
30
40
Time (Months)

NICE National Institute for Health and Care Excellence

Professional organisation submission

Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer ID1676

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NCRI-ACP-RCP-RCR**
3. Job title or position	[redacted]

4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NCRI-ACP-RCP-RCR**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	**No**

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To cure the condition
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Traditionally, improvement in overall survival is considered practice changing. A Hazard ratio of ~ 0.8 or lower for OS would be seen as practice changing in this indication (This was HR used for introduction of neo-adjuvant chemotherapy based on OE02 trial).
8. In your view, is there an unmet need for patients and	Oesophageal cancer is a cancer of unmet need. Of around 9000 cases diagnosed per year, ~20% have resectable disease (CRUK website accessed 1/3/2021:

healthcare professionals in this condition?	https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer#heading-Five). 3-year survival is only 57.4% after curative surgery (NOGCA audit 2021: https://www.nogca.org.uk/content/uploads/2021/02/REF217_NOGCA_2020-Annual-Report-FINAL-V2.0.pdf), therefore further improvement in treatments are necessary.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Treatment varies depending on histology and site of tumour. For squamous cell cancers of the oesophagus, the treatment options are 1) neo-adjuvant chemoradiotherapy followed by surgery 2) definitive chemoradiotherapy 3) preoperative chemotherapy (2 cycles cisplatin-capecitabine) followed by surgery [where surgery is considered, option 1 is preferred over option 3] For adenocarcinoma oesophagus/gastro-oesophageal junction, surgery is the mainstay of treatment. Peri-operative treatment consists of either neo-adjuvant chemoradiotherapy or peri-operative chemotherapy which is mainly used for gastro-oesophageal tumour (perioperative FLOT [5FU, Leucovorin, Oxaliplatin, Docetaxel] combination is favoured over ECX [Epirubicin, cisplatin, capecitabine] combination). Following surgery and neo-adjuvant / peri-operative treatment, patients undergo follow up (ie current there is no recommended maintenance treatment)
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines NG83

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway for management is broadly well defined. For Squamous cell cancer, there is a difference in opinion between NHS professionals whether neoadjuvant chemoradiotherapy followed by surgery or definitive chemoradiotherapy is the preferred modality, they are broadly considered to be equivalent choices (and both are discussed as options with patients) For adenocarcinoma of the gastro-oesophageal junction, surgical based treatment is considered standard of care. Both neoadjuvant chemoradiotherapy followed by surgery and peri-operative FLOT chemotherapy are considered acceptable treatment options
• What impact would the technology have on the current pathway of care?	Embracing the technology would imply adjuvant treatment with nivolumab for 1 year (2 weekly in the first 16 weeks then 4 weekly). This translates to upto 16 additional visits for immunotherapy, which will have implications for patients and NHS services. A small proportion of the patients will experience serious side-effects which will need to be managed including hospitalisation (in Checkmate 577, the incidence of Grade 3-4 toxicity was 8% in the Nivolumab arm compared to 3% in placebo, but hospitalisation rate for toxicity was not specified)
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Nivolumab is used widely in the NHS for other clinical indications, although it is not used for oesophageal cancer. Its use as adjuvant treatment for oesophageal cancer will lead to extension of treatment duration for patients with oesophageal cancer treated with curative intent.
• How does healthcare resource use differ between the technology and current care?	There will be extension in use of healthcare resources (chemotherapy services) as the technology requires administration of additional doses of treatment (Nivolumab) for upto 1 year.
• In what clinical setting should the technology be	This technology is likely to be delivered in secondary care (chemotherapy units)

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Introduction of this therapy will not require any additional equipment as Nivolumab is currently given in oncology centres for other indications. However, there will be implications on resources as this is an additional indication to be managed within oncology units. Additional test will be required to monitor for side-effects related to immunotherapy.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Checkmate 577 demonstrated a doubling of disease-free survival from 11 months to 22.4 months (HR 0.69) and a 31% reduction in recurrence or death - which was statistically significant and is considered clinically meaningful benefit.
• Do you expect the technology to increase length of life more than current care?	Although the data from Checkmate 577 is not available, the improvement in disease free survival demonstrated in the trial (HR 0.69) is likely to lead to a survival benefit
• Do you expect the technology to increase health-related quality of life more than current care?	Nivolumab is a relatively well tolerated treatment. Checkmate 577 showed that patient reported outcome based on EQ-5D-3L visual analogue scale showed broadly similar overall health status and utility index between Nivolumab treated and non-treated patients. However, it is to be noted that patients who develop recurrence after surgery is likely to experience deterioration in Quality of life due to disease status or palliative chemotherapy. As Nivolumab demonstrated a 31% reduction in risk of recurrent disease or death, it is likely that this will lead to direct benefit in terms of Quality of life.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No specific group was identified where the technology (adjuvant Nivolumab) was more or less effective as per Forrest plot analysis of subgroups.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It is not more 'difficult' as immunotherapy is administered as an intravenous infusion and is used within NHS for other indications. However, the protracted course of treatment for up to 1 year (in the trial, median duration of adjuvant immunotherapy was 10 months) will have resource implications. Patients on immunotherapy will require regular blood tests to monitor organ function including endocrine function. CT scan monitoring will be required during treatment to rule out disease progression (6-month disease free survival in the intervention arm of Checkmate 577 was 72%, ie ~30% will still progress, which will be detected mostly through CT scans.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The use of trial inclusion/exclusion criteria may be applied to start treatment, and disease progression or serious toxicity (as per trial protocol) as criteria for discontinuation. Treatment related toxicity may require treatment discontinuation. In Checkmate 577, treatment discontinuation due to toxicity was seen in ~9% of subjects. Establishing toxicity and severity would require additional testing (usually bloods, but for pneumonitis, CT scan).
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	NO
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	The technology has a favourable therapeutic window as it has demonstrated good efficacy without significant toxicity or adverse impact on quality of life. Its impact on disease-free survival (doubling of median DFS) is clinical meaningful although overall survival outcomes are awaited.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Immunotherapy has been a step-change in many cancer sites and is of emerging importance in gastro-oesophageal cancer. It is a low-toxicity regimen. There are not many interventions in oesophageal cancer that have shown a HR of 0.69 with high statistical significance and doubling of disease-free survival. However, the impact on overall survival is also required.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, Improvement in survival is a patient group with particularly poor prognosis (median disease free survival 11 months)
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Nivolumab is a very well-tolerated treatment with high grade adverse events seen in <10% of cases. Checkmate 577 show no adverse effect on patient's quality of life compared to placebo.
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, neo-adjuvant chemoradiotherapy followed by surgery is a standard option in this patient group. However, there are other standards used in the UK, including definitive chemoradiotherapy (squamous cell carcinoma), pre-operative chemotherapy and peri-operative chemoradiotherapy
• If not, how could the results be extrapolated to the UK setting?	It will be difficult to extrapolate results if alternative standards of care are used however potential ways to extrapolate results are suggested below. The clinical trial used a very specific patient group: post-surgery, R0 resection, those who had residual pathological disease post chemoradiotherapy (expected to be around 70% in case of adenocarcinoma and 50% in case of SCC). 1)Patients (SCC) who have had definitive chemoradiotherapy instead of surgery will not fulfil the surgical criteria, however if they have residual disease on re-staging endoscopy without metastatic disease on imaging (60-70%; Crosby et al, doi: 10.1016/S1470-2045(13)70136-0) could be considered equivalent group. 2) Patients who had FLOT chemotherapy (adenocarcinoma gastro-oesophageal junction) – proportion of patients with residual disease post FLOT is slightly higher (84%; Al Batran et al, doi: 10.1016/S1470-2045(16)30531-9) than those receiving chemoradiotherapy, adenocarcinoma cohort (77%; van Hagen et al, doi: 10.1056/NEJMoa1112088). Therefore, these treatment groups could be considered comparable, and the same criteria applied to select patients for the technology

	3)patients who receive pre-op chemotherapy (Cisplatin-capecitabine or ECX) – complete path response is <10%, so >90% of the patients will have residual disease, which is much higher than those receiving chemoradiotherapy, hence unlikely to be comparable groups (so result cannot be extrapolated).
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcome is overall survival. Disease-free survival was the primary end-point of the study but median overall survival and overall survival at 1, 2 and 3 years were measured as secondary end-points. The primary end-point has been reported, the secondary outcomes are awaited.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not aware of any such data
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	Comparator arm was neo-adjuvant chemoradiotherapy (for oesophageal and gastro-oesophageal junctional tumours). Currently perioperative FLOT is also considered a standard of care for gastro-oesophageal junctional tumours (but not oesophageal cancer) based on randomised phase III trial by Al-Batran et al (doi: 10.1016/S0140-6736(18)32557-1). The ESOPEC trial is currently evaluating peri-operative FLOT vs neo-adjuvant chemoradiotherapy in oesophageal cancer but last patient last follow up is not expected until June 2024 (https://www.clinicaltrials.gov/ct2/show/NCT02509286)
21. How do data on real-world experience compare with the trial data?	Real world data for this specific patient population (R0 resection with pathological residual disease on resected specimen) has not been published separately.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None specifically, however it should be noted that several categories of patients were excluded in the trial because of contra-indication to immunotherapy, including patients with known HIV/AIDS and certain auto-immune conditions.
22b. Consider whether these issues are different from issues with current care and why.	Not applicable

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Key messages
23. In up to 5 bullet points, please summarise the key messages of your submission. • Technology shows clinically relevant improvement in disease free survival which is statistically highly significant • The treatment is well tolerated with no adverse effect on Quality of life, and toxicity is acceptable • It addresses need is a particular patient population which has poor prognosis (median DFS 11 months) • Overall Survival data is not available – therefore impact on overall survival is currently unknown •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer [ID1676]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Guts UK Charity
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Guts UK are a charity that fundraises for research and provides information to help people manage diseases and conditions affecting the digestive tract, liver and pancreas. The charities mission is to • Provide expert information: Information is power! When armed with information, patients can take control of their health and make informed decisions. We do this by information leaflets sent to patients and sold to hospitals, our website and social media accounts. We also have a biannual magazine. • Raise public awareness: Our research shows that 58% of people are embarrassed to talk about their digestive condition or symptoms. 51% of people delay seeking advice for their symptoms for over 6 months. When the Guts UK roadshow comes to town, we empower people to seek help. We also fund science of digestion events to increase knowledge. Fund life-changing & life-saving research: Guts UK is the only UK charity funding research into the digestive system from top to tail. It's time the UK got to grips with guts!
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	To be fully transparent with this process Guts UK are founder members of the Less Survivable Cancers Taskforce (LSCT) and whilst Guts UK have not received any direct funding from the manufacturers in the last 12 months LSCT have. As LSCT is a separate concern no details of funding amounts can be provided as this is commercially sensitive information.

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	Guts UK has no links at all with the tobacco industry
5. How did you gather information about the experiences of patients and carers to include in your submission?	We asked the leaders of support groups for people living with oesophageal cancer and cancer of the gastro-oesophageal junction to get in touch to share their story of living with or caring for someone diagnosed with these cancers. Understandably it is difficult for people to input time into submissions with cancer, so we also searched for qualitative studies for quality of life and life experience of people diagnosed with these cancers to understand their experience. In particular quality of life in respect to living with a possibility of re-occurrence and how a treatment that could be used in this area might improve the quality of their life.
Living with the condition	
6. What is it like to live with the condition? What do carers	Oesophageal cancer and cancer between the stomach and gullet are two of six less survivable cancers, for which there are no screening tools to identify them widely used, and as early symptoms are vague, people are frequently diagnosed late, when treatment options are limited. The chance of surviving beyond five years with oesophageal cancer is approximately 15 out of 100 people diagnosed. Often patients and their families have limited time together, as many as 7 in 10 (Humphreys E et al 2020) people are

experience when caring for someone with the condition?	diagnosed at a stage (III or IV) when it has spread to the lymph nodes and has spread to nearby organs and distant body sites. These cancers are difficult to experience and lead to a poor quality of life therefore having a preventive option after treatment is potentially of great benefit. Fear, worry, or concern relating to the possibility that cancer will come back or progress is long term and can negatively affect quality of life. It can be a significant problem if people experience more side effects of treatment in oesophageal cancer and are having symptoms later post treatment such as strictures. Fear of recurrence also is an additional burden for carers who have an unmet need about managing concerns about cancer recurrence (N. Haj Mohammad, et al 2015). More than a third of carers of people with oesophageal cancer, where the treatment is curative experience moderate or high carer burden for up to three years after treatment. Carers and family members also have the added concern that the patient often has eating problems so are concerned with nutrition and can often see the weight loss quicker than the patient realises themselves. Knowing that a new treatment may help with increasing outcomes and / or reduce the likelihood of a cancer returning will certainly help in many cases.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Currently with the pandemic causing delays in diagnosis and treatment patients and cares are very concerned and know that there will be a backlog of patients coming out of the pandemic which will cause concerns as did the prospect of going to the hospital for treatment knowing they were at risk of Covid. Before Covid the diagnosis of this cancer was down to either the GP referring for endoscopy or a patient presenting at secondary care for treatment, and patients and carers all know how important diagnosing cancer early is the key to the best outcomes, this still applies now. Current treatments are a worry for many, the possible side effects can impact on QoL and wellbeing during treatment especially those with nutrition and / or poor fitness issues. Patients and Carers in the majority do understand that the treatment is needed and the only route open to them for this cancer.

8. Is there an unmet need for patients with this condition?	Yes, extending life and reducing the recurrence of the cancer once diagnosed. Early awareness and diagnosis is key.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	There is an unmet need as there is no current treatment that has shown that it can delay or prevent recurrence of cancer of the gullet or the junction between the gullet and stomach in this population. The current treatment is to watch and wait to see if it continues to grow or returns in the future, which causes anxiety, which is severe in some people, is challenging to live with and effects QoL and wellbeing. It is therefore important if there is a treatment available that can be given to improve the bodies own immune system that shows increased survival and has a role in prevention this is an important treatment to consider.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	All will consider and be concern about the possibility of extra side effects added to standard treatment. Also as we move to lift Covid restrictions there will be concerns of being at more risk due to the treatment. Research is looking at evidence suggesting cancer patients may derive less benefit from Covid vaccination due to current and new treatments.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Yes, it will be the patients diagnosed earlier with little or no malnutrition present and a reasonably level of fitness, possibly this will be the younger patients who might benefit more. Reason being is that they will be more able to cope with the extra treatment.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Gastro-oesophageal junction cancer cancer is increasing in many different ethnic communities within the UK now, something that GPs need to be aware of as the symptoms are not always clear and / or defined. There will be barriers to early identification of gastro-oesophageal junction cancer and possibly understanding of treatment in some population groups.

Other issues	
13. Are there any other issues that you would like the committee to consider?	Earliest start of treatment after diagnosis. Timely follow up appointments to check on wellbeing and assessing the impact of being on a prevention treatment and what is the effect of any reduction of anxiety through people being on a treatment rather than watch and wait. Consider the long-term effect of the treatment.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Oesophageal cancer and cancer between the stomach and gullet are two of six less survivable cancers, for which there are no screening tools to identify them widely used, and as early symptoms are vague, people are frequently diagnosed late, when treatment options are limited.
- Fear, worry, or concern relating to the possibility that cancer will come back or progress is long term and can negatively affect quality of life for both the person with cancer and their carers.
- This treatment is different to other treatments commonly used as it is immunotherapy which acts by a different mechanism to increase the bodies own immune system to reduce rates of recurrence.
- There is an unmet need, as there is no current treatment that has shown that it can delay or prevent recurrence of cancer of the gullet or the junction between the gullet and stomach in this population.
- A treatment that shows increased survival and has a role in prevention, where there is no current treatment currently available, is an important treatment to consider.

Thank you for your time.

NICE National Institute for Health and Care Excellence

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Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer [ID1676]. A Single Technology Appraisal

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None of the authors has any conflicts of interest to declare.

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Rider on responsibility for report

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Contributions of authors

Matt Stevenson and Andrew Rawdin critiqued the health economic analysis submitted by the company. Emma Simpson summarised and critiqued the clinical effectiveness data reported within the company's submission. John Stevens and Martin Orr critiqued the statistical aspects of the submission. Mark Clowes critiqued the company's search strategy. All authors were involved in drafting and commenting on the final report. Doctors Hayat and Sripadam acted as clinical advisors.

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Abbreviations

AEs	Adverse events
AIC	Akaike Information Criterion
ALT	ALanine aminoTransferase
AST	ASpartate aminoTransferase
BIC	Bayesian Information Criterion
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence interval
CrI	Credible Interval
CRT	ChemoRadiation Therapy
CS	Company Submission
DFS	Disease-Free Survival
DMFS	Distant-Metastasis Free Survival
DSA	Deterministic Sensitivity Analyses
DSU	Decision Support Unit
ECOG	Eastern Co-operative Oncology Group
ECOG PS	Eastern Co-operative Oncology Group Performance Score
EQ-5D-3L	EuroQol 5 Dimensions 3 Levels
EQ-5D VAS	EuroQol 5 Dimensions Visual Analogue Scale
ERG	Evidence Review Group
ESMO	European Society of Medical Oncology
FACT-E	Functional Assessment of Cancer Therapy - Esophageal
[redacted]	[redacted]
GEJ	Gastroesophageal Junction
GEJC	Gastroesophageal Junction Cancer
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
ITT	Intention To Treat
IV	Intravenous(ly)
IWRS	Interactive Web Response System
KM	Kaplan-Meier
N/A	Not Applicable
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

OC	Oesophageal Cancer
OS	Overall Survival
PAS	Patient Access Scheme
PD-1	Programmed cell Death 1 (receptor)
PD-L1	Programmed Death Ligand 1
PFS 2	Progression Free Survival after the next line of the subsequent therapy
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analysis
PSA	Probabilistic Sensitivity Analyses
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
ROW	Rest Of the World
SAE	Serious Adverse Event(s)
SCC	Squamous Cell Carcinoma
SLR	Systematic Literature Review
STA	Single Technology Appraisal
ypN	Post-surgical lymph node staging following Preoperative radiotherapy or chemotherapy

1. Executive summary

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs) which are specified in terms of cost per quality-adjusted life years (QALYs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. The results of the ERG's exploratory analyses are presented in Section 1.6. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the view of the ERG, and do not necessarily reflect the opinion of NICE.

1.1 Overview of the ERG's key issues

Key issues identified by the ERG that impact on the incremental costs and quality-adjusted life years (QALYs) are summarised in Table 1.

Table 1: Overview of the ERG's key issues

ID1676	Summary of issue*
Issue 1	The data used for disease-free survival (DFS) when fitting distributions
Issue 2	The distribution chosen to represent DFS
Issue 3	The duration of DFS at which a 'cure' can be assumed
Issue 4	The average age of patients treated in the UK
Issue 5	That above the age of 75 years, patients had the same utility independent of whether their disease had recurred
Issue 6	Potential underestimation of the costing of adjuvant-nivolumab treatment within the model
Issue 7	The source of utility data

*All detailed in Section 4.3.3

The key differences between the company's preferred assumptions and the ERG's preferred assumptions relate to:

(i) **The most appropriate distribution to use for DFS.** The company selected a 1 knot spline distribution to model DFS. However, the ERG notes that the Generalised-F distribution had lower values on both the Bayesian Information Criterion and the Akaike Information Criterion and there was strong evidence that this was the better distribution in fitting the observed data. There was also no indication based on the underlying hazards or clinical plausibility that the Generalised-F distribution was inappropriate.

(ii) **The duration of DFS at which a patient could be considered 'cured'.** The company selected a duration of 3 years, however the clinical advice provided to the ERG stated that 5 years may be more appropriate, and DFS events were observed in CheckMate 577 after 3 years.

(iii) **The duration of adjuvant nivolumab treatment.** The company capped the use of adjuvant nivolumab treatment at 12 months, although a small proportion of patients continued treatment beyond this point. The ERG preferred a maximum treatment duration of 63 weeks so that any clinical benefits that were associated with extended treatment were appropriately costed. At the fact check stage the company provided further information suggesting that the elongated treatment duration was due to dose delays which were not incorporated in its model, meaning that the costs used by the ERG may be an over-estimation.

(iv) **The source of utility data.** The company used utility data from Szende *et al*, which is associated with broad age bands and with no loss in utility above the age of 75 years. The ERG believed that this is implausible and used utility values reported by Ara and Brazier instead.

(v) **The disutility of the post-recurrence health state compared to the disease-free health states.** The company's model assumes that the utility for people over 75 years of age is independent of whether disease has progressed. The ERG does not believe that this is plausible.

Additionally, the ERG believes that the most recent data for DFS should be used within the company's model, although it acknowledges that the company did not have these before its original submission.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival (OS)) and quality of life, using QALYs. In the model, adjuvant nivolumab treatment increases QALYs compared with routine surveillance by increasing both expected OS and the average quality of life for patients, whilst alive, as disease progression is also delayed. In the model, the costs associated with adjuvant nivolumab treatment compared with routine surveillance are greater, primarily due to the acquisition costs of nivolumab.

The assumptions within the company's base case modelling that the ERG believes are either incorrect, or uncertain, and that impact most on the ICER, expressed as the additional cost per QALY gained, are provided in Table 1.

1.3 The decision problem: summary of the ERG's key issues

The ERG has no key issues with the decision problem as addressed by the company, but notes that the population has been changed to be more in line with the population in CheckMate 577 and that OS data were immature and therefore not explicitly modelled.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The key evidence for clinical effectiveness within the company submission (CS) comprises one randomised controlled trial (RCT) of adjuvant nivolumab (n=532) versus placebo (n=262) which was relevant to the decision problem: CheckMate 577. This RCT was ongoing at the time of writing, and data were from a pre-specified interim analysis. OS data were not available. At the data cut-off, the hazard ratio (HR) for DFS was 0.69 (96.4% confidence interval (CI) 0.56, 0.86) p=0.0003, statistically significantly favouring nivolumab over placebo. The Kaplan-Meier estimated median DFS was 22.41 months (95% CI 16.62, 34.00) in the nivolumab arm, and 11.04 months (95% CI 8.34, 14.32) in the placebo arm. All cause adverse events of grade 3-4 were experienced by 183 (34.4%) patients in the nivolumab group, and 84 (32.3%) patients in the placebo group. All cause serious adverse events of any grade were experienced by 158 (29.7%) patients in the nivolumab group, and 78 (30.0%) patients in the placebo group.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

This section expands on the issues listed in Table 1.

Issue 1. The data used for disease-free survival (DFS) when fitting distributions

Report section	Sections 4.3.3 and 4.4.3.1
Description of issue and why the ERG has identified it as important	Since its submission, the company has received more recent DFS data. The ERG believes that this should be used in an updated model.
What alternative approach has the ERG suggested?	-
What is the expected effect on the cost-effectiveness estimates?	-
What additional evidence or analyses might help to resolve this key issue?	-

Issue 2. The distribution chosen to represent DFS

Report section	Sections 4.3.3 and 4.4.3.1
Description of issue and why the ERG has identified it as important	The company selected a 1 knot spline distribution to model DFS. However, the ERG notes that the Generalised-F distribution had lower values on both the Bayesian Information Criterion and the Akaike Information Criterion. There was also no indication based on the underlying hazards or clinical plausibility that the Generalised-F distribution was inappropriate.
What alternative approach has the ERG suggested?	The use of the Generalised-F distribution to model DFS.
What is the expected effect on the cost-effectiveness	This decreased the company's base case ICER from £22,766 to

estimates?	£17,729.
What additional evidence or analyses might help to resolve this key issue?	Further data on DFS. The ERG notes that more recent data on DFS have become available to the company since its submission (see Issue 1).

Issue 3. The duration of DFS at which a 'cure' can be assumed

Report section	Sections 4.3.3 and 4.4.3.1
Description of issue and why the ERG has identified it as important	The company selected a 'cure' point at 3 years of DFS. However, clinical advice to the ERG suggests that 5 years is more appropriate. The ERG also notes that some DFS events occur after 3 years.
What alternative approach has the ERG suggested?	Setting the 'cure' point to 5 years.
What is the expected effect on the cost-effectiveness estimates?	This increased the company's base case ICER from £22,766 to £27,114.
What additional evidence or analyses might help to resolve this key issue?	A longer duration of DFS data to better estimate the time point at which there are assumed to be no further disease-related events.

Issue 4. The average age of patients treated in the UK

Report section	Sections 4.3.3 and 4.4.3.1
Description of issue and why the ERG has identified it as important	The company used data directly from CheckMate 577 for average patient age (60.5 years). However, the clinical advice provided to the ERG suggests that patients in UK practice would be older than this, on average. During the Fact Check process the company referenced an audit which suggested a media age of 67 years compared with 62 years in CheckMate 577.
What alternative approach has the ERG suggested?	-
What is the expected effect on the cost-effectiveness estimates?	Increasing the mean age would increase the ICER. Illustrative results indicated that the company's base case ICER would increase from £22,766 to £27,275 if the mean age used was 65 years, rather than 60.5 years.
What additional evidence or analyses might help to resolve this key issue?	Audit data, including adenocarcinoma patients, may provide a more accurate estimate of the average age of patients suitable for adjuvant nivolumab treatment.

Issue 5. That above the age of 75 years, patients had the same utility independent of whether their disease had recurred

Report section	Sections 4.3.3 and 4.4.3.1
Description of issue and why the ERG has identified it as important	The structure of the company's model means that above 75 years of age, patients have the same utility in both the disease-free and the post-recurrence health states. The ERG believes it is implausible that, on average, patients would not have a higher

	utility if they remained in the DFS state rather than being in the post-recurrence disease state.
What alternative approach has the ERG suggested?	-
What is the expected effect on the cost-effectiveness estimates?	Ensuring that the utility for those in the post-recurrence state is likely to decrease the ICER. Illustrative results indicated that the ERG's base ICER would decrease from £17,440 to £16,977 if the utility for recurrence was set at 0.65 rather than 0.747.
What additional evidence or analyses might help to resolve this key issue?	Amending the model so that the average utility associated with patients in the recurrence state is always lower than that of patients who have not recurred, although this relationship over time may be uncertain.

Issue 6. Potential underestimation of the costing of adjuvant-nivolumab treatment within the model

Report section	Sections 4.3.3 and 4.4.3.1
Description of issue and why the ERG has identified it as important	The company capped the duration of adjuvant nivolumab treatment at 12 months, although in CheckMate 577 some patients had a longer duration of treatment.
What alternative approach has the ERG suggested?	To use the duration of treatment observed in CheckMate 577
What is the expected effect on the cost-effectiveness estimates?	This increased the company's base case ICER from £22,766 to £23,052.
What additional evidence or analyses might help to resolve this key issue?	-

Issue 7. The source of utility data

Report section	Sections 4.3.3 and 4.4.3.1
Description of issue and why the ERG has identified it as important	The company used utility data from Szende *et al*. which is associated with broad age categories and no decrease in utility after 75 years of age.
What alternative approach has the ERG suggested?	The ERG prefers to use the data reported in Ara and Brazier which does allow utility to decrease after 75 years.
What is the expected effect on the cost-effectiveness estimates?	This decreased the company's base case ICER from £22,766 to £22,280.
What additional evidence or analyses might help to resolve this key issue?	-

1.6 Summary of ERG's preferred assumptions and resulting ICER

The ERG altered the company's base case as follows: using a Generalised-F distribution for OS; changing the duration of DFS to 5 years before a 'cure' was assumed; using a mean patient age of 65 years; assuming a maximum duration of nivolumab treatment of 63 weeks; and using utility data reported by Ara and Brazier. The results are shown in Table 2. The ERG base case ICER (£21,298) was lower than the company's (£22,766) primarily due to the use of the Generalised-F distribution. Reverting back to the 1 knot spline, but maintaining the other ERG changes increased the ICER to £32,011.

Table 2: Summary of ERG preferred assumptions and deterministic ICER for nivolumab compared to routine surveillance

Exploratory analysis			
	Incremental QALYs	**Incremental cost**	**ICER**
Company's updated base case	[redacted]	[redacted]	**£22,766**
EA1: using the Generalised-F distribution for DFS	[redacted]	[redacted]	£17,729
EA2: assuming a 'cure' point at 5 years of DFS rather that at 3 years	[redacted]	[redacted]	£27,114
EA3: using a mean age of 65 years	[redacted]	[redacted]	£27,275
EA4: assuming a maximum duration of adjuvant nivolumab treatment of 63 weeks	[redacted]	[redacted]	£23,052
EA5: using utility data from Ara and Brazier	[redacted]	[redacted]	£22,280
ERG's preferred analysis (combining EA 1-5)*	[redacted]	[redacted]	**£21,298**
EA6: (the ERG preferred analysis using a 1 knot spline)	[redacted]	[redacted]	£32,011

EA – exploratory analysis; ICER - incremental cost-effectiveness ratio; QALY - quality-adjusted life year
** The probabilistic value was £21,310*

The impact on the ICER of incorporating distributions fitted to the newer DFS data is unknown.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

Section B.1.3.1 of the company submission (CS)[1] contains an accurate overview of the health problem. Gastroesophageal cancers are categorised by location and histology. Oesophageal cancer (OC) originates in the inner lining of the upper, middle or lower parts of the oesophagus, whereas gastroesophageal junction (GEJ) cancer (GEJC) originates close to, either above or below, the point at which the oesophagus joins the stomach. Two histological subtypes are predominant, squamous cell carcinoma (SCC) and adenocarcinoma; contrary to the global population, the most common type of OC in the UK is adenocarcinoma.[2]

Survival following OC in the UK is poor, due to diagnosis of disease at a late stage, with an estimated 16% of patients alive at five years.[3] Median survival post-recurrence of OC and GEJC is reported as being less than six months in the Netherlands.[4]

The company anticipate that nivolumab as monotherapy will be indicated for [redacted]

2.2 Critique of company's overview of current service provision

The description of current service provision in the UK in Section B.1.3.2 of the CS is adapted from the pathway presented by Lordick *et al*.[5] which is included within the European Society for Medical Oncology (ESMO) guidelines and appears accurate. Figure 3 of the CS is reproduced in Figure 1. The company comments that the treatment provided is dependent on the size, type, location and stage of the cancer, and comprises a combination of chemotherapy, radiotherapy and surgery. The company reports that clinical advice provided as part of an advisory board indicates that practice '*varies widely*' in the UK. Currently no adjuvant treatments are commonly used in the post-surgery setting for patients with squamous cell OC, with routine surveillance being the mainstay of treatment, as recommended in ESMO,[5] NICE[6] and National Comprehensive Cancer Network (NCCN)[7] guidelines for patients who have received neoadjuvant chemoradiation and present without cancer at resection margins. For patients with adenocarcinoma, NCCN guidelines include post-operative chemo(radio)therapy for some patients, although clinical advice to the company suggested that this does not happen in the UK. [redacted]

The company contend that the use of adjuvant nivolumab instead of routine surveillance would reduce the risk of relapse and improve long-term survival. The proposed positioning of adjuvant nivolumab is shown in Figure 1.

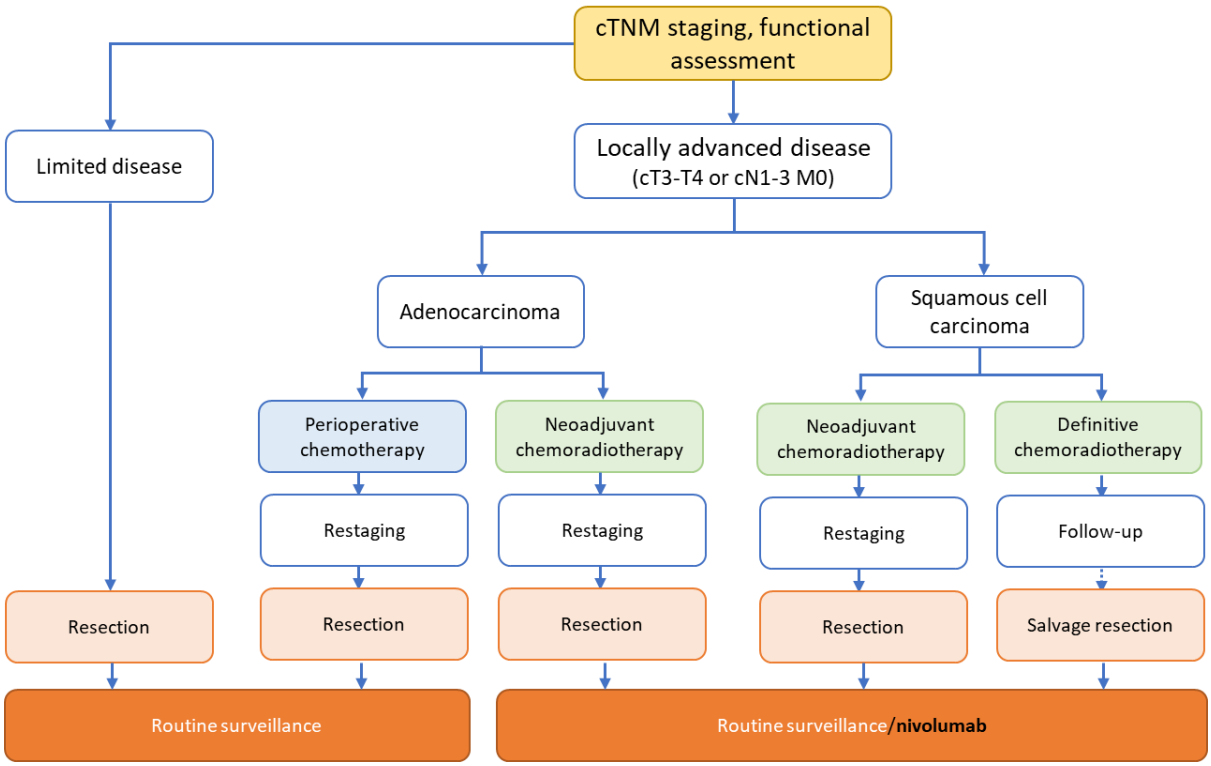


Figure 1: The treatment pathway for local / local regional resectable OC in the UK provided by the company. (reproduced from Figure 3 of the CS)

2.3 Critique of company's definition of the decision problem

Table 3 details the differences between the NICE scope[8] and the CS[1] as stated by the company.

Table 3: Decision problem (adapted from Table 1 of the CS)

	Scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with resected OC or GEJC	[redacted]	To be more in line with the population in the CheckMate 577 study.
Intervention	Nivolumab	As final scope	-
Comparators	Routine surveillance	As final scope	-
Outcomes	Overall survival Disease free survival Adverse effects of treatment Health-related quality of life	All bar overall survival	The company states that overall survival data were not available at the time of submission due to data immaturity.
Subgroups to be considered	None	As final scope	-
Special considerations	None	As final scope	-

2.3.1 Population

The population in the NICE scope is adults with resected OC or GEJC. The company has amended the population in the decision problem to [redacted], stating that the "*evidence presented in this submission is derived from the pivotal CheckMate 577 trial, which included patients with resected OC or GEJ cancer who have received chemoradiotherapy followed by complete resection.*"

2.3.2 Intervention

Nivolumab (Opdivo®) is a fully human immunoglobin G4 monoclonal antibody that acts as a programmed cell death 1 (PD-1) immune checkpoint inhibitor, preventing tumour cells from evading destruction. Within resected OC and GEJC, the company propose the use of adjuvant nivolumab monotherapy [redacted]. Nivolumab treatment is expected to be provided for a maximum duration of one year with a dose of 240mg administered intravenously (IV) fortnightly for the first 16 weeks, and then every four weeks at a dose of 480mg IV. All administrations take 30 minutes. [redacted]

Nivolumab is indicated for multiple disease areas and is associated with a patient access scheme (PAS) that provides a discount of [redacted], resulting in costs of [redacted] per 240mg dose and [redacted] per 480mg dose.

2.3.3 Comparator

The specified comparator was routine surveillance. The company states that this is follow-up appointments quarterly in the first year after resection, every six months in the following two years and then annually in the fourth and fifth years at which point a patient is discharged. The follow-up meetings do not include investigations unless the patient presents with symptoms suggestive of recurrence. Further details on resource use are provided in Section 4.2.3.4.

2.3.4 Outcomes

The NICE scope lists overall survival (OS), Disease-free survival (DFS), adverse effects (AEs) of treatment and health-related quality of life (HRQoL) as outcomes to be reported. The company included all of these except for OS results, stating that OS "*is a secondary endpoint in the pivotal trial, CheckMate 577, however OS data are not yet available at the time of submission as the data have not reached sufficient maturity.*"

2.3.5 Subgroups

The NICE scope did not list any subgroups that warranted exploration. The company did not provide analyses related to subgroups.

2.3.6 Special considerations

The NICE scope did not list any special considerations including issues related to equity or equality that should be explored. The company did not claim that special considerations were relevant to this single technology appraisal (STA).

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to identify relevant evidence for this STA.

3.1.1 Searches

Appendix D of the CS reports a systematic literature review of RCTs of adjuvant therapies for OC or GEJC. Searches covering the key databases recommended by NICE (Embase, MEDLINE and CENTRAL) were conducted in two phases: August 2019 and November 2020. The same search strategy was used for each phase.

Embase and MEDLINE were searched together via ProQuest. While the ERG does not normally recommend searching databases simultaneously, it notes that on this occasion the search strategy has been carefully tailored for optimal retrieval on each source by including appropriate subject headings from both Medline (MeSH) and Embase (Emtree).

Conference proceedings were excluded from the database searches, but the company stated that supplementary searches were run of key congresses including the American Society of Clinical Oncology, ESMO and the American Association for Cancer Research since 2018 (clarification response A6[9]).

No additional trial registers were searched other than CENTRAL (clarification response A7[9]); the ERG would advise searching the World Health Organisation International Clinical Trials Registry Platform and ClinicalTrials.gov for future SLRs of clinical evidence (Glanville *et al*[10]).

Some checking was conducted of reference lists by the company to mitigate the risk of missing any studies (clarification response A8[9]). An English language limit was applied to the searches.

The original CS included an error, with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) chart for appendix D actually being that of the economic review. The company supplied an amended version of appendix D containing the correct PRISMA chart with their response to the ERG's clarification letter.

The ERG is broadly satisfied with the quality of the clinical searches and considers it unlikely that relevant studies eligible for inclusion have been overlooked.

3.1.2 Inclusion criteria

The company conducted an SLR to identify clinical effectiveness and safety evidence relevant to the final NICE scope (CS Appendix D). The company undertook a broad review of randomised controlled trial (RCTs) in adults with OC or GEJC, designed to cover any adjuvant therapy (systemic treatment; radiotherapy; or chemoradiotherapy), with therapies compared with each other or placebo (CS Appendix D). The SLR inclusion criteria included the effectiveness (OS, DFS) and safety outcomes from the final NICE scope. Health-related quality of life (HRQoL) data were sought in a separate SLR, CS Appendix G). Study design was restricted to RCTs (CS Appendix D). The ERG considers this to be generally appropriate given that RCTs represent a higher quality of evidence than other study types.

Study selection was conducted by two researchers (CS Appendix D), as is good practice for systematic reviews.

3.1.3 Critique of data extraction

Data were extracted by one reviewer, and checked by another (CS Appendix D), as is good practice for systematic reviews. CheckMate 577 outcome data were checked against the publications and CSR and found to be accurate. [11] [12] [13] [14]

3.1.4 Quality assessment

Quality items assessed by the company (CS Section B.2.5 and CS Appendix D) were taken from the Centre for Reviews and Dissemination guidelines for undertaking reviews in health care.[15] These are standard and appropriate criteria for assessing the risk of bias in RCTs. Quality assessment was checked by the ERG against information provided by the company, the CSR, trial protocol CheckMate 577 and publications (Table 4).[11] [12] [13] [14, 16]

Patients were randomly assigned in a 2:1 ratio for nivolumab to placebo. Randomised sequence generation and allocation concealment were by a centralised interactive voice and web response system. This indicates a low risk of selection bias.

Randomisation stratification factors were:

1) PD-L1 status (≥ 1% vs < 1% or indeterminate/non-evaluable)

2) Pathologic lymph node status (positive [≥ ypN1] vs negative [ypN0]) [ypN refers to post-surgical lymph node staging following Preoperative radiotherapy or chemotherapy [17]]

3) Histology (squamous vs adenocarcinoma).

It would have been informative to stratify by cancer location (OC versus GEJC) as treatment response could vary. However the correlation between histology and location would mean that this is partially

accounted for as GEJC/lower oesophagus cancers are mostly adenocarcinoma whereas SCC tend to develop in the upper and middle part of the oesophagus).[18,19] Location (OC or GEJC) was balanced between treatment arms (see Table 8).

There was a low risk of bias with respect to balance between groups, as baseline characteristics appeared similar and there were no unexpected imbalances in drop-outs between groups.

There was blinding of patients and physicians and site staff, meaning outcome assessmetns were blinded. This indicates a low risk of performance bias and detection bias. An intention-to-treat (ITT) analysis was provided by the CS for the interim analysis of DFS.

CheckMate 577 is ongoing and therefore final results have not yet been collected, so it cannot be assessed if the authors measured more outcomes than they published. However, data from the clinical cut-off date for the interim analysis for the outcomes from the NICE final scope, DFS, AEs and HRQoL were provided by the company in the CS and accompanying documents. An ITT analysis was provided for DFS. DFS data were provided from the interim analysis. The interim DFS analysis was planned for when there had been at least 374 DFS events.[11, 14] The interim analysis, database lock July 2020, last patient data collected May 2020, occurred following 396 DFS events. [11, 14] The population for HRQoL measures was all randomized subjects who have an assessment at baseline and at least 1 subsequent assessment while on treatment. The safety population of the CheckMate 577 trial comprised all treated patients.

[redacted]

Table 4: Quality assessment of CheckMate 577

Question	CS assessment (CS Table 11) Grade (yes/no/not clear/NA)	ERG assessment	ERG support for judgement
Was randomisation carried out appropriately?	Yes	Yes	Randomised through Interactive Web Response System (IWRS)
Was the concealment of treatment allocation adequate?	Yes	Yes	Allocation by a central IWRS
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Baseline characteristics appear balanced between groups
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Patients and clinicians and site staff blinded
Were there any unexpected imbalances in dropouts between groups?	No	No	No. Dropouts appear balanced between the groups
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	NA	Study ongoing, not all outcomes complete and so could not be published (at time of writing)
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes, for primary outcome	ITT DFS published Kelly 2020 [12 14] HRQoL not ITT Van Cutsem 2021 [13]

ITT: intention-to-treat; NA: not applicable

3.1.5 Evidence synthesis

Not applicable, only one study included.

3.2 Included study of nivolumab

The CS clinical SLR identified one RCT of nivolumab which was relevant to the decision problem: CheckMate 577 (NCT02743494) (CS Clarification response A9[9]). This formed the key evidence for clinical effectiveness and safety within the CS.

The trial was of good methodological quality, however as the trial was ongoing only interim analyses were available. The company consider the interim analysis of DFS as final because it met its pre-specified statistical significance criteria (CS Clarification response A4[9]). OS data were not available to either the trial investigators or the team working on the clinical submission. At the time of clinical data cut-off, [redacted]

The company identified six other ongoing studies of nivolumab in OC or GEJC (CS Clarification response A10[9]). Four of these (NCT03662659, NCT02746796, NCT03143153 and NCT02872116) were not relevant to the positioning in the treatment pathway stated in the decision problem of the final NICE scope. Two studies (NCT03006705 and NCT02935634) had comparators of combination chemotherapy, that did not match the comparator of the final NICE scope.

The ERG does not believe that any relevant published RCTs of nivolumab that could have provided effectiveness data have been omitted from the CS.

3.2.1 Study design CheckMate 577

CheckMate 577 is an ongoing Phase III randomised (2:1), multicentre, international double blind, placebo-controlled (CS Section B.2). The study compared adjuvant nivolumab or placebo in patients with complete resection of OC or GEJC following neoadjuvant chemoradiation therapy (CRT) (

Table 5).

Nivolumab was administered at a dose of 240 mg IV every two weeks for eight cycles followed by 480 mg IV every four weeks. The company stated that treatment was continued up to a year, or until disease recurrence, unacceptable toxicity, or withdrawal of consent (CS Section B.2), however, a small proportion of patients had a treatment duration in excess of 1 year.

Table 5: CheckMate 577 study characteristics

Study	**Population**	**Intervention (n randomised)**	**Comparator (n randomised)**	Primary outcome
CheckMate 577 NCT02743494 CA209-577 2015-005556-10 (EudraCT Number)	Resected OC or GEJ cancer	Nivolumab 240 mg every 2 weeks IV for 8 cycles (i.e., 16 weeks) followed by 480 mg IV every 4 weeks for a total of a year or until recurrent disease, unacceptable toxicity, or consent withdrawal n=532	Placebo Every two weeks IV for eight cycles followed by IV every 4 weeks for a total of a year for a total of a year or until recurrent disease, unacceptable toxicity, or consent withdrawal n=262	DFS, time from randomisation to first recurrence or death, whichever occurs first. Assessed by investigator

Randomisation was stratified by histology (SCC vs adenocarcinoma), pathologic lymph node status (positive vs negative) and tumour cell PD-L1 status (≥ 1% vs < 1% or indeterminate/non-evaluable). Randomisation of patients took place from July 2016 (CS Section B.2.3.1.1) to August 2019.[11 14]

The primary outcome was investigator-assessed DFS, defined as time from randomisation to first recurrence or death, whichever occurs first (CS Section B.2.3).

Secondary outcomes were: OS, defined as the time from randomisation to death; and OS rates at 1-, 2- and 3-years following randomisation (CS Section B.2.3).

OS had originally been a co-primary outcome but was changed to a secondary outcome following a protocol revision reported August 2019[20.14] [redacted]

Exploratory outcomes were: safety and tolerability; Distant-metastasis free survival (DMFS), defined as the time from randomisation to the first distant recurrence or death; PD-L1 status as predictive

biomarker; progression free survival after the next line of the subsequent therapy (PFS2) defined as the time from randomisation to the date of investigator-defined documented objective disease progression on the subsequent next-line therapy or start of second subsequent next-line therapy or death due to any cause, whichever occurs first; HRQoL measures EuroQol 5 Dimensions 3 Levels (EQ-5D-3L) and Functional Assessment of Cancer Therapy - Esophageal (FACT-E) (CS Section B.2.3).

At time of writing, CheckMate 577 was ongoing. OS data from CheckMate 577 were not available to the trial investigators of the team producing the CS (clarification question B4[9]). In response to clarification question A4[9] the company stated that *"The OS interim analysis is planned when 80% of OS events are observed, projected for* [redacted] *The final OS analysis is planned when 460 OS events are observed, projected for* [redacted].

The CS provided data from the pre-specified DFS interim analysis, data cut-off at July 2020 (for DFS, PFS2, HRQoL and AE) (CS Section B.2). The company consider this the final DFS analysis as it met its pre-specified statistical significance criteria (CS Clarification response A4[9]).

The company provide references to support the use of DFS as a surrogate outcome for OS in adjuvant treatment for gastric cancer[21] and in neoadjuvant treatment of gastro-oesophageal adenocarcinoma.[22] More data would be beneficial for adjuvant immune-oncology therapies as DFS is not uniformly a suitable surrogate. The ERG notes that DFS has been reported as not being a good surrogate for OS in neoadjuvant treatment of GEJC.[23]

Two abstracts have been published from the CheckMate 577 study: Kelly *et al* 2020 [12]; and Van Cutsem *et al* 2021. [13] Between the time of company submission, and submission of ERG report, a further paper on CheckMate 577 was published (Kelly *et al* 2021).[14]

Key study eligibility criteria are shown in Table 6. Patients were adults (≥18 years) with Stage II or Stage III OC or GEJC, who had completed neoadjuvant CRT and complete resection (CS Section B.2.3).

Table 6: Inclusion and exclusion criteria for CheckMate 577 (Copied from CS Table 7)

Key inclusion criteria	Key exclusion criteria
• Men or women of at least 18 years of age • Stage II or Stage III (per AJCC 7th edition) carcinoma of the oesophagus or GEJ and histologically confirmed predominant adenocarcinoma or squamous cell carcinoma • Completed pre-operative (neoadjuvant) chemoradiotherapy followed by surgery. Platinum based chemotherapy should be used. • Complete resection (R0) and surgically rendered free of disease with negative margins on resected specimens. • Residual pathologic disease i.e., non-pathCR of their cancer with at least ypN1 or ypT1 listed on the pathology report of the resected specimens. • ECOG PS score of 0 or 1 • All patients must have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomisation.	• Patients who do not receive concurrent chemoradiotherapy prior to surgery. • Patients who only receive chemotherapy or only radiation prior to surgery • Patients with cervical oesophageal carcinoma. • Patients with Stage IV resectable disease. • Patient who received treatment directed against the resected cancer after complete resection • Patients with previous malignancies unless a complete remission was achieved at least five years prior to study entry and no additional therapy is required or anticipated to be required during the study period (exceptions are noted in the protocol) • Patients with active, known or suspected autoimmune disease. • Patients with a condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration. • Patients with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity. • Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

CTLA: cytotoxic T-lymphocyte-associated protein 4; ECOG PS: Eastern Cooperative Oncology Group Performance Score; pathCR: pathological complete resection; PD-1: programmed cell death 1; PD-L1: programmed death ligand 1

Source: CheckMate 577 protocol [16]

According to clinical advice, in the UK population, cervical OC would be treated, whereas these patients were excluded from the RCT. Otherwise the trial inclusion/exclusion criteria were relevant to the UK population.

Concomitant treatment with topical, inhalational, adrenal replacement or brief course corticosteroids was allowed. Patients were not allowed immunosuppressants, concurrent anti-neoplastic therapy, or live vaccine (CS Section B.2.3).

3.2.2 Effectiveness study results CheckMate 577

The CS reported data from the pre-specified interim analysis, after 396 DFS events, data cut-off at July 2020, at which median follow-up was 24.4 months (CS Section B.2.6.3). [redacted]

Median duration of study drug exposure was 10.1 months (range, 0.03 to 14.2) for the nivolumab arm, and for the placebo arm 9.0 months (range, 0.03 to 15.0).[14]

At this interim analysis, 507 of 532 patients (95.3%) randomised to nivolumab, and 248 of 262 patients (95.4%) randomised to placebo, were continuing within the study (CS Section B.2.6). At the time of the interim analysis, 31 (5.8%) patients randomised to nivolumab, and 19 (7.3%) patients randomised to placebo, remained on study treatment (CS Section B.2.6). The most common reasons for discontinuation were treatment completion (nivolumab 43.0%, placebo 38.1%), and disease recurrence (nivolumab 28.0%, placebo 43.5%). Study drug toxicity resulted in discontinuation for 10.7% of the nivolumab arm and 3.1% of the placebo arm, with AE considered unrelated to study drug accounting for 2.8% of the nivolumab arm and 3.5% of the placebo arm.

Subsequent therapy was received by 157 (30%) in the nivolumab arm, of whom 125 (23.5%) had subsequent systemic therapy, and 111 (42%) of the placebo arm received subsequent therapy, with subsequent systemic therapy in 89 (34.0%) (Table 7) (CS Section B.2.6).[14]

Table 7: CheckMate 577 Subsequent systemic therapies (adapted from CS Table 15)

	Nivolumab	Placebo
Patients randomised, n	532	262
Patients with any subsequent therapies, n (%)[14]	157 (30)	111 (42)
Radiotherapy, n (%)	43 (8)	41 (16)
Surgery, n (%)	28 (5)	20 (8)
Subsequent systemic therapy, n (%)	125 (23.5)	89 (34.0)
Subsequent systemic therapies received, n (%) (CS Table 15)		
Immunotherapy	4 (0.8)	19 (7.3)
Anti-PD1	[redacted]	[redacted]
Investigational agent	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Anti-PDL1	[redacted]	[redacted]
Avelumab	[redacted]	[redacted]
Anti-CTLA4	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]
Other immunotherapy	[redacted]	[redacted]
Targeted therapy	13 (2.4)	11 (4.2)
Bevacizumab	[redacted]	[redacted]
Investigational agent	[redacted]	[redacted]
Ramucirumab	[redacted]	[redacted]
Other systemic anticancer therapy – experimental	[redacted]	[redacted]
Chemotherapy[a]	123 (23.1)	85 (32.4)
Other[b]	[redacted]	[redacted]
Number of lines of subsequent therapy		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
≥ 4	[redacted]	[redacted]

Source: CheckMate 577 CSR [11], Kelly *et al* 2021 [14]

[a] Most common chemotherapies were fluorouracil and oxaliplatin.

[b] Mostly supportive treatments, including primarily folinic acid, but also zoledronic acid, and denosumab.

Baseline characteristics are shown in Table 8. The baseline characteristics appeared well balanced between groups (CS Section B.2.3). The median age was 62.0 years (range: 26 - 86 years), and most patients were white (81.6%) and male (84.5%) (CS Section B.2.3). There were 38.2% of patients from Europe, 32.1% from USA/Canada, 13.4% from Asia, and 16.4% from the rest of the world (ROW).[11]

Most patients had adenocarcinoma (70.9%). Most patients (71.8%) had baseline PD-L1 status < 1%. [11]

[redacted]

According to clinical advice, study participants had similar pathology types and stage distribution to a UK population although the UK eligible population may be older than the trial population, but this is unlikely to substantially impact on the treatment efficacy results. CS clarification response B20[9] suggests that of UK OC patients who received chemoradiotherapy and surgical resection, 42.9% of patients are aged 60-69 years and 73.9% are aged <70 years.[24] At the Fact Check stage, the company provided data from the National Oesophago-Gastric Cancer Audit[25] which gives a median age for patients in England and Wales with oesophageal squamous cell carcinoma with a planned treatment modality of surgery of 67 years (inter quartile range 60–73) which is greater than that observed in CheckMate 577 (62.0 years).

[redacted]

According to clinical advice, the eligible UK population would have a lower percentage of male patients than in the RCT. CS clarification response B20[9] suggests 68.6% of a UK OC population who received chemoradiotherapy and surgical resection are male.[24]

Table 8: Baseline Characteristics CheckMate 577 (copied from CS Table 9)

Baseline characteristic		Nivolumab	Placebo
Cohort size		532	262
Age	Median (range), years	62.0 (26-82)	61.0 (26-86)
	< 65 years, n (%)	333 (62.6)	174 (66.4)
Sex, n (%)	Female	83 (15.6)	40 (15.3)
	Male	449 (84.4)	222 (84.7)
Race, n (%)	White	432 (81.2)	216 (82.4)
	Asian	83 (15.6)	34 (13.0)
Geographic location, n (%)	US/Canada	167 (31.4)	88 (33.6)
	Europe	202 (38.0)	101 (38.5)
	Asia	77 (14.5)	29 (11.1)
	ROW	86 (16.2)	44 (16.8)
ECOG PS, n (%)	0	308 (57.9)	156 (59.5)
	1	224 (42.1)	106 (40.5)
Histological type, n (%)	Adenocarcinoma	376 (70.7)	187 (71.4)
	Squamous cell carcinoma	155 (29.1)	75 (28.6)
	Other	1 (0.2)	0

Baseline PD-L1 status, n (%)	≥ 1 %	89 (16.7)	40 (15.3)
	< 1 %	374 (70.3)	196 (74.8)
	Indeterminate/non-evaluable	69 (13.0)	26 (9.9)
Disease at initial diagnosis, n (%)	OC	320 (60.2)	155 (59.2)
	GEJ cancer	212 (39.8)	107 (40.8)
Disease stage at initial diagnosis, n (%)	Stage I	0	0
	Stage II	179 (33.6)	99 (37.8)
	Stage III	351 (66.0)	163 (62.2)
	Stage IV	0	0
	Not reported	2 (0.4)	0
Disease at study entry, n (%)	OC	311 (58.5)	151 (57.6)
	OC lower third	101 (38.0)	96 (36.6)
	OC middle third	82 (15.4)	46 (17.6)
	OC upper third	27 (5.1)	9 (3.4)
	GEJ	221 (41.5)	111 (42.4)
	GEJ type I	91 (17.1)	49 (18.7)
	GEJ type II	99 (18.6)	46 (17.6)
	GEJ type III	26 (4.9)	14 (5.3)
	GEJ not reported	5 (0.8)	2 (0.8)
Pathologic TN classification at study entry: tumour, n (%)	ypT0	31 (5.8)	16 (6.1)
	ypT1	83 (15.6)	33 (12.6)
	ypT2	119 (22.4)	73 (27.9)
	ypT3	286 (53.8)	138 (52.7)
	ypT4	10 (1.9)	2 (0.8)
	Unknown	3 (0.6)	0
Pathologic TN classification at study entry: nodes, n (%)	ypN0	227 (42.7)	109 (41.6)
	≥ ypN1: ypN1	186 (35.0)	87 (33.2)
	≥ ypN1: ypN2	94 (17.7)	49 (18.7)
	≥ ypN1: ypN3	25 (4.7)	16 (6.1)
	Unknown	0	1 (0.4)

ECOG PS: Eastern Corporative Oncology Group Performance Score; GEJ: gastroesophageal junction; OC: oesophageal cancer; PD-L1: programmed death ligand 1; ROW: rest of world

Source: CheckMate 577 CSR [11]

Disease-free survival

At the interim analysis (data cut-off July 2020), there were [redacted] DFS events in the nivolumab arm, and [redacted] DFS events in the placebo arm (CS Section B.2.6.3) (Table 9).

Kaplan-Meier survival functions are shown in Figure 2. The hazard ratio, stratified by randomisation stratification factors, was 0.69 (96.4% CI 0.56, 0.86) p=0.0003, statistically significantly favouring nivolumab over placebo. [12]

Kaplan-Meier estimated median DFS was 22.41 months (95% CI 16.62, 34.00) in the nivolumab arm, and 11.04 months (95% CI 8.34, 14.32) in the placebo arm (CS Section B.2.6.3).[12]

Table 9: DFS CheckMate 577 (adapted from CS Table 13)

DFS	Nivolumab	Placebo
Randomised patients	532	262
Evaluable patients	532	262
Median DFS (95% CI), months	22.41 (16.62, 34.00)	11.04 (8.34, 14.32)
6-month DFS rates (95% CI), %	72.3 (68.2, 76.0)	63.4 (57.2, 69.0)
DFS Events, n (%)	[redacted]	[redacted]
Type of event: recurrence, n (%)	219 (41.2)	147 (56.1)
Local recurrence, n (%)	33 (6.2)	20 (7.6)
Regional recurrence, n (%)	32 (6.0)	24 (9.2)
Distant recurrence, n (%)	154 (28.9)	103 (39.3)
Type of event: death without recurrence, n (%)	[redacted]	[redacted]

CI: confidence internal; DFS: disease free survival; Source: CheckMate 577 CSR [11] Kelly *et al* 2021[12]

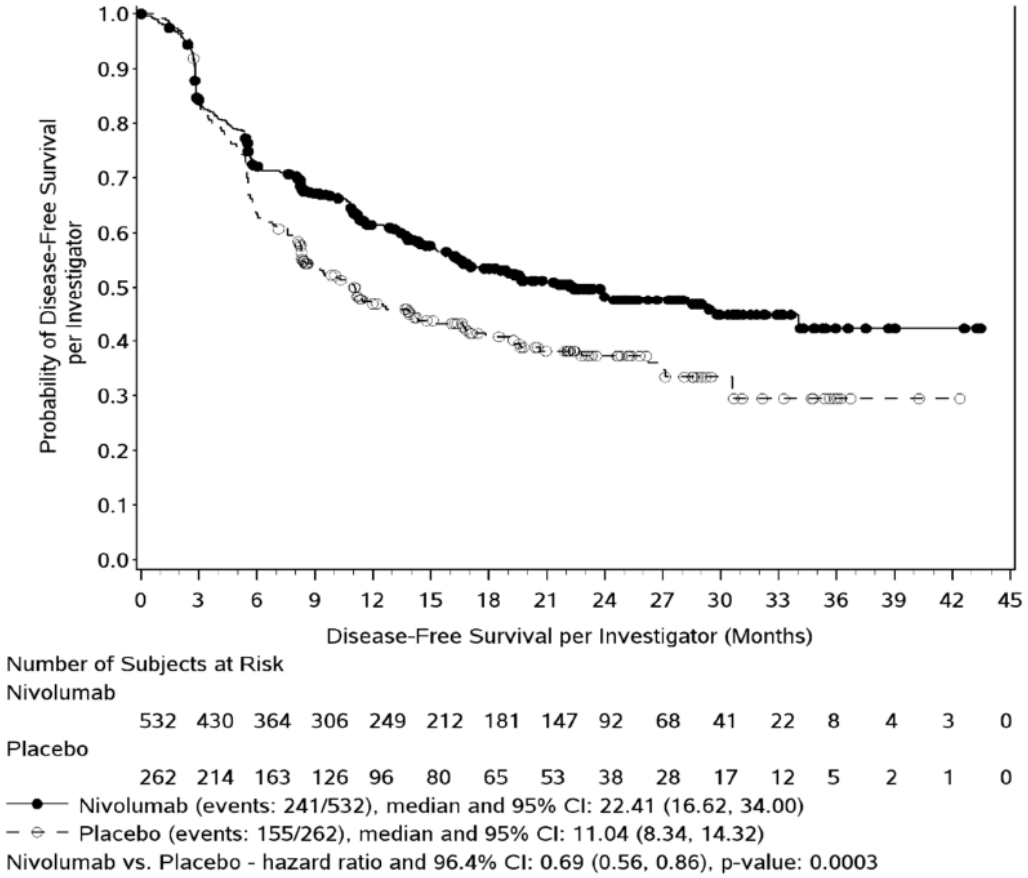


Figure 2: Kaplan-Meier plot of DFS in all randomised patients CheckMate 577 (copied from CS Figure 6)

Subgroups

No subgroups of interest were listed in the final NICE scope.

[redacted]

Although not powered to test for an interaction between treatment and subgroups, subgroup analyses unadjusted for randomisation stratification factors showed a hazard ratio (HR) <1 for almost all pre-specified subgroups (CS Section B.2.7). [redacted]

Distant metastasis-free survival

There were [redacted] DMFS events in the nivolumab arm, and [redacted] DMFS events in the placebo arm (CS Section B.2.6.3) (

Table 10). The HR, stratified by randomisation stratification factors, was 0.74 (95% CI 0.60, 0.92).[14] Median DMFS was 28.32 months (95%CI 21.26, NA) in the nivolumab arm, and 17.61 months (95%CI 12.45, 25.40) in the placebo arm (CS Section B.2.6.3).[14]

Table 10: DMFS and PFS2 (adapted from CS Table 13)

Endpoint		Nivolumab	Placebo
Randomised patients		532	262
Evaluable patients		532	262
DMFS	Median DMFS (95% CI), months	28.32 (21.26, N/A)	17.61 (12.45, 25.40)
	6-month DMFS rates (95% CI), %	[redacted]	[redacted]
	Events, n (%)	[redacted]	[redacted]
PFS2	Median PFS2 (95% CI), months	[redacted]	[redacted]
	Events	[redacted]	[redacted]
	Type of event, death	[redacted]	[redacted]
	Type of event, progression on subsequent systemic therapy	[redacted]	[redacted]
	Type of event, start of second subsequent systemic therapy	[redacted]	[redacted]

CI: confidence internal; DMFS: distant metastasis-free survival; N/A: not applicable; PFS2: progression free survival on subsequent systemic therapy

Source: CheckMate 577 CSR [11], Kelly *et al* 2021[14]

Progression free survival on subsequent systemic therapy

For patients who did not receive subsequent systemic therapy, PFS2 was defined as the time between randomisation and death, or the last known alive date; [redacted] (CS Section B.2.6.3). For patients who received subsequent systemic therapy, PFS2 was defined as the time between randomisation and progression per investigator assessment on the subsequent systemic therapy, second subsequent systemic therapy, or death from any cause, whichever occurred first; [redacted] (CS Section B.2.6.3).

The HR, stratified by randomisation stratification factors, was [redacted] (95%CI [redacted]). (

Table 10). Median PFS2 was [redacted] in the nivolumab arm, and was [redacted] in the placebo arm (CS Section B.2.6.3).

3.2.3 Adverse events

The safety population of the CheckMate 577 trial comprised all treated patients; 532 patients treated with nivolumab group, and 260 patients with placebo (CS Section B.2.9). The median number of nivolumab doses received was [redacted] and for placebo the median number of doses was [redacted] (CS Section B.2.9). AEs were counted if reported between first dose and 30 days following last dose study treatment [14], and immune-mediated AEs were reported within 100 days of last dose (CS Section B.2.9).

All cause AEs of any grade were experienced by 510 patients (95.9%) in the nivolumab group, and 243 patients (93.5%) in the placebo group (

Table 11 and CS Section B.2.10). The most frequently reported any grade AEs in nivolumab-treated patients were: diarrhoea (29.1%), fatigue (27.1%), nausea (22.7%), cough (18.4%), and vomiting (15.0%). Type and frequency of all cause any grade AEs were similar in the placebo group: diarrhoea (29.2%), fatigue (24.2%), nausea (21.2%), cough (18.5%), dysphagia (16.5%) and vomiting (16.2%). All cause AEs of any grade considered treatment-related were more frequent in the nivolumab group (70.7%) than the placebo group (45.8%). [12] Grades of AEs were defined according National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. All cause AEs of grade 3-4 were experienced by 183 (34.4%) patients in the nivolumab group, and 84 (32.3%) patients in the placebo group (CS Section B.2.10).

Table 11: AEs observed in CheckMate 577[11]

	Nivolumab (N = 532)			Placebo (N = 260)		
Mean doses received	[redacted]			[redacted]		
Cumulative dose (mg) Mean (Standard Deviation)	[redacted]			Not applicable		
Safety event	**Any grade**	**Grade 3–4**	**Grade 5**	**Any grade**	**Grade 3–4**	**Grade 5**
Overall all-cause AEs, n (%)	510 (95.9)	183 (34.4)	9 (1.7)	243 (93.5)	84 (32.3)	6 (2.3)
AEs considered treatment-related, n (%)	376 (70.7)	71 (13.3)	1 (0.2) *	119 (45.8)	15 (5.8)	0 (0.0)
Serious adverse events Total patients with an event, n (%)	158 (29.7)	107 (20.1)	9 (1.7)	78 (30.0)	53 (20.4)	6 (2.3)
SAEs considered treatment-related, n (%)	40 (7.5)	29 (5.5)	1 (0.2)*	7 (2.7)	3 (1.2)	0 (0.0)
All-cause AEs leading to discontinuation, n (%)	68 (12.8)	38 (7.1)	[redacted]	20 (7.7)	16 (6.2)	[redacted]
AEs considered treatment-related leading to discontinuation, n (%)	48 (9.0)	26 (4.9)	1 (0.2)*[11]	8 (3.1)	7 (2.7)	0 (0.0)[11]

*Cardiac arrest "*this event was deemed not to be treatment-related by the investigator after the database lock based on further evaluation of the fatal event."(CS Section B.2.9)* [14] CSR [11]

Serious AEs (SAEs) were defined as events which were: fatal; life-threatening; resulting in hospitalisation or prolongation of existing hospitalisation; resulting in persistent or significant disability/incapacity; a congenital anomaly/birth defect; considered medically important based upon

appropriate medical and scientific judgment; or suspected transmission of an infectious agent via the study drug (CS clarification response A3[9]). All cause SAEs of any grade were experienced by 158 (29.7%) patients in the nivolumab group, and 78 (30.0%) patients in the placebo group (CS Section B.2.10).

The most frequently reported all-cause SAEs of any-grade for nivolumab treated patients were: pneumonia (3.0%); malignant neoplasm progression (2.3%); pneumonia aspiration (1.3%); pneumonitis (1.1%); and dysphagia (1.1%). The most frequently reported all-cause SAEs of any-grade for placebo were: malignant neoplasm progression (3.1%); pneumonia (1.9%); dysphagia (1.9%); pleural effusion (1.5%); pneumothorax (1.2%); dyspnoea (1.2%); diaphragmatic hernia (1.2%); and oesophageal stenosis (1.2%). All cause SAEs of any grade considered treatment-related were more frequent in the nivolumab group (7.5%) than the placebo group (2.7%).[12]

The most commonly reported drug-related select AEs of any grade for nivolumab treated patients were: diarrhoea (16.5%); pruritus (10.0%); rash (9.8%); aspartate aminotransferase (AST) increased (5.5%); and alanine aminotransferase (ALT) increased (4.7%). In the placebo group, the most commonly reported drug-related select AEs of any grade were: diarrhoea (15.0%); rash (3.8%); and AST increased (3.8%). The most commonly reported immune mediated AEs (Table 12) of any grade for nivolumab treated patients were: hypothyroidism/thyroiditis (11.1%); rash (7.9%); hyperthyroidism (6.6%); and pneumonitis (4.5%). For the placebo group, the most commonly reported immune mediated AEs of any grade were: pneumonitis (1.5%); rash (1.5%); hepatitis (1.2%); and hypothyroidism/thyroiditis (1.2%).

Table 12: Select AEs, immune-mediated AEs and other events of special interest reported in CheckMate 577 (copied from CS Table 20)

Safety parameters	No. of patients (%)			
	Nivolumab (N = 532)		Placebo (N = 260)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
All-cause select AEs				
Skin	169 (31.8)	7 (1.3)	48 (18.5)	1 (0.4)
Gastrointestinal	157 (29.5)	6 (1.1)	77 (29.6)	3 (1.2)
Endocrine	101 (19.0)	5 (0.9)	8 (3.1)	0
Hepatic	79 (14.8)	14 (2.6)	31 (11.9)	6 (2.3)
Pulmonary	29 (5.5)	6 (1.1)	5 (1.9)	1 (0.4)
Hypersensitivity/Infusion Reactions	15 (2.8)	1 (0.2)	5 (1.9)	0
Renal	12 (2.3)	1 (0.2)	7 (2.7)	0
Treatment-related select AEs				
Skin	130 (24.4)	7 (1.3)	28 (10.8)	1 (0.4)
Endocrine	93 (17.5)	5 (0.9)	6 (2.3)	0
Gastrointestinal	91 (17.1)	4 (0.8)	40 (15.4)	3 (1.2)

Safety parameters	No. of patients (%)			
	Nivolumab (N = 532)		Placebo (N = 260)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Hepatic	49 (9.2)	6 (1.1)	18 (6.9)	4 (1.5)
Pulmonary	23 (4.3)	6 (1.1)	4 (1.5)	1 (0.4)
Hypersensitivity/Infusion Reactions	10 (1.9)	0	3 (1.2)	0
Renal	7 (1.3)	1 (0.2)	2 (0.8)	0
All-causality non-endocrine IMAEs within 100 days of last dose treated with immune modulating medication				
Rash	42 (7.9)	5 (0.9)	4 (1.5)	1 (0.4)
Pneumonitis	24 (4.5)	9 (1.7)	4 (1.5)	1 (0.4)
Diarrhoea/Colitis	10 (1.9)	4 (0.8)	2 (0.8)	1 (0.4)
Hepatitis	6 (1.1)	4 (0.8)	3 (1.2)	3 (1.2)
Nephritis and Renal Dysfunction	2 (0.4)	1 (0.2)	1 (0.4)	0
Hypersensitivity	1 (0.2)	0	1 (0.4)	0
All-causality endocrine IMAEs within 100 days of last dose with or without immune modulating medication				
Hypothyroidism/Thyroiditis	59 (11.1)	2 (0.4)	3 (1.2)	0
Hyperthyroidism	35 (6.6)	0	1 (0.4)	0
Adrenal Insufficiency	5 (0.9)	2 (0.4)	1 (0.4)	0
Diabetes Mellitus	3 (0.6)	2 (0.4)	0	0
Hypophysitis	1 (0.2)	0	0	0
All-causality OESIs within 100 days of last dose with or without immune modulating medication				
Myocarditis	3 (0.6)	3 (0.6)	0	0
Pancreatitis	1 (0.2)	1 (0.2)	0	0
Guillain-Barré Syndrome	1 (0.2)	1 (0.2)	0	0

AE: adverse event; IMAE: immune mediated adverse event; OESI: other event of special interest; Source: CheckMate 577 CSR table 8.1-1 [11]

All cause AEs of any grade leading to discontinuation were experienced by 68 (12.8%) patients in the nivolumab group and 20 (7.7%) patients in the placebo group. The most frequent of these were: in the nivolumab group pneumonitis (1.9%), malignant neoplasm (0.9%), rash (0.6%), and myocarditis (0.6%); for the placebo group malignant neoplasm (1.5%) and pneumonitis (0.8%) (CSR).[11] Treatment-related AEs leading to discontinuation were experienced by 9% of the nivolumab group, and 3% of the placebo group (Kelly 2020).[12]

3.2.4 HRQoL

The patient reported outcome analysis population comprised randomised patients who had an assessment at baseline and at least one post-baseline assessment (CS Section B.2.4).

The EuroQol 5 dimensions 3 level Visual Analogue Scale (EQ-5D VAS) is a patient-reported outcome measure that ranges from 0 (worst health) to 100 (best health). Mean EQ-5D-VAS score in the nivolumab arm was 70.4 at baseline (n=509) and 83.1 at week 53 (n=48).[13] Mean EQ-5D-VAS score

in the placebo arm was 69.1 at baseline (n=251) and 85.7 at week 53 (n=21). There was some improvement shown in both groups, which was considered clinically meaningful (defined as a change of at least seven points) at some time points.[14] There was no formal statistical testing of between-arm differences (CS Section B.2.6).

FACT-E is a patient reported outcome measure that ranges from 0 (worst health) to 176 (best health). Baseline data, from 499 patients from the nivolumab arm, and 253 patients from the placebo arm (CS Section B.2.6), indicated that baseline scores were similar between arms. There was no formal statistical testing of between-arm differences (CS Section B.2.6). At week 53, data were available for 45 nivolumab, and 20 placebo patients. FACT-E total mean scores had changed from baseline[13] from 133.40 to 134.58 for the nivolumab arm, and from 134.03 to 144.03 in the placebo arm (CS Section B.2.6). There was some improvement, although not clinically meaningful (defined as a change of 9.5 points or more), shown in both groups. [14]

3.3 Critique of the indirect comparison and/or network meta-analysis

No indirect comparison or network meta-analysis was conducted in the submission.

3.4 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

3.5 Conclusions of the clinical effectiveness section

The ERG does not believe that any published RCTs relevant to the decision problem that could have provided effectiveness data have been omitted from the CS. The key evidence for clinical effectiveness within the CS comprised one RCT of adjuvant nivolumab (n=532) versus placebo (n=262) which was relevant to the decision problem: CheckMate577. The RCT was of good methodological quality. This RCT was ongoing at the time of writing, with reported data coming from an interim analysis. OS data were not available to trial investigators or those in the company working on the submission.

According to clinical advice, study participants had similar pathology types and stage distribution to a UK population although, the UK eligible population is expected to be slightly older and with a lower percentage of male participants than in the RCT. [redacted]

At the clinical data cut-off, the DFS HR was 0.69 (96.4% CI 0.56, 0.86) p=0.0003, which statistically significantly favoured nivolumab over placebo. Kaplan-Meier estimated median DFS was 22.41 months

(95% CI 16.62, 34.00) in the nivolumab arm, and 11.04 months (95% CI 8.34, 14.32) in the placebo arm.

For DMFS, the hazard ratio, stratified by randomisation stratification factors, was 0.74 (95% CI 0.60, 0.92). For PFS2, the hazard ratio, stratified by randomisation stratification factors, was [redacted].

All cause AEs of grade 3-4 were experienced by 183 (34.4%) patients in the nivolumab group, and 84 (32.3%) patients in the placebo group. All cause SAEs of any grade were experienced by 158 (29.7%) patients in the nivolumab group, and 78 (30.0%) patients in the placebo group. The most frequently reported all-cause SAEs of any-grade for nivolumab-treated patients were: pneumonia (3.0%); malignant neoplasm progression (2.3%); pneumonia aspiration (1.3%); pneumonitis (1.1%); and dysphagia (1.1%). The most frequently reported all-cause SAEs of any-grade for placebo were: malignant neoplasm progression (3.1%); pneumonia (1.9%); dysphagia (1.9%); pleural effusion (1.5%). For nivolumab-treated patients, the most commonly reported immune mediated AEs of any grade were: hypothyroidism/thyroiditis (11.1%); rash (7.9%); hyperthyroidism (6.6%); and pneumonitis (4.5%). For the placebo group, the most commonly reported immune mediated AEs of any grade were: pneumonitis (1.5%); rash (1.5%); hepatitis (1.2%); and hypothyroidism/thyroiditis (1.2%). For nivolumab treated patients, the most commonly reported drug-related select AEs of any grade were: diarrhoea (16.5%); pruritus (10.0%); and rash (9.8%). In the placebo group, the most commonly reported drug-related select AEs of any grade were: diarrhoea (15.0%); and rash (3.8%). HRQoL, measured by FACT-E and EQ-5D-3L VAS, improved for both groups, with numerically similar results for both treatment arms. Significance for HRQoL was not tested.

4 COST EFFECTIVENESS

This chapter presents a summary and critique of the company's health economic analyses of adjuvant nivolumab treatment compared to routine surveillance for [redacted]. Section 4.1 presents a critique of the company's review of existing health economic analyses. Section 4.2 summarises the methods and results of the company's model. Sections 4.3 and 4.4 present the critique of the model and additional exploratory analyses undertaken by the ERG, respectively. Section 4.5 presents a discussion and critique of the available economic evidence.

4.1 Company's review of published cost-effectiveness studies

The company undertook a SLR to identify relevant cost-effectiveness studies from published literature and from previous NICE technology appraisals.

4.1.1 Company's search objective and methods

Appendices G-I of the CS report the SLRs of economic, cost and utility evidence respectively. All three reviews used the same search strategy, which is reported in Appendix G of the CS.

Databases searched included MEDLINE, Embase and Econlit (all via ProQuest). As with the clinical SLR, there were two phases of searching; only the 2020 update was reported in Appendix G, but the company provided further details of the initial phase (from 2018) in their clarification response.[9] The company also confirmed that that they had searched the National Health Service (NHS) Economic Evaluation Database in this initial phase (this source was not included in phase 2 since it is no longer being updated). Supplementary searches were undertaken of relevant conference proceedings and international HTA websites.

Noting that the SLR of HRQoL (Appendix H) identified no utility studies in the specific adjuvant population, the ERG queried whether the company had considered searching for studies of HRQoL in the broader population of oesophageal cancer. The company responded that they had decided not to do this since "*It was believed that expanding the search to a broader population would result in HRQoL / utility data that would not match with the state of wellbeing of the population of interest and therefore could not support any decisions for selecting utility inputs for the economic model.*" (clarification response, B36)[9].

Overall, the ERG is satisfied that these searches were well designed and executed and are unlikely to have missed any relevant studies meeting the stated inclusion criteria.

4.1.2 Eligibility criteria for the company's review of published economic evaluations

The inclusion and exclusion criteria used by the company are presented in Appendix G, Table G-1 of the CS. The ERG considers the inclusion criteria to be appropriate to capture recent and relevant published evidence.

4.1.3 Findings of the cost effectiveness review

Details on the review process are provided in Appendix G of the CS. Seventeen citations, representing seventeen unique studies were identified as previously published cost-effectiveness analyses that were deemed relevant to the decision problem. These were summarised in Table 21 of the CS. A further 19 studies were identified that could provide information on health care resource use. None of the identified cost-effectiveness analyses included adjuvant nivolumab as a treatment option.

4.1.4 Conclusions of the cost effectiveness review

As the company's searches did not identify any relevant studies including adjuvant nivolumab treatment, the company developed a *de novo* health economic model which is detailed in Section 4.2 and critiqued in Section 4.3.

4.2 Description of company's health economic analysis

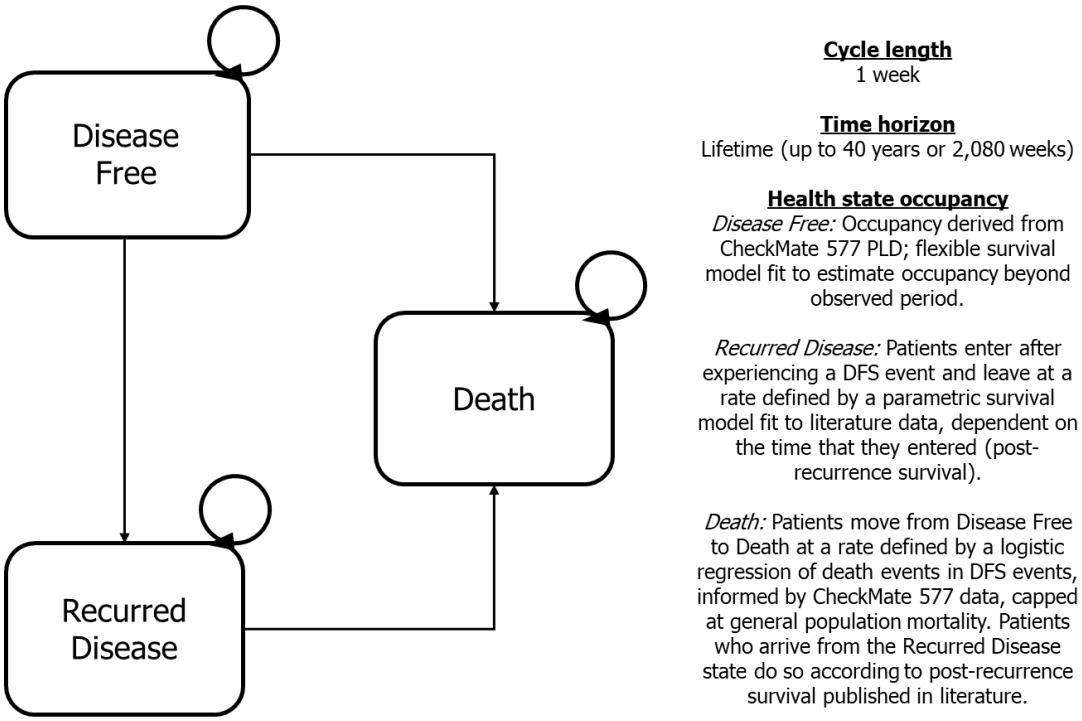
Following the clarification process, the company submitted an updated model which is exclusively focussed upon from Section 4.2.1 onwards. In addition to errors that were identified by the ERG and subsequently fixed by the company, the company also, when answering a clarification question (B27),[9] identified that there was an error in the scaling used for parametric distributions. This resulted in the original model generating a large discrepancy between the ICERs produced when using the distribution preferred by the company for DFS and those produced by the parametric distributions, with some of the results of the parametric distributions being three times greater. Following the correction of the model, these ICERs were much more similar.

4.2.1 Model overview

The company's model evaluates the use of adjuvant nivolumab monotherapy in patients with OC or GEJC who have received chemoradiotherapy followed by surgery compared to routine surveillance. The analysis has adopted a payer (NHS) perspective with the majority of costs inflated to a 2020 price year. The model employs a 40-year time horizon, with weekly time cycles to consider the lifetime of each patient. Both costs and benefits were discounted at a rate of 3.5% per annum. Half cycle correction was not undertaken but the ERG did not consider this a limitation given the weekly time cycle.

4.2.2 Model structure and logic

The model schematic supplied by the company has been replicated in Figure 3.



DFS: disease-free survival; PLD: patient-level data

Figure 3: Company's model structure (replicated from Figure 14 of the CS)

All patients begin in the disease-free state of the model. From this health state three events can occur within a time cycle: i) remaining within the disease-free health state, ii) recurrence of disease, in which case the patient is moved to the recurred disease state, or iii) death (from either disease (OC or GEJC) related reasons or from other causes) in which case the patient is moved to the absorbing death state. Once in the recurred disease state the only events that can happen are remaining in the recurred disease state or moving to the death state. The distributions used to govern movement between health states were dependent on the treatment patients received (adjuvant nivolumab treatment or routine surveillance), with an exception for patients who enter the recurred disease state, who are assumed to have the same probabilities of death regardless of initial treatment.

4.2.3 Evidence used to inform the company's model parameters

4.2.3.1 Initial patient characteristics at model entry

The deterministic base case model assumes that all patients enter the model at 60.5 years of age, with 84.5% of patients being male, which is in line with patients enrolled in CheckMate 577.

4.2.3.2 Time-to-event parameters

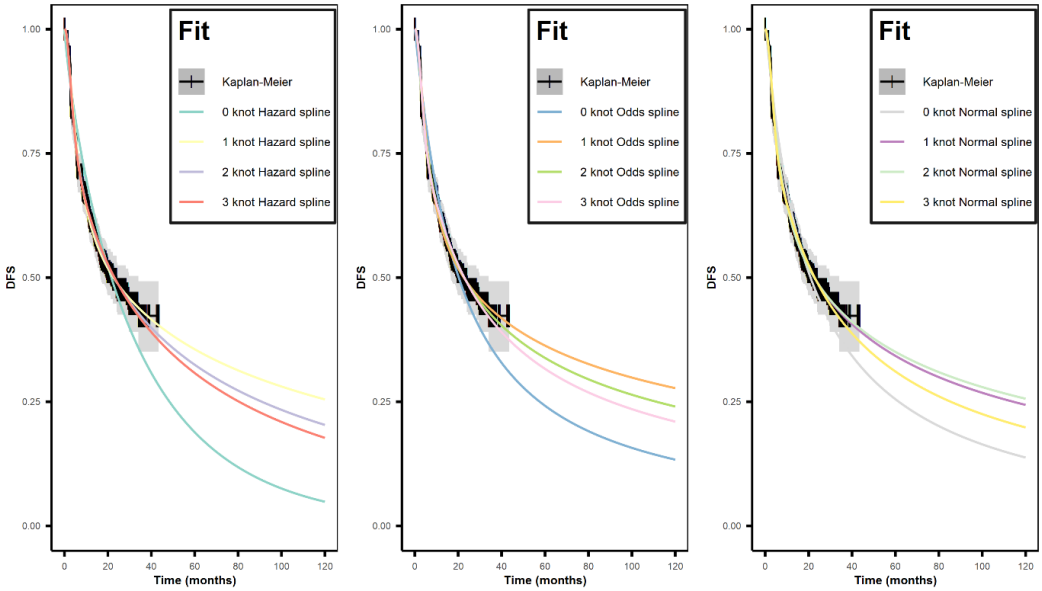
4.2.3.2.1 Disease-free survival (DFS) events

DFS events were defined as either disease recurrence or death, with the time defined as the duration between the randomisation date and the date of the first event as observed in CheckMate 577. The company explored the use of parametric survival functions, spline models, mixture models and semi-parametric models, which used parametric models after a defined cut-point. Separate models were used for the nivolumab arm and the routine surveillance arm.

The company stated the goodness-of-fit was evaluated using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) alongside a visual inspection of the fit over the observed period and consideration of the log cumulative hazard plot. Plausibility of the extrapolation was assessed '*through consideration of the long-term hazard profile and the extrapolated mean survival estimates*.' The company stated that '*the nivolumab and routine surveillance arms of CheckMate 577 demonstrated a high initial hazard during the initial study period, with a substantial number of events occurring immediately after study entry.*'

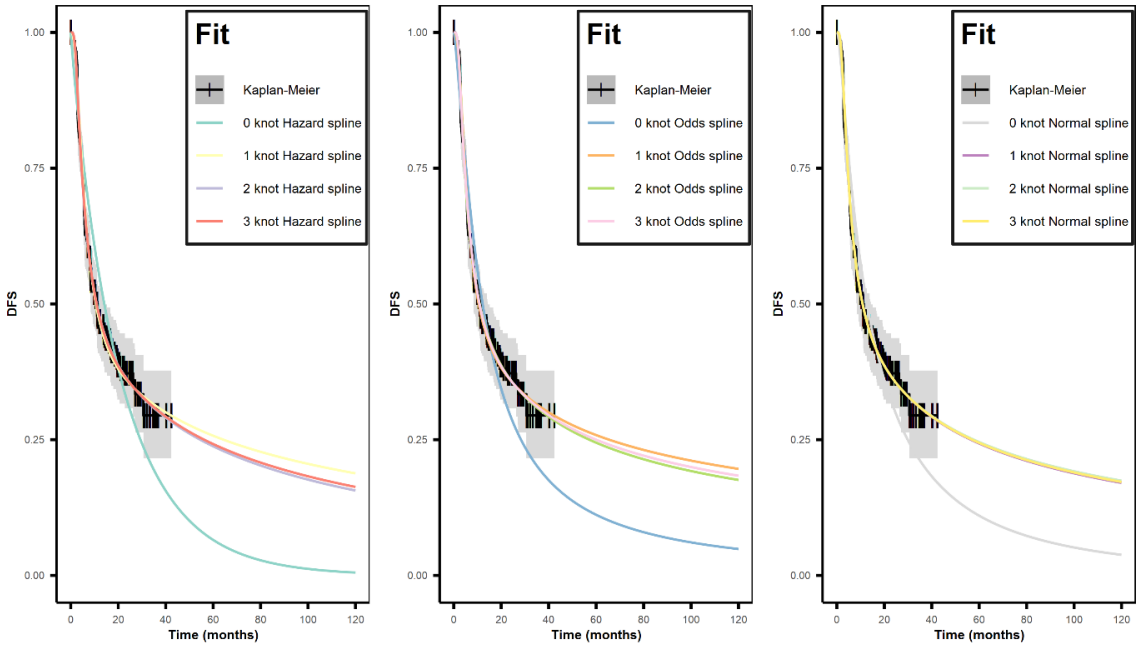
The company believed that the parametric and mixture parametric models did not '*adequately reflect either this early change in hazard or the long-term outcomes for patients.*' Semi-parametric models were deemed not to be the best approach as '*semi-parametric models with cut-points before approximately 15 months were also not able to fit the data well, as early cut points fall within the time when the hazard is changing too rapidly to provide a reliable fit. Semi-parametric models with later cut points fit the data better, but the extrapolation depended on a low number of events, which undermines the confidence in the shape of the curve*' although these models were explored in scenario analyses. The company's preferred approach was to use a log-normal spline model with one knot which the company stated '*validated well to the observed data and to the expected disease trajectory for both the nivolumab and routine surveillance arms.*' The company noted that the chosen splines had a high mean but noted that in '*the base case, it is assumed that all patients who remain disease free after three years would experience recurrence and death events at the rate of the general population ….. Therefore, the high means are constrained in the model by general population mortality. The most important factor in model choice therefore becomes the fit in the initial three years.*'

The fit of the spline models to the data observed in Checkmate 577 are provided in Figure 4 for the nivolumab arm and in Figure 5 for the routine surveillance arm.



Fit Name	AIC	BIC	Median (Months)	Mean (Months)
0 knot Hazard spline	2121.69	2142.80	21.57 (18.47, 25.50)	35.75 (29.72, 43.58)
1 knot Hazard spline	2063.14	2094.80	22.55 (17.34, 32.27)	180.14 (75.82, 805.54)
2 knot Hazard spline	2060.54	2102.75	22.90 (18.14, 30.80)	95.02 (45.21, 329.63)
3 knot Hazard spline	2062.39	2115.16	23.04 (18.39, 30.56)	75.50 (41.60, 269.09)
0 knot Odds spline	2100.38	2121.48	20.24 (16.97, 24.54)	393.92 (131.47, 4188.36)
1 knot Odds spline	2062.09	2093.75	22.55 (17.22, 32.28)	N/A
2 knot Odds spline	2060.71	2102.93	22.78 (17.99, 30.89)	N/A (109.54, N/A)
3 knot Odds spline	2061.25	2114.02	22.81 (18.37, 30.25)	N/A (96.50, N/A)
0 knot Normal spline	2083.52	2104.63	20.90 (17.46, 25.49)	75.39 (53.56, 110.87)
1 knot Normal spline	2065.42	2097.08	22.74 (17.69, 30.94)	403.31 (134.01, 4067.82)
2 knot Normal spline	2067.75	2109.96	22.61 (17.66, 31.58)	588.18 (98.04, 9637.31)
3 knot Normal spline	2061.80	2114.57	22.83 (18.43, 30.01)	154.12 (60.17, 1356.29)

Figure 4: Investigator-assessed DFS for nivolumab: spline models (reproduced from Figure 17 in Appendix M of the CS)



Fit Name	AIC	BIC	Median (Months)	Mean (Months)
0 knot Hazard spline	1249.88	1268.15	14.12 (11.87, 16.86)	21.31 (17.36, 26.50)
1 knot Hazard spline	1183.45	1210.86	10.57 (8.56, 13.66)	202.61 (49.13, 7100.08)
2 knot Hazard spline	1181.91	1218.45	10.92 (8.67, 14.47)	96.22 (33.50, 2566.38)
3 knot Hazard spline	1183.20	1228.88	10.90 (8.72, 14.44)	109.35 (33.64, 3947.44)
0 knot Odds spline	1223.05	1241.32	12.15 (10.01, 14.84)	44.42 (27.62, 85.06)
1 knot Odds spline	1181.74	1209.15	10.50 (8.36, 13.68)	N/A
2 knot Odds spline	1181.79	1218.34	10.90 (8.63, 14.43)	N/A (87.79, N/A)
3 knot Odds spline	1183.11	1228.79	10.83 (8.67, 14.41)	N/A (96.18, N/A)
0 knot Normal spline	1212.17	1230.44	12.75 (10.60, 15.45)	28.29 (20.94, 40.19)
1 knot Normal spline	1181.26	1208.67	10.92 (8.64, 14.28)	360.25 (64.17, 13344.54)
2 knot Normal spline	1183.22	1219.77	10.86 (8.62, 14.27)	430.29 (55.97, 19113.70)
3 knot Normal spline	1185.20	1230.89	10.87 (8.63, 14.46)	387.22 (50.01, 17272.59)

Figure 5: Investigator-assessed DFS for routine surveillance: spline models (reproduced from Figure 18 in Appendix M of the CS)

As stated, the company's base case model assumed that after three years being in the disease-free state that patients had the mortality risk associated with the average age- and sex-matched member of the general population. That is, the patient was effectively 'cured' after 3 years of DFS.

The company provides some validation of its chosen survival curve by showing that the median value of the distributions used were similar to those observed in CheckMate 577 being 22.74 months compared with an observed median of 22.40 months for the nivolumab arm, and being 10.92 months compared with an observed median of 11.00 for the routine surveillance arms. The ERG notes that these values are favourable to nivolumab and unfavourable to routine surveillance but acknowledges the

potential volatility of a median. Further validation of observed and modelled DFS was provided in Tables 27 and 28 of the CS, this validation is discussed further in Section 4.3.3.

4.2.3.2.1.1 The proportion of DFS events that result in death

A DFS event can be one of two events: disease progression or death. Within the model it was necessary to estimate what proportion of events were death and what proportion were disease progression. In the company's base case, the proportion of events were estimated separately for the nivolumab arm and the routine surveillance arm from CheckMate 577 patient-level data. The model selected for use was a logistic model with time as a single, linear covariate. Further brief details were provided in Clarification Response B25.[9]

A plot of the proportion of DFS events that are estimated to be death in the first 3 years is provided in Figure 6. This figure was generated by the ERG, and shows that a higher proportion of events in the nivolumab arm are estimated to be deaths, although it should be noted that there are fewer DFS events in the nivolumab arm. The company provided a sensitivity analyses assuming that the probability of a DFS event being death was constant for each arm, although these constant values were greater than all values in the initial 3-year period and so this was disregarded by the ERG.

Figure 6: The proportion of DFS events that are estimated to be deaths

4.2.3.2.2 Time to death from the recurred disease state

Survival post-recurrence were not available to the company from CheckMate 577 and thus an alternative source was used to estimate this distribution. The chosen source was Lou *et al*.[27] which

detailed survival of a cohort of patients who had undergone surgical resection for OC between 1996 and 2010 at the Memorial Sloan-Kettering Cancer Center in New York. Data presented in Lou *et al*. were digitised to create patient-level data using the Guyot *et al*. algorithm,[28] with parametric models fitted to these data. Figure 22 in the CS has been reproduced in Figure 7; the company has confirmed that the y-axis should be labelled survival probability rather than 'recurrence free' probability. The company selected the Gompertz distribution as the most appropriate for use in the base case with this distribution assumed to apply to patients regardless of whether they had received adjuvant nivolumab treatment or routine surveillance.

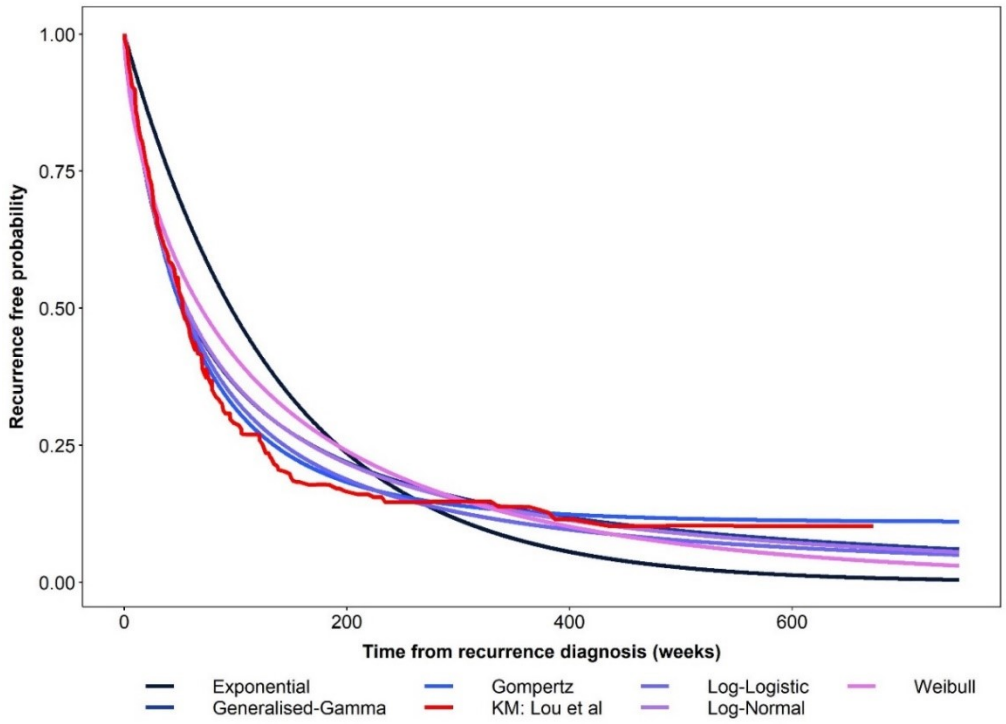


Figure 7: The estimated probability of survival post-recurrence (reproduced from Figure 22 of the CS)

The company states that the cohort represents a "*mixed group of patients with both adenocarcinoma and squamous cell carcinoma histologies, as a heterogeneous group of patients who have experienced recurrence, receiving any and all further lines, may progress and experience death at different times*" and that "*these data were therefore considered representative of the CheckMate 577 study population and the likely survival trajectory after disease recurrence*." The company did not comment in the CS on the generalisability of either the geographical location or the time period in which the data were collected, however, did provide additional data in Table 7 of its clarification response, and suggested '*our review of more recent analyses than Lou et al in comparable populations, including UK-specific*

publications for advanced oesophagogastric adenocarcinoma patients, suggests that any improvements in the standard of care have not translated to better post-recurrence survival outcomes.' Whilst the ERG notes that the data in Lou *et al.* are collected between 1996 and 2010, it is content that these are suitable for use in decision making.

4.2.3.2.3 Time to death after three years within the DFS health state

For patients who have been within the DFS health state for three years it is assumed that the patient has the same mortality risk as an average age- and sex-matched person using 2019 values from England and Wales.[29] An abridged table of annual probability of mortalities by sex and age is provided in Table 29 of the CS.

4.2.3.2.4 Time on adjuvant nivolumab treatment

Time on nivolumab treatment is modelled directly from the data observed in CheckMate 577 with the exception that in the company's base case no patient is assumed to have a treatment duration of greater than 12 months. This assumption is relaxed in a scenario analysis. Figure 8 reproduces Figure 24 of the CS which shows the duration of nivolumab treatment and the DFS associated with treatment. The ERG comments that there is a steep decline in those on treatment approaching 12 months, but that a small proportion of patients had treatment for longer than 12 months.

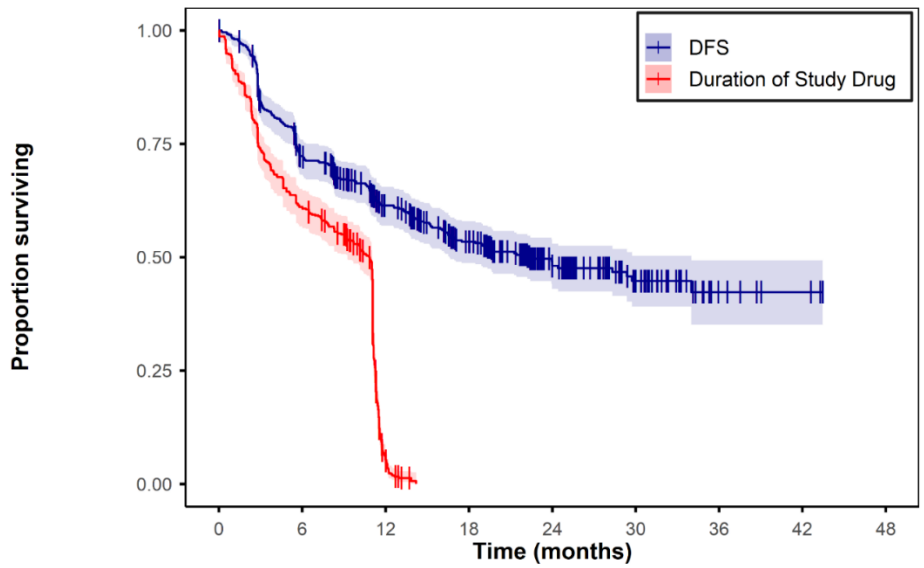


Figure 8: Time until adjuvant nivolumab treatment (reproduced from Figure 24 of the CS)

4.2.3.3 Health-related quality of life

EQ-5D-3L data were collected within CheckMate 577[13] for patients in the disease-free health state. However, the baseline values for both the nivolumab arm (0.820) and the routine surveillance arm (0.831) were greater than for the age- and sex-matched population value as estimated by Szende *et al.*[30]

Given these data the company elected to use age- and sex-matched values for those in the disease-free survival state.

Data on utility post-recurrence was also collected in CheckMate 577, however, there was a considerable amount of missing data, and the values observed were higher than the value estimated by Szende *et al*.[30] for an age- and sex-matched population. The company conducted a pragmatic literature review of previous NICE Technology Appraisals. The value selected for use in the base case (0.747) was taken from patients within the control arm of an STA of nivolumab in patients with previously treated unresectable advanced oesophageal cancer.[31] Alternative values were used in sensitivity analyses. The model assumed that the utility in the post recurrence state was the minimum value of the age- and sex-matched value or 0.747. This assumption resulted in utilities being the same for the disease-free survival state and the post-recurrence state for patients aged 75 years and over. The company acknowledged this situation, but highlighted that when lower values for post-recurrent utility was used the ICER became more favourable to adjuvant nivolumab treatment, and chose not to amend their model.

The company included disutility associated with adverse events due to nivolumab treatment. This disutility (0.007) whilst on treatment was not explicitly linked to specific adverse events, but was calculated as the difference in utilities observed in CheckMate 577 between the nivolumab and the routine surveillance arms.[13]

The estimates for health state utility values applied in the company's model are summarised in Table 13.

Table 13: Health state utility values used in the company's base case analysis

Health state	Utility value
Disease-free (both arms)	[redacted]*
Post-recurrence (both arms)	0.747†
Treatment related disutility – nivolumab	-0.007

* Age and sex dependent, value is presented for a cohort of patients aged 60.5 years with 84.5% male.

†Assumed to be the lower of 0.747 and the value for disease-free

4.2.3.4 Resource use and costs

The following sections detail the drug acquisition costs, drug administration costs, disease management costs, subsequent treatment costs, and the costs associated with managing adverse events used within the model.

4.2.3.4.1 Drug acquisition costs

Nivolumab is available in a 10 mg/mL concentration for IV infusion in 4 mL (40 mg), 10 mL (100 mg) and 24 mL (240 mg) vials. The list prices of these vials are £439.00, £1,097.00 and £2,633.00 respectively. Nivolumab treatment is expected to be provided for a maximum duration of one year with a dose of 240mg administered intravenously (IV) fortnightly for 16 weeks, and then four-weekly at a dose of 480mg IV. All administrations take 30 minutes. The company has proposed a PAS which takes the form of a simple price discount of [redacted]; this results in a drug acquisition cost of [redacted] for patients who receive nivolumab for a 12-month period. Routine surveillance has been assumed to have no drug acquisition costs.

4.2.3.4.2 Drug administration costs

Administration costs for nivolumab were taken from NHS Reference Costs 2018/19 as a weighted average of SB123Z HRG codes, which report costs dependent on whether the administration was a day case, an outpatient, or other, and was inflated to 2020 values. The cost used in the model was £252.73 per nivolumab administration. Routine surveillance was not associated with administration costs.

4.2.3.4.3 Disease management costs

The resource use, unit costs and weekly cost for both the disease-free and post-recurrence health states are detailed in

Table **14**. The weekly costs used in the model and the terminal care costs are presented in Table 15. There is a marginal discrepancy between the values in

Table **14** and Table 15 which the ERG believes to be due to some of the values in

Table **14** not being uplifted for inflation. The ERG is content that the values reported in Table 15 are sufficient for decision making.

Table 14: Type of resources, frequencies and unit costs for disease management costs used in the model for both nivolumab and routine surveillance

Resource	Weekly frequency of resource use	Unit cost	Weekly total
Disease-free			
Scans (CT/MRI)	0.0833*	£132.85	£11.07
Oncologist visits (ongoing monitoring)	0.0833*	£280.00	£23.33
Post-recurrence			
Clinician consultation	0.153	£187.36	£28.67
CT scan	0.092	£97.15	£8.94
Full blood count	0.221	£2.79	£0.62
Renal function test	0.162	£1.10	£0.18
Hepatic function test	0.170	£1.10	£0.19
Hospitalisation	0.095	£534.07	£50.74
Palliative care specialist nurse	0.359	£76.74	£27.55

CT: Computerised tomography; MRI: Magnetic resonance imaging.

* For the initial year only. Resource use halves at the start of the second year and then halves again at the start of the third year. This value is used until the end of the fifth year, when resource use is assumed to terminate.

Table 15: Weekly health state costs used in the model independent of initial treatment

Health State	Mean weekly health state cost
Disease-free	
First 52 weeks	£36.14
Weeks 53 to 104	£18.07
Weeks 105 to 260	£9.04
Subsequent weeks	£0.00
Post-recurrence	£119.53
Terminal costs	£8,364.08

4.2.3.4.4 Subsequent treatment costs

The model includes the costs of subsequent treatments following recurrence. The assumed costs, which are shown in Table 16, were independent of whether a patient received nivolumab treatment.

Table 16: Second-line treatment costs

Description	Oxaliplatin	5-Fluorouracil (5-FU)	Capecitabine	Cisplatin (in addition to capecitabine)	Cisplatin (in addition to fluorouracil)
Weeks between treatment cycles	2	1	12	1	4
Costs per treatment cycle					
Drug cost	£19.21	£2.91	£79.03	£6.81	£11.02
Administration cost	£252.73	£252.73	£0.00	£252.73	£252.73
Total cost per treatment cycle	£271.94	£255.64	£79.03	£259.54	£263.75
Proportional weighting	50%	50%	50%	25%	25%

Note: The dose of capecitabine is twice per day for fourteen days every 21 days.

4.2.3.4.5 Costs associated with the management of adverse events

Incidence rates and management costs for AEs included in the model are specified in

Table **17**. Three conditions (lymphocyte count decreased, pruritus and psoriasis are assumed to have no cost implications.

Table 17: Incidence rates and unit costs for Grade 3-5 AEs used in the model

Adverse event	Frequency of adverse event over the treatment period		Unit cost	Costs associated with an adverse event	
	Nivolumab	Routine surveillance		Nivolumab	Routine surveillance
Pneumonitis	[redacted]	[redacted]	£641.27[32]	£15.56	£3.84
Fatigue	[redacted]	[redacted]	£205.03[32]	£3.11	£0.00
Lymphocyte count decreased	[redacted]	[redacted]	£0.00[32]	£0.00	£0.00
Rash	[redacted]	[redacted]	£62.86[32]	£0.76	£0.38
Colitis	[redacted]	[redacted]	£3,193.34[33]	£29.06	£0.00
Interstitial lung disease	[redacted]	[redacted]	£641.27*	£5.84	£0.00
Myocarditis	[redacted]	[redacted]	£558.54**	£5.08	£0.00
Pruritus	[redacted]	[redacted]	£0.00	£0.00	£0.00
Psoriasis	[redacted]	[redacted]	£0.00	£0.00	£0.00

* assumed equal to pneumonitis ** assumed equal to hyperthyroidism [32]

4.2.4 Model evaluation methods

The CS presents the results of the base case analyses in terms of ICERs (cost per QALY gained) for nivolumab versus routine surveillance

The distributions used for the PSA undertaken by the company are presented in Table 44 of the CS. The results of the PSA are additionally presented as points on a cost-effectiveness plane and as cost-effectiveness acceptability curves (CEACs).

4.2.5 Company's model validation and verification

The CS reports that assumption and parameter values used in the models were validated by clinical experts, and that model outcomes were validated against published outcomes.

4.2.6 Company's cost-effectiveness results

The probabilistic and deterministic results presented in this section are based on the updated version of the company's model submitted in response to the clarification and the fact check process.

Central estimates of cost-effectiveness

The central estimates of cost-effectiveness generated using the company's model for the comparison of adjuvant nivolumab compared with routine surveillance are presented in Table 18. The probabilistic

version of the model suggests that adjuvant nivolumab therapy is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient; generating an ICER of £22,822 per QALY gained. The deterministic version of the model produces a slightly lower ICER of £22,766 per QALY gained. The model appears relatively linear based on the similarity of the deterministic and probabilistic estimates.

The company presents disaggregated outcomes, costs incurred, QALYs accrued and life years accrued by different elements or states in the model, these results are presented in Table 19. The additional costs are primarily associated with the acquisition cost of nivolumab whilst the bulk of the QALY gain is due to a longer time spent alive in the disease-free health state.

Table 18: Company's results - Base Case Analysis, nivolumab versus routine surveillance

Description	Total life years accrued	QALY accrued	Total costs incurred	Incremental			ICER
				Life years	QALYs	Cost	
Probabilistic model							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,822
Deterministic model							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,766

QALYs: Quality-adjusted life years ICER: Incremental cost-effectiveness ratio

Table 19: Base case disaggregated outcomes

Description	Nivolumab	Routine surveillance	Incremental
Disaggregated costs (discounted)			
Disease-free health state	[redacted]	[redacted]	[redacted]
Disease-free health state (long term)	[redacted]	[redacted]	[redacted]
Post-recurrence health state	[redacted]	[redacted]	[redacted]
Death state	[redacted]	[redacted]	[redacted]
Treatment (nivolumab)	[redacted]	[redacted]	[redacted]
Modelled second line treatment	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
Disaggregated QALYs (discounted)			
Disease-free health state	[redacted]	[redacted]	[redacted]
Disease-free health state (long term)	[redacted]	[redacted]	[redacted]
Post-recurrence health state	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
Clinical outcomes (undiscounted, years)			
Median disease-free survival	[redacted]	[redacted]	[redacted]
Mean disease-fee survival	[redacted]	[redacted]	[redacted]
Median overall survival	[redacted]	[redacted]	[redacted]
Mean overall survival	[redacted]	[redacted]	[redacted]
Time in health state (undiscounted, years)			
Disease-free health state	[redacted]	[redacted]	[redacted]
Disease-free health state (long term)	[redacted]	[redacted]	[redacted]
Post-recurrence health state	[redacted]	[redacted]	[redacted]

Notes: QALYs: Quality-adjusted life years

The distribution of patients amongst health state across time is shown in Figure 9 for nivolumab treatment and in Figure 10 for routine surveillance.

Figure 9: Company's base case survival curves for adjuvant nivolumab treatment (model traces)

Figure 10: Company's base case survival curves for routine surveillance (model traces)

4.2.8 Company's PSA

As shown in Table 18 the company's probabilistic estimate of the ICER was £22,822. The company also presented scatterplots and CEACs for adjuvant nivolumab compared with routine surveillance in its clarification response. The company's base case model, estimates that adjuvant nivolumab treatment is below a willingness-to-pay threshold of £20,000 per QALY gained on [redacted] of occasions and that adjuvant nivolumab treatment is below a willingness-to-pay threshold of £30,000 per QALY gained on [redacted] of occasions.

Figure 11 presents the company's base case CEAC for nivolumab versus routine surveillance.

Figure 11: Company's base case CEAC. Nivolumab versus routine surveillance (adapted from the company's model)

4.2.9 Company's DSA

Deterministic sensitivity analyses (DSAs) are presented for adjuvant nivolumab compared with routine surveillance using tornado plots. Most of these analyses are performed by assuming 20% variability on parameters, assuming 80% of the parameter value as a lower bound and 120% of a parameter value as an upper bound. The exceptions are the annual discount rates for costs and benefits where the lower bound of zero and an upper bound of 0.06 are assumed and the percentage of the patient cohort which are assumed to be male where a lower bound of 0% and an upper bound of 100% are assumed.

Following the clarification process, the company presented revised results for the DSA, these results are presented in Figure 12; only analyses that impact on the ICER are included. Only one sensitivity analysis performed by the company increased the ICER to greater than £30,000 which was assuming that patients were 72.6 years at the time of adjuvant nivolumab treatment.

Figure 12: Tornado diagram showing the company's DSA (reproduced from Figure 2 of the company's clarification response)

4.2.10 Company's scenarios analyses

The company performed multiple scenario analyses, with those deemed most relevant by the ERG detailed here. Further analyses are presented in the CS[1] and response to clarification questions.[9] Where pertinent analyses were not provided by the company following the updating of the model, these were run by the ERG. The company scenarios detailed in the ERG report are: using the Generalised-F distribution to predict disease-free survival; increasing the period before the patient is considered cured; assuming nivolumab treatment can be extended to 63 weeks; using utility data from Ara and Brazier[34] rather than Szende *et al*.[30]; using Kaplan Meier data directly to estimate DFS; and varying the utility assumed post-recurrence. The results of these analyses are presented in Table 21 to Table 25 respectively. In none of these analyses did the ICER increase above £30,000 per QALY gained. For reference, the company's base case analysis produced an ICER of £22,766.

The ERG comments that some scenario analyses, which may *a priori*, be thought to markedly affect the ICER, did not, for example, the distribution related to survival post-recurrence. The company examined using different distributions to represent the post-recurrence survival reported by Lou *et al*.[27] and using post-recurrence data from the Netherlands[35] (with different distributions fitted to these data).

Table 20: Scenario analysis using the Generalised-F distribution for disease-free survival

Description	Life years	QALYs	Costs
Nivolumab	[redacted]	[redacted]	[redacted]
Routine surveillance	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]

ICER			£17,729

QALYs: Quality adjusted life years ICER: Incremental cost-effectiveness ratio

Table 21: Scenario analysis results assuming that general population risks applied after five years of disease-free survival rather than from 3 years

Description	Life years	QALYs	Costs
Nivolumab	[redacted]	[redacted]	[redacted]
Routine surveillance	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]
ICER			£27,114

QALYs: Quality adjusted life years ICER: Incremental cost-effectiveness ratio

Table 22: Scenario analysis results assuming that nivolumab treatment has a maximum duration of 63 weeks

Description	Life years	QALYs	Costs
Nivolumab	[redacted]	[redacted]	[redacted]
Routine surveillance	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]
ICER			£23,052

QALYs: Quality adjusted life years ICER: Incremental cost-effectiveness ratio

Table 23: Scenario analysis results using utility data from Ara and Brazier rather than Szende *et al*

Description	Life years	QALYs	Costs
Nivolumab	[redacted]	[redacted]	[redacted]
Routine surveillance	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]
ICER			£22,280

QALYs: Quality adjusted life years ICER: Incremental cost-effectiveness ratio

Table 24: Scenario analysis using the Kaplan Meier data directly to represent DFS

Description	Life years	QALYs	Costs
Nivolumab	[redacted]	[redacted]	[redacted]
Routine surveillance	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]

ICER			£20,248

QALYs: Quality adjusted life years ICER: Incremental cost-effectiveness ratio

Table 25: Scenario analysis results using a range of values for post-recurrence utility

Description	ICER
Post recurrence utility value: 0.747 (base case)	£22,766
Post recurrence utility value: 0.70	£22,478
Post recurrence utility value: 0.65	£22,154
Post recurrence utility value: 0.60	£21,841
Post recurrence utility value: 0.55	£21,535
Post recurrence utility value: 0.50	£21,239
Post recurrence utility value: 0.45	£20,950
Post recurrence utility value: 0.42	£20,781

ICER: Incremental cost-effectiveness ratio

4.3 Critical appraisal of the company's health economic analysis

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic model upon which this was based. These included:

- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Examination of the correspondence between the description of the model reported in the CS and the company's executable model.
- Replication of the base case results, PSA, DSAs and scenario analyses presented within the CS.
- Where possible, checking of parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

4.3.1 Model verification

The ERG believes the company's updated version of the model to be generally well programmed and free from major errors, and that the model structure and parameter values used are appropriate for the decision problem.

4.3.2 Adherence of the company's model to the NICE Reference Case

The company's economic analysis of adjuvant nivolumab treatment in OC and GEJC is generally in line with the NICE Reference Case. The ERG's summary of the adherence of the company's model to the NICE Reference Case is provided in Table 26. The ERG believes that the company's model structure can be used in decision making.

Table 26: Adherence of the company's economic analyses to the NICE Reference Case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The company has amended the population in the decision problem to [redacted], stating that the "*evidence presented in this submission is derived from the pivotal CheckMate 577 trial, which included patients with resected OC or GEJ cancer who have received chemoradiotherapy followed by complete resection.*"
Comparator(s)	As listed in the scope developed by NICE	✔
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	✔
Perspective on costs	NHS and PSS	Only an NHS perspective was applied
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	✔
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	✔
Synthesis of evidence on health effects	Based on systematic review	The company assumed that those in the DFS state had a utility equal to the age- and sex-matched population. The utility for those in the post-recurrence health state was selected following a pragmatic literature review, although this was not adjusted as patients aged and was replaced by the DFS value if this were lower. The disutility associated with adjuvant nivolumab treatment (0.007) was estimated from the CheckMate 577 study.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	✔
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	✔
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	✔
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✔

Element	Reference case	ERG comments
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	✔ (Although only an NHS perspective was used)
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	✔

4.3.3 Main issues identified within the critical appraisal

Box 1 summarises the main issues identified within the ERG's critical appraisal of the company's revised economic analyses.

Box 1: Main issues identified within the critical appraisal undertaken by the ERG

(1) That the most recent DFS data have not been considered in generating distributions.

(2) Selection of the 1 knot spline model rather than the Generalised-F distribution for modelling DFS

(3) Assumption of a 'cure' at 3 years of DFS rather than at 5 years

(4) That the average age of patients in the UK are anticipated to be older than those recruited to CheckMate 577

(5) That above the age of 75 years, patients had the same utility independent of whether they were in the DFS health state or the post-recurrence health state

(6) Potential underestimation of the costs of adjuvant-nivolumab treatment within the model

(7) Use of the utility data from Szende *et al*., rather than from Ara and Brazier

The rationales for the items listed in Box 1, are provided below.

1. The most recent DFS data have not been considered in generating distributions

Additional data were provided by the company within the clarification process, taken from an updated data cut (February 2021) which was received by the company after its submission. The updated data are shown in Figure 13. The ERG believes that the company should fit distributions to the newer data and use these in its modelling.

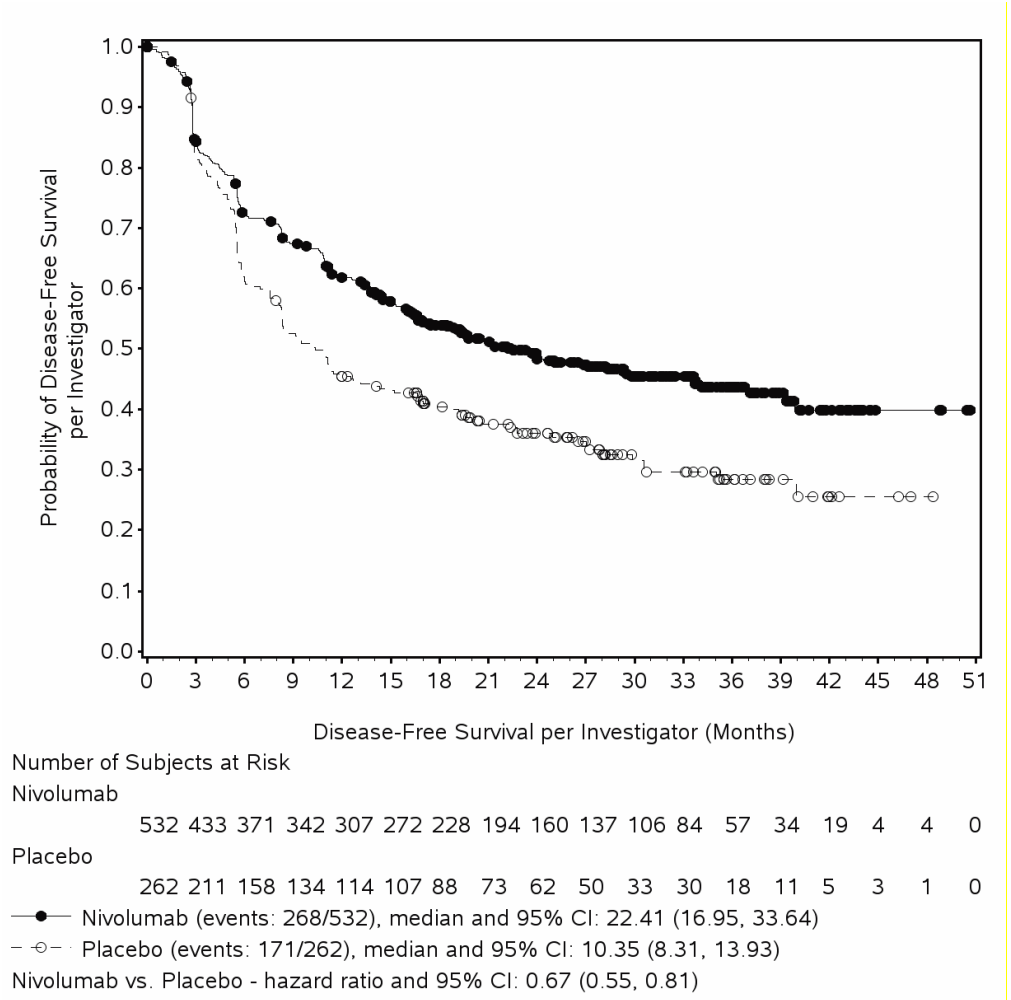


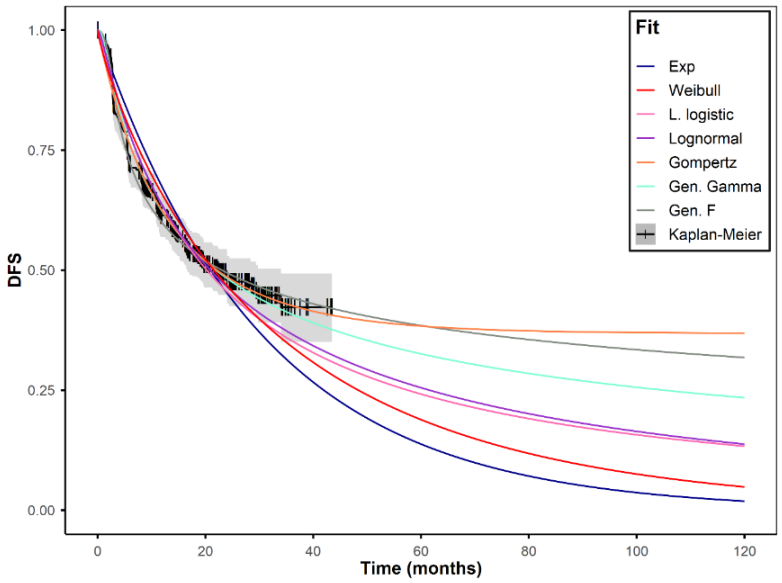
Figure 13: Updated DFS data (February 2021). Reproduced from Figure 7 of the company's clarification response)

2. Selection of the 1 knot spline model rather than the Generalised-F distribution for modelling DFS

As detailed in Section 4.2.3.2.1 the company used a 1 knot spline model to model DFS. However, the ERG believes that the Generalised-F distribution should be preferred. The BIC for the 1 knot spline model was 2097.08 for the nivolumab arm and 1208.67 for the routine surveillance arm, but were 2063.75 and 1188.79 respectively for the Generalised-F distribution, indicating strong evidence that the Generalised-F distribution fitted better to the observed data.[36] A similar advantage for the Generalised-F distribution compared to the 1 knot spline model was observed when comparing AIC values. As the observed data covered a period slightly over 40 months in duration, and the company assumed a 'cure' at 3 years, the ERG does not believe that extrapolated values should carry much weight in the model choice. There was also no indication based on the underlying hazards or clinical plausibility that the Generalised-F distribution was inappropriate.

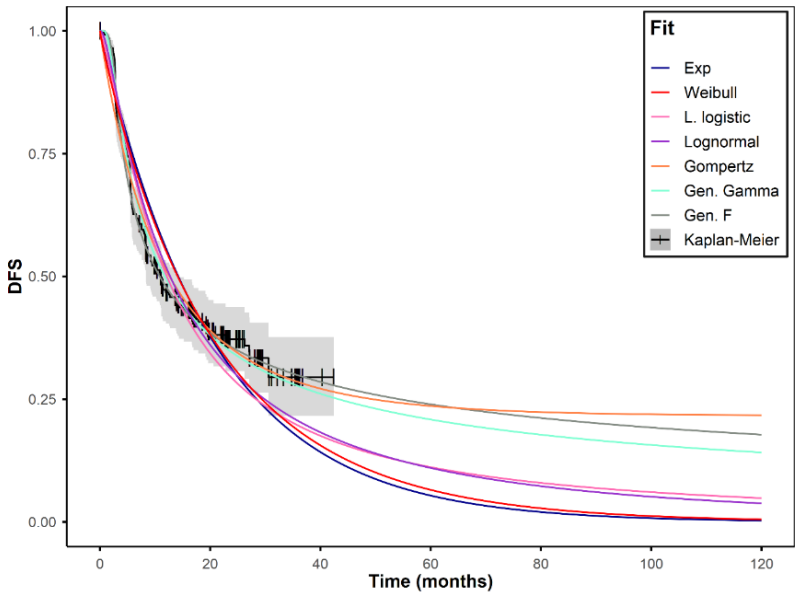
The ERG does not agree with the company that '*the generalised F model is not explicitly recommended by NICE TSD 14*[37]' as this document states that '*other more weakly structured, flexible models [are] available …… These have not been used in NICE Appraisals as yet, but are potentially very useful.*'

The fit of parametric distributions to the data observed in Checkmate 577 are provided in Figure 14 for the nivolumab arm and in Figure 15 for the routine surveillance arm. The Generalised-F distribution appears to visually fit the data well.



Fit Name	AIC	BIC	Parameters	Median (Months)	Mean (Months)
Exp.	2127.62	2131.89	lambda: 0.0330	20.98 (18.30, 24.28)	30.27 (26.40, 35.03)
Weibull	2121.69	2130.25	shape: 0.8584; scale: 33.0558	21.57 (18.47, 25.50)	35.75 (29.73, 43.58)
Gompertz	2094.14	2102.70	shape: -0.0535; rate: 0.0534	22.16 (17.77, 30.76)	N/A
L. logistic	2100.38	2108.93	shape: 1.0516; scale: 20.2428	20.24 (16.99, 24.54)	393.92 (131.47, 4188.4
ognormal	2083.52	2092.08	mu: 3.0395; sigma: 1.6020	20.90 (17.46, 25.49)	75.39 (53.56, 110.87)
en. Gamma	2071.69	2084.52	mu: 2.4381; sigma: 1.7821; Q: -0.9972	21.96 (17.60, 28.84)	N/A (108.77, N/A)
Gen. F	2046.64	2063.75	mu: 1.1323; sigma: 0.4760; Q: -6.7388; P: 14.0601	23.07 (17.01, 33.37)	N/A (38.41, N/A)

Figure 14: Investigator-assessed DFS for nivolumab: parametric distributions (reproduced from Figure 6 in Appendix M of the CS)



Fit Name	AIC	BIC	Parameters	Median (Months)	Mean (Months)
Exp.	1248.56	1252.13	lambda: 0.0487	14.22 (12.02, 16.88)	20.52 (17.35, 24.35)
Weibull	1249.88	1257.02	shape: 0.9468; scale: 20.7897	14.12 (11.87, 16.86)	21.31 (17.36, 26.50)
Gompertz	1232.17	1239.31	shape: -0.0477; rate: 0.0730	12.64 (10.33, 15.76)	N/A
L. logistic	1223.05	1230.19	shape: 1.2989; scale: 12.1505	12.15 (10.01, 14.84)	44.41 (27.59, 85.13)
Lognormal	1212.17	1219.31	mu: 2.5453; sigma: 1.2628	12.75 (10.60, 15.45)	28.29 (20.94, 40.18)
Gen. Gamma	1187.64	1198.34	mu: 1.7564; sigma: 1.1688; Q: -1.5152	11.78 (9.54, 14.89)	N/A (71.40, N/A)
Gen. F	1174.52	1188.79	mu: 1.0854; sigma: 0.2823; Q: -7.2939; P: 15.5229	10.85 (8.77, 14.63)	N/A (101.87, N/A)

Figure 15: Investigator-assessed DFS for routine surveillance: parametric distributions (reproduced from Figure 7 in Appendix M of the CS)

Comparisons of the observed data to the modelled estimates from the 1 knot spline model and the Generalised-F are provided within Table 27; observed data for DFS was not explicitly reported at 3 years. At 3 time points reported (6 months, 1 year, and 2 years) the Generalised-F model looked as good, if not a better fit to the observed data, than the 1 knot spline, acknowledging that goodness-of-fit measures will be a better gauge than 3 discrete points.

As patients in the DFS state at 3 years are assumed to have the general mortality hazard beyond this time point, any inaccuracy in the proportion in DFS at three years could have considerable consequences for the incremental cost-effectiveness ratio (ICER). The use of the Generalised-F distribution results in a greater number of patients in DFS at 3 years (43.2% of patients for adjuvant nivolumab and 29.2% for routine surveillance) than the values estimated using the 1 knot spline (40.1% and 28.9% respectively).

Table 27: The comparison of DFS between the data observed in CheckMate 577 and that produced by the company's base case model

	DFS at 6 months	DFS at 1 year	DFS at 2 years
Adjuvant nivolumab treatment			
Observed	72.2%	61.4%	48.1%
Log-normal 1 knot spline (model results) – Company preferred	73.2%	59.5%	46.9%
Generalised-F – ERG preferred	72.1%	59.3%	48.5%
Routine surveillance			
Observed	63.4%	46.7%	37.2%
Log-normal 1 knot spline (model results)	63.7%	45.9%	34.3%
Generalised-F – ERG preferred	64.3%	47.5%	34.8%

DFS: disease free survival

In the company's scenario analysis, it was seen the use of the Generalised-F distribution reduced the ICER from an ICER of £22,766 to an ICER of £17,729. (Table 20). Additionally, newer DFS data have been obtained by the company (see point 1) after the initial submission. As stated, distributions fitted to the newer data would be preferred by the ERG.

3. Assumption of a 'cure' at 3 years of DFS rather than at 5 years

Clinical advice to the ERG suggested that they would be more confident that a patient could be considered 'cured' at 5 years rather than 3 years. Figure 13 indicated that few, but some, events were occurring after 3 years, although it is unknown whether these were recurrence or death events.

Using 5-years to define a 'cure' point rather than 3-years was shown to increase the ICER from £22,766 to an ICER of £27,114 (Table 21). This was because the percentages of patients considered 'cured' at 5 years were reduced from 40.1% to 31.6% in the adjuvant nivolumab arm and from 28.9% to 22.5% in the routine surveillance arm.

4. That the average age of patients in the UK are anticipated to be older than those recruited to CheckMate 577

Clinical advice provided to the ERG indicated that patients in CheckMate 577 are younger than those treated in UK practice. At the Fact Check stage the company provided data from the National Oesophago-Gastric Cancer Audit[25] which gives a median age for patients in England and Wales with oesophageal squamous cell carcinoma with a planned treatment modality of surgery of 67 years (inter quartile range 60–73). Data for adenocarcinoma patients were not available. This supports the clinical

advice provided to the ERG, although the company states that the median age in CheckMate 577 (62.0 years) falls within the published inter quartile range of the National Oesophago-Gastric Cancer Audit.

Figure 12 shows that the ICER is sensitive to the assumed age of the population with the ICER rising to £37,462 when the population age was set to 67 years rather than 60.5 years. The 72.6 years of age value, however, represented an increase of 20% rather than an informed value and at Fact Check stage the company provided data suggesting a median age of 67 years.

5. **That above the age of 75 years, patients had the same utility independent of whether they were in the DFS health state or the post-recurrence health state**

The structure of the company's model means that above 75 years of age, patients have the same utility in both the disease-free and the post-recurrence health states. The ERG believes it is implausible that, on average, patients would not have a higher utility if they remained in DFS rather than having had recurrent disease. Scenario analyses presented by the company show that the ICER decreases if the post-recurrence utility is reduced. (Table 25).

6. **Potential underestimation of the costs of adjuvant-nivolumab treatment within the model**

Within CheckMate 577 a small proportion of patients received adjuvant nivolumab treatment for longer than the 12 months assumed within the model. The ERG cannot discount the possibility that the increased nivolumab treatment may have had a beneficial effect on the patient which would be incorporated into the modelled DFS distributions. In order that the benefits are represented by the actual costs incurred the ERG prefers the company's scenario analysis which allows treatment up to a period of 63 weeks, based on the observed time on treatment. Allowing for treatment up to 63 weeks increased the ICER from £22,766 to an ICER of £23,052 (Table 22). At the fact check stage the company provided further information suggesting that the elongated treatment duration was due to dose delays which were not incorporated in its model, meaning that the costs used by the ERG may be an over-estimation.

7. **Limitations regarding the use of utility data from Szende *et al***

The company states that it chose to use data from Szende *et al*. as they were newer than those of Ara and Brazier, but that the company considered the two sources as comparable. The ERG prefers Ara and Brazier, primarily because there are broad age categories in Szende, which results in utility being constant beyond the age of 75 years which is considered implausible. This may be important when the limitation associated with the utility estimated in the post-recurrence state (see point 5) is explored. The ERG notes that for the initial period in the model (from ages 60 to 71 years) the utility values are estimated to be higher in Ara and Brazier.

4.4 Exploratory analyses undertaken by the ERG

4.4.1 Overview of ERG's exploratory analyses

The ERG undertook exploratory analyses to address five of the key points identified within the critical appraisal (Section 4.3.3). These four points (Issues 2, 3, 4, 6 and 7) were ones where the ERG felt confident that these changes would provide a more accurate answer. The methods used for these analyses are detailed in Section 4.4.2, with the results produced contained in Section 4.4.3.1

Analyses could not be robustly undertaken by the ERG for the remaining points (Issues 1 and 5). For these, the estimated directional change in the ICER is provided, if known, along with illustrative results, where appropriate, are presented in Section 4.4.3.2.

The ERG's preferred base case combined all of the five ERG exploratory analyses. This base case should be taken with moderate caution due to factors (Issues 1 and 5) which could affect the ICER and that have not been incorporated in this central estimate.

4.4.2 ERG's exploratory analyses - methods

ERG exploratory analysis 1: Using the Generalised-F distribution for DFS

To implement this exploratory analysis the ERG used the drop-down boxes within the company's model to select the Generalised-F distribution for both nivolumab and routine surveillance.

ERG exploratory analysis 2: Using a 'cure' point at five years DFS

To implement this exploratory analysis the ERG used the functionality built in to the company's model, by changing 'intRemCycleTrt' and 'intRemCycleCtrl' to a value of 5.

ERG exploratory analysis 3: Assuming a mean age of 65 years for each patient.

At the Fact Check stage the company contested the ERG's statement that the anticipated population was likely to be greater than the 60.5 years assumed in the model and highlighted data indicating that the median age for patients in England and Wales with oesophageal squamous cell carcinoma with a planned treatment modality of surgery of 67 years (inter quartile range 60–73 years[25]) compared with 62 years in CheckMate 577. These data support an older population. The ERG has run an analysis assuming a mean of 65 years of age (for simplicity, approximately adding the difference in medians (5.0 years) to the mean age in the company's base case)

ERG exploratory analysis 4: Allowing a maximum of 63 weeks of nivolumab treatment

To implement this exploratory analysis the ERG used the drop-down box within the company's model to select 'Nivolumab 63 weeks' rather than 'Nivolumab 52 weeks' for 'Treatment Arm: First Line'.

ERG exploratory analysis 5: Using utility data from Ara and Brazier rather than Szende *et al*.
To implement this exploratory analysis, the ERG selected Ara and Brazier rather than Szende *et al*. for 'Utility Decrements Source'. However, the ERG noticed an error within the model in the implementation of different utility sources, which it resolved. The answers reported by the company in Table 11 of the clarification response[9] matched the values generated by the ERG - it is thus likely that the company did not save the amended model prior to dispatch. The ERG amended the company's model by changing 'rngAgeUtility,2,' to 'rngAgeUtility,4,' in cells BD11:BF2099 in both the 'Treatment Trace' and the 'Control Trace' worksheets.

4.4.3 ERG's exploratory analyses - results

4.4.3.1 Quantitative changes to the company's base case

Table 28 presents the results of the ERG's deterministic exploratory analyses. Each individual change (ERG exploratory analysis 1 to 5) is applied relative to the company's base case in, with all of the individual changes combined to form the ERG's preferred base case.

As shown in Table 28, using the company's deterministic model, the ICER for adjuvant nivolumab treatment versus routine surveillance is estimated to be £22,766 per QALY gained. Under the ERG's preferred base case, the ICER for is estimated to be £21,298 per QALY gained. The probabilistic ICER is £21,310 per QALY gained in the ERG's base case.

The ICER when using the Generalised-F distribution was fairly insensitive to whether the 'cure' point was set to 3 years or 5 years of DFS, which was explained by the relatively constant absolute difference in DFS at both time points. At 3 years the difference was 14.0% (43.2% - 29.2%) and at 5 years the difference was 13.8% (36.6% - 22.8%). This difference was more pronounced for the 1 knot spline being 11.2% (40.1% - 28.9%) at 3 years and 9.1% (31.6% - 22.5%) at 5 years. To inform the NICE committee, an exploratory analysis was conducted changing the distribution used for DFS to the 1 knot spline within the ERG base case. In this analysis, the ICER increased to £32,011.

Table 28: Results of the ERG's deterministic exploratory analyses

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,766
ERG exploratory analysis 1 (using the Generalised-F distribution for DFS)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,729
ERG exploratory analysis 2 (assuming a 'cure' point at 5 years of DFS rather that at 3 years)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,114
ERG exploratory analysis 3 (assuming a mean age of 65 years)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,275
ERG exploratory analysis 4 (assuming a maximum duration of adjuvant nivolumab treatment of 63 weeks)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,052
ERG exploratory analysis 5 (using utility data from Ara and Brazier)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,280
ERG preferred base case (a combination of ERG exploratory analyses 1-5)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,298
ERG exploratory analysis 6 (the ERG base case using a 1 knot spline)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,011

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years
For information, the ERG's preferred probabilistic ICER is £21,310

4.4.3.2 Qualitative / semi-qualitative changes to the ERG's base case ICER

The sections paragraphs discuss changes to the ERG's base case ICER where the ERG deemed it could not provide a robust answer based on lack of data for selected parameters. For reference, the ERG's deterministic base case ICER is £21,298.

4.4.3.2.1 That the company's model did not use distributions fitted to the most recent DFS data
After the company had made its submission, it received additional DFS data (up to February 2021). The ERG would have preferred that the company refit distributions to the new data to provide a better representation of the ICER under current knowledge. It is not known whether the new data cut would favour, or disfavour, adjuvant nivolumab treatment, nor is the magnitude of any change in ICER known.

4.4.3.2.2 That the utility of patients aged 75 years, or over, are independent of whether they have had recurrent disease
The ERG has attempted to mitigate this limitation be reducing the utility in the post-recurrence disease state to an arbitrary value of 0.65 which is lower than the population value in Ara and Brazier until the patient reaches 95 years of age. Using a value of 0.65 for the post-recurrence utility the the ERG's base case ICER decreases to £20,688 (incremental costs £[redacted]; incremental QALYs [redacted]).

4.5 Discussion

The model submitted by the company was implemented to a good standard. The ERG, however, preferred alternative assumptions to those used by the company which consisted of using the Generalised-F distribution to model DFS rather than a 1 knot spline, to assume a 'cure' point at 5 years of DFS rather than at 3 years, aligning the costs of nivolumab treatment with the duration of treatment observed in the CheckMate 577 study rather than being capped at 1 year, and to use utility data from Ara and Brazier rather than Szende *et al*. Collectively, these changes reduced the company's deterministic ICER from £22,766 to £21,298, although maintaining the 1 knot spline resulted in an ICER of £32,011. Probabilistic ICERs were similar to the deterministic values.

There were a number of factors that could affect the ICER where the ERG could not provide a robust estimate although assuming a lower utility value for those with post-recurrent disease decreases the ICER, as would any delayed doses that have not been included in the company's model. The ERG cannot estimate the direction of the change in the ICER if more recent DFS data were used to fit survival distributions.

5 END OF LIFE

The NICE End of Life criteria are:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The company's base case analysis estimates that patients receiving routine surveillance would live for considerably longer than 24 months and therefore it makes no claim that End of Life criteria should be applied in this STA. The ERG agrees with this viewpoint.

6 OVERALL CONCLUSIONS

The key evidence for clinical effectiveness within the CS comprised one RCT (CheckMate577) of adjuvant nivolumab (n=532) versus placebo (n=262). This RCT was ongoing at the time of writing and OS data were not available to the trial investigators or staff preparing the CS. At the data cut-off, the HR for DFS was 0.69 (96.4% CI 0.56, 0.86), statistically significantly favouring nivolumab over placebo. The Kaplan-Meier estimated median DFS was 22.41 months (95% CI 16.62, 34.00) in the nivolumab arm, and 11.04 months (95% CI 8.34, 14.32) in the placebo arm. All cause SAEs of any grade were experienced by 158 (29.7%) patients in the nivolumab group, and 78 (30.0%) patients in the placebo group.

The model submitted by the company was implemented to a good standard, although the ERG preferred alternative assumptions to those used by the company. Incorporating the assumptions preferred by the ERG decreased the deterministic ICER of adjuvant nivolumab compared with routine surveillance from £22,766 in the company's base case to £21,298 in the ERG's base case (£21,310 probabilistic). Using the company preferred 1 knot spline model instead of the ERG-preferred Generalised-F distribution increased the deterministic ICER to £32,011. However, the most recent DFS data were not considered when fitting survival models, although the ERG acknowledges that these were received by the company after its submission. The impact on the ICER of incorporating distributions fitted to the newer DFS data is unknown.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer [ID1676]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 7 June 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Using AIC/BIC to compare distributions fitted to DFS

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.1 page 8 The ERG noted that "…the Generalised-F distribution had lower values on both the Bayesian Information Criterion and the Akaike Information Criterion and there was strong evidence that this was the better distribution in fitting the observed data." However, the company believes that the AIC/BIC alone do not constitute strong evidence, without taking other factors into consideration.	The company proposes the text be amended to read: ""…the Generalised-F distribution had lower values on both the Bayesian Information Criterion and the Akaike Information Criterion, providing some evidence that this was the better distribution in fitting the observed data, although the AIC/BIC should not be the sole basis for selecting distributions."	Analyst degree of freedom is not accounted for by the information criteria, therefore they should not be solely relied upon to select the best fitting distributions. The characteristics of the models themselves should be given consideration, particularly with respect to the observed hazard function and any a priori knowledge of the processes underlying the events being modelled, including clinical plausibility and consideration of potential modifications of the event-driving process.	The ERG believes that there is strong evidence that the Generalised-F distribution fits the observed data better than other distributions and has now added in a reference to support this. We agree that the decision of an appropriate distribution should not only be based on goodness of fit and have added text to this effect. "*There was also no indication based on the underlying hazards or clinical plausibility that the Generalised-F distribution was inappropriate.*" In addition, we have stated in the ERG report that "*As the observed data covered a period slightly over 40 months in duration, and the company assumed a 'cure' at 3 years, the ERG does not believe that extrapolated values should*
Section 1.5 page 10 The ERG noted that "…the Generalised-F distribution had lower values on both the Bayesian Information Criterion and the Akaike Information Criterion" However, the company believes that the AIC/BIC alone do not constitute strong evidence, without taking other factors into consideration.	As above.	As above.	

Section 4.3.3 page 65 The ERG states "The BIC for the 1 knot spline model was 2097.08 for the nivolumab arm and 1208.67 for the routine surveillance arm, but were 2063.75 and 1188.79 respectively for the Generalised-F distribution, indicating strong evidence that the Generalised-F distribution fitted better to the observed data." However, the company believes that the AIC/BIC alone do not constitute strong evidence, without taking other factors into consideration.	The company proposes the text be amended to read: "The BIC for the 1 knot spline model was 2097.08 for the nivolumab arm and 1208.67 for the routine surveillance arm, but were 2063.75 and 1188.79 respectively for the Generalised-F distribution, providing some evidence that the Generalised-F distribution fitted better to the observed data."	As above.	*carry much weight in the model choice.*"

Issue 2 The average age of patients treated in the UK

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.5 page 11 "…it is anticipated that patients in UK practice would be older than this [CheckMate 577 population], on average" The available evidence suggests that the CheckMate 577 population is	The company proposes the text be amended to read: "…it is anticipated that patients in UK practice may be slightly older, but comparable, to the population in the CheckMate 577 trial"	Although patients with OC in the UK are likely to be older than those recruited to CheckMate 577, those eligible for treatment with nivolumab within the proposed indication are likely to be of a comparable age. The National Oesophago-Gastric Cancer Audit 2017 (https://www.nogca.org.uk/content/uploads/2017/12/NOGCA-Annual-Report-2017.pdf) gives a median age for patients in England and Wales with oesophageal squamous cell carcinoma with a planned treatment modality of surgery of 67 (IQR 60–73). Data for adenocarcinoma patients were not available; nevertheless, the median age of patients in	This is not a factual error, although additional details have been added to the report. Additionally, in the light of the audit data, the ERG base case has been changed to use an age of 65 years rather than 60.5 years.

comparable in age to those patients in the UK who would be eligible for nivolumab.		CheckMate 577 was 62.0, which falls within the IQR of the national average for oesophageal squamous cell carcinoma patients who were suitable to undergo surgery i.e. the subset of oesophageal squamous cell carcinoma patients eligible for treatment with nivolumab.	
Section 4.3.3 pages 64 and 68 "…the average age of patients in the UK are likely to be older than those recruited to CheckMate 577" The available evidence suggests that the CheckMate 577 population is comparable in age to those patients in the UK who would be eligible for nivolumab.	The company proposes the text amended to read: "…the average age of patients in the UK are likely to be slightly older, but comparable, to those recruited to CheckMate 577"	As above.	
Section 3.2.2 page 29 The ERG states: "CS clarification response B20 suggests that in a UK OC population 42.9% of patients are aged 60-69 years and 73.9% are aged <70 years." This statement misrepresents the data	The company proposes the text be amended to read: "CS clarification response B20 suggests that of UK OC patients who received chemoradiotherapy and surgical resection, 42.9% of patients are aged 60-69 years and 73.9% are aged <70 years."	The figures cited in the CS clarification response B20 are not for the overall UK OC population, as implied, but for those UK patients with OC who had received chemoradiotherapy and undergone resection i.e. those represented by the CheckMate 577 trial.	Change made as requested.

cited in the clarification response, which are not for the overall UK OC population.			

Issue 3 Method for applying utility rankings

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.5 page 12 (issue 5) The ERG suggests "Restructuring the model so that utility rankings are maintained as patients age would provide a more accurate answer." However, it is not necessary to restructure the model in order to address this issue.	The company suggests the alternative approach/additional evidence resolution be changed to either: Set "Age-Dependent Utility Decrements" to "Yes" on the 'Model Control' worksheet Or Set "Age-Dependent Utility Decrements" to "Yes" and set utility value for the Disease Free health state to the appropriate value from Ara and Brazier on the 'Model Control' worksheet	It is not necessary to restructure the model in order to apply the change to the rankings – this functionality already exists in the model, as follows. Setting "Age-Dependent Utility Decrements" to "Yes" will use utility decrements and not apply a hard limit based on baseline utility for patients age. This was not done in the base case as it would lead to the disease free health state having higher utility than the general population for that age. In order to both maintain the health state utility rankings and ensure utility does not exceed the general population the "Age Dependent Utility Decrements" should be set to "Yes" and the disease free utility should be changed to match the general population utility for the baseline age, derived from Ara and Brazier or Szende et al (re ERG	Our comment may have been ambiguous, and thus we have amended the text. The rankings we were highlighting was between the utilities associated with people who have had a recurrence and people who have not had a recurrence. The proposed solution does not appear to ensure that the average utility is lower in patients with a recurrence.

		report issue 7).	

Issue 4 Nivolumab treatment duration and dosing

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.5 page 12 In Issue 6 the ERG suggests that the company's model underestimates the costing of adjuvant nivolumab by not including patients treated past 12 months. This may be true, but it should also be acknowledged that the ERG's solution is likely to overestimate this cost.	The company requests the ERG acknowledge that this method overestimates the costing of adjuvant nivolumab treatment as it ignores the dose delays which appear to be a significant cause of patients treated past 12 months.	It is likely that those patients who had a total time on treatment greater than 12 months were due to dose delays i.e. these patients did not receive additional nivolumab doses, but rather they received the same number of doses spread over a slightly longer time period. The CSR in CS appendix E table S.4.2.1 shows the dose delays for treated patients, which align closely to patients treated past 12 months. Furthermore, table S.4.1 in the CSR (CS appendix E) shows the maximum number of doses of nivolumab received by any patient was [redacted] The Company is content to incorporate time on treatment into the model but this should be done in parallel with a dose modifier to ensure that dose delays are accounted for.	Additional text has been added to make the point raised by the company.

Section 4.3.3 page 69 The ERG states "Within CheckMate 577 a small proportion of patients received adjuvant nivolumab treatment for longer than the 12 months assumed within the model. The ERG cannot discount the possibility that the increased nivolumab treatment may have had a beneficial effect on the patient which would be incorporated into the modelled DFS distributions." The increased time on treatment experienced by a few patients does not necessarily mean increased nivolumab.	The company requests that the ERG removes the reference to 'increased nivolumab treatment'.	The company acknowledges that a small proportion of patients had a longer time on treatment than 12 months, however, it is anticipated that this is likely due to dose delays (see above). Therefore, stating that patients have 'increased nivolumab treatment' does not necessarily reflect the clinical reality.	The text has been amended to '*elongated treatment duration'*.

Issue 5 Proportion of patients with adenocarcinoma versus squamous cell carcinoma

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.5 page 13 The ERG states that "The proportion of patients with adenocarcinoma is likely to be greater in the UK than in patients recruited for CheckMate 577" The available data suggest that the proportion of patients with adenocarcinoma in CheckMate 577 is reflective of the UK setting.	The company proposes the text be updated to read: "the proportion of patients with adenocarcinoma recruited to CheckMate 577 is reflective of the proportion diagnosed in the UK."	The proportion of patients in CheckMate 577 with adenocarcinoma was 71%, with 29% patients having squamous cell carcinoma. The evidence is that this is reflective of the proportions in the UK. From a Global Burden of Disease study cited in the original Company submission: UK age-standardised estimated incidence in 2018 of 4.5 per 100,000 person years for	Based on the data provided by the company we have removed text related to a greater proportion of patients with adenocarcinoma in the UK from the report.

		adenocarcinoma compared with 2.1 for oesophageal squamous cell carcinoma (Arnold et al 2020). This gives a ratio of 0.68:0.32 for adenocarcinoma:squamous cell carcinoma. From an England-specific source (Offman et al 2018, doi 10.1038/s41416-018-0047-4): The three-year moving average centred around 2012 was 4,661 oesophageal adenocarcinoma cases and 2,295 oesophageal squamous cell carcinoma cases (67% and 33%, respectively), with modelling projecting 71% oesophageal adenocarcinoma and 29% oesophageal squamous cell carcinoma for 2032.	
Section 4.3.3 page 69 "The UK has a higher proportion of adenocarcinoma, relative to adenocarcinoma and SCC combined, than the ROW and CheckMate 577 only had a small number of patients from the UK." The available data suggest that the proportion of patients with adenocarcinoma in CheckMate 577 is reflective of the UK setting.	The company proposes the text be updated to read: "Although the UK has a higher proportion of adenocarcinoma, relative to adenocarcinoma and SCC combined, than the ROW, the proportion of patients with adenocarcinoma recruited to CheckMate 577 is reflective of the proportion diagnosed in the UK."	See above.	

Issue 6 Proposed indication

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 2.1 page 15 "The company anticipate that nivolumab as monotherapy will be indicated for [redacted]" This statement does not accurately represent the prognosis for the indicated population.	The company proposes the text be revised to reflect that although patients with [redacted]	Patients who have residual pathologic disease (i.e. non-pathCR) have a worse prognosis than those who achieve pathologic complete response (pathCR). From the company submission: Non-pathCR has been demonstrated to predict a significantly lower rate of both DFS and OS in patients treated with neoadjuvant CRT followed by surgical resection.[11,33,34] In the CROSS trial, 42% patients without pathCR after CRT experienced a recurrence, compared to 17% patients with pathCR after CRT.[35] The high risk of recurrence is particularly significant in light of the very poor post recurrence survival, with only a short time from recurrence to death.[12,16]	It was deemed simplest to remove the final sentence of the redacted text from our report.

Issue 7 Sex of UK patients relevant to the proposed indication

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 3.2.2 page 29 "CS clarification response B20 suggests 68.6% of a UK OC	The company proposes the text be revised to read: "CS clarification response B20 suggests 68.6% of a UK OC population who received chemoradiotherapy and surgical resection are	The figures cited in the CS clarification response B20 are not for the overall UK OC population, as implied, but for those UK patients	Change made as requested

population are male." This statement misrepresents the data cited in the clarification response, which are not for the overall UK OC population.	male."	with OC who had received chemoradiotherapy and undergone resection i.e. those represented by the CheckMate 577 trial.	

Issue 8 Treatment of patients with GEJC

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 2.2 page 15 and section 3.5 page 38 [redacted]	The company acknowledges that this is correct but notes that this does not impact on effectiveness of nivolumab for the indication of interest. Hence, the company proposes that text pertaining to the treatment of [redacted] be removed or amended to reflect that this would not impact on clinical or cost-effectiveness.	The company agrees that treatment of [redacted]. However, the indication for nivolumab is fairly specific in terms of [redacted]. Hence, although this pathway excludes some patients from nivolumab use in UK clinical practice, it would not impact on clinical or cost-effectiveness.	We have added sentences to say that this comment does not impact on the clinical or cost-effectiveness estimates.

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Technical engagement response form

Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer [ID1676]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments**: 5pm, Wednesday 21 July 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Bristol-Myers Squibb Ltd.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td>Key issue 1: The data used for disease-free survival (DFS) when fitting distributions</td><td>Yes – the survival analysis has been updated using the CheckMate 577 [redacted] database lock (DBL), described in Appendix 1. The utility analysis has also been updated based on the CheckMate 577 [redacted] DBL, described in Appendix 2. The cost effectiveness analysis for the updated base case includes both the updated survival and utility analysis.</td><td>The Company has used disease free survival (DFS) data from the CheckMate 577 [redacted] DBL, which was not available at the time of the original Company Submission. Survival analysis was undertaken on the updated DFS data using the approach outlined in the original Company Submission; an updated survival analysis report can be found in Appendix 1, and discussion of the distribution selected to represent DFS in the updated base case can be found in response to key issue 2, below.

In parallel, the utility analysis has also been updated using data from the CheckMate 577 [redacted] DBL aligned with the approach outlined in the original Company Submission; an updated utility analysis report can be found in Appendix 2. The updated utility analysis was consistent with that used in the original Company Submission; as seen in Table 1, differences to the observed mean utility per state were minimal.

Table 1. Summary of difference in mean utility
<table>
<tr><th>Dataset</th><th colspan="2">Nivolumab
Mean (95% CI)</th><th colspan="2">Routine surveillance
Mean (95% CI)</th></tr>
<tr><td></td><td>[redacted] DBL</td><td>Jul 2020 DBL</td><td>[redacted] DBL</td><td>Jul 2020 DBL</td></tr>
<tr><td>All pre-recurrence</td><td>0.843
(0.833, 0.853)</td><td>0.843
(0.832, 0.853)</td><td>0.851
(0.836, 0.866)</td><td>0.851
(0.836, 0.866)</td></tr>
<tr><td>On treatment pre-recurrence</td><td>0.843
(0.832, 0.855)</td><td>0.844
(0.832, 0.855)</td><td>0.850
(0.833, 0.868)</td><td>0.851
(0.834, 0.868)</td></tr>
<tr><td>On treatment post-recurrence</td><td>0.741
(0.709, 0.774)</td><td>0.746
(0.715, 0.777)</td><td>0.776
(0.733, 0.820)</td><td>0.766
(0.718, 0.814)</td></tr>
<tr><td>All pre-recurrence (exclude baseline)</td><td>0.848
(0.835, 0.856)</td><td>0.845
(0.834, 0.856)</td><td>0.853
(0.837, 0.869)</td><td>0.853
(0.838, 0.869)</td></tr>
<tr><td colspan="5">CI: confidence interval; DBL: database lock</td></tr>
</table>
</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response
		Results from the updated DFS and utility analyses have been incorporated into the cost-effectiveness model and are included in the revised company base case. Details of the impact of this updated analysis on the updated base case ICER can be found in the response to key issue 2. Further details regarding how utilities are handled in the model can be found in the responses to key issues 5 and 7.
Key issue 2: The distribution chosen to represent DFS	**Yes** – the survival analysis has been updated using the CheckMate 577 [redacted] database lock (DBL), described in Appendix 1.	The model has been updated to use the updated DFS distributions and disease-free utilities in the nivolumab and routine surveillance arms (see response to key issue 1). As shown in Appendix 1, parametric extrapolations provided a notably poor fit to the observed data. Of these extrapolations, only generalised F distributions provided an appropriate fit to the updated DFS data; spline models provided an acceptable alternative. The generalised F distribution has been used in the updated company base case, aligned to the ERG preferred distribution. Using the new DBL ([redacted]) data, the original company base case analysis (provided in the Company Submission) can be updated using disease free utility input, the generalised F distribution for the updated DFS data and updated logistic regression predicting events among the DFS composite endpoint that were deaths (i.e. not recurrence) in the first three years. When all other parameters are maintained as in the original base case analysis (as outlined in the Summary of changes to the company's cost-effectiveness estimate(s)), the resultant ICER is £17,601 from the Company's original base case of £22,766.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 3: The duration of DFS at which a 'cure' can be assumed	**Yes** – evidence from the updated CheckMate 577 [redacted] DBL has been used to support the assumption of general population mortality at three years	In the original Company Submission model, all patients in the disease free health state assumed general population mortality risk and no risk of disease recurrence after three years. This was based on two lines of evidence: 1. The CheckMate 577 trial (July 2020 DBL) showed that after approximately two years the risk of DFS events becomes very low and was comparable in both the nivolumab and placebo (routine surveillance) arms.[1] This was supported by assessment of the [redacted] DBL: only [redacted] events occur following 36 months, despite [redacted] patients at risk in the nivolumab arm and [redacted] patients in the routine surveillance arm. This would strongly indicate cure at three years in both treatment arms. 2. Clinical advice to the company suggested that all patients would be considered disease free following resection, but that the underlying hazard may not converge to the general population rate for approximately three to five years. Therefore, three years was chosen in the original base case model to reflect both the trial data and clinical advice. This has been reflected in the updated base case analysis.

Key issue 4: The average age of patients treated in the UK	**Yes**	The average age of patients in the CheckMate 577 trial,[1] which was used in the base case model in the original Company Submission, was 60.5 years. Although patients with OC in the UK are likely to be older than those recruited to CheckMate 577, those eligible for treatment with nivolumab within the proposed indication are likely to be of a comparable age. Although the Company has not been able to identify published data regarding the average age for UK patients who would be eligible for treatment within this indication, the following sources of evidence were used as a guide: • National Cancer Registration and Analysis Service and Cancer Research UK (NCRAS/CRUK): Of those patients who receive chemoradiotherapy (CRT) and surgical resection, 42.9% of patients are aged 60–69 years and 73.9% are aged < 70 years.[2] • Lou et al (2013),[3] the study used in the Company Submission to inform post-recurrence survival, considered a cohort of patients who had undergone surgical resection for OC, the majority of whom had received neoadjuvant therapy; the mean age was 63 years. • Clinical experts contacted to inform technical engagement cited registry data obtained from their own practice, which stated that mean age for this patient population was 63 years. Additionally, an analysis was undertaken to assess the impact of adjusting the CheckMate 577 data to reflect the age distribution of patients with OC who had received CRT and surgical resection, per the NCRAS/CRUK dataset.[2] Using the method of moments (as in a matching-adjusted indirect comparison[4,5]) the weighted proportion of patients in each age subgroup within CheckMate 577 ([redacted] DBL) was matched to that in the NCRAS/CRUK[2] dataset. This resulted in an increase in mean age from [redacted] years to 62.66 years, with a small reduction in the effective sample size from 794 to 728.3 (Table 2). The effective sample size is indicative of the statistical power of the adjusted population, and its similarity to the unadjusted sample size indicates that the age distribution given by NCRAS/CRUK is well represented within the CheckMate 577 sample. The influence of these weights upon observed DFS within CheckMate 577 was minimal (** *Figure 1*), indicating that the models upon the unadjusted CheckMate 577 population are representative of patients with the NCRAS/CRUK age distribution. *Table 2. Age distribution of patients with OC treated with chemotherapy, tumour resection and radiotherapy – England (NCRAS/CRUK)[2] and CheckMate 577*

Variable	NCRAS/CRUK (2013–2015) – oesophageal cancer, chemotherapy + tumour resection + radiotherapy - receiving	CheckMate 577 ([redacted] DBL)	
		Unadjusted	Age-adjusted*
N/ESS	532	794	728.3
Age (years)			
Mean	NR	[redacted]	62.66
SD	NR	[redacted]	9.254
< 50 (%)	8.30	[redacted]	8.30
50–59 (%)	22.70	[redacted]	22.70
60–69 (%)	42.90	[redacted]	42.90
70–79 (%)	25.80	[redacted]	25.80
≥ 80 (%)	0.40	[redacted]	0.40

**Patient-level data weighted by method of moments to match weighted proportions within all age categories to NCRAS/CRUK dataset.*
DBL: database lock; ESS: effective sample size (sum of weights)^2 / sum(weights^2); SD: standard deviation

[redacted]

Figure 1. Age-adjusted CheckMate 577 DFS, matching via method of moments the age distribution of NCRAS/CRUK (2013–2015)[2]

Considering the available evidence, the ERG preference of 65 years is likely a conservative estimate of the mean age of the UK OC population eligible for treatment with nivolumab. In reflection of the new evidence identified from the literature, consultation with clinical experts and the new analysis of the CheckMate 577 data described above, the Company considers the most plausible mean age to be 62.66 years, aligning with the NCRAS/CRUK data. The Company base case has been updated to use a mean age of 62.66 years. Updating only the age in the base case analysis results in an ICER of £24,714, from the original base case analysis of £22,766.

Key issue	Does this response contain new evidence, data or analyses?	Response
		Given the average age of patients in the CheckMate 577 trial, this is considered to be a conservative assumption; the Company also presents scenarios using the trial mean age (60.5 years) and the ERG preference (65 years).
Key issue 5: That above the age of 75 years, patients had the same utility independent of whether their disease had recurred	**No**	To address this issue, the mechanism by which age-related utility interacts with the model has been changed from an optional functionality to apply a decrement to the application of an age-related factor. In the base case in the original Company Submission, age-related utility decrements were not applied; instead, the model imposed a limit on health state utility to not exceed general population utility (N.B. in the original Company Submission, the general population utility was based on Szende et al[6]). This led to utilities for disease free and recurred disease being equal past 75 years. The updated model now includes an age-related utility factor, based on data from Ara and Brazier[7] (see also response to key issue 7). The updated base case analysis uses: • General population utility, adjusted for age using the Ara and Brazier[7] adjustment factor; • Post-recurrence utility, adjusted for age using the Ara and Brazier[7] adjustment factor. As the general population utility and post-recurrence utility are adjusted for age at the same rate, the post-recurrence utility always remains below the health state utility for patients without recurrence.

Key issue 6: Potential underestimation of the costing of adjuvant-nivolumab treatment within the model	**Yes** – new analysis of data from CheckMate 577 has been used to develop a dose frequency modifier.	CheckMate 577[1] and the nivolumab Summary of Product Characteristics (SmPC)[8] included a maximum total treatment duration of 12 months. However, during CheckMate 577, a subgroup of patients received their last dose of nivolumab more than 12 months after initiating treatment. CheckMate 577 allowed nivolumab dose delays for management of adverse events but did not allow skipping doses. Hence, those patients who had a total time on treatment greater than 12 months were due to dose delays i.e. these patients did not receive additional nivolumab doses, but rather they received the same number of doses spread over a slightly longer time period. The CSR in Company Submission appendix E table S.4.2.1 shows the dose delays for treated patients, which align closely to patients treated past 12 months. Furthermore, table S.4.1 in the CSR (Company Submission appendix E) shows the maximum number of doses of nivolumab received by any patient was [redacted] The original company base case analysis assumed that all patients stopped treatment at 12 months, aligned with the SmPC and CheckMate 577.[1,8] However, the preferred ERG assumption for modelling time on treatment removed this stopping rule. For this reason, the updated company base case analysis removes the stopping rule but includes a dose modifier to account for dose delays. The dose modifier was calculated using the updated CheckMate 577 [redacted] DBL, as the percentage of nivolumab doses administered versus those predicted by time on treatment. This percentage ([redacted]) was calculated as the ratio of the sum of the dispensed doses of nivolumab over the nivolumab intention-to-treat cohort versus that expected by consideration of the difference between the treatment end and treatment start dates of each patients, under a schedule of one dose per fortnight for the first 9 doses (up to week 16, inclusive) and one dose per four weeks thereafter to treatment end. To reflect the requirement of the nivolumab SmPC for adjuvant therapy,[8] the Company has included the 12 month stopping rule as a scenario. Adding these changes to the model resulted in an ICER of £22,702 from the company base case of £22,766.
Key issue 7: The source of utility data	**Yes** – this analysis uses the preferred ERG method;	The original Company Submission used utilities from a publication by Szende et al (2014)[6] in preference to those reported by Ara and Brazier (2010)[7]. The Company considered the two

Key issue	Does this response contain new evidence, data or analyses?	Response
	however, the inputs are derived from the updated CheckMate 577 [redacted] DBL.	publications to be comparable but chose the Szende et al[6] utilities as the more recent of the two options. The ERG prefers to use the utilities reported by Ara and Brazier,[7] which permits the utility to decrease after 75 years. The Company agrees to use the ERG's preferred approach. Note that the inputs are derived from the updated CheckMate 577 [redacted] DBL, as described in the response to key issue 1, and the response to key issue 5 provides additional detail regarding the implementation of these utilities above the age of 75. The changes made to address key issue 5 and 7 resulted in the base case ICER changing to £22,112 from the company base case of £22,766.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
No additional issues identified.			

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Original company base case analysis (post clarification question response)	Not applicable	Not applicable	ICER: £22,766

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Key issue 1: The data used for disease-free survival (DFS) when fitting distributions	**T**he original company base case analysis applied data from the CheckMate 577 July 2020 DBL.	The survival analysis has been updated using the CheckMate 577 [redacted] database lock (DBL), described in Appendix 1. The utility analysis has also been updated based on the CheckMate 577 [redacted] DBL, described in Appendix 2. The cost effectiveness analysis for the updated base case includes both the updated survival and utility analysis. Note: in line with the original base case analysis, this analysis uses the following assumptions that have been modified in the updated base case analysis: • Spline DFS extrapolations • Time on treatment applies 12-month stopping rule in line with CheckMate 577[1] and SmPC[8] • No treatment modifier to reflect dose delays • Baseline age: 60.5 years • Utility inputs based on Szende et al (2014)[6] and general population utility cap.	ICER: £19,242

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Key issue 2: The distribution chosen to represent DFS	**T**he original company base case analysis applied DFS extrapolations based on data from the CheckMate 577 July 2020 DBL and using a distribution of a lognormal spline with 1 knot.	The survival analysis has been updated using the CheckMate 577 [redacted] database lock (DBL), described in Appendix 1. Further, the DFS inputs was updated to use generalised F extrapolations. Note: in line with the original base case analysis, this analysis uses the following assumptions that have been modified in the updated base case analysis: • Time on treatment applies 12-month stopping rule in line with CheckMate 577[1] and SmPC[8] • No treatment modifier to reflect dose delays • Baseline age: 60.5 years • Utility inputs based on Szende et al (2014)[6] and general population utility cap.	ICER: £17,601

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Key issue 4: The average age of patients treated in the UK	The original company base case analysis applied a baseline mean age of 60.5 years	The mean age at baseline has been changed to 62.66 years. Note: in line with the original base case analysis, this analysis uses the following assumptions that have been modified in the updated base case analysis: • CheckMate 577 July 2020 DBL • Spline DFS extrapolations • Time on treatment applies 12-month stopping rule in line with CheckMate 577[1] and SmPC[8] • No treatment modifier to reflect dose delays • Utility inputs based on Szende et al (2014)[6] and general population utility cap.	ICER: £24,714
Key issue 5: That above the age of 75 years, patients had the same utility independent of whether their disease had recurred and **Key issue 7:** The source of utility data	The original company submission took the minimum utility between age related general population utility and health state utility Additionally, the original company submission used utilities from a publication by Szende et al (2014)[6] in preference to those reported by Ara and Brazier (2010)[7].	All health states are now adjusted to reflected age-related utility values. The new submission uses Ara and Brazier to produce an age related utility decrement factor. Note: in line with the original base case analysis, this analysis uses the following assumptions that have been modified in the updated base case analysis: • CheckMate 577 July 2020 DBL • Spline DFS extrapolations • Baseline age: 60.5 years • Time on treatment applies 12-month stopping rule in line with CheckMate 577[1] and SmPC[8] • No treatment modifier to reflect dose delays	ICER: £22,112

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Key issue 6: Potential underestimation of the costing of adjuvant-nivolumab treatment within the model	The original submission assumed treatment ended at 52 weeks based on a stopping rule implemented during CheckMate 577 and reflected in the SmPC.[1,8] Dose delays were not reflected in the analysis.	The updated base case analysis includes extended treatment to reflect all time on treatment in combination with a dose modifier to account for the delayed doses. Note: in line with the original base case analysis, this analysis uses the following assumptions that have been modified in the updated base case analysis: • CheckMate 577 July 2020 DBL • Spline DFS extrapolations • Baseline age: 60.5 years • Utility inputs based on Szende et al (2014)[6] and general population utility cap.	ICER: £22,702

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Company's preferred base case following technical engagement Note: this includes the following amendments: • CheckMate 577 [redacted] DBL • Generalised F Spline DFS extrapolations • Baseline age: 62.66 years • No time on treatment stopping rule • Treatment modifier to reflect dose delays • Utility inputs based on Ara and Brazier (2010)[7] • Health state utilities reflecting age-adjusted utility values	**Incremental QALYs:** [redacted]	**Incremental costs:** [redacted]	ICER: £16,668

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Appendix 3 Cost-effectiveness analysis (February 2021 database lock)

Table of Contents

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Tables and Figures

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1 Summary of cost-effectiveness results

Note: all incremental cost-effectiveness ratios (ICERs) presented below apply the updated patient access scheme (PAS) for nivolumab of [redacted] and are based on the February 2021 database lock (DBL), unless specified otherwise.

Table 1 presents the summary of cost-effectiveness outcomes. Each row represents the cumulative impact of the additional assumption and it runs from the NICE submission company base case down to the updated company base case. Table 1 also presents the impact of Evidence Review Group (ERG) assumptions and ERG requested analyses on cost effectiveness. All scenarios resulted in cost-effective ICERs that were below the £30,000 per quality-adjusted life year (QALY) threshold.

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Table 1. Summary of changes to cost-effectiveness outcomes when applying cumulative changes to model assumptions

Model change	Assumption	ICER (cost/QALY) after cumulative impact of model change
		nivolumab vs routine surveillance
Company base case (following correction in response to ERG clarification questions)		
0		**£22,766**
Issue 2: Using generalised F distribution		
1		£17,729
Issue 3: Patients assume general population mortality at 5 years instead of 3 years		
2		£17,570
Issue 4: Baseline age 65 years		
3		£21,316
Issue 6: Assuming a maximum duration of adjuvant nivolumab treatment of 63 weeks		
4		£21,593
Issue 7: Using utility data from Ara and Brazier (ERG base case)		
5		**£21,298**
Issue 3 and 4: Patients assume general population mortality at 3 years and baseline age changed to 62.66 years		
6		£19,281
Issue 1: Updated with new trial data and using generalised F distribution		
7	Updated disease-free utility input, disease free survival and death on recurrence with data from CheckMate 577 February 2021 DBL.	£17,094
Issue 5: updated general population limiter/age-dependent utility factor		
8	Updated age-dependent utility to use a factor rather than a decrement, now included in the base case. Allows users to select whether they want to limit health state utility to general population.	£16,951
Issue 6: Added dose frequency modifier and extended duration of treatment to equal the recorded ToT		
9	The treatment now lasts as long as the ToT curve allows for, however this includes delayed treatments rather than reflecting additional doses received. To adjust for these delayed doses the cost has been reduced by a calculated multiplier derived from CheckMate 577 data.	£16,668
Company base case post-technical engagement – thereafter "base case"		
-	**Company base case**	**£16,668**

DBL: database lock; ICER: incremental cost-effectiveness ratio; PSA: probabilistic scenario analyses; QALY: quality-adjusted life year; ToT: time on treatment

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1.1 Base case results

1.1.1 Base case incremental cost-effectiveness analysis results

The results of the base case analysis are summarised in Table 2.

In terms of comparator treatment, the model predicts a median overall survival (OS) of [redacted] years for routine surveillance. An accrual of [redacted] discounted QALYs for routine surveillance, was predicted over the modelled time horizon. By comparison, it was predicted that the use of nivolumab will result in up to an additional [redacted] discounted QALYs (total: [redacted] discounted QALYs) and up to an additional [redacted] undiscounted life years (total: [redacted] undiscounted life years). It was estimated that patients receiving nivolumab would spend [redacted] years in the disease-free health state, with a subsequent [redacted] years in the recurred disease health state, indicating that nivolumab is associated with significant incremental benefit in time spent disease free and a small decrease in time spent with recurred disease.

Total discounted costs associated with nivolumab (with PAS), accrued over the modelled time horizon, were predicted to be [redacted]. By comparison, total discounted costs associated with routine surveillance was notably lower at [redacted]. Incremental discounted costs were [redacted], under base case assumptions. The resulting ICER estimate for nivolumab was £16,668 per QALY gained. Therefore, the base case ICER is below a £30,000 per QALY willingness-to-pay (WTP) threshold and nivolumab can be considered a cost-effective use of NHS resources.

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Table 2. Base case analysis results

	Component	Nivolumab	Routine surveillance	Incremental
Disaggregated costs (discounted)	Disease free	[redacted]	[redacted]	[redacted]
	Disease free (long term)	[redacted]	[redacted]	[redacted]
	Recurred disease	[redacted]	[redacted]	[redacted]
	Death	[redacted]	[redacted]	[redacted]
	Treatment	[redacted]	[redacted]	[redacted]
	Modelled 2nd line	[redacted]	[redacted]	[redacted]
	AEs	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
Disaggregated QALYs (discounted)	Disease free	[redacted]	[redacted]	[redacted]
	Disease free (long term)	[redacted]	[redacted]	[redacted]
	Recurred disease	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
Clinical outcomes (years, undiscounted)	Median DFS	[redacted]	[redacted]	[redacted]
	Mean DFS	[redacted]	[redacted]	[redacted]
	Median OS	[redacted]	[redacted]	[redacted]
	Mean OS	[redacted]	[redacted]	[redacted]
Time in health state (years, undiscounted)	Disease free	[redacted]	[redacted]	[redacted]
	Disease free (long term)	[redacted]	[redacted]	[redacted]
	Recurred disease	[redacted]	[redacted]	[redacted]

AE: adverse event; DFS: disease free survival; OS: overall survival; QALY: quality-adjusted life year

1.2 Sensitivity analyses

In order to assess the impact of parameters on the model outcomes, probabilistic sensitivity analyses (PSA) and deterministic sensitivity analyses (DSA) have been used to vary the data inputs by a set amount. Uncertainty around the input data has been assessed using probabilistic analyses, while alternative assumptions have been examined in scenario analyses.

1.2.1 Probabilistic sensitivity analysis

In the PSA, a non-parametric bootstrapping approach was taken, sampling values from distributions around the means of input parameters in the model. Sampling utilises information of the mean and standard error of parameters to derive an estimated value using an appropriate distribution (costs: gamma; age and survival parameters: normal; utilities,

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probabilities and proportions: beta). These analyses are used to estimate the overall uncertainty that exists in the model results due to uncertainty in the chosen input parameters.

The majority of parameters included in the PSA are sampled independently, with the exception of semi-parametric survival estimates, where parameters associated with individual survival function are sampled using a common random number.

Several inputs are derived from sources where it has not been possible to ascertain standard errors. To assess uncertainty surrounding these inputs, the standard error has been assumed to be 20% of the mean value for the purposes of the PSA.

1,000 simulations of the model were deemed enough for the model results to converge to a sufficient degree of accuracy.

1.2.1.1 PSA results

The scatterplot for the base case analysis, arising from 1,000 simulations of the model with all parameters sampled, is presented in Figure 1, while the cost-effectiveness acceptability curve (CEAC) is presented in Figure 2. Based on these analyses, the probability that nivolumab versus routine surveillance is cost-effective at a WTP threshold of £30,000 per QALY is [redacted]%, with the mean ICER being £17,511 (Table 3).

Table 3. PSA results

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)			**£17,511**

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

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Figure 1. ICER scatterplot: nivolumab versus routine surveillance

Figure 2. CEAC: nivolumab versus routine surveillance

1.2.2 Deterministic sensitivity analysis

Results of the DSA are presented in Figure 3 and demonstrate the impact of specific parameters on ICER estimates. In all scenarios, the ICER for nivolumab versus comparators remained below the £30,000 per QALY WTP threshold.

Plausible alternative scenarios have been investigated further in section 1.2.3.1, in order to assess the impact of the uncertainty in the analysis.

Figure 3. DSA tornado plot: nivolumab versus routine surveillance

1.2.3 Scenario analysis

1.2.3.1 Alternative time points at which general population risk is assumed

In the new base case, after three years, disease free patients start to assume a general population risk of disease free mortality, based on clinical advice received by the Company. The ERG believes that five years is more plausible, therefore this is presented here as a scenario (Table 4). In this scenario, nivolumab remains cost effective at a WTP threshold of £30,000 per QALY.

Table 4: Scenario analysis results – general population risk at five years

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£16,611
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year			

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1.2.3.2 Alternative discounting

In anticipation of potential revisions to the reference case, the results where discounting for cost and benefits is 1.5% are also presented (Table 5).

Table 5. Discounting for costs and benefits at 1.5%

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£12,859
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year			

1.2.3.3 Variability in post recurrence utility

There is reason to believe that the post recurrence utility value in the base case may be higher than patients might expect to experience. However, no alternative source has been found to inform this health state aside from a previous cost-effectiveness study in gastric cancer patients.[1,2] As described in the original Company Submission B.3.4, this paper reported the post recurrence utility to be 0.42. In order to aid decision making, the post recurrence utility was arbitrarily varied from the study reported value of 0.42 to the base case value, in order to understand the impact that this may have on the results of the cost-effectiveness model and therefore the decision that might be made should the true post recurrence value be different. In all scenarios examined, the decision would not change; nivolumab remains cost-effective (Table 6). Therefore, while knowing the true value may be difficult at this stage, the base case remains robust to changes. In addition, it is likely that the base case is overestimating the true ICER and should be considered conservative.

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Table 6: Scenario analysis results – variations in post recurrence utility

Post recurrence utility value	ICER	Decision
0.42	£15,151	Cost-effective
0.45	£15,279	Cost-effective
0.5	£15,496	Cost-effective
0.55	£15,720	Cost-effective
0.6	£15,950	Cost-effective
0.65	£16,187	Cost-effective
0.7	£16,432	Cost-effective
0.747 (base case)	£16,668	Cost-effective
ICER: incremental cost-effectiveness ratio		

1.2.3.4 Alternative DFS fits

The generalised F fits provided superior fitting to all other methods examined (see Technical Engagement Response Appendix 1). The results of alternative parametric models are displayed below (Table 7). In all scenarios examined, the decision regarding the cost-effectiveness of nivolumab would not change, demonstrating that the deterministic values are robust to the underlying assumptions and methods.

Table 7: Scenario analysis results - alternative DFS fits

Nivolumab DFS model	Routine surveillance DFS model	ICER
Log-normal two knot spline	Log-normal two knot spline	£20,333
Exponential	Exponential	£16,921
Gompertz	Gompertz	£18,548
L.logistic	L.logistic	£15,074
L.normal	L.normal	£15,332
Weibull	Weibull	£15,910
DFS: disease free survival; ICER: incremental cost-effectiveness ratio		

1.2.3.5 Alternate baseline age

The updated Company base case has a baseline age of 62.66 years. Based on evidence from the literature, new analysis of data from CheckMate 577 and clinical expert opinion (see technical engagement response form for details), the Company believes 62.66 years is a plausible and conservative assumption. The original Company base case used the mean age from the CheckMate 577 trial, which was 60.5 years. Given the evidence from CheckMate 577, which is based on a relevant patient population, a baseline age of 60.5

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years is presented as a scenario (Table 8). The ERG base case preferred a baseline age of 65, therefore this is also included as a scenario (Table 9).

Table 8: Baseline age 60.5

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life Years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£15,162
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year			

Table 9: Baseline age 65

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life Years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£18,632
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year			

1.2.3.6 Removed dose modifier and kept 12 month stopping rule

In the updated Company base case, time on treatment is permitted to extend beyond 12 months, reflecting that some patients received nivolumab over a longer period than 12 months due to dose delays. The CheckMate 577 protocol allowed dose delays for management of adverse events, but did not permit dose modifications or dose skipping, therefore the additional time on treatment reflects delayed doses, not additional doses. To account for these dose delays, a dose modifier has also been added to the updated Company base case.

An alternative scenario is to assume that nivolumab dosing is priced as if it were on the intended schedule and that treatment stops at 52 weeks, as per the nivolumab Summary of Product Characteristics. All other extensions to treatment time can be assumed to be caused by dose delays and therefore should not be associated with any additional costs. This approach is presented here as a scenario (Table 10). In this scenario, which includes a 12-month stopping rule and does not include a dose modifier, nivolumab remains cost effective.

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Table 10: 12 month stopping rule without dose modifier

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life Years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)	-	-	£16,462
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year			

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer [ID1676]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Wednesday 21 July 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with oesophageal or gastro-oesophageal junction cancer and current treatment options	
About you	
1. Your name	**Somnath Mukherjee**
2. Name of organisation	**Oxford University Hospital NHS Trust**
3. Job title or position	**Consultant Clinical Oncologist**
4. Are you (please tick all that apply):	☐ **X** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **X** a specialist in the treatment of people with oesophageal or gastro-oesophageal junction cancer? ☐ a specialist in the clinical evidence base for oesophageal or gastro-oesophageal junction cancer? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ **X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes **I was involved in writing the organisation (**NCRI-ACP-RCP-RCR**) submission, and Part 1 remains unchanged upto question 23; q24 onwards new responses have been added** **I have added comments in part 2.**
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**none**
The aim of treatment for oesophageal or gastro-oesophageal junction cancer	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To cure the condition
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	Traditionally, improvement in overall survival is considered practice changing. A Hazard ratio of ~ 0.8 or lower for OS would be seen as practice changing in this indication (This was HR used for introduction of neo-adjuvant chemotherapy based on OE02 trial).

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in oesophageal or gastro-oesophageal junction cancer?	Oesophageal cancer is a cancer of unmet need. Of around 9000 cases diagnosed per year, ~20% have resectable disease (CRUK website accessed 1/3/2021: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer#heading-Five). 3-year survival is only 57.4% after curative surgery (NOGCA audit 2021: https://www.nogca.org.uk/content/uploads/2021/02/REF217_NOGCA_2020-Annual-Report-FINAL-V2.0.pdf), therefore further improvement in treatments are necessary.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Treatment varies depending on histology and site of tumour. For squamous cell cancers of the oesophagus, the treatment options are 1) neo-adjuvant chemoradiotherapy followed by surgery 2) definitive chemoradiotherapy 3) preoperative chemotherapy (2 cycles cisplatin-capecitabine) followed by surgery [where surgery is considered, option 1 is preferred over option 3] For adenocarcinoma oesophagus/gastro-oesophageal junction, surgery is the mainstay of treatment. Peri-operative treatment consists of either neo-adjuvant chemoradiotherapy or peri-operative chemotherapy which is mainly used for gastro-oesophageal tumour (perioperative FLOT [5FU, Leucovorin, Oxaliplatin, Docetaxel] combination is favoured over ECX [Epirubicin, cisplatin, capecitabine] combination). Following surgery and neo-adjuvant / peri-operative treatment, patients undergo follow up (ie current there is no recommended maintenance treatment)

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines NG83
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway for management is broadly well defined. For Squamous cell cancer, there is a difference in opinion between NHS professionals whether neoadjuvant chemoradiotherapy followed by surgery or definitive chemoradiotherapy is the preferred modality, they are broadly considered to be equivalent choices (and both are discussed as options with patients) For adenocarcinoma of the gastro-oesophageal junction, surgical based treatment is considered standard of care. Both neoadjuvant chemoradiotherapy followed by surgery and peri-operative FLOT chemotherapy are considered acceptable treatment options
• What impact would the technology have on the current pathway of care?	Embracing the technology would imply adjuvant treatment with nivolumab for 1 year (2 weekly in the first 16 weeks then 4 weekly). This translates to upto 16 additional visits for immunotherapy, which will have implications for patients and NHS services. A small proportion of the patients will experience serious side-effects which will need to be managed including hospitalisation (in Checkmate 577, the incidence of Grade 3-4 toxicity was 8% in the Nivolumab arm compared to 3% in placebo, but hospitalisation rate for toxicity was not specified)
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Nivolumab is used widely in the NHS for other clinical indications, although it is not used for oesophageal cancer. Its use as adjuvant treatment for oesophageal cancer will lead to extension of treatment duration for patients with oesophageal cancer treated with curative intent.
• How does healthcare resource use differ between	There will be extension in use of healthcare resources (chemotherapy services) as the technology requires administration of additional doses of treatment (Nivolumab) for upto 1 year.

the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This technology is likely to be delivered in secondary care (chemotherapy units)
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Introduction of this therapy will not require any additional equipment as Nivolumab is currently given in oncology centres for other indications. However, there will be implications on resources as this is an additional indication to be managed within oncology units. Additional test will be required to monitor for side-effects related to immunotherapy.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Checkmate 577 demonstrated a doubling of disease-free survival from 11 months to 22.4 months (HR 0.69) and a 31% reduction in recurrence or death - which was statistically significant and is considered clinically meaningful benefit.
• Do you expect the technology to increase length of life more than current care?	Although the data from Checkmate 577 is not available, the improvement in disease free survival demonstrated in the trial (HR 0.69) is likely to lead to a survival benefit
• Do you expect the technology to increase health-related quality of life more than current care?	Nivolumab is a relatively well tolerated treatment. Checkmate 577 showed that patient reported outcome based on EQ-5D-3L visual analogue scale showed broadly similar overall health status and utility index between Nivolumab treated and non-treated patients. However, it is to be noted that patients who develop recurrence after surgery is likely to experience deterioration in Quality of life due to disease status or

	palliative chemotherapy. As Nivolumab demonstrated a 31% reduction in risk of recurrent disease or death, it is likely that this will lead to direct benefit in terms of Quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No specific group was identified where the technology (adjuvant Nivolumab) was more or less effective as per Forrest plot analysis of subgroups.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It is not more 'difficult' as immunotherapy is administered as an intravenous infusion and is used within NHS for other indications. However, the protracted course of treatment for up to 1 year (in the trial, median duration of adjuvant immunotherapy was 10 months) will have resource implications. Patients on immunotherapy will require regular blood tests to monitor organ function including endocrine function. CT scan monitoring will be required during treatment to rule out disease progression (6-month disease free survival in the intervention arm of Checkmate 577 was 72%, ie ~30% will still progress, which will be detected mostly through CT scans.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The use of trial inclusion/exclusion criteria may be applied to start treatment, and disease progression or serious toxicity (as per trial protocol) as criteria for discontinuation. Treatment related toxicity may require treatment discontinuation. In Checkmate 577, treatment discontinuation due to toxicity was seen in ~9% of subjects. Establishing toxicity and severity would require additional testing (usually bloods, but for pneumonitis, CT scan).
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	NO
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The technology has a favourable therapeutic window as it has demonstrated good efficacy without significant toxicity or adverse impact on quality of life. Its impact on disease-free survival (doubling of median DFS) is clinical meaningful although overall survival outcomes are awaited.

• Is the technology a 'step-change' in the management of the condition?	Immunotherapy has been a step-change in many cancer sites and is of emerging importance in gastro-oesophageal cancer. It is a low-toxicity regimen. There are not many interventions in oesophageal cancer that have shown a HR of 0.69 with high statistical significance and doubling of disease-free survival. However, the impact on overall survival is also required.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, Improvement in survival is a patient group with particularly poor prognosis (median disease free survival 11 months)
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Nivolumab is a very well-tolerated treatment with high grade adverse events seen in <10% of cases. Checkmate 577 show no adverse effect on patient's quality of life compared to placebo.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, neo-adjuvant chemoradiotherapy followed by surgery is a standard option in this patient group. However, there are other standards used in the UK, including definitive chemoradiotherapy (squamous cell carcinoma), pre-operative chemotherapy and peri-operative chemoradiotherapy
• If not, how could the results be extrapolated to the UK setting?	It will be difficult to extrapolate results if alternative standards of care are used however potential ways to extrapolate results are suggested below. The clinical trial used a very specific patient group: post-surgery,

	R0 resection, those who had residual pathological disease post chemoradiotherapy (expected to be around 70% in case of adenocarcinoma and 50% in case of SCC). 1)Patients (SCC) who have had definitive chemoradiotherapy instead of surgery will not fulfil the surgical criteria, however if they have residual disease on re-staging endoscopy without metastatic disease on imaging (60-70%; Crosby et al, doi: 10.1016/S1470-2045(13)70136-0) could be considered equivalent group. 2) Patients who had FLOT chemotherapy (adenocarcinoma gastro-oesophageal junction) – proportion of patients with residual disease post FLOT is slightly higher (84%; Al Batran et al, doi: 10.1016/S1470-2045(16)30531-9) than those receiving chemoradiotherapy, adenocarcinoma cohort (77%; van Hagen et al, doi: 10.1056/NEJMoa1112088). Therefore, these treatment groups could be considered comparable, and the same criteria applied to select patients for the technology 3)patients who receive pre-op chemotherapy (Cisplatin-capecitabine or ECX) – complete path response is <10%, so >90% of the patients will have residual disease, which is much higher than those receiving chemoradiotherapy, hence unlikely to be comparable groups (so result cannot be extrapolated).
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcome is overall survival. Disease-free survival was the primary end-point of the study but median overall survival and overall survival at 1, 2 and 3 years were measured as secondary end-points. The primary end-point has been reported, the secondary outcomes are awaited.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not aware of any such data
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Real world data for this specific patient population (R0 resection with pathological residual disease on resected specimen) has not been published separately.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	None specifically, however it should be noted that several categories of patients were excluded in the trial because of contra-indication to immunotherapy, including patients with known HIV/AIDS and certain auto-immune conditions.

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. Is the eligible population in England expected to differ to the population in CheckMate 577?	The eligible population will not differ from CheckMate 577
25. Would people with cervical oesophageal carcinoma be included in the eligible population? If so, would the treatment efficacy expect to differ in people with this condition?	Primary management of patients with cervical oesophageal cancer is radical chemoradiotherapy, not surgery. Therefore they will not be appropriate for this intervention. Most clinical trials of oesophageal cancer/gastro-oesophageal junctional cancers have excluded cervical oesophageal cancer as they are considered more like Head and Neck cancers (and some centres are treated by Head and Neck oncologists rather than oesophageal oncologists, and may be treated with higher radiation dose than thoracic oesophageal cancers). The outcomes are different.
26. What proportion of people with oesophageal or gastro-oesophageal junction cancer who experience disease recurrence would have subsequent systemic therapies? What type of systemic	Recurrence following neoadjuvant chemoradiation and surgery is seen in 35% of cases in the CROSS trial (mixed population of SCC and adenocarcinoma) (Oppedijk, J Clin Oncol, 2014 Feb 10;32(5)385-91. In NEOSCOPE (adenocarcinoma-only population), progression was demonstrated in 32% cases (Mukherjee et al, Eur Jr Cancer, 2021 Jun 19;153:153-161). However this is based on recurrence rate in an unselected population who had chemorad and surgery (this would have included those who had complete response, which is 25-30% in

therapies would be given in clinical practice?	adenocarcinoma, 50% in SCC). Patient population in CHECKMATE 577 were selected group with residual disease post chemorad and therefore likely to have a worse prognosis and higher chance of recurrence Although I am not aware of any data on 2nd line therapy, I estimate about 50-60% of those who recur would be eligible for systemic therapy. For adenocarcinoma, it would usually be a combination of epirubicin, oxaliplatin and capecitabine (EOX) for HER2-ve patients and Herceptin, cisplatin and capecitabine for HER2 positive patients. For SCC, the chemotherapy combination is cisplatin/capecitabine or oxaliplatin/capecitabine
27. After progression on first-line treatment, would you expect a worse prognosis for people who received nivolumab or routine surveillance?	It is difficult to answer this, as there is no data. At the moment it is unknown whether there is a specific subgroup who truly benefit from immunotherapy (no subgroups could be identified based on known parameters in CHECKMATE 577 – but that does not mean one does not exist), and if such a subgroup exist, and we don't know whether their chemo-responsiveness is different. However, it is likely (personal view) that patients who have progressed despite adjuvant Nivolumab will have worse outcome.
28. Would you expect a proportion of patients to receive a lifelong benefit after treatment with Nivolumab? Please provide an estimate of this proportion if possible.	Looking at the DFS survival curve in the CHECKMATE 577 study and reading off the curve, the DFS curve for standard flattens out at around 30month time point with about 25-30% remaining disease free. For the Nivolumab survival curve, the curve flattens out with about 40-45% patients remaining disease free. Most recurrences in oesophageal/gastro-oesophageal cancers occur within 3 years (likely earlier in this 'high risk' group where there was residual disease post chemoradiation) – and this period has been captured in the DFS curves. This to suggests that a greater proportion of patients are being cured through Nivolumab and therefore have life-long benefit (in the order of 10-15%) – although a statistical opinion on this point needs to be taken as well.

29. Would you expect to give Nivolumab until progression or for a limited cycle or duration?	For limited period (upto 1 year) as per CHECKMATE 577 trial protocol. This period should not be extended as there is no evidence to support prolonged course of adjuvant Nivolumab.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Issue 1: The data used for disease-free survival (DFS) when fitting distributions.	
Issue 2: The distribution chosen to represent DFS	
Issue 3: The duration of DFS at which a 'cure' can be assumed	Most events in Oesophageal cancer would happen within 3 years, and most studies including the CROSS trial which is the basis for current standard of care (and including CHECKMATE 577) shows relative flattening of curve after 3 years. There will always be events with relapses being reported after 5 years, but 3 year would be a reasonable time point. Moreover, this group (persistent disease at surgery despite neoadjuvant chemorad) is a relatively worse group where we would expect events to occur earlier. So I consider 3 year as a reasonable duration of DFS at which for most patients 'cure' can be assumed.

Issue 4: The average age of patients treated in the UK	Not all patients will be suitable for Nivolumab given an year of additional treatment, and in clinical practice there will be some selection (as happens with clinical trials), so in clinical practice, I believe the patients who will actually receive Nivolumab will be similar to that reported in the trial. It should be noted that the trial protocol did not specifically define an age cut-off.
Issue 5: That above the age of 75 years, patients had the same utility independent of whether their disease had recurred	
Issue 6: Potential underestimation of the costing of adjuvant-nivolumab treatment within the model	1. Please consider additional comments in 'any important issues' section while estimating costs. 2. All patients will not complete total treatment due to toxicity and other issues, hope this was taken into consideration 3. While factoring in the 'eligible' population, only patients with residual disease on resected pathology (and not all patients who have had curative resection) should be eligible – this should be factored into calculations (as this limits the number of eligible patients to a smaller group which will have costing implications)
Issue 7: The source of utility data	
Are there any important issues that have been missed in ERG report?	I wanted to highlight that the eligible patients are only those with completely excised tumour who still have residual disease left on the resected pathological sample. 50% of SCC and 25-30% of adenocarcinoma patients have complete pathological response (no residual disease left on resected sample) and as per CHECKMATE 577, these patients would not have been eligible for Nivolumab. This makes the population

	eligible for Nivolumab considerable smaller (and I am not sure whether this has been taken into account while doing the cost-utility modelling). The ERG document (Sec 2.2, Fig 1) the flow-sheet also proposes adjuvant nivolumab following salvage resection in patients who receive definitive chemoradiotherapy. This may be a reasonable approach if the salvage is primary (ie response assessment with imaging and endoscopy performed after definitive chemorad shows local residual disease and the patient proceeds to immediate oesophagectomy). This is because RT dose for definitive chemorad is not too different from that of neoadjuvant chemorad. However if the patient is found to have complete response on CT and endoscopy following definitive chemorad, and subsequently, months or years down the line found to have local recurrence and is then treated with salvage surgery, benefit of Nivolumab in that group is unknown as was not a part of CHECKMATE 577 study. Currently ERG proposes infusions to be capped to 63 weeks. In my view, the duration of treatment of nivolumab should NOT be capped to x weeks or x months, given sometimes infusion may need to be delayed because of toxicity etc. I believe the '63 weeks' identified in trial data by ERG is most likely to have risen from unintended delays. The protocol clearly states that intention was 2 weekly infusions x 16 weeks (ie 8 infusions if all goes to plan) then 4 weekly infusions thereafter upto a total duration of 1 year. Assuming 52 weeks in a year, there would be 52-16=36 weeks of 4 weekly infusions (ie 9 infusions in this latter period). So the intended number of infusions in the trial was 8+9=17 (assuming everything went to plan). I would have thought, to eliminate ambiguity regarding infusions, rather than use a cap of ' 63 weeks', maybe use a cap of total number of infusions to 17 (and accept that due to toxicity/scheduling issues, this may spill beyond 52 weeks). If for example as currently proposed by ERG, a cap of 63 weeks was used and the patient was not delayed in anyway, this would have added 3 further infusions (and corresponding unnecessary costs)

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Technology shows clinically relevant improvement in disease free survival which is statistically highly significant
- The treatment is well tolerated with no adverse effect on Quality of life, and toxicity is acceptable
- It addresses need is a particular patient population which has poor prognosis (median DFS 11 months)
- Overall Survival data is not available – therefore impact on overall survival is currently unknown, but likely to have survival benefit given the DFS results

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer [ID1676]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Wednesday 21 July 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with oesophageal or gastro-oesophageal junction cancer and current treatment options	
About you	
1. Your name	**Professor Anne Thomas**
2. Name of organisation	**University of Leicester**
3. Job title or position	**Professor of Cancer Therapeutics**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with oesophageal or gastro-oesophageal junction cancer? ☐ a specialist in the clinical evidence base for oesophageal or gastro-oesophageal junction cancer? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NIL**
The aim of treatment for oesophageal or gastro-oesophageal junction cancer	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To cure the condition
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	To improve the overall survival In operable adenocarcinoma with a perioperative chemotherapy approach this is a median survival of 50 months in the FLOT4-AIO German study. In the Dutch CROSS study which studied neo adjuvant chemoradiotherapy in both squamous cell and adenocarcinoma the median survival was 49.4months.

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in oesophageal or gastro-oesophageal junction cancer?	Oesophageal cancer, including gastro-oesophageal junctional tumours (GOJ), is a global healthcare problem and has been designated a cancer of unmet need by CRUK. The majority of patients present with stage 4 (incurable) cancer and for those that undergo potentially curative surgery the long term survival is only approximately 30%.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Treatment varies depending on histology and location of tumour. Chemoradiotherapy is only possible when the primary tumour is relatively short in length (<10 cm) and there is no significant involvement of the cardia (top of the stomach). This therefore excludes most junctional tumours and only includes tumours confined to the oesophagus For squamous cell cancers of the oesophagus, the treatment options are 1) neo-adjuvant chemoradiotherapy followed by surgery 2) definitive chemoradiotherapy 3) preoperative chemotherapy (2 cycles cisplatin-capecitabine) followed by surgery. For gastro-oesophageal adenocarcinoma (including GOJ) surgery alone is considered for stage I disease. For bulky stage II and III perioperative chemotherapy is administered around the time of the surgery. The most effective drugs are FLOT 5FU, Leucovorin, Oxaliplatin, Docetaxel but this does have associated adverse effects and may be difficult to administer as a complete course of treatment

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines NG83 ESMO guidelines 2016
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Specialist MDTs exist to treat these patients throughout England so treatment pathways are fairly well aligned. There is some divided opinion with regard the role of trimodality treatment (surgery and chemoradiotherapy) in Squamous cell carcinoma of the oesophagus versus definitive chemoradiotherapy. Some oncologists use more neoadjuvant ECX/EOX (epirubicin, cisplatin or oxaliplatin and 5FU) than FLOT chemotherapy
• What impact would the technology have on the current pathway of care?	The patients would have longer adjuvant therapy than they do now. This technology would be added on to the end of the current pathway with increase in duration of therapy for these patients.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Nivolumab is used widely in the NHS for the treatment of cancers such as melanoma and lung cancer. The current care pathways for these tumours would be used to treat the oesophageal patients eg. Patient alert cards, education re side effects
• How does healthcare resource use differ between the technology and current care?	Patients would have an additional years worth of treatment with nivolumab which would be given every 2 weeks initially and then every 4 weeks
• In what clinical setting should the technology be used? (For example,	Secondary care chemotherapy units

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There would need to be investment into capacity in chemotherapy suites to accommodate these additional patient attendances. This would mean more pharmacy time, chair time with chemotherapy nurse support.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Checkmate 577 is a large well designed global randomised study. The median disease free survival was 22.4 months in all comers (ie irrespective of PDL1 status). The hazard ratio was 0.69 (96.4% CI 0.56-0.86).
• Do you expect the technology to increase length of life more than current care?	Yes. Checkmate 577 needs further follow up to report OS. To date the median distant metastasis-free survival curves are very encouraging with clear separation between those patients treated with nivolumab and those treated with placebo. 28.3months versus 17.6 months (HR 0.74 95% CI 0.60-0.92)
• Do you expect the technology to increase health-related quality of life more than current care?	Health related quality of life was recorded in Checkmate 577 using FACT-E and EQ-5D-3L. 90% of data was collected and there was no deterioration in health of the patients on nivolumab. Moreover, when these patients relapse their quality of life does plummet. With the reduction of risk of recurrence of 31%, we can predict that quality of life will be maintained in patients as their risk of recurrence diminishes.
14. Are there any groups of people for whom the technology would be more or less effective	The pre-planned subgroup analysis did not show that any group benefitted more than another allowing for the small numbers in some of the groups (eg black race). Tumour-cell PD-L1 expression did not discriminate responses.

(or appropriate) than the general population?	
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	In Checkmate 577 the incidence of serious adverse events related to nivolumab was 8% compared to 3% in the placebo group. It is to be expected that some patients will therefore get immune-related toxicities which will need to be managed by steroids and potentially hospital admissions. Patients will need additional blood tests and CT scanning through the period of time they are on treatment. Currently patients are not routinely scanned once they have completed treatment. There is no doubt that this is a long time for patients to be on treatment but post Ivor Lewis oesophagectomy, patients often have regular hospital visits to deal with the morbidity of the operation itself.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patient selection will need to mirror the selection of patients as described in the inclusion and exclusion eligibility criteria of the Checkmate 577 study. Patients will need to be of good PS and in practice a number of patients will not be eligible for this treatment due to poor performance status and or co-morbidities. Additional screening of patients for HIV and Hep B and C will need to be done as well as thyroid function testing and cortisol levels.

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	NO
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. These data clearly define a patient population who may benefit from this technology. Although the overall survival data from Checkpoint 577 is awaited; the DFS and distant metastasis-free survival curves look very encouraging with clear separation and an encouraging plateauing tail indicating the potential of long term survival at a level yet to be achieved in this patient population
• Is the technology a 'step-change' in the management of the condition?	Absolutely
• Does the use of the technology address any particular unmet need of the patient population?	Yes. Current outcomes for this patient group are poor despite patients enduring very intense chemotherapy/radiotherapy and surgery.
19. How do any side effects or adverse effects of the technology	Immune-mediated adverse results will be seen in up to 10% of patients. With the knowledge of using this technology already in other cancer treatment algorithms, there is a wealth of experience with the management of the side

affect the management of the condition and the patient's quality of life?	effects. Patient education will be key and appropriate support from the specialist team. No significant negative impact on quality of life is predicted.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the Checkmate 577 trial cohort reflects the clinical care of this patient group who undergo trimodality treatment in the UK.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival is a secondary outcome of the trial and has yet to be reported. The disease free survival is very impressive with an doubling from 11 months to 22.4 months; moreover with a tolerable safety profile which is very important for this group of patients who undergo a complex and difficult treatment programme
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not	NO

apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	NO
22. How do data on real-world experience compare with the trial data?	It is very difficult to get accurate comparative real world data as the National Audit in OG cancer doesn't provide the detail of this specific cohort of patients with R0 disease after a trimodality approach to treatment. [redacted]
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	NO
23b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	

24. Is the eligible population in England expected to differ to the population in CheckMate 577?	NO
25. Would people with cervical oesophageal carcinoma be included in the eligible population? If so, would the treatment efficacy expect to differ in people with this condition?	Yes if these patients were going to be treated on this pathway. Occasionally very high cervical tumours are treated with the involvement of the ENT surgeons as well.
26. What proportion of people with oesophageal or gastro-oesophageal junction cancer who experience disease recurrence would have subsequent systemic therapies? What type of systemic therapies would be given in clinical practice?	We endeavour to give all patients with recurrence palliative systemic treatment. Inevitably, some patients have deteriorating performance status are not fit enough for treatment or indeed patients choose not to have treatment. Approximately 80% of patients will have treatment. Platinum based chemotherapy regimens are the standard first line options for recurrent metastatic gastro-oesophageal cancer but this does depend on the time to progression. If patients progress within 12 months of their original surgery then there is little chance of remaining sensitive to platinum agents. In adenocarcinoma there are no standard second line treatment options and some oncologists may use a taxane or irinotecan based regimen or indeed refer for clinical trials. Nivolumab is licensed and approved by NICE for use in patients with metastatic squamous cell carcinoma of the oesophagus following prior fluorouracil and platinum containing regimens. This therefore represents a new standard of care option for these patients.
27. After progression on first-line treatment, would you expect a worse prognosis for people who	At the moment there are no data to definitely answer this question and thus we think the prognosis is likely to be the same in both groups

received nivolumab or routine surveillance?	
28. Would you expect a proportion of patients to receive a lifelong benefit after treatment with Nivolumab? Please provide an estimate of this proportion if possible.	Yes, without the OS data it is difficult to be exact but there is a 26% reduction in risk of metastatic- disease free survival provided in Checkmate 577 at around 30 months with the survival curves plateauing at this point. The attrition of patients between 3 and 5 years of follow up after trimodality treatment is small with most recurrences happening within 3 years of surgery. Therefore, it is expected that a proportion of patients will be cured with lifelong benefit due to the provision of adjuvant nivolumab. This proportion will not be more than 26%.
29. Would you expect to give Nivolumab until progression or for a limited cycle or duration?	Up to 1 year as defined in the trial if toxicity was acceptable and the patient had stable disease on imaging

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Issue 1: The data used for disease-free survival (DFS) when fitting distributions.	No comment
Issue 2: The distribution chosen to represent DFS	No comment
Issue 3: The duration of DFS at which a 'cure' can be assumed	Most recurrences happen within 3 years of surgery therefore patients surviving for 3 years and beyond are deemed cured. Very few recurrences happen between 3 and 5 years.

Issue 4: The average age of patients treated in the UK	Trimodality treatment is only offered to the fittest patients with oesophago-gastric cancer. It is not possible to gain this information from the National OG Audit data. [redacted]
Issue 5: That above the age of 75 years, patients had the same utility independent of whether their disease had recurred	No comment
Issue 6: Potential underestimation of the costing of adjuvant-nivolumab treatment within the model	No comment
Issue 7: The source of utility data	No comment
Are there any important issues that have been missed in ERG report?	No

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- There is an unmet need to improve outcomes of gastro-oesophageal patients treated with radical intent
- Adjuvant nivolumab provides a step change improvement in outcomes in the Checkmate 577 study
- The patient population in the Checkmate 577 is representative of UK patients undergoing trimodality treatment
- The addition of adjuvant nivolumab to existing trimodality regimens is tolerable
- Capacity will be needed in chemotherapy suites to deliver the technology but the patients numbers will be small ~150 per year in the UK

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer [ID1676]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**David Chuter**

2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	GUTS UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Our lives are completely changed by the effects of this cancer and treatment, eating normally has gone, we struggle to eat well so quality of life is affected and correct nutrition can be a problem long and short term. Many patients are diagnosed late and malnutrition is common due to swallowing or eating issues so it can be hard to cope with the treatment, often a feed tube is needed before treatment starts. Patients do live in fear of the cancer returning or spreading to other parts of the body during or after treatment, this never goes away. Carers and family members do have added concerns when seeing their loved ones losing weight and often see the weight loss before the patient, they also may have the full worry of financial issues if the patient or carer cannot work and just coping with surrounding family and friends can be hard.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Just coming out of the pandemic patients and carers are aware of likely delays of treatment as in the national media every day, also there is the fear of hospital visits because of Covid19. Everyone know early diagnosis is key for better treatment options and outcomes but the concern is getting the referral from the GP early enough, especially the younger patients presenting with the most common symptoms but GPs often dismiss heartburn and ingestion in patients below 60 as considered not at risk to this cancer or the precursor of Barretts Oesophagus. The current care and treatments do vary between Hospitals Trusts and the options are often limited due to late referral and / or diagnosis, too many present to A&E now with late stage cancer.
10. Is there an unmet need for patients with this condition?	Extending life and survivorship is the main unmet need and is governed by early awareness and diagnosis. Quality of life and wellbeing during treatment and after, be it end of life or palliative care or survivorship, is again down to early diagnosis and getting nutrition and exercise right from the start. Presenting late stage especially with younger patients.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Once diagnosed many patients will search online and be shocked by the survival figures, many will look for the best treatment and trial available but others will be concerned about the added risk of extra side effects of new treatment technologies to the standard treatments. As a patient myself, at the time of diagnosis my biggest worry was the treatment but if I knew it may help me survive even a few months longer I would have gone for it.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	There will be concerns over Covid being more of a danger when using this combination of treatment. Added side effects. Possibilities that quality of life may be reduced. Carers and family members may see the patient struggling to cope with the treatment. Feeling that the technology is untested.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Yes. Younger patients diagnosed early and without other health complications. Any age patients with very little or no malnutrition at diagnosis and with reasonably fitness level. These patients will be able cope with the treatment and possibly have less side effects.
Equality	
14. Are there any potential equality issues that should be taken into account when	Many communities are sometimes reluctant to visit their GP, it may be ethnic, social standing or lack of awareness reasons. Younger patients due to accepting symptoms are normal and down day to day stress and eating habits, also because GPs may not trigger a referral with a younger patient.

considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	Earliest start of treatment but ensuring the patient can cope, nutrition and fitness is key. Quality of Life and Wellbeing must be part of the normal follow ups and hospital visits, can be done by telephone and virtual platform but must be timely. We do not know the long term effect of this combination treatment so data must be collected into survivorship, this will mean follow ups for longer than standard treatment.
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • Patient is fit for the treatment. • Early diagnosis especially by GP of younger patients. • Quality of life is checked in a timely manner during treatment. • Nutrition and fitness / exercise is important to cope with the treatment • Must extend life with good quality of life.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer [ID1676]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments**: 5pm, Wednesday 21 July 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NCRI-ACP-RCP-RCR**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	• Response
Key issue 1: The data used for disease-free survival (DFS) when fitting distributions	**No**	
Key issue 2: The distribution chosen to represent DFS	**No**	
Key issue 3: The duration of DFS at which a 'cure' can be assumed	**Yes**	• Most events in Oesophageal cancer would happen within 3 years, and most studies including the CROSS trial which is the basis for current standard of care (and including CHECKMATE 577) shows relative flattening of curve after 3 years. There will always be events with relapses being reported after 5 years, but 3 year would be a reasonable time point. Moreover, this group (persistent disease at surgery despite neoadjuvant chemorad) is a relatively worse group where we would expect events to occur earlier. So, we would consider 3 year as a reasonable duration of DFS at which for most patients' 'cure' can be assumed.
Key issue 4: The average age of patients treated in the UK	**Yes**	• Not all patients will be suitable for Nivolumab given it is a year of additional treatment, and in clinical practice there will be some selection (as happens with clinical trials), so in clinical practice, I believe the patients who will actually receive Nivolumab will be similar to that reported in the trial. It

		should be noted that the trial protocol did not specifically define an age cut-off.
Key issue 5: That above the age of 75 years, patients had the same utility independent of whether their disease had recurred	**No**	
Key issue 6: Potential underestimation of the costing of adjuvant-nivolumab treatment within the model	**Yes**	ERG identified that patients received treatment more than 1 year. This is most likely to have risen from unintended delays. The protocol clearly states that intention was 2 weekly infusions x 16 weeks (ie 8 infusions if all goes to plan) then 4 weekly infusions thereafter up to a total duration of 1 year. Assuming 52 weeks in a year, there would be 52-16=36 weeks of 4 weekly infusions (ie 9 infusions in this latter period). So, the intended number of infusions in the trial was 8+9=17 (assuming everything went to plan). If the infusions were delayed due to toxicity etc, it would appear that the total treatment time was greater than 1 year. Our experts suggest, to eliminate ambiguity regarding infusions, rather than use a cap of '63 weeks' as proposed by ERG, using a cap of total number of infusions to 17 (and accept that due to toxicity/scheduling issues, this may spill beyond 52 weeks). There is a potential for *over-estimation* of cost if following hasn't been considered: • All patients will not complete total treatment (1 year) due to toxicity and other issues. In CHECKMATE 577, the median duration of treatment was 10 months. It is not clear if this hope this has been taken into consideration during cost-estimations • While factoring in the population eligible for nivolumab, only patients with residual disease on resected pathology (and not all patients who have had curative resection) should be eligible – this should be factored into

		calculations (as this limits the number of eligible patients to a smaller group which will have costing implications)
Key issue 7: The source of utility data	**No**	

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

• Additional issue 1: **Duration of Nivolumab treatment**	• Section 1.1 (iii) page 9	• Yes	• ERG preferred a maximum treatment duration of 63 weeks. As alluded to in response to Key Issue 6 above, the additional weeks beyond 1 year does not represent additional infusions of nivolumab, it is due to delays in treatment. So maximum number of infusions (17) rather than duration of treatment in time units should be recommended. In the CHECKMATE 577 trial, the median duration of treatment was 10 months. It is not clear whether this was factored into costings.

• Additional issue 2: **Eligibility of Nivolumab for patients undergoing salvage oesophagectomy**	• Section 2.2 (Fig 1) pg 15	• Yes	For patients receiving radical chemoradiotherapy (where primary surgery is not intended) – salvage surgery is offered if a) patients have persistent disease despite chemoradiotherapy or b) patients have no evidence of disease after completion of chemorad, but subsequently develop locally recurrent disease at a later stage. The current algorithm proposed by the fig 1 does not differentiate between a) and b) in terms of eligibility for adjuvant nivolumab. Patients who receive immediate salvage surgery (ie a) – is very similar to neo-adjuvant chemoradiotherapy and surgery as in the CHECKMATE 577 cohort, and it is reasonable to allow nivolumab in this cohort. However, patients who receive salvage at a later date (ie b) – the benefit of nivolumab is not proven as this cohort has not been evaluated in CHECKMAT 577 and therefore it may not be appropriate to offer nivolumab in this cohort as this is essentially recurrent disease

• Additional issue 3: **Population eligible for Nivolumab**	• Section 2.3.1 (page 16)	• Yes	• Scope issued by NICE is 'adults with resected OC or GEJC'. However, CHECKMATE 577 did not include all patients with resected OC or GEJC – only those patients whose resected samples contained residual disease. This is a subset of patients undergoing resection (as ~50% of patients with Squamous cell cancer and ~25-30% with adenocarcinoma undergo complete pathological response and would not have been eligible for trial treatment). This should be considered while calculating ICER and making recommendations.

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER

• Insert key issue number and title as described in the ERG report	• Briefly describe the company's original preferred assumption or analysis	• Briefly describe the change(s) made in response to the ERG report	• Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
• ..	• ..	• ..	• [INSERT / DELETE ROWS AS REQUIRED]
• Company's preferred base case following technical engagement	• Incremental QALYs: [QQQ]	• Incremental costs: [£££]	• Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer [ID1676]. A Single Technology Appraisal. Response to the company's Technical Engagement Report response

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Neither author has any conflicts of interest to declare.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Stevenson M and Rawdin A. Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer [ID1676]. A Single Technology Appraisal. Response to the company's Technical Engagement Report response. School of Health and Related Research (ScHARR), 2021.

Contributions of authors

Matt Stevenson and Andrew Rawdin critiqued the company's response to the technical engagement report and produced the ERG's base case analysis. Both authors were involved in drafting and commenting on the final report.

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1) Introduction.

This report serves as a critique and discussion of the company's response to the Technical Engagement Report[1] (TER) that was produced following the Evidence Review Group (ERG) report relating to Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer.[2] The ERG and company are largely in agreement with the assumptions within the company's model and the data used to populate it. The one exception is whether a cure could be assumed after 3 years of disease-free survival (DFS), which is the company's base case, or after 5 years' DFS, which is the ERG's preference. For conciseness, the majority of the additional data provided by the company in its response to the TER[1] are not reproduced here.

The following sections detail the: changes made to the company's base case following the TER; the resulting base case incremental cost-effectiveness ratio (ICER); the ERG's base case ICER; and conclusions.

2) Changes made to the company's base case following the TER

The company addressed the seven key issues raised in the TER. These are summarised in Table 1. Full details of the changes are provided in the company's response.[1]

Table 1: The ERG's summary of changes made by the company to its base case in response to the TER.

Issue Number	Changes made by the company to its base case	ERG critique
1	The company has used more mature data (from a database lock of February 2021) within its survival analysis	The ERG agrees with this change
2	The company has changed the distribution for DFS to a Generalised-F distribution	The ERG agrees with this change
3	None – the company maintains a cure at 3 years DFS within its base case.	The ERG maintains its preference for a cure to be considered at 5-years of DFS rather than 3.
4	The company has increased the mean age to 62.66 years	The ERG believes this is a plausible value and a better estimate than the 60.5 years originally used.
5 and 7	The company has age-adjusted utilities in all health states and have used Ara and Brazier to estimate utility in the general population	The ERG agrees with these changes
6	The company has added dose modification to take into account that treatment after 12 months was due to missed doses not additional treatment	The ERG agrees with this change

3) The company's new base case ICER

The changes documented in Table 1 resulted in a change in the company's probabilistic base case ICER, which is shown in Table 2. For reference, the deterministic ICER is £16,668

Table 2: The company's new base case probabilistic ICER.

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)			**£17,511**

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

The company estimates that the probability that the ICER is below £30,000 per QALY is [redacted] using 1000 iterations.

4) The ERG's new base case ICER

The ERG altered only one parameter from the company's base case, which related to the time after DFS at which the patient would be considered cured. This is due to different interpretations of the underlying data. The company states that for the most mature dataset "*only* [redacted] *events occur following 36 months, despite* [redacted] *patients at risk in the nivolumab arm and* [redacted] *patients in the routine surveillance arm. This would strongly indicate cure at three years in both treatment arms.*" In contrast, the ERG believes that if patients were truly cured then death would only be due to background mortality rates and the data provided by the company indicate rates greater than for a general population aged approximately 66 years. Additionally, clinical advice provided to the ERG suggested that a period of 5 years of DFS would be preferable, whilst clinical advice to the company suggested that "*the underlying hazard may not converge to the general population rate for approximately three to five years.*" For these reasons, the ERG prefers assuming a cure after 5 years of DFS

As shown in Table 3, the ERG's new base case has a probabilistic ICER of £17,613; for reference, the deterministic ICER is £16,611. The ERG estimates that the probability that the ICER is below £30,000 per QALY is [redacted] using 1000 iterations.

Table 3: The company's new base case probabilistic ICER.

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)			**£17,613**

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

In writing this document the ERG realised it had not provided an analysis where the mortality rate of 'cured' patients was higher than that of the general population, as is often assumed in NICE appraisals. Whilst this does not form part of the ERG base case, an analysis has been run to pre-empt potential questions from the committee. In this analysis the probability of death was increased by an arbitrary 10% for all patients aged 68 years and over (assuming a starting population approaching 63 years and 'cure' at 68 years). This analysis resulted in a deterministic ICER of £17,105, which was formed from an incremental cost of [redacted] and [redacted] incremental QALYs. This moderate increase in the ICER, of less than £500, indicates that the results were robust to assumptions regarding increased mortality compared with the general population after 'cure'.

5) Conclusions

The company estimate a probabilistic ICER of £17,551 (£16,668 deterministic). The ERG's estimates are similar, with a probabilistic ICER of £17,613 (£16,611 deterministic). Both the company and the ERG estimate that the probability of the ICER being below £30,000 per QALY gained is very high.

6) References

1. Bristol-Myers Squibb Ltd. Comments on the Technical Engagement Report. 2021.
2. Stevenson M, Simpson E, Stevens J, Rawdin A, Orr M, Clowes M, *et al.* Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer [ID1676]. A Single Technology Appraisal. 2021.

Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer [ID1676]. A Single Technology Appraisal. Addendum

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Declared competing interests of the authors

Neither author has any conflicts of interest to declare.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Stevenson M and Rawdin A. Nivolumab for adjuvant treatment of oesophageal or gastro-oesophageal junction cancer [ID1676]. A Single Technology Appraisal. Addendum. School of Health and Related Research (ScHARR), 2021.

Contributions of authors

Matt Stevenson and Andrew Rawdin produced the additional results requested by NICE. Both authors were involved in drafting and commenting on the final report.

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1) Introduction.

This report provides additional analyses requested by NICE at the pre-meeting briefing. These fall into three categories.

1) Providing the incremental costs, life years, and QALYs associated with the deterministic ERG base case. Previously, these were provided for only the probabilistic ERG base case, with both ICERs reported.
2) Providing a sensitivity analysis changing the mean age in the ERG deterministic base case to 65 rather than 62.66 years
3) Providing a sensitivity analysis where the mean age was changed to 65 years and a standardised mortality ratio (SMR) of 1.10 was applied to those patients considered 'cured' in the ERG deterministic base case. Cured patients were those who had disease-free survival for a period of 5 years.

2) Documenting the incremental costs and QALYs within the ERGs base case.

As shown in Table 1, the ERG's deterministic base case has a ICER of £16,611; for reference, the probabilistic ICER is £17,613, which is the approach that the ERG believes is most appropriate for decision making.

Table 1: The ERG's base case deterministic ICER.

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)			**£16,611**

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

3) A sensitivity analyses assuming that the mean age for patients was 65 years.

Table 2 provides deterministic results when the mean age of patients was increased from 62.66 years to 65 years. This change increases the ERG's base case deterministic ICER from £16,611 to £18,574.

Table 2: The ERG's base case deterministic ICER with patient mean age increased to 65 years.

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)			**£18,574**

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

4) A sensitivity analyses assuming that the mean age for patients was 65 years and applying an SMR of 1.1 to patients considered 'cured'.

Table 3 provides deterministic results when the mean age of patients was increased from 62.66 years to 65 years and also applying an SMR of 1.1 to patients considered 'cured'. This change increases the ERG's base case deterministic ICER from £16,611 to £19,169.

Table 3: The ERG's base case deterministic ICER with patient mean age increased to 65 years and applying an SMR of 1.1 to patients considered 'cured'.

Outcome	Nivolumab	Routine surveillance	Incremental
Costs	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (Cost/QALY)			**£19,169**

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

5) Conclusions

The ERG's additional analyses produced deterministic ICERs below £20,000, although the probabilistic ICERs are anticipated to be higher, as in the ERG base case the probabilistic ICER was 5% higher than the deterministic value.